HIV Care Continuum in Jimma, Southwest Ethiopia: A Multiphase Mixed Methods Study

by

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Thesis
Submitted to Flinders University
for the degree of Doctor of Philosophy in Public Health

Doctor of Philosophy in Public Health

College of Medicine and Public Health

17.04.2019

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ABBREVIATIONS, ACRONYMS AND GLOSSARY

AHR	Adjusted hazard ratio
AIDS	Acquired immune deficiency syndrome
ANC	Antenatal care
AOR	Adjusted odds ratio
ART	Antiretroviral therapy
ART_{HP}	ART in health post
ART_{PC}	ART in private clinics
CAGs	Community ART groups
CD4	Cluster of differentiation 4
CDC	Centres for diseases control
CHR	Crude hazard ratio
COR	Crud odds ratio
CSA	Central statistical agency
EMR	Electronic medical records
EPHA	Ethiopian Public Health Association
FDRE	Federal Democratic Republic of Ethiopia
GBD	Global burden of diseases
GDP	Global domestic production
H2H	House-to-house HIV testing
HAART	Highly active antiretroviral therapy
HAPCO	HIV/AIDS prevention and control office
HCC	HIV care continuum
HCT	HIV care and treatment

HEP	Health extension program
HEWs	Health extension workers
HIV	Human immune-deficiency virus
HSDP	Health sector development program
IDUs	Injected drug users
JHC	**Jimma Health Center**
JUTH	**Jimma University Teaching Hospital**
LP	Late presentation for HIV care
LTFU	Lost to follow-up
MSH	Management Science for Health
MSF	Médicins Sans Frontières
MSM	Men who have sex with men
NCD	Non-communicable diseases
NGO	Non-governmental organizations
OPD	Outpatient department
OSSA	Organization Service for Social Aid
PEPFAR	The United States President's emergency plan for AIDS relief
PITC	Provider initiated HIV testing and counselling
PMTCT	Prevention of HIV transmission from mother to child
POC	Point of care
RCT	Randomized clinical trial
SHT	Self-HIV testing
SNNPR	Southern Nations, Nationalities and Peoples Region
SSA	sub-Sahara Africa

STIs Sexually transmitted infections

Tb Tuberculosis

TTLT Teach, test, link and trace model

UNAIDS The Joint United Nations Programme on HIV/AIDS

VCT Voluntary counselling and testing for HIV

WHO World Health Organization

Glossary

Terms ***Definitions***

AIDS is a condition that describes an advanced stages of HIV infection characterized by low immunity, multiple OIs and/or HIV-related cancers.

ART is a type of drug used to treat HIV infection and is provided lifelong in combinations with other ARTs.

CAGs is a program in which HIV patients on ART form a group, and collects ART medications from the clinic on a rotating basis to distribute to the other community members. Each patient should also visit a health facility twice a year to receive clinical services, and anytime when feeling unwell.

CD4 is a group of T-lymphocytes that helps to show the status of immune system in an HIV infection patient, and the CD4 count is a test that measures the level CD4 cells the HIV patient has in his/her blood.

Discontinuation is interrupting ART intake either for short or long periods or total stoppage.

H2H H2H is an HIV testing program in which HIV testing is performed in house of individual to be tested. The testing may be performed by peer educators, HEWs or trained lay counsellors.

Health centre is a health facility at the primary care level that provides preventive and curative services by health officers, nurses, and laboratory and pharmacy professionals. Each health centre coordinates five health posts and provides basic health care services for about 25,000-40,000 people.

Health post is the lowest health facility level at the primary health care level and based in kebele, the lowest administrative unit in Ethiopia, that provides basic preventive packages, family planning and delivery. Each health post serves 3,000-5,000 population. The professionals deployed in health post are called HEWs.

HEWs are trained (one year) female cadres of community-based health workers who are in charge of a health post. Each health post employs 2-3 HEWs.

Immunologic failure is failure to gain immunity after starting ART**.**

LP is a delay in HIV diagnosis or linkage to ART care.

OIs are superimposed infections (to HIV) that occur in immunocompromised patients. These infections occurred more frequently in those group of patients.

PITC is HIV testing program through the recommendation of the health care provider who come to visit a health facility.

PMTC is an intervention program that HIV transmission from an HIV-positive mother to her infant.

POC is testing or provision of care at the time and place of patient care.

SHT is an HIV testing program whereby a person collects a specimen from him- or herself, to conduct HIV testing and interpret the status by oneself.

TTLT is a full package program that provides HIV counselling and testing, ART linkage and tracing of lost patients from ART care services.

VCT is a client-based HIV testing program in which individuals actively seek HIV testing and counselling services at a health facility.

Executive Summary

Introduction: The HIV care continuum framework aims to provide a linked continuum of care through diagnosis, effective treatment and patient monitoring. Significant progress has been achieved in the antiretroviral therapy (ART) era, but several challenges have also hampered its ultimate success. These include: late HIV care presentation (LP), discontinuation from pre-ART and ART, poor adherence to ART and immunological failure. The aims of this thesis were four-fold, to: (i) review the available evidence on ART discontinuation in Ethiopia, (ii) examine the whole continuum of HIV care, (iii) explore the facilitators, barriers and solutions of HIV care and treatment (HCT), and (iv) develop consensus-based solutions for improving access to and utilization of HCT in Southwest Ethiopia.

Methods: The thesis employed a mixed-methods study in four phases: (i) systematic review and meta-analysis of ART discontinuation in Ethiopia, (ii) retrospective cohort study in Southwest Ethiopia of predictors of LP, ART discontinuation, HIV related immunologic failure and mortality, (iii) qualitative study to explore the facilitators, barriers and solutions for HIV care from the perspectives of HIV patients, care providers, community advocates and program managers from Southwest Ethiopia, and (iv) consensus-development study using a Nominal Group Technique (NGT), involving service providers, researchers, governmental and non–governmental HIV program managers, to identify possible solutions (identified from the qualitative study) for improving access to HCT. Ethics approvals were obtained from Flinders University of South Australia and Jimma University of Southwest Ethiopia.

Results

(i) The systematic review and meta-analysis identified risk factors for discontinuation as: rurality, poor literacy, alcohol consumption, tobacco smoking, mental illness and functional incapacity.

(ii) The 12-year retrospective cohort study (n=5299 patients with HIV) found the following. LP (in 65% of participants) led to poor outcomes and was associated with risk factors such as being younger, female, Tb/HIV co-infected and no history of HIV testing among adults but not in children. Discontinuation rate from ART care was 22.3% and the problem increased with time. Predictors of ART discontinuation comprised being female, having an immunological failure, having Tb/HIV co-infection, and no previous history of HIV testing. Immunologic failure was seen in 20% of participants and its magnitude increased with time. Similarly, predictors of immunologic failure included being: female, late presenters for HIV care, and

CD4 <200 cells/mm3. The cumulative incidence of HIV mortality was 6.2%, and CD4 count <200 cells/μL, WHO clinical stage 3 or 4, having immunologic failure, bedridden functional status, and no history of HIV testing. Using the above continuum of care as surrogate measures, the performance of Southwest Ethiopia to the UNAIDS 90-90-90 targets was 35-66-65.
(iii) The qualitative study included semi-structured interviews with 35 participants (10 HIV patients, nine HIV care providers, 11 community advocates and five HIV program managers/policy makers). Facilitators for HIV care were found to be new programs, knowledge and trust in ART and support. Emerging barriers were fear of being seen by others, availability, role of tradition, free ART as expensive, poor knowledge and trust in ART care system and fragmented health care system. The suggested solutions included strengthening existing programs, implementing new programs (self-HIV testing, house-to-house HIV testing, community ART distribution, and *teach, test, link and trace* model), decentralizing and integrating services (ART in health post, ART in private clinics), and filling gaps in legislation (in issues related with disclosure and traditional healing practices).
(iv) The consensus method included 18 experts, who identified the following possible solutions: filling gaps in legislation, self-HIV testing and *teach-test-link-trace* model.

Conclusions: This thesis shows that poor HIV care outcomes were prevalent in Southwest Ethiopia, and the UNAIDS performance was very low compared to the global target. The HCT programs were affected by patient-, HIV care provider-, community- and policy-level barriers. The involvement of multidisciplinary teams is recommended to act on the complex issue, and call for the implementation of the suggested solutions from these studies. However, a large-scale study would be required before implementing the solutions from the experts.

Key Words: HIV care continuum, late presentation for HIV care, discontinuation, lost to follow up, retention, attrition, immunologic failure, mortality, UNAIDS 90-90-90, meta-analysis, cohort, qualitative study, nominal group technique, mixed method

DECLARATION

I certify that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief, it does not contain any material previously published or written by another person except where due reference is made in the text.

17/04/2019

Hailay Abrha Gesesew **Date**

PUBLICATIONS RELATED TO THE THESIS

Original published papers:

1) **Hailay A Gesesew,** Lillian Mwanri, Paul Ward, Kifle W Hajito, Garuma T Feyissa. Factors associated with discontinuation of anti-retroviral therapy among adults living with HIV/AIDS in Ethiopia: a systematic review protocol. JBI Database of Systematic Reviews & Implementation Reports 2016, 14 (2): 27-36.
2) **Hailay Abrha Gesesew**, Paul Ward, Kifle Woldemichael Hajito, Garruma Tolu Feyissa, Leila Mohammadi, Lillian Mwanri. Discontinuation from antiretroviral therapy: a continuing challenge among adults in HIV care in Ethiopia: a systematic review and meta-analysis. PLOS ONE, 2017, 12 (1): e0169651.
3) **Hailay Abrha Gesesew**, Paul Ward, Kifle Woldemichael, Lillian Mwanri. Late presentation for HIV care in Southwest Ethiopia in 2003-2015: Prevalence, trend, outcomes and risk factors. BMC Infectious Diseases, 2018, 18:59.
4) **Hailay Abrha Gesesew**, Paul Ward, Kifle Woldemichael Hajito, Lillian Mwanri. Prevalence, trend and risk factors for ART discontinuation among HIV-infected adult patients in Ethiopia in 2003-2015. PLOS One, 2017, 12(6): e0179533.
5) **Hailay Abrha Gesesew**, Paul Ward, Kifle Woldemichael, Lillian Mwanri. Immunological failure in HIV-infected adult patients from 2003 to 2015 in Southwest Ethiopia. BMJ Open, 2018, 8(8): e017413.
6) **Hailay Abrha Gesesew**, Paul Ward, Kifle Woldemichael, Lillian Mwanri. Early mortality among patients accessing antiretroviral therapy programs in Ethiopia in 2003-15. PLOS One, 2018, 13(6): e0198815.

Conference presentations:

1) **Hailay G**, Paul W, Kifle W, Lillian M. HIV care continuum outcomes in Southwest Ethiopia—Barriers, facilitators and new solutions: A qualitative inquiry followed by NGT. ICOPH 2018, Bangkok, Thailand, 19-21 July 2018 (***Oral presentations***)
2) **Hailay G**, Paul W, Kifle W, Lillian M. HIV care continuum outcomes in Southwest Ethiopia—Barriers, facilitators and solutions: A qualitative inquiry followed by NGT. 2018 ASMR SA conference, Adelaide, Australia, 06 June 2018 (***Oral presentations***)
3) **Hailay G**, Paul W, Kifle W, Lillian M. HIV care continuum outcomes in Southwest Ethiopia: Old barriers, facilitators and new solutions. 29th EPHA Conferences, Addis Ababa, Ethiopia, 26-29 Feb 2018 (***Oral presentations***)

4) **Hailay G**, Paul W, Kifle W, Lillian M. HIV care continuum outcomes: does Southwest Ethiopia meet the UNAIDS targets? 29th EPHA Conferences, Addis Ababa, Ethiopia, 26-29 Feb 2018 (***Oral presentations***)
5) **Hailay G**, Paul W, Kifle W, Lillian M. HIV care continuum outcomes in Southwest Ethiopia: Old barriers and new solutions. Workshop, Central Jimma Hotel, Jimma, Ethiopia, 21 Dec 2017 (***presenter, and organizer***)
6) **Hailay G**, Paul W, Kifle W, Lillian M. ART discontinuation among HIV patients in Ethiopia in 2003–2015: prevalence, trend and risk factors. 7th Asia Pacific STD and Infectious Diseases Congress, Osaka, Japan, 23-25 Oct 2017 (***Oral presentations***)
7) **Hailay G**, Paul W, Kifle W, Lillian M. HIV care continuum outcomes: does Southwest Ethiopia meet the UNAIDS targets? 7th Asia Pacific STD and Infectious Diseases Congress, Osaka, Japan, 23-25 Oct 2017 (***Oral presentations***)
8) **Hailay G**, Paul W, Kifle W, Lillian M. Prevalence, trend, outcomes and risk factors for late presentation for HIV care in Ethiopia, 2003–2015. 7th Asia Pacific STD and Infectious Diseases Congress, Osaka, Japan, 23-25 Oct 2017 (***Oral presentations***)
9) **Hailay G**, Paul W, Kifle W, Lillian M. HIV care continuum outcomes: does Southwest Ethiopia meet the UNAIDS targets? 9th IAS Conferences on HIV Sciences, Paris, France, 23-26 July 2017 (**e-*Poster presentations***)
10) **Hailay G**, Paul W, Kifle W, Lillian M. Antiretroviral therapy discontinuation among HIV infected adults in Ethiopia in 2003–2015: prevalence, trend and risk factors. STI & HIV World Congress 2017, Rio De Janerio, Brazil. STI (BMJ Journals), 2017, 93(Suppl 2):A127-A127. (**e-*Poster presentations)***
11) **Hailay G**, Lillian M, Paul W, Kifle W. Prevalence, trend, outcomes and risk factors for LP in Ethiopia, 2003–2015. STI & HIV World Congress 2017, Rio De Janerio, Brazil. STI (BMJ Journals), 2017, 93(Suppl 2):A126-A126. (**e-*Poster presentations***)
12) **Hailay G**, Paul W, Kifle W, Lillian M. HIV care continuum outcomes in Ethiopia: surrogates for UNAIDS 90–90–90 targets for ending HIV/AIDS. STI & HIV World Congress 2017, Rio De Janerio, Brazil. STI (BMJ Journals), 2017, 93(Suppl 2):A126-A127. (**e-*Poster presentations)***
13) **Hailay G.** HIV journey from 1984-2030: heading to ending HIV/AIDS Epidemic (World AIDS Day, 2016), Adelaide, Australia, 25 Nov 2016 (***Oral presentations***)
14) **Hailay G**, Paul W, Kifle W, Lillian M. ART Discontinuation in Ethiopia: a systematic review and meta-analysis (2016 State Population Health Conference), Adelaide, Australia, 22 Oct 2016 (***Oral presentations***)

ACKNOWLEDGEMENTS

First and foremost, I would like to express my sincere gratitude to my supervisors Associate Professor Lillian Mwanri, Professor Paul Ward and Professor Kifle Woldemicahel for their unreserved supportive supervision, wonderful mentoring, and timely feedback throughout the years. I am thankful to them for extending my theoretical and practical comprehension, providing valuable ideas during the design of the project, publications and every aspect of the thesis. The thesis would not have been such complex but interesting without their support. They open my door to be a mixed methods researcher. Lillian's travel to Ethiopia to attend the NGT workshop as expert, Paul's travel to Thailand to attend my oral presentation, and Kifle's outstanding stage leader during the fieldwork were unforgettable moments. I am grateful for all these and I say, THANK YOU VERY MUCH. I have been very fortunate to work with these outstanding individuals who have not only been my supervisors but also my mentors. I look forward to learning and working with them in the future.

I am very grateful for Flinders University, College of Medicine and Public Health and the Discipline of Public Health for the generous *Australian Government Research Training Program (RTP) Scholarship*, other scholarships, awards and research grants which enable me to study my PhD in Australia and successfully conduct my fieldwork in Ethiopia. I also want to extend my gratitude to the Australian Federation of University Women South Australia Inc. Trust Fund (AFUW- SA) for awarding me the 2017 (AFUW- SA) bursary award. I am thankful for Jimma University, Jimma University Teaching Hospital and Jimma Health Centre for their support which enabled me to undertake the fieldwork. I would like to pass my gratitude to the study participants who shared their valuable information and stories explored in this thesis.

Many thanks also go to Dr Pamela Lyon, a research and word specialist, whose unfailing support improved my writing, presentation and communication skills and she did this for free. Thank you also goes to Eileen Clark for editing my PhD thesis. Thank you, my friends, - Amanuel Tesfay, Aderajew Niguse and Mubarek Abera- from Jimma University for facilitating the administrative work to obtain the data from Ethiopia, before and after my fieldwork. I owe Amanuel specifically significantly for the sleepless nights he spent exporting the SQL data to excel and SPSS. I am also grateful for my PhD student colleagues, and Flinders University staff. Lastly but not least, I am intensely grateful to my family, parents and siblings for their love, support and prayers- they were inspiring and motivating. This work is dedicated to them especially for my parents who themselves did not get an opportunity to go to school but always believed in education as a key for improving quality of life.

Chapter 1

Introduction

CHAPTER 1 - INTRODUCTION

1.1 Background

1.1.1 Global epidemiology of HIV

Human immunodeficiency virus (HIV) is an extraordinary known global epidemic which has affected individuals of all ages, sexes, races and income status[1]. Globally, between 1980 and 2015, almost 78 million people have been infected by HIV, and about half of these people have died[2]. According to the latest estimates of Global Burden of Diseases (GBD 2016), across the world 2.1 million people had new HIV infections, 38.8 million people had HIV infection, and 1.2 million people died due to the virus in 2015[3]. High income countries contributed the least to these figures, including 0.02% to the total number of new infections, 0.04% to the total number of people with HIV, and 0.03% to the total number of deaths in 2015[3].

While Africa contributes only 11% of the global population and 1.5% of the health workforce, the continent accounted for 65% of adult and 90% of paediatric HIV infections, the highest contribution of all regions[2]. The highest rates of HIV in sub-Saharan Africa (SSA) were recorded in the Southern Africa countries. In 2015, countries such as South Africa, Botswana, Swaziland, Lesotho, Namibia, and Zimbabwe had an estimated HIV prevalence of 10% of the total population[3]. Ethiopia contributed 2% to the total number of HIV-infected people in Africa in 2013[4].

The epidemiology of HIV peaked in the early 1990s; however, the trend has been declining in most countries in the last three decades. Figure 1.1 describes the epidemiological trend of HIV from 1990-2015[5]. For example, the chart shows that the number of global new infections in 1997 were 3.5 million per year but it was reduced to 2.1 million per year in 2015. Similarly, AIDS-related deaths declined from 2 million in 2004/5 to 1.1 million in 2015. The graph also demonstrates a continuing increase in the number of HIV infected people but a slow rate after 2000s in comparison to the 1990s.

1.1.2 Ethiopia: country profile and health service structure

Country profile

The Federal Democratic Republic of Ethiopia (FDRE) is a landlocked country located in East Africa, covering an area of 1.2 million square kilometres[6]. Ethiopia shares borders with Eritrea to the north and north east, Djibouti and Somalia to the east, the Republic of Sudan and South Sudan to the west, and Kenya to the south. The nation has nine regional states and two chartered cities and about 80% of the population is in rural areas.

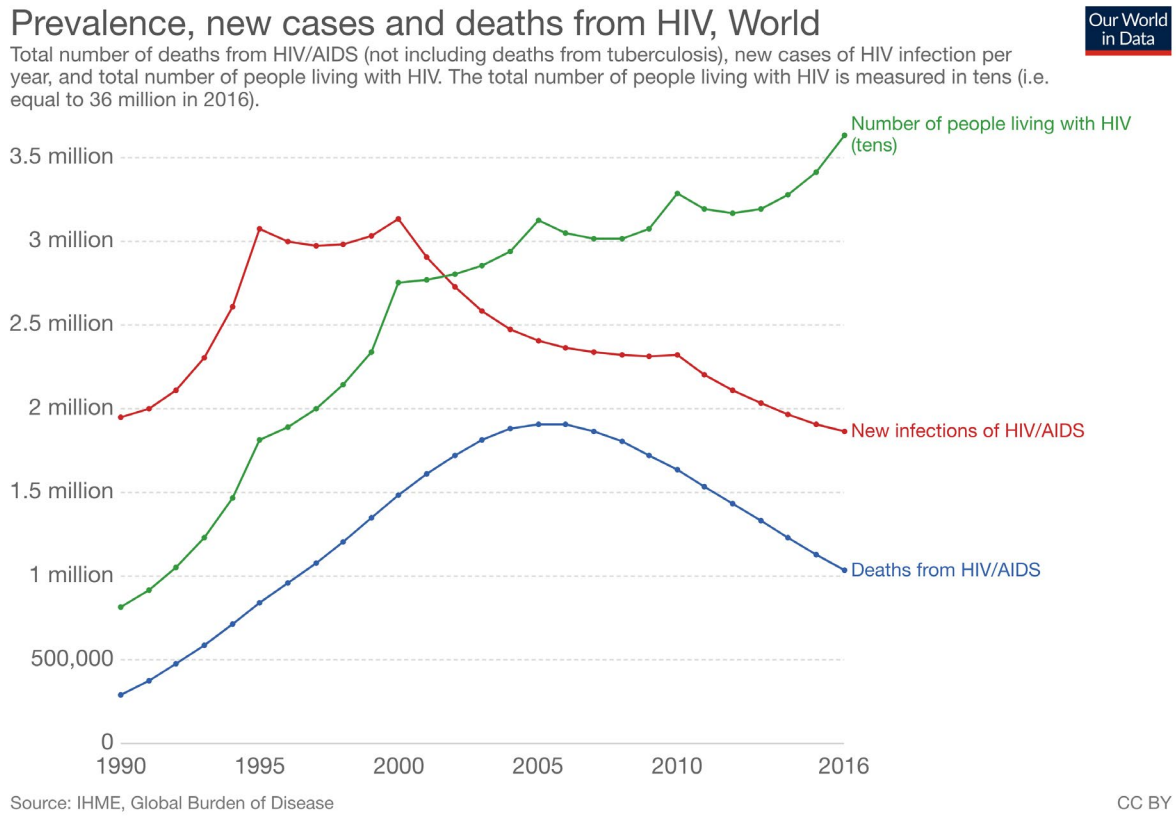

Figure 1-1: Global number of HIV/AIDS mortality, new infections, and people living with HIV (1990-2016)

According to the central statistical agency (CSA 2007)[7], Ethiopia is the second most populous country in Africa, next to Nigeria, with an estimated population over 102 million. Demographically, 44% of the population is aged under 15 years, and the estimated male to female ratio is 101 to 100. The Ethiopian economy is based on agriculture providing 40.5% of gross domestic product (GDP), 81% of exports and 85% of labour force. While primary education is free in Ethiopia, the estimated adult literacy status in 2015 was 49%[8].

Health Service Structure

Ethiopia has a vision to attain a universal health coverage through primary health care. The country has a three-tier health system, namely primary, secondary and tertiary level of health care (Figure 1.2)[9]. As shown in Figure 1.2, health centre and health post are the gateways to primary level health care in the country. Health centres provide preventative and curative services delivered by health officers, nurses, and laboratory and pharmacy professionals. A health centre coordinates five health posts and serves about 25,000-40,000 people. Health posts are based in kebele (lowest administrative unit in Ethiopia) and serve 3,000-5,000 population.

The professionals deployed in health post are called health extension workers (HEWs) and provide Health Extension Program (HEP) packages that include preventive programs, family planning and delivery services. Two or three HEWs are deployed in one health post based on the distribution and total number of households[9]. The current health system of Ethiopia is summarized in figure 1.2.

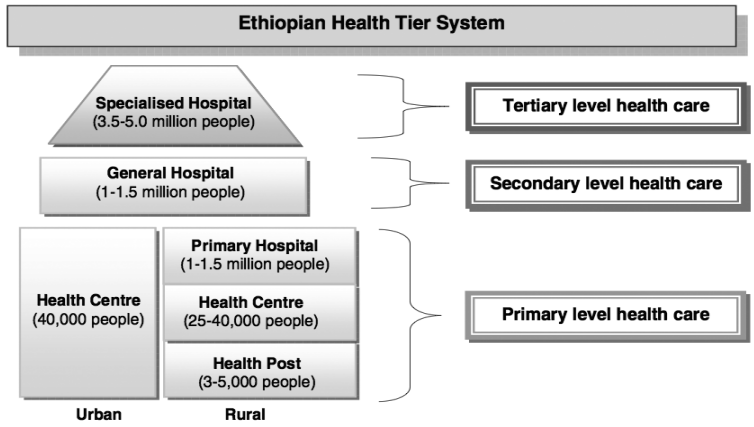

Figure 1-2: Ethiopia health tier system (adopted from HSDP IV, 2014/5)

In recent years, Ethiopia has shown marked improvement in most key health indicators, and availability and accessibility of the basic health services. Between 2000 and 2016, there was a reduction in under five mortality rates from 166 to 67 per 1000 live births, neonatal mortality rates from 49 to 29 per 1000 live births and maternal mortality ratio from 871 to 412 per 100,000 live births[10]. The total government and private expenditure on health, health professional density per population and life expectancy at birth are also improved through time[10]. Furthermore, the number of health posts and health centres increased from 76 and 412 in 1996/7[9] to more than 16000 and 3500 in 2016[11] respectively.

Ethiopia collaborated with its development partners[12] in a number of innovative programs and structures to achieve the improvements noted above. The HEP is one of the widely acknowledged innovative programs in which 16 essential health packages (Annex 1.1) are implemented through house-to-house visit [13 14]. The program has contributed significantly to the reduction of maternal and child mortality, with a motto of '*No mother should die while giving birth*' [13]. Health development army (HDA) is another program that strengthened the local health systems. In this, over three million volunteers, predominantly women, have been trained by the HEWs to perform 'multi-purpose' health promotion activities such as community empowerment and disease prevention[15]. Members of HDA are organized by their

neighbourhood, and are commonly named "one-to-five" networks to denote five-member households and a leader. "One-to-five" networks have different names in different regional states in Ethiopia such as '*tokko-shenni'* in Oromia. About five or six "one-to-five" networks are grouped in one team to have a total of 25-30 households, a team called "one-to-thirty"[16]. Both "one-to-five" and "one-to-thirty" networks are supervised by the HEWs in the kebele[17].

Despite the improvements in health care services and outcomes, the burden of morbidity and mortality in Ethiopia remains high[18]. Lower respiratory infections, HIV/AIDS, diarrheal diseases and tuberculosis (Tb) were the top four diseases that caused deaths in 2005. A decade later, in 2016, diarrheal diseases, lower respiratory infections, ischemic heart disease and Tb were the top four diseases that caused deaths, and HIV was the sixth killer disease[19]. The epidemiology of HIV and care services in Ethiopia are described in section 1.1.3.

1.1.3 Ethiopia: HIV and HIV care services

Similar to other countries in SSA, Ethiopia has also been threatened by the HIV/AIDS epidemic, which in Ethiopia is generalized and heterogeneous[20]. The overall prevalence among adults is 0.9%, in pregnant women is 0.4%, and in women with concurrent sexual partners (five or more) is more than 6%[10]. The prevalence of HIV in women (1.2%) is twice as higher than men (0.6%), and is seven times greater in urban settings (2.9%) than rural settings (0.4%). The burden of HIV is also disparate by region ranging from <0.1 % in Somali regional state to 4.8% in Gambela regional state. In 2016, a total of 19,743 people died of AIDS related causes in the country and about 792,840 children lost either or both of their parents due to HIV [21 22]. As shown in Figure 1.3, the magnitude of HIV in Ethiopia has been decreasing in the recent years.

HIV is not curable disease; however, a lifelong treatment called antiretroviral therapy (ART) was introduced in 1990s to halt the manifold impacts of the virus [23]. Many local, national and international organizations including HIV/AIDS Prevention and Control Office (HAPCO), President's Emergency Plan for AIDS Relief (PEPFAR), Management Science for Health (MSH), Global Fund to fight AIDS, Tb and Malaria, and others are investing their resources to increase ART coverage[12]. Ethiopia introduced ART in 2003 for the first time at cost of patients, and two years later ART started to be provided for free[24]. A total of 535,069 people has 'ever started' on ART, and 375,811 people were on ART in over more than 1000 health facilities in 2014/5[20]. As a result of ART treatment, in 2017 it was reported that HIV incidence, AIDS related mortality and overall HIV prevalence had fallen by 95%, 73% and 29% respectively over the past 14 years[25].

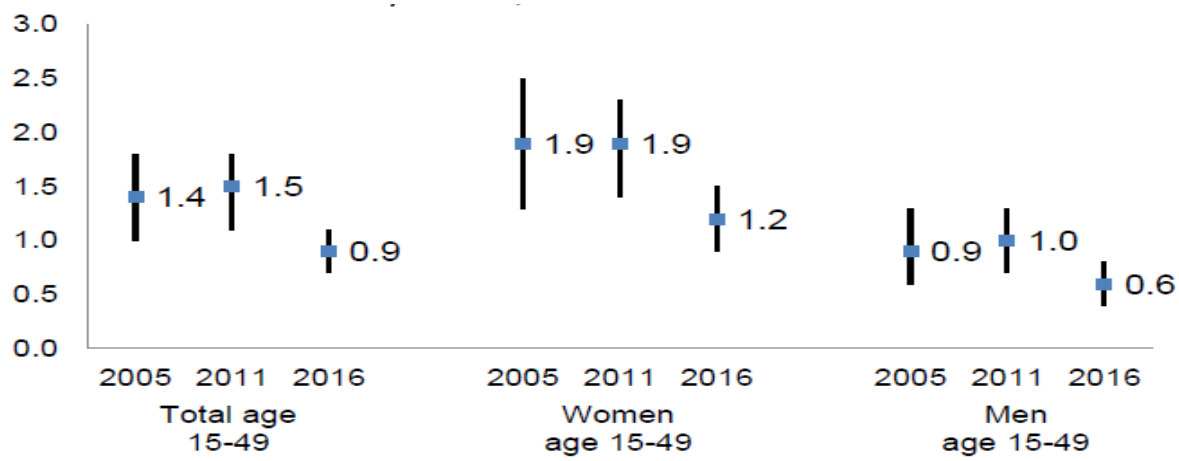

Figure 1-3: Percentage of HIV positive patients in Ethiopia (2005-16)

Ethiopia has been implementing a wide range of HIV related programs with a range of services including preventative, treatment and care, national systems strengthening and programme management, orphan and vulnerable children support, and enabling environment activities[26]. Prevention thematic area have included: voluntary counselling and testing (VCT), prevention of mother to child transmission (PMTCT), behavioural change communication and community mobilization. Treatment and care themes have included ART, laboratory monitoring, provider-initiated testing and counselling (PITC), nutritional support, palliative care and home-based care activities. In 2002, the Ethiopian HAPCO was established to coordinate these activities and this system was decentralized from federal to '*woreda'* (district) level[21]. HAPCO has also branches in higher institutions[21].

Ethiopia has implemented a public health approach to accelerate mega-scale provision of HIV counselling and testing and ART services. These include decentralizing and integrating services, shifting of task, delivering free service at the point of care (POC), strengthening supply management and evaluating progress [27 28]. A number of development partners have been participants in planning and implementation of major initiatives and programs for HIV treatment, prevention, care and support in Ethiopia and Africa[12]. For example, "3 by 5" initiative[29] was designed to treat 3 million people in 2005. "Getting to Zero"[30] was a theme of the 2015 World AIDS Day commemoration targeting to achieve "Zero new HIV infections. Zero discrimination. Zero AIDS-related deaths." "Treat all"[31] is a strategy that eloquently promote the universal HIV care coverage to ensure that all HIV positive individuals received ART irrespective of their CD4 count, World Health Organization (WHO) clinical stage or viral load. The "90-90-90" targets[32] was recently launched by The Joint United Nations Program on HIV/AIDS (UNAIDS). It is one the most ambitious goal which targets at 90% of people living

with HIV knowing their HIV status, 90% of HIV diagnosed patients receiving sustained treatment, and 90% of those on ART achieving viral suppression[32].

Despite the efforts mentioned above, there are numerous gaps and challenges in timely initiation of ART, ART retention in care and prevention of HIV related mortality in Ethiopia[20] [27]. Furthermore, there are significant inequities in the nation particularly in ART coverage, which varies between children (23%) and adults (60%), females (54%) and male (69%), and from 5.6% to 93% among regions[20]. Somali, Gambela, Afar and Oromia regional states have the lowest ART coverage in the nation. To help HIV patients fully benefit from ART, attain national goals and use resources most effectively, Ethiopia uses the HIV care continuum (HCC) framework initially incepted by the Centres for Disease Control and prevention (CDC) in Atlanta, USA, in 2013[33].

The HCC comprises HIV testing and diagnosis, ART eligibility, long term ART retention, and achieving and maintaining viral suppression through ARV adherence. The sequence of HCC is shown in figure 1.4. Linking to HIV care begins when a person has a positive test for HIV. Next, individuals are assessed for ART eligibility based on their CD4 count testing and/or WHO clinical staging. While the WHO clinical staging is diagnosed immediately, the CD4 count involves obtaining a blood sample and sending it for processing, with results received after a couple of weeks. However, following the introduction of test and treat strategy in 2016[34], no CD4 count measurement is needed in hospitals and selected health centers, but eligibility assessment for ART based on their CD4 count testing and/or WHO clinical staging is still applied in most health centers in the country. Once eligible and ready for ART, then the patient starts the treatment and is expected to take it for the remainder of his or her life. The ultimate goal of ART intake is to reduce the number of viral counts in the bloodstream (viral suppression) and achieve immunological gain.

As described in figure 1.4, if an HIV infected patient fails to pass through each step in the HCC (designed in grey), there will be a respective negative consequence (designed in dotted lines, circles or rectangles in red). Specifically, if a patient is not diagnosed or linked to HIV care timely, the negative outcome will be late presentation for HIV care; if a patient failed to remain in care, the negative outcome will be ART discontinuation; if a patient on ART failed to achieve virological suppression, the negative outcome will be clinical, immunological or virological failure; and finally, a patient may die. Each negative outcome is discussed further in section 1.2.

A theoretical framework on HIV Care Continuum in Southwest Ethiopia, 2018

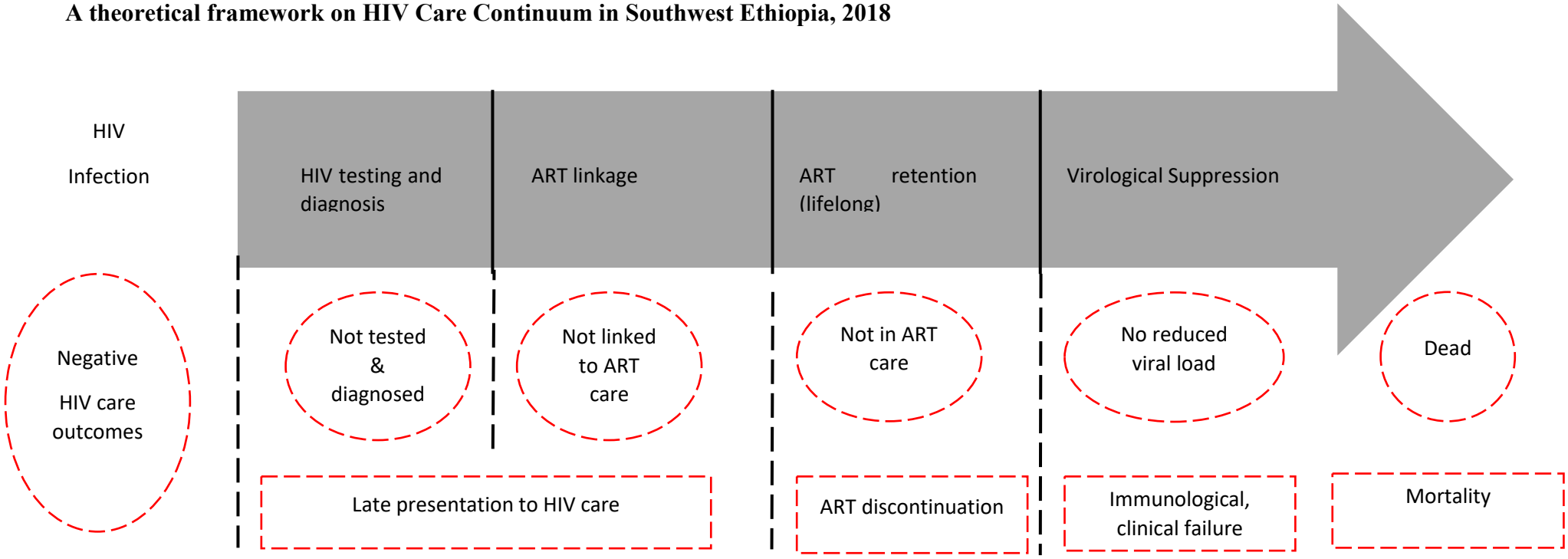

Figure 1-4: HIV care framework for assessing negative outcomes of HIV care and treatment, Southwest Ethiopia, 2018 (Adapted based on Kranzer et al, 2012)

The box with grey arrow shows the steps on the pathway of HIV care: HIV testing and diagnosis, ART linkage, lifelong ART retention and virological suppression. The dotted lines, circles or rectangles in red outside the grey arrow show negative outcomes in the pathway of HIV care: late presentation for HIV care, ART discontinuation, immunological, clinical or virological failure, and mortality[1].

[1] This figure needs to be viewed in colour.

1.2 Problem statement

The HCC is a series of stages from the time a person is diagnosed with HIV through assessment for ART eligibility, retention in care, and immunologic success and virologic suppression via treatment adherence[33 35]. Many activities have attempted to address negative HIV outcomes in the continuum[36], especially after the advent of ART[23]. Nevertheless, there have been challenges at every stage of the continuum. These include late HIV care presentation (LP)[37 38], discontinuation of pre-ART and ART[39 40], poor ART adherence[41-43], immunologic[44 45], clinical[46 47], treatment[46 47] and virologic[48 49] failures. These are the major challenges in the ART era.

LP can result from delayed HIV diagnosis and/or delays in accessing HIV care[50]. Although there are different definitions of LP, most are derived from the threshold for ART eligibility[51]. For example, LP may be defined as having a baseline CD4 count below 200 or 350 cells/mm3 and/or AIDS defining disease[52-54]. There are also other measurements for LP[55 56]. LP has been acknowledged as a challenge to achieving the UNAIDS 90-90-90 targets[4 57 58] and it can lead to several complications. It is associated with high risk of HIV transmission[59], resistance to ART drugs[59] and medical care costs[60]. LP has been reported as a significant problem across the globe, with a magnitude of between 35–65% in Africa[61 62], 72–83.3% in Asia[38] and 15–66% in Europe[63 64]. In Ethiopia, there are limited studies of the magnitude of LP. One study from northern part of the country found a LP prevalence of 68.8%[65]. There have been several studies assessing determinants of LP [52-54], but all except one are from the northern part of the country. No studies have been found to date assessing the outcomes of LP, and the problem has not been investigated among children in Ethiopia. It is, therefore, imperative to understand LP contextually as part of efforts to end the AIDS epidemic.

In Ethiopia, attrition – interruption of active engagement in ART for any reason including death – has been identified as the most common challenge in the continuum[66 67]. After thirty years of targeted HIV diagnosis and 20 years after ART rollout, attrition has remained a constant challenge in the country. Evidence shows that discontinuation from ART (hereafter discontinuation) is the main contributor to attrition, and to poor quality of life and mortality among HIV infected patients on ART[68-70]. Discontinuation is a challenge to the success of ART programs and has been recognized as a barrier to meeting the second 90 of the UNAIDS targets, because it interrupts the sustainable intake of the treatment. Discontinuation includes interruption to ART when patients are lost to follow up (LTFU), if they default, or if they stop medication while remaining in care[71]. Discontinuation diminishes the immunologic

benefit of HIV treatment and aggravates HIV related complications such as AIDS related re-admission, morbidity, drug resistance, and mortality[71 72]. Several studies have been conducted to determine the rate of discontinuation. The global rate ranges from 5%–60%[73-79], while previous studies in Ethiopia have reported that the magnitude of discontinuation ranges between 9.8%[80] and 31.4%[81].

The available literature in Ethiopia shows that demographic, behavioural and clinical factors affect discontinuation[82-84]. Nevertheless, these studies show conflicting associations, and predisposing factors are still poorly understood. In addition, there has been no published systematic review and meta-analysis to demonstrate the conflicting associations in particular, and the predictors of discontinuation in general. One systematic review[85] carried out on ART non-adherence in Ethiopia did not specifically identify predictors of LTFU, default or stopping treatment. Until a comprehensive understanding of these factors is obtained, efforts to enhance retention rates would be *ad hoc* and cost ineffective. In addition, the lack of high-quality data on the relationship between discontinuation and its contributing factors is a challenge that prevents HIV/AIDS control programs from delivering accurate data to inform tailored intervention strategies.

As described above, discontinuation is prevalent; nevertheless, few studies have assessed the problem contextually. Only two studies[82 86], both using case control designs, have been conducted in the southwest part of Ethiopia. These studies only assessed predictors of defaulting and the magnitude of discontinuation was not determined. The major contributor to ART discontinuation, LTFU, was also not measured. Additionally, there is little information on child ART discontinuation in Ethiopia despite a growing amount evidence from other countries[87-89].

Immunologic failure is another challenge in the sequence of HCC[90-92]. WHO has set definitions for immunologic failure among children and adults[93]. Through ongoing viral replication, immunologic failure enhances the risk of resistant mutations that challenges the efficacy of available or future drug options[94]. Being a surrogate marker for virological failure[95 96], immunologic failure influences the performance of the third 90 of the UNAIDS targets[32]. The magnitude of immunologic failure is significant: 23–33.1% in Europe[90], 9–18% in Asia[91 97], 11–39% in Africa[98] and 6.8–21% in Ethiopia[92 99]. There have been a few studies investigating immunologic failure in Ethiopia but all of them were conducted in the northern and western parts of Ethiopia, and no study has been conducted in the Southwest region of the country. Only two studies have assessed immunologic failure among children, one of which was conducted in Southwest Ethiopia[100]. In this, only 96 children were followed and only for

three years, and these shortcomings could lead to spurious or biased estimates.

Further to LP, ART discontinuation and immunologic failure, HIV related mortality is another problem observed in the era of universal ART. Mortality estimates in 2015 indicated 0.3 million deaths in high-income countries and 0.9 million deaths in low- and middle-income countries[3]. Evidence shows that deaths mainly occur in the first two years of ART follow up[101 102]. There have been numerous studies of the predictors of mortality in Ethiopia[101-104] and these show an incidence rate of 3.2–10.3%[101 102]. Synthesizing the studies conducted in Ethiopia, the following gaps were observed: i) early mortality, i.e. mortality in the first two years of ART follow up, was not assessed despite high mortality occurring in this period; ii) no studies assumed that death could be an outcome for discontinued patients, instead all studies that assessed predictors of mortality considered discontinuation as censored. Previous work found that 40–86% of lost patients failed to re-engage with care[105], and 50% of lost patients were found dead[70 106]; iii) no studies were undertaken in Southwestern Ethiopia; and iv) short follow-up periods and small sample sizes were used in previous retrospective cohort studies.

Considering HCC as a whole, it is possible to assess Southwest Ethiopia's performance as measured by the UNAIDS 90-90-90 targets. Since the inception of these targets in 2014, few countries have reported progress towards achieving them, and Sweden is the only country to have reached them, achieving 90-97-95[107]. Yemen was the poorest performer, with 11% and 3% achievement respectively for the first and second markers[108] while SSA overall achieved 45-86-76[4]. Like other SSA countries, Ethiopia adopted the UNAIDS 90-90-90 targets in 2014[109]; however, limited information is available about progress. One study, a time series analysis covering 26 years and published in 2018, reported a 67-88-86 performance[110]. A 2017 UNAIDS HIV update also reported an estimated performance of 67-59-61[111].

When considering the overall picture, it is possible to see that research is lacking into key factors leading to negative HCT outcomes. While some patient-related characteristics are recorded, we do not know why these individuals were at risk of negative HCC outcomes, because behavioural factors at the individual level have not been explored. Furthermore, studies elsewhere have revealed factors that influence HCC beyond individual levels. These include institution level factors such as lack of ART trained health professionals[112-115], lack of transport[116-119], and cost of ART[119]; community level factors such as stigma[120-122] and traditional healing[123-126]; and program level factors such as political commitment[127 128] and lack of coordinated HIV care activities[129]. However, there have been no comprehensive studies in Ethiopia that explore challenges to HCT from the viewpoints of stakeholders at these levels. Additionally, no studies have investigated these stakeholders' views on what could be done to

rectify negative HIV care outcomes. Furthermore, methodologically, there have been no mixed methods studies despite the value of such designs in addressing the complex nature of HCT.

This research project was designed to address the gaps in knowledge identified above. In **phase one,** a systematic review and meta-analysis was planned to review the available evidence on factors associated with discontinuation among HIV patients in Ethiopia. The systematic review and meta-analysis was designed to identify the following: (i) adequacy of existing evidence, (ii) geographic distribution of existing studies; (iii) outcomes of discontinuation, including immunologic failure or death; (iv) effects of LP on discontinuation. A further literature search was conducted to see whether any studies have been conducted in the region on the whole continuum of HIV care and found none.

Considering the clinical and public health importance of the above-mentioned gaps and implications, in **phase two** of the project, the negative outcomes of the whole HIV care and treatment (HCT) cascade was aimed to assess using 12 years' retrospective data from Jimma University Teaching Hospital (JUTH) in Southwest Ethiopia. The negative outcomes to be investigated comprise LP, discontinuation, immunologic failure and HIV mortality in children and adults.

As a result, in **phase three** of this project, facilitators, barriers and solutions implicated at each stage of HCT were studied from the perspectives of patients with HIV, HIV care providers, community advocates and HIV care program managers from Southwest Ethiopia. The aim of this phase was to discover enablers of and challenges to HCT, and then propose new solutions that could facilitate progress towards achieving the UNAIDS 90-90-90 treatment targets. To assess the relevance, feasibility and acceptability of these proposed solutions, in **phase four** of the project, a nominal group technique (NGT) approach was used with a panel of experts including academics, service providers and HIV program managers, who were asked to rank and evaluate expert advice from key stakeholders. The outcomes from this NGT were used to improve practice, guide future HIV policy development and generate new research ideas for further studies to improve responses to the 90-90-90 targets.

In summary, this multi-phase project was designed to assess the complex characteristics of the HCC through reviewing the available evidence, assessing status and predictors of all HCC outcomes, further exploring the facilitators and barriers to the cascade, and recommending solutions after discussing with panels of experts.

1.3 Significance and originality

This study will contribute to the better outcome of HCT not only in Southwest Ethiopia but also in Ethiopia and beyond. This work, in a nutshell, contributes to improve the number of people who know their HIV status, number of diagnosed HIV patients accessing HIV treatment sustainably, and number of HIV patients with clinical and immunological successes. The primary beneficiary targets of this study are HIV patients, HIV care providers, policy makers and researchers.

For HIV patients, the identified facilitators and barriers along with the suggested solutions will help to enhance their knowledge and decision to know their HIV status early, improve the trust in ART care, encourage consistent ART utilizations and improve quality of life. For HIV care providers, the findings will help them to identify and prioritize vulnerable patients with high likelihood of negative HIV outcomes by considering contextual factors. This also helps the health workers to conduct targeted HIV testing to diagnose patients timely, and targeted counselling to reduce attrition and enhance consistent ART utilization. For policy makers, the barriers from the analysis will help them to design a new strategy to meet the UNAIDS targets. The findings will foster them to recognize the strengths and weaknesses of the existing strategies, programs and policies. For future researchers, the suggested solutions require further robust and large-scale studies before implementation. This study will also serve as a springboard in conducting new studies and further investigations.

The thesis produced a significant original contribution to the HIV community. The significant original contribution to knowledge of the current project includes: 1) use of sequential multiphase mixed methods; 2) assessment of the whole sequence of HCC; 3) identification of barriers and recommended new solutions at each stage of HIV care evaluating the relevance, feasibility and acceptability of each solution using a consensus method study; and 4) positive response to the implementation of translating the findings to produce output in terms of potential strategies to improve the HCC.

1.4 Research questions, aims and objectives

1.4.1 Research Questions

i. What available evidence/implications of ART discontinuation is there in Ethiopia?
ii. What is the epidemiology of negative HCT outcomes in Southwest Ethiopia?
iii. What are the facilitators, barriers and solutions for HCT in Southwest Ethiopia?
iv. To what extent are the solutions in question–iii, relevant, feasible and acceptable?

1.4.2 Aims and objectives

The project has four aims.

Aim 1: reviewing discontinuation among adult patients with HIV

To identify the best available evidence on predictors of HIV treatment discontinuation among adult HIV patients aged 15 years old and above in Ethiopia.

Aim 2: assessing HCC outcomes

i. To assess LP among patients with HIV enrolled in ART clinics of JUTH and Jimma Health centre (JHC) from 2003-15
ii. To assess discontinuation among patients with HIV enrolled in ART clinics of JUTH and JHC from 2003-15
iii. To assess immunologic failure among patients with HIV enrolled in ART clinics of JUTH and JHC from 2003-15
iv. To assess mortality among patients with HIV enrolled in ART clinics of JUTH and JHC from 2003-15
v. To estimate Jimma, Southwest Ethiopia's performance to the UNAIDS 90-90-90 targets

Aim 3: exploring facilitators, barriers, and solutions for

i. To explore facilitators for HIV diagnosis, ART linkage and retention in care from the perspectives of HIV patients, HIV care providers, community advocates and HIV care system administrators in Southwest Ethiopia
ii. To explore barriers to HIV diagnosis, ART linkage and retention in care from the perspectives of HIV patients, HIV care providers, community advocates and HIV care system administrators in Southwest Ethiopia
iii. To explore ways improving HIV diagnosis, ART linkage and retention in care from the perspectives of HIV patients, HIV care providers, community advocates and HIV care system administrators in Southwest Ethiopia

Aim 4: Recommending policy and practice to address the UNAIDS 90-90-90 targets

1.5 Thesis structure

The thesis has nine chapters. Chapter one is the introductory part of the project. It consists of background, problem statement, significance and originality, and research questions, aims and objectives. Chapter two is the literature review and it comprises nine sections. Section one and two introduce the overview of the chapter, and development of ART and treatment outcomes.

Section three to six discuss the series of HIV care comprising LP, discontinuation, immunologic failure and mortality respectively. Section seven presents the literature review on the performance on the UNAIDS treatment targets. Section eight presents the model that guided the study. The chapter is concluded by summarizing the literature in the last section. Chapter three describes the methodology of the thesis, and methods that answered each research question sequentially. The chapter has six sections. The first section is introduction of the chapter, and the second section is about the study setting and period. The third section is scientific inquiry of mixed methods. Section four to seven present methods for research questions one to four respectively. The last two sections deal with the ethics and result dissemination of the project.

Chapter four to seven present the findings (and respective discussion) of the studies in the project. Chapter four presents findings from systematic review and meta-analysis. The review from this chapter was published in PLOS ONE[130], and the extended version is presented in the thesis. Chapter five presents findings from retrospective cohort study. Similarly, four papers[131-134] were published from the cohort findings and extended version of these papers are presented in thesis. Chapter six presents findings from qualitative study and chapter seven presents findings from the NGT. A general discussion of the whole project is presented in Chapter eight, while Chapter nine discusses conclusions and recommendations, and implications for policy, research and program. The checklists, guides, ethical forms and copies of published papers are appended.

Chapter 2

Literature review

CHAPTER 2 - LITERATURE REVIEW

2.1 Introduction

In Chapter two I review relevant literature on HIV treatment outcomes among HIV patients on ART. This chapter provides background for the systematic review and meta-analysis chapter presented in Chapter four that specifically focuses on ART discontinuation in Ethiopia. The problem statement described in Chapter one shows the whole range of HCC outcomes are assessed in the project, hence all of these are covered in this literature review, using existing global evidence with a special focus on Ethiopia. Demographic, clinical, institutional, and behavioural characteristics affecting each stage of HCC outcome are explored, guided by the HCC framework.

The Chapter includes nine sections. In the first section, the global and national epidemiology of HIV are introduced while the second section the advent of ART in treating and preventing HIV is described. Sections three to six present burdens, trend, predictors, and interventions of LP, discontinuation, immunologic failure and mortality among patients with HIV. The seventh section focuses on the UNAIDS 90-90-90 treatment targets. Section eight summarises the literature review. The final section of the chapter demonstrates the model used in this thesis.

A systematic search of English language publications was conducted to assess HCC outcomes including LP, discontinuation, immunologic failure and mortality. The search timeframe was between 1995 and 2018, with 1995 being a significant year when ART utilisation commenced. Search terms for each outcome were developed to find relevant articles in selected databases and search engines including Pub-med, Medline, SCOPUS, CINHAL, Web of Science, ProQuest, and The Cochrane Library.

The search terms were categorized into three concepts as follows:

(i) “human immunodeficiency virus”, HIV, “antiretroviral therapy”, ART, HAART, and “HIV treatment”,

(ii) trend, predictor, factor, barrier, facilitator, enabler, solution, intervention, and “ways to improve”, and

(iii) “late HIV diagnosis”, “late HIV testing”, “delayed HIV diagnosis”, “delayed HIV testing”, “late HIV care presentation”, “delayed HIV care presentation”, discontinu*, “lost to follow up”, LTFU, dropout, default*, “immunologic failure”, “clinical failure”, “virological failure”, “treatment failure”, attrition, mortality, death, and “UNAIDS 90-90-90”.

The Boolean operator system comprising the words "AND' and/or "OR" was employed to limit, broaden and/or redefine the search strategy for outcomes of interest. The keywords in each search concept were linked with 'OR', and searching concepts (i), (ii) and (iii) were linked with 'AND'. Additionally, articles with full text and their relevant references were also considered during reviewing. Besides, grey literature and other relevant un/published documents, guidelines, policies and strategies were searched manually. Content analysis of all available material was conducted to identify patterns and themes which were further described below corresponding to the series of HCC.

2.2 Development of anti-retroviral therapy and treatment outcomes

The development of ART has been indispensable in prolonging life of people with HIV[135]. Introduced in 1987, zidovudine (AZT) was the first drug against HIV[23]. It was effective in viral suppression, but at $12,000/person a year, was among the most expensive drug therapy ever[136]. Since the invention of ART, more than 20 drugs against the virus have been approved based on clinical efficacy and effect on plasma HIV RNA concentration[137]. The treatment regimen changed, however, at the end of 1995, from mono/dual to triple therapy, now called highly active ART (HAART), following the acceptance of the first protease inhibitor [23].

ART is not curative; however, the treatment reduces the number of viruses in the blood and controls their multiplication, even to the point of undetectable status (viral load suppression). Treatment increases the number of CD4 cells, boosting the immune system. Viral load suppression and the increased CD4 count help to reduce the development of opportunistic infections (OIs), improve quality of life and survival. ART drugs are classified in to six classes: Nucleoside/nucleotide reverse-transcriptase inhibitors (NRTI), non-nucleoside reverse-transcriptase inhibitors (NNRTI), protease inhibitors (PI), fusion inhibitors or "entry inhibitors" (FI), CCR5 antagonists and integrase inhibitors (II). Under WHO recommendations, HAART involves a combination of at least three different ARV drugs for ART- naïve adults:

- AZT+3TC+EFV
- AZT +3TC+NVP
- TDF +3TC or FTC + EFV
- TDF +3TC or FTC + NVP, where

(AZT/ZDV=zidovudine, 3TC=lamivudine, EFV=efavirenz, NVP=nevirapine, TDF=tenofovir disoproxil fumarate, FTC=emtricitabine) [138].

Currently, the preferred first line regimens for adult include TDF + FTC + EFV; ZDV+ 3TC+ EFV; or ZDV+3TC+ NVP. However, if treatment failure is detected, first line regimens are used. TDF + 3TC + LPV/r (Lopinavir) or ATV/r (Atazanavir) are the preferred second line drugs if AZT was used in the first line ART, but if TDF was used in the first line ART, AZT + 3TC + LPV/r or ATV/r are the preferred second line regimens. For children, ABC (Abacavir) + 3TC + LPV/r or AZT + 3TC + LPV/r are the recommended ART drugs. If children develop treatment failure, the optional second line regimens include AZT + 3TC + EFV or ABC or TDF + 3TC + EFV.

In Ethiopia, ART program was first offered in July 2003 in few public hospitals and patients were charged, but after two years ART became a free service [24]. The current treatment protocol in Ethiopia is based on the *National Guidelines for Comprehensive HIV Prevention, Care and Treatment:* FDRE, Ministry of Health version 2014[139] which was based on the WHO ART treatment guideline version 2010[138]. According to the Ethiopian *National Guidelines for Comprehensive HIV Prevention, Care and Treatment* protocol[139], eligibility criteria for adults who are HIV positive to commence ART has been revised four times and is as follows:

- CD4 cell count <200, 200-350, and < 500 cells/mm3 before 2012, 2012-2015 and 2015-late 2016 irrespective of WHO clinical stage respectively
- WHO clinical stage 3 or 4 irrespective CD4 cell count, and
- Pregnant, breast feeding women, sero-discordant couples or diagnosed with active irrespective CD4 cell count.

ART is recommended for all children with HIV irrespective of WHO clinical stage and CD4 cell count. However, a test and treat strategy that allows every HIV positive to start ART was launched in Ethiopia since the end of 2016[31], but the strategy is yet to be rolled over across the country.

ART was provided free of charge in 22 hospitals in Ethiopia in 2005 through the aid of Global Fund, World Bank, and PEPFAR and other partners[24 140]. The service was expanded from four facilities in 2003 to 913 in 2013[24 141]. The number of people on ART has also been increasing dramatically in the last decades[20]. The number of patients ever started on ART increased from 900 in 2004/5[142] to 535,069 in 2014/15[20].

At a global or national level, the success of ART programs depends on the following indicators[20]: (i) access, utilization, coverage and equity of ART, (ii) early presentation for ART care programs, (iii) retention in ART care, and (iv) early identification of treatment failure and shift to second-line regimens. Therefore, in each of these indicators, significant impediments

have been observed including: ART inequity, LP, ART attrition, immunologic failure, and mortality. The literature review about these negative outcomes is presented in the next sections.

2.3 Late presentation for HIV care

2.3.1 Definitions and burdens of late presentation for HIV care

Timely presentation to HIV care determines the effectiveness of ART. Time to present for HIV care, early or late, occurs at different points of HIV testing/diagnosis, linkage after diagnosis, and assessment for eligibility has been completed[37 51-56 143-145]. The term timely presentation is used arbitrarily and is not clearly defined. However, LP occurs when a person: (i) is tested or diagnosed with HIV late, because the person was not aware of the (risk of) infection; (ii) does not seek HIV testing despite being aware of the (risk of) infection; (iii) comes late to link with ART eligibility assessment after diagnosed with HIV; and (iv) starts ART late after being eligible for ART[50 143]. Currently, the rationale for the measurements of LP is based on duration between HIV diagnosis and presentation to ART care[55 56 143], observation of AIDS defining illnesses[37 52-54 144 145], and criteria for ART eligibility[51].

A number of clinical definitions for LP have been presented. In earlier times, LP was defined as a baseline CD4 count was below 200 cells/mm3 and/or with an AIDS defining illnesses[37 52-54 144 145]. When the CD4 based criteria for ART eligibility was revised, LP was defined as a baseline CD4 count below 350 or 500 cells/mm3 and/or with an AIDS defining illnesses[37 52-54 144 145]. Others used LP if indicators of advanced AIDS stage are observed either before or during HIV diagnosis [146], and after six [55 143] or 12 months [56] of HIV diagnosis. The available clinical definitions of LP are conservative, and could not differentiate between delayed presentation before HIV diagnosis, between HIV diagnosis and initial entry to care, and between initial entry to care and ART start. Furthermore, the definitions differ between countries.

The rationale for LP measurement in Ethiopia is based on ART eligibility criteria[54]. Before 2012, LP was defined if the baseline CD4 count was below 200 cells/mm^3 irrespective of the baseline status of WHO clinical stage, or if the baseline WHO clinical stage was 3 or 4 irrespective of the baseline CD4 status[52 53]. Between 2012 and 2015, LP was defined if the baseline CD4 count was below 350 cells/mm^3 irrespective of the baseline status of WHO clinical stage, or if the baseline WHO clinical stage was 3 or 4 irrespective of the baseline CD4 status[54]. Between 2015 and late 2016, LP was defined if the baseline CD4 count was below 500 cells/mm3 irrespective of the baseline status of WHO clinical stage, or if the baseline WHO clinical stage was 3 or 4 irrespective of the baseline CD4 status[147]. After the end of 2016, a

new program called test and treat strategy program was launched, which requires commencement of ART immediately up on diagnosis.

LP has been reported to be an important problem globally, nationally and locally. In the United States and Canada, prevalence of LP was reported at 41%-66% in the period between 2000 and 2010[148]. For example, 41% of HIV patients presented late in the southern US in 2006[59]. More than half (54%) of patients in a North American Cohort Collaboration on Research and Design had a baseline CD4 count of below 350 cells/mm^3[148]. In Washington, two- thirds (66%) of patients were diagnosed AIDS within one year of HIV diagnosis between 1997 and 2006[148]. In Calgary of Canada, 39% of HIV patients presented with a CD4 count <200 cells/mm^3 at their first visit[149].

In Europe, the magnitude of LP has been reported to be high, between 15-66% [63 64]. A collaborative study in Europe reported that 54% of HIV patients had a baseline CD4 count below 350 cells/mm3 or diagnosis of AIDS indicators within six months of diagnosis[150]. In Switzerland, a total of 44.4%-58.6% of HIV patients presented with baseline CD4 count below 350 cells/mm3 in 2016[64]. Similarly, 54% of HIV patients in Italy presented with baseline CD4 count below 350 cells/mm3 in 2016[151]. In Belgium, 43% of HIV patients presented late, baseline CD4 count below 350 cells/µl[152].

Although LP was high in developed countries, the trend declined recently. For example, in Ireland, LP reduced from 66% in 2002 to 33% in 2014[153]. In the collaborative research in Europe, LP declined from 57% in 2000 to 52% in 2010/11[150]. The burden of LP in these countries varies across different population groups. LP was higher in African immigrants[148 154] and Latinos[155] and was higher in heterosexuals than men who have sex with men (MSM)[148 154 155].

In Asia, LP was also highly significant problem ranging from 36.3%- 79.1%[38 156]. For example, in India in 2012, 46% of newly diagnosed patients presented with baseline CD4 count below 200 cells/µl, and 69% presented with baseline CD4 count below 350 cells/µl[157]. More than half of HIV patients in China also presented with baseline CD4 count below 350 cells/mm3 in 2012[37]. In a multi-centre (22 sites) regional study in Asia (13 countries), about 80% of HIV patients presented with either baseline CD4 count below 200 cells/mm3 or AIDS diagnosis before ART initiation in 2007, but this fell to 36.3% in 2011[156]. Similar to the US, Canada and Europe, the trend of LP in Asia is also declining[37 38 156]. LP was also low in homosexuals[38].

In Africa, the magnitude of LP has been reported to be between 33.6%-79%[158]. For instance, in South Africa, 34%, 33% and 79% of HIV patients had a baseline CD4 count of

below 100, 200 and 500 cells/mm3 respectively[158 159]. In Harare, 67% patients presented with baseline CD4 count of below 200 cells/mm3 and 71% patients presented with WHO clinical stage of 3 or 4[160]. More than one third (40%) of HIV patients in Kenya in 2011 presented with baseline WHO clinical stage 3 or 4[161]. Although there is no study that show the trend of LP in Africa, the trend of baseline CD4 count of patients is improving gradually[61]. In Ethiopia, there were no adequate data that show the burden of LP. One cross-sectional study from northern part of the country has reported a prevalence of 69%[65]. Another situational analysis in Southwest Ethiopia reported that 33-38% of HIV patients had baseline CD4 counts of below 200 cells/mm3 or WHO clinical stage of 3 or 4[52]. Few studies reported the outcomes of LP, principally poor outcomes for patients including immunologic failure[152 162], LTFU[150 151], drug resistance[59] and death[54].

In this review, the variation in the definitions of LP limits direct comparisons; however, it was found high in low-, middle- and high-income countries. The levels are falling although the information on this was limited. Unlike studies in Africa, most studies in middle-and high-income countries identified patients' sexuality when measuring LP and found that it occurred less often in homosexuals. This may signify that a higher proportion of homosexuals know that they are at higher risk to HIV infection, and as such, have the need to know HIV status early. Like countries in Africa and others, LP in Ethiopia was high. Nevertheless, the burdens and trend associated with it have not been researched in detail in different contexts. Less is also known about the magnitude of LP in children.

2.3.2 Predisposing factors for late presentation for HIV care

The literature review has revealed that LP can be predicted by a number of factors: age[38 156-158 161 163], sex[64 151 160-162 164 165], marital status[52 157 161], education[52 157 161], unemployment[161], residence[146 158 166], income[159 160], availability of and access to HIV testing[145 159], testing strategies[37 167], comorbidities[52 163], sexuality[38 150-152 154], injectable drug users (IDU)[38 145 146 151 156], having contact with sex workers[52 163], HIV related stigma[52 145 160 168], fear of non-disclosure[161], alcohol consumption[52 161 163 169], traditional healing[121], culture[170-172], and year of enrollment in ART care[38 59 155 156 163].

Several studies assessed the association of age and LP[38 156-158 161 163]. These studies reported being old age as a risk factor to LP. For example, the odds of LP among patients aged 41-<50 years with HIV were double those of patients aged younger than 30 years in the multi-site study in Asia-Pacific region[38]. Likewise, the risk of LP of patients aged 50+ years with HIV in South Africa was double that of patients aged below 20 years[158]. Older adults in

Ethiopia were also at a higher risk of LP[163]. There are different reasons why older people presented late for HIV care services. Some studies suggested that older patients with HIV did not show symptoms related to HIV until after long period of infection and once their immunity has been compromised[158]. Furthermore, these patients are more likely to be diagnosed after admission because they perceived that they had lesser risk of HIV infection[58]. Previous studies have shown that people who perceived themselves to be healthy were reluctant to seek health care[145 154].

Gender was also another factor in LP, but findings were mixed. Most studies found that LP was high in men than women[160 161 165 173]. For example, a study in South Africa reported males were at three times greater risk of LP[173]. Other study in SSA found a 70% increase of LP in males[161]. Evidence showed that women had high possibility of HIV testing soon after their husband were diagnosed with HIV, thereby seeking HIV care services early than their men[174]. "Front door" services were more available for women than men. Moreover, further evidence showed women had higher self-perception illness and access health care than men, which in turn facilitates early diagnosis. Conversely, other studies reported that women were vulnerable to LP than men[64 164]. Women have low knowledge of HIV and care services [54], high perception of stigma and discrimination[175] and greater use of traditional healing[53 54] than men, and these may lead to delayed HIV care. Patriarchal cultural norms that depict women as dependant on men for most of their lives also influenced their access to health care services, particularly HIV care services[170-172].

Marital status was a significant predictor of LP. Studies from Ethiopia[52] and Uganda[161] found that divorced or separated people were four and two times at risk to present late for HIV care respectively. This finding was also supported by study from India[157]. When people get divorced, they might feel annoyance or even depression, and this may be followed by economic hardship[52] which leads to delayed seeking of care.

Educational status was another factor in LP. Evidence from Uganda stated that people who completed only lower grades had 50% higher risk to LP than those who completed higher grades[161]. Conversely, a study in Ethiopia found that people who could formally read and write were about four times at risk of LP than people who could not read and write[52]. This could be due to the fear of stigma, as people with high literacy status might have higher contact with many people at work or school, thereby leading to higher perceived stigma.

Income, employment status, residence, and availability and access of HIV testing[145 159] were also other factors associated with LP. A study in Zimbabwe found that people with higher monthly income presented early than those with lower monthly income[160]. Unemployed

people were at 50% higher risk of presenting late to HIV care than employed people[161]. Structural barriers could be the reason why people with lower income, unemployed status or lower education status were more likely to present late to seek HIV care services[146 158 166]. Furthermore, a study in South Africa revealed that people who had to travel more than five kilometers distance to reach an HIV clinic were three times more likely to present late than those who travel short distances[159]. A study from Vietnam also supported this finding[145]. Even so, it is evident that people from rural dwelling invest substantial time and resources to visit hospital[161].

LP was also linked with HIV testing strategies[37 167]. A finding from Zambia suggested that provider-initiated HIV testing and counselling (PITC) did not facilitate early diagnosis[167]. In the same way, the odds of LP in PITC was high when compared to VCT in China[37]. Because clients of PITC are mostly at clinical risk, such clinical risk-based HIV testing program may miss a timely diagnosis i.e. most patients do not come to clinics until they become sick[176]. Therefore, PITC was not found to facilitate early presentation for HIV care.

Heterosexuals, IDUs, and alcohol consumers presented late to the HIV care. Numerous studies, all of them outside Africa, assessed the association between sexuality and LP[38 150-152 154], and interestingly, all found heterosexuals as delayed presenters. For example, a multicenter study in Asia revealed that homosexuals were 55% less at risk to LP than heterosexuals[38]. Similarly, heterosexuals in Belgium were twice at risk to LP than homosexuals[152]. Previous studies indicated that homosexuals had higher repeated testing rate than heterosexuals, and this may contribute for early HIV diagnosis and presentation to care[177 178]. All studies that assessed the link between IDUs and LP found IDUs to be late presenters[38 145 146 151 156]. In a study performed in Vietnam, for example, IDUs were three times at risk to LP[145]. An Italian study also confirmed this, with IDUs at higher risk (27%) of LP[151]. Evidence shows that most IDUs are detained in prison for drug related offenses, and they have less access to HIV testing services[145]. Furthermore, there are fewer referrals to ART clinics, which, in turn, leads to late entry into care[179].

Three studies [52 161 169] that assessed the relationship between alcohol consumption and LP found different results. The Ethiopian study[52] found alcohol to be a risk factor, a Ugandan[161] study found to be a protective factor while a Cameroonian study[169] reported no association. Alcohol consumers could be at higher risk of LP as they might get in to difficulty or not want to stop consuming alcohol, which is not recommended for patients on ART[53]. On the contrary, alcohol drinkers may present for repeated testing because they perceive themselves at higher risk, and this subsequently leads to early diagnosis[52].

Perceived or fear of HIV related stigma and discrimination and utilization of tradition healing negatively affected early HIV care presentation. Several studies showed that fear of stigma negatively affects timely HIV diagnosis and entry to care[52 53 145 160]. A study from Zimbabwe revealed that people who experienced stigma as a result of HIV positive status had higher odds of entering late into care compared with those who did not experience stigma[160]. Additionally, the qualitative component of mixed study in Ethiopia found stigma was as a major barrier to timely HIV diagnosis and entry into care[52]. Use of traditional healing was also found to create a significant barrier for delayed HIV diagnosis and entry into HIV care. Qualitative studies from Ethiopia[121] and South Africa[126] confirmed this finding.

Other barriers such as comorbidities or other chronic illnesses and calendar year were also linked with LP. For example, a study from Ethiopia found that patients with depression were more likely to present late to HIV care than those without depression[163]. Another study from Ethiopia found that patients who had other comorbid illnesses were at three times higher risk to delay for HIV care[52]. Most patients with chronic illnesses were diagnosed HIV at advanced stages and showed signs and symptoms of WHO clinical stage 3 or 4[52 53]. Patients with mental illness have limited access to HIV testing and other HIV care services because they are dependent on their caregivers. This may lead to delayed diagnosis or presentation to ART clinic. The calendar year when patients enrolled was also another predictor of LP. In an Ethiopian study, patients who enrolled recently (2013-14) were at 86% less risk to LP compared to those who enrolled before 2008[163]. Similar to this, a cohort from Asia revealed that patients who enrolled after 2011 had 85% less risk to LP than those who enrolled before 2007[156]. This is not surprising as decentralization of HIV care services, launching of new HIV testing programs, and overall awareness to health care service utilization were improved in the recent times[20 27 68 142].

In general, socio-demographic, socio-economic, socio-cultural, clinical, institutional, and behavioral factors all influenced LP. Most of the studies were conducted outside Ethiopia, and pieces of evidence were from quantitative studies. Socio-cultural barriers were not explored well in Africa, and even less so in Ethiopia. The great majority of predictors or barriers were identified as characteristics of patients. For some factors such as gender, education and alcohol consumption, there were contradictory association with LP. Other predictors were studied in limited contexts. For example, the influence of being heterosexual or homosexual on LP was assessed in Europe, Asia, US and Canada but not in Africa.

2.3.3 Interventions for improving late presentation for HIV care

LP can be improved before and after HIV diagnosis. As stated in section 2.3.1, LP occurs if there is delay before diagnosis, between diagnosis and primary engagement with care, and between primary engagement with care and ART initiation. Therefore, interventions focused on these points of care. WHO has described the framework of HIV testing at health institution or community level[180]. At health facility level, the service may be provided in clinic setups such as outpatient department, antenatal care (ANC), Tb clinic, and sexually transmitted infection (STIs) clinic[180]. Additionally, the health facility level testing may be conducted in settings other than clinic, such as in VCT or other drop in services for hard-to-reach population[180].

Studies have shown the positive impact of VCT on the uptake of HIV testing and early HIV diagnosis. For example, a trial in Zimbabwe[181] and Zambia[182] found 12- and 5- fold increases in testing uptake in the intervention arm (received VCT in addition to the available service in clinic) versus control arm (clinic test service available). As part of VCT, HIV testing services were provided in ANC, Tb and STI clinics and these have been implemented in Africa including Ethiopia[183-187]. Although PITC is another HIV testing strategy, studies found PITC contributed less for early diagnosis[37 167].

At community level, HIV testing services could be delivered at events, churches, workplaces, schools, nightclubs, and outreach sites for hard-to-reach population, and home-based HIV testing either door to door or for index families[180]. The acceptability of community-based HIV testing was examined in a systematic review of 61 studies[188]. The review found that participants who were tested at community level had higher baseline CD4 count and WHO clinical stage of 1 or 2 compared to those who were tested in a facility. Furthermore, engagement following diagnosis was also found high in community- than facility- based testing[189]. HIV testing services at household level were described in different studies in Africa. For example, South Africa[190] and Zambia[191] implemented home-based HIV testing and acknowledge its impact in early diagnosis.

Recently, HIV-self testing has emerged as an alternative option to HIV testing at facility or community level. This screening program involves collecting a specimen, performing a test and interpreting the result by oneself. Studies have assessed the acceptability and benefit of HIV-self testing in USA[192-195], Europe[196-199] and Asia [200-203]. A few African countries, but not in Ethiopia, have also introduced this program, and results reveal a promising benefit for early diagnosis. Kenya[204], Malawi[205] and Zimbabwe[206] are among the countries that have been implementing the program.

Interventions to improve delayed entry were reported by few studies. Decentralization and task shifting were found effective in increasing HIV testing coverage and ART initiation as reported from studies in Ethiopia[207] and Malawi[208 209]. POC CD4 measurement was also another solution that prevent pre-ART LTFU, and Uganda[210], Mozambique[211] and South Africa[212] found this very effective. Another intervention to address delayed entry to care was home visit by expert patients or peer educators, and this was found helpful in studies from South Africa and Malawi[190], and Kenya[213].

Although this review illustrates that there have been numerous studies identifying predictors of LP, there have been few studies investigating ways to improve or overcome these predictors. Most available solutions for improving LP were directed at improving coverage of HIV testing, with a few designed to improve linkage to ART care after diagnosis. Approaches that improved HIV testing and counselling included facility-based, community-based, and self-HIV testing, with the emphasis in current literature on community-based and self-testing models. Although promising, the implementation and evaluation of these models are yet to be explored in Africa. In Ethiopia, community-based approaches are introduced[214], at least in a pilot stage, but none was for self-HIV testing.

2.3.4 Summary

To conclude, the burden of LP was significant, outcomes were poor and there were many factors influencing the problem. Most of these were focused on characteristics of individuals including sociodemographic and economic status, behavioural and cultural norms. Findings were consistent across a large body of literature but there were inconsistent findings on the relationship between some factors and LP. Although not numerous, there were interventions to improve LP at different levels: facility, community and self. Most recent attention has been directed at community-level interventions with the majority of these aimed at improving HIV testing. Few studies assessed how to improve delayed entry to treatment after early diagnosis.

Contextually, in Africa the burden, predictors and interventions of LP were not explored adequately and even less so in Ethiopia. Furthermore, little evidence is available on children rather than adults, homosexuals and other hard-to-reach populations rather than heterosexuals, and interventions rather than magnitude and predictors.

2.4 Discontinuation from antiretroviral therapy

2.4.1 Definitions and burdens of discontinuation

Whilst ART has brought a dramatic change to the life of patients with HIV, it is a lifelong prescription, and this is not easy for every HIV patient [71 215]. As such, discontinuation has been

an ongoing impediment since the start of the program both globally[77 216 217] and in Ethiopia[218-220]. Discontinuation refers to interruption in taking ART at different times after ART initiation[71]. This may occur for periods of months, or take the form of LTFU, defaulting, total stoppage or transferring out while remaining in care[71].

Disparate definitions are available for LTFU and defaulting. LTFU, for example, has been defined as patients discontinue for more than one, three or even six months[71]. A study that aimed to provide a standard definition for LTFU by analysing data from 111 facilities in Latin America, Africa and Asia recommended LTFU should be used if more than six months have elapsed since the last clinic visit[221].

Defaulting was described as patients being without drugs for one week; non-attendant at clinic for one, two, three, four, or six months; missed appointments for one, two or three appointments; and missed for two, three, seven and 14 days after appointments[222]. There have been different definitions of defaulting or LTFU from ART based on setting, program and duration. For instance, a multi-site study in East Africa confirmed the presence of 14 different measurements for defaulting[222]. Definitions in Ethiopia was also not consistent. The operational definition for LTFU was missing appointments for one, two, three or 12 months[80 83 84 218-220 223] while defaulting was missing appointments for more than two months[82 86].

There were also no standard definitions for discontinuation in the literature, with definitions ranging from length of time that a patient was without drugs, non-attendance at ART clinic, or number of missed appointments. Additionally, the available definitions for discontinuation are limited in the era of new ART prescription programs. For example, there was no any definition of LTFU or defaulting for patients being treated under the 'Appointment Spacing Model', that allows patients to receive pills for six months' treatment at one visit.

Discontinuation is an important problem worldwide and nationwide. Although it has changed over time, discontinuation was roughly recorded to be a problem between 5%-60% in high-income countries in the US, Europe and Canada[73]. For example, 60% of HIV patients in US interrupted their medication in 2011[73], and 28% UK patients in a ten-year longitudinal study discontinued their treatment[74]. In Asia, the magnitude of discontinuation was about between 9% and 34%[75 76]. For example, 9%-24% patients in China withdrew from ART care[75], while a study conducted in India showed an overall dropout rate of 38 per 100 person years [77].

In Africa, discontinuation ranged between 13.7%-57.4%[78 79]. The attrition rate in Malawi, for example, was 33 and 36 person-years for hospitals and health centres respectively [224]. In Ethiopia, discontinuation was as prevalent as in the other countries, ranging between 9.8%-

31.4%[80 81]. Studies conducted in North[225], South[84], and Northwest[81] Ethiopia reported that the proportions of LTFU were 9.8%, 28% and 31.4% respectively.

While still of major importance, many studies have found a decrease in discontinuation[226-230]. For example, a six months LTFU in Vietnam decreased from 16.2 to 8.9 per 100 person years [227]. This may be due to introduction of significant community-based HIV care service programs. However, in a few studies the rate of discontinuation had increased[229 231]. A five years study in Zimbabwe revealed that the trend of LTFU increased almost linearly from delivery to five years[231]. This could be related with the dramatic increase in number of patients on ART, which could also lead to interruption of ART through shortage of physical and human resources and other structural barriers.

The literature review showed that the problem was disparate by population, sample size, follow-up period and operational definitions. There were differences in discontinuation rates between homosexuals and heterosexuals, and children and adults. Sample size in studies could be large or small, and follow-up periods could be short or long. The inconsistent definitions provided in section 2.4.1 also significantly contributed to differences in extent of discontinuation. Furthermore, patients who discontinued their treatment faced poor outcomes, with poor quality life, increasing HIV transmission, economic burden and drug resistance[72 77], and these patients re-engaged less with care, as revealed by a tracing study[105].

Thus, the burden of discontinuation was high, the trend was inconsistent, outcomes were poor, and the problem peaked in the first months of ART follow-up globally. In Ethiopia, the problem has not been assessed in detail in children, and available studies were limited to few regional states. There were inadequate data showing trend in discontinuation. Different reasons were provided for these gaps, and are presented in section 2.4.2.

2.4.2 Predisposing factors for discontinuation

Discontinuation was found to be affected by a range of factors including: age[84 102 106 219 232-234], sex[80 81 106 218 219 235-237], residence[86 238 239], education[125 126 219], baseline functional status[84 86 236], baseline WHO clinical stage[220 236 240 241], baseline CD4 count[219 230 242], Tb/HIV co-infection[106 218 241 243], mental illness[82 86 125 235], alcohol consumption[86 241 244], substance use[126 245], traditional beliefs or alternative medicine[121 125 126 214 246], stigma[116 214 244 247 248], knowledge to ART[83 121 246 249], and access to health care[82 116 125 126 230 235 244].

Age[84 102 106 219 232-234] was one predictor of discontinuation. For example, studies by Berheto et al and Wubshet et al found older patients with HIV at higher risk of LTFU[84 106]. Conversely, Melaku et al and Gwynn et al reported the odds of LTFU among younger adults

were high compared with older adults[219 232]. In a study from Kenya, dropouts were more likely among younger adults[233], unlike findings from Ethiopia[102] and Uganda[234]. Younger adult patients with HIV could be more likely to discontinue their treatment because they lacked skills to foresee complications arising from stopping treatment for short or longer periods, and might decide to discontinue treatment[84]. Most young patients might also not be married, meaning that they would not get support from their partners to remind them to take the treatment consistently, which could have its own contribution to discontinuation. In addition, the transition from pediatric to adult ART care could also be another challenge for young adults to adapt the system by themselves. On the other hand, older adults might be busy with family activities and this could interrupt taking treatments regularly. Furthermore, older adults may be affected by chronic diseases than young adults[250], and interfering ART care.

Another factor associated with discontinuation was gender[80 106 218 219 235-237]. The evidence on the relationship between gender and discontinuation was heterogeneous. In some studies, a high risk of discontinuation among females was identified[232 237 251]. For example, a multicenter study in Cameroon, Cote d'Ivoire, Kenya, Mozambique, Rwanda, South Africa, Uganda, Zambia, and Thailand found that LTFU was higher in females (8.4%) than males (7.1%). Research shows that the two main barriers of retention, stigma[120 122 252 253] and usage of traditional healing [124 126], were high in females. On the other hand, several studies found high risk of discontinuation in males[66 81 219 235 254]. For example, a systematic review of qualitative studies found that males were reluctant to continue ART[235]. This may be because of there being few national programs, or low health seeking behavior and low adherence among male patients with HIV[255 256].

Residence[86 238 239] and education[125 126 219] were other factors linked with discontinuation. Patients living in rural settings faced difficulty in taking their medication regularly. A study conducted by Megerso and colleagues[238] confirmed this, reporting that the odds of discontinuation among rural residents was three times higher than urban residents. Studies conducted by Deribe et al. and Geng et al. supported this finding[257]. Unsurprisingly, having less access because of cost or transportation, low awareness of long term ART benefits because of lesser literacy status, and the greater availability of traditional healing over modern medicine contributed to high discontinuation in rural dwellers[117 118]. Level of education also affected discontinuation status among patients with HIV. A study from Ethiopia found that people who never attended school had lower rates of discontinuation than who those had completed primary, secondary or tertiary level[219], while a qualitative study in South Africa found that people with less education were less likely to have regular attendance at ART appointments[126].

This may not be surprise because the reality of sustainable ART compliance requires understanding, where the level of literacy matters[126]. Knowledge of ART as a challenge for ART retention was also revealed by numerous studies[83 121 246 249].

The rate of discontinuation was different by the baseline status of functionality[84 86 236], WHO clinical stage[220 236 240 241] and CD4 count[219 230 242]. Discontinuation rate was elevated among bedridden HIV patients [86 236], advanced WHO clinical stage[220 236 240 241] and low baseline CD4 count[219 230 242]. Being severely ill, immunocompromised or showing symptoms of AIDS interrupt the regular use of ART[258 259]. Furthermore, patients with bedridden functional status, advanced WHO stage, and low CD4 count were more likely to develop OIs and manifold comorbidities [258 260], which could interfere with taking ART.

Several studies also found that chronic illnesses such as Tb/HIV co-infection[106 218 241 243] and mental illness[82 86 125 235] affected discontinuation. According to Bucciardini et al, the risk of discontinuation among Tb/HIV patients was double compared to HIV patients alone[218]. This was confirmed by studies in African countries including Ethiopia[106 241 243]. The intricate relationship between Tb and HIV could lead to prompt progression to advanced HIV stage, and interferes regular ART intake [261]. The double stigma and pill burden from both diseases could also be additional factors in discontinuation in patients with Tb/HIV. The rate of discontinuation was found high in patients with mental illness. For example, the odds of discontinuation among patients with mental illness in Ethiopia was high compared to those with no mental illness[257]. This is consistent with a review study reporting a significant challenge to ART retention among patients with mental illness[125]. The serious bidirectional combination of both diseases could impede the consistent ART intake[262]. Additionally, the double stigma could even more of a challenge to ART continuation[262 263].

A range of studies also mentioned alcohol consumption[86 241 244] and substance use[126 245] as barriers to discontinuation. The study by Deribe et al. found six times higher risk to discontinuation among heavy alcohol drinkers compared to non-drinkers[257]. In a qualitative study, Loeliger et al found that drinking alcohol, smoking tobacco, taking marijuana and sniffing glue or other illicit drugs interfere ART retention[126]. Patients with HIV who drink alcohol and use substances may refugee in or use these as 'escapism' to deceive themselves about having the disease[126]. In particular, because patients on ART are not allowed to drink alcohol, heavy alcohol drinkers may decide to stop their medicine[53].

Traditional healing[121 125 126 214 246] and stigma[116 214 244 247 248] were identified in several studies as two common barriers to ART retention. For example, in qualitative studies from Ethiopia[121] and South Africa[126], the impact of traditional healers was shown to undermine

efforts to retain patients on ART. Other studies corroborated this finding[125 214 246]. Likewise, stigma severely affected ART retention. A qualitative study in Kenya found that enacted HIV related stigma could lead to stress or other mental illnesses, as a result of which patients may suspend or permanently stop taking their medicine[247]. Another review study also confirmed the importance of perceived stigma when accessing care[116]. The fear of stigma or exposure to other people in combination with the cultural norms could affect the decision to initiate or maintain ART[248]. Additionally, patients may delay the start of treatment, and this delayed presentation could expose patients to several other chronic diseases, interrupting ART intake[160].

Access to health care services[82 116 125 126 230 235 244] was mentioned as another barrier to ART retention. For example, Asefa et al. revealed that HIV patients who live in distant places were less likely to consistently continue their treatment than patients living near the place[82]. Other studies found that long delays in seeing a physician or obtaining ART from the pharmacy, and stockouts affected discontinuation[264 265]. In a study by Sarnquist et al, affordability and insurance as barriers to ART retention were mentioned by 17% and 15% of study participants. Therefore, distance, long waiting time, inability to afford treatment and having no health insurance negatively affect access to ART care and thereby retention in care.

Finally, additional factors for discontinuation among children included caregiver relationship and nutritional status of the child. The risk of LTFU among children was higher if biological mother was their primary care giver than grandmother[266], which could be due to the workload differences between mother and grandmother. Severely underweight children were at higher risk to discontinue from treatment than well-nourished children because malnutrition affects ART compliance and associated benefits[266 267].

The literature review has shown that demographic, economic, clinical, cultural, behavioral and structural barriers influenced discontinuation. Of the numerous studies assessed factors associated with discontinuation, few of them were from Ethiopia. Of these studies in Ethiopia, the vast majority were concentrated in limited regions of the country. In addition, most studies assessed the problem in adult HIV patients, not in children or older people. Although comparisons are inconsistent due to different definitions, some studies showed conflicting association between variables (age and gender) and outcomes. There were only a few qualitative studies, and most studies included in the literature review were retrospective; as such their ability to explore barriers beyond the clinical and non-clinical characteristics of patients was limited.

2.4.3 Interventions for discontinuation

Only a few studies assessed interventions to reduce discontinuation from ART. One program designed to improve the HCC was a *seek-test-treat-succeed* model[268]. In this, early access to care and treatment literacy is enhanced (*seek*) and testing uptake and timely linkage are improved (*test*). Likewise, early and sustainable HIV treatment involving volunteers or community health workers is improved (*treat*) with task shifting, improving sustainable retention and re-linkage (*succeed*).

Service integration was also another solution to reduce discontinuation. For example, integrating the ART care schedule of women and their children improved through circumventing logistical problems[125]. Another solution involved using traditional healers as an entry point to modern medicine because many people give credibility to traditional healing practices[125].

Other suggested interventions for enhancing retention included introducing new technologies and reducing stigma. Introducing new technologies such as using mobile information technology during the appointments, helped patients with HIV to remember their ART schedule[269]. South Africa introduced a disability grant providing incentives for severely ill people to come back to care[270]. Reducing stigma by involving HIV positive patients in campaigns to raise awareness through sharing their experiences was found to be very effective in one study[271].

A systematic review found use of POC CD4 testing, community-supported programs and patient tracing were effective means of increasing retention in care[272]. An observational study found that POC CD4 testing reduced discontinuation from 64% to 33%[211]. Utilization of patient tracer, HIV positive social worker/peer educators assigned to trace and re-link to care, helped to re-engage lost patients at low cost[273]. Another systematic review and network meta-analysis found that short message service (SMS) text messages, multiple interventions, cognitive behavioural therapy and supporter interventions were effective interventions for ART adherence[274].

Generally speaking, although a number of barriers have been identified, few studies across the world, and even fewer in Ethiopia have assessed ways to reduce discontinuation. In this literature review, *seek-test-treat-succeed* model, service integration, implementing new technologies, stigma reduction, cognitive behavioural therapy, supporter interventions, POC CD4 testing and community-based activities were identified as strategies to improve retention in care.

2.4.4 Summary

To summarize, discontinuation occurred in considerable numbers of patients although the trend has reduced over time. The literature review revealed individual or community related barriers including demographic, economic, clinical, cultural, behavioural and structural factors. However, few studies reported interventions for promoting retention. Research on all aspects of discontinuation – burden, predictors and interventions – was lacking in Ethiopia, and the available evidence was concentrated in a few regions. Discontinuation among children was almost never addressed nationally.

2.5 HIV related immunologic failure

2.5.1 Definitions and burdens of immunologic failure

WHO has provided definitions for immunological failure for children and adults[93]. For a child younger than five years old, immunologic failure is defined if the CD4 count of a child persists < 200 cells/mm^3 or CD4 percentage continues to be <10% after six months of ART treatment. For a child five years and older, immunologic failure is defined if the CD4 count of the children remains below 200 cells/mm^3 after six months of ART treatment. For adolescent and adult, immunologic failure is diagnosed if a patient's CD4 count falls to (or below) the baseline level. Additionally, immunologic failure is also diagnosed if the CD4 count of the patient persists below 100 cells/mm^3 after six months of ART treatment. Lastly, immunologic failure is also measured if CD4 count falls below 50% of peak on-treatment value[97].

The main function of immunologic failure is to monitor the effect of ART through assessing the achievement of virological suppression and subsequently diagnosing treatment failure. Nevertheless, several studies argue the sensitivity and specificity of immunologic failure as defined above do not correctly reveal virological failure or *vice-versa*. For example, one systematic review reported that existing definitions of immunologic failure had low positive predictive value and high negative predictive value for diagnosing virological failure[275]. Therefore, because of such limitations of immunologic failure, the WHO suggested performing targeted viral load testing to confirm treatment failure for those with immunological failure in countries like Ethiopia, where virological monitoring is not available or routinely performed[34].

Immunologic failure is one of many impediments affecting people's expectations of benefit in the era of universal ART [276] [277]. For instance, in Asia, the magnitude of immunological failure was 9%-33.5%[91] [97]. In China and Thailand, 30% and 34% of patients respectively were diagnosed with immunologic failure[278] [279]. In Africa, immunological failure

ranged between 8% and 57%[234 280]. For example, in Uganda, 8 and 38 failures per 100 patients were recorded at 12 and 24 months respectively after treatment initiation[234]. However, immunologic benefit has improved over time. For example, six-month viral load suppression among children in Uganda was 80.6, 85.2 and 81.1 % who started their treatment in calendar years 2007, 2008 and 2009 respectively [281]. A multi-country study in Africa also revealed significant declines (81% to 63%) in the proportions of children with severe immunosuppression at baseline [282].

In Ethiopia, the burden of immunological failure was between 6.8%-27%[283 284]. Studies in Western Ethiopia[100], South Ethiopia[285] and northern Ethiopia[286] found an immunologic failure prevalence of 11.5%, 17.6% and 22% in 2009, 2015 and 2014 respectively. Although there are no published data on the trend of immunologic failure in Ethiopia, different studies at different points of time show that immunologic failure is increasing.

Generally, the burden of immunologic failure is an important problem, with reported rates varying from 6.8% to 57%. The rate has declined in Asia and Africa but seems to be rising slightly in Ethiopia. The differences in magnitude between countries could be due to differences in definition or timing of measurement of immunologic failure. For example, some studies reported immunologic failure at 6 months, while others used 12 or 24 months. All studies cited in the literature review that assessed immunologic failure were in relation to first line ART drugs and none assessed immunologic failure of second line ART drugs. The studies on immunologic failure in Ethiopia were concentrated in central and north Ethiopia.

2.5.2 Predisposing factors for immunological failure

Unlike LP and discontinuation, there were very few articles about immunologic failure. The literature review identified the following as factors affecting immunologic failure: age[217 287 288], sex[98], education[289], unemployment[289], low baseline CD4 count[98 289-292], advanced WHO clinical stage[290 291], poor adherence[293], treatment supporter[293], non-disclosure[92], and risk behaviour[294].

Age was one determinant factor for immunologic failure, with high rates seen in older adults[217 287 288]. This may be due to age-related compromise of the immune system[288] and delayed HIV diagnosis [295] among older adults. Most studies that assessed the association of gender and immunologic failure did not show a statistically significant relationship [296-298], except one that found high rate in females [98]. It has been noted that reduction in viral counts for females is greater over time than for males even if they have higher viral loads[299].

Education and employment were other variables associated with immunologic failure. For example, Babo et al. found that patients with HIV who had formal education were at five

times higher risk than those who were not able to read and write[289]. Although this is a surprising finding and may need further exploration, it is plausible to hypothesise that educated people would have high likelihood of high and frequent mobility because of different commitments, and ART intake would thus be interrupted. However, to the contrary, Babo et al. indicated that the odds of immunologic failure among unemployed patients with HIV was five times higher than for employed patients[289]. This may be associated with lack of money because the associated costs may affect the regular intake of medication needed to obtain immunologic benefit. This study, however, did not assess the link between education and employment where the majority of educated participants were not employed.

The rate of immunologic failure was also high if the baseline CD4 count was low[98 289-292] and WHO clinical stage was advanced[290 291]. Kassa et al [290] found that the risk of immunologic failure among patients with baseline CD4 count above 100 cells/mm^3 were 80% less than for those with below 100 cells/mm^3. This study [290] also found that patients with baseline WHO clinical stage 3 or 4 were at four times higher risk of developing immunologic failure than those with WHO clinical stage 1 or 2. Patients with low CD4 count or advanced WHO clinical stage were easily vulnerable to OIs or other chronic illnesses, and this deterred ART intake and effectiveness of the treatment[258 260 261].

Poor adherence[293], lack of treatment supporter[293] and non-disclosure[92] affected immunologic failure. A study from Tanzania revealed that the odds of immunologic failure among non-compliant patients was significantly higher (13 times) than compliant patients[293]. Similarly, this study found very high odds (27 times) of immunologic failure among patients with no treatment supporter, someone who would support or observe treatment for a patient on ART to ensure that the patient take the treatment on time, daily[293]. Bayou et al found there was 57% lesser risk of immunologic failure among patients who disclosed their HIV status to at least one person[92]. Non-disclosure has been reported to limit receiving the required support (e.g. psychological support, reminding treatment intake, earning money or other resources for associated costs) from others, and this further predisposes patients to non-adherence. Such non-adherence limits the immunological gain from the treatment[300].

Finally, sexual risk behaviours were related with immunologic failure[294]. For example, a study by Dragsted et al. reported that the risk of immunologic failure was high in IDUs compared to homosexual, bisexual or heterosexual contacts. There could be several reasons why IDU was a predictor to immunologic failure. For example, IDUs could have high rates of mental illness which is highly stigmatized, and is associated with comorbid illnesses and/ or drug use. The complexity of these factors could negatively influence ART compliance and

subsequently immunological success[301]. Furthermore, since most IDUs are known to have drug dependency problems and may lack money, which often lead them to committing crime and imprisonment. These factors may subsequently undermine the retention in care leading to poor ART benefit[301].

Thus, immunological failure was affected by sociodemographic, economic, clinical and behavioral factors. Unlike LP and discontinuation, there were few studies on immunologic failure globally. Studies in Ethiopia were also geographically skewed and most of them were performed in only few regions of the nation. Furthermore, the literature review revealed that there were limited studies that assessed factors linked with immunologic failure among children and older adults, immune vulnerable age groups.

2.5.3 Interventions for immunologic failure

Four different interventions for immunologic failure were reported in four different studies. A randomized controlled trial (RCT) in Uganda found that patients who had support from a peer or health worker had higher virological suppression rates than those who did not[302]. Similarly, in another RCT in Uganda, home-based ART care was found to be as effective as facility-based ART care in gaining immunological benefit[303]. An RCT in South Africa revealed that the rate of virological suppression or immunologic gain under a new program called 'directly observed therapy (DOT)' for ART was 73% compared to 68% in the self-ART group[304]. In an RCT from Nigeria, use of treatment partner-assisted therapy compared with standard of ART care improved virological suppression at the earlier follow up[305]. In summary, treatment supporter, home-based ART care, DOT for ART and treatment partner-assisted therapy were the interventions to reduce immunologic failure.

2.5.4 Summary

Immunologic failure was an important problem with extent ranging as high as 57%. Nevertheless, in the present literature review only studies reporting immunologic failure for first line ART drugs were identified. Factors affecting immunologic failure including patient characteristics such as demographic, economic, clinical and behavioural were identified. Global evidence on immunologic failure is scarce, and the existing evidence in Ethiopia is geographically biased. Furthermore, evidence on groups vulnerable to HIV and immunologic failure is scarce. To enhance immunologic success, individual-, home- and facility-based programs have been tested but no interventions for immunologic failure have been reported in Ethiopia.

2.6 HIV related mortality

2.6.1 Definition and burdens of HIV mortality

HIV related mortality (hereafter mortality) refers to death due to any cause in the reporting period[306]. Despite the scaling up of ART coverage, HIV/AIDS continued to become among the top ten causes of death list of causes[307]. Literature shows that Southern Africa had the highest crude mortality rates followed by East and West Africa, Central Africa, Latin America and Asia Pacific[308]. A multi-centre study found a cumulative mortality of 5%, 15% and 17% in Europe, North America and South Africa, respectively[309]. These studies reported that the death rate was high in the first 12 months of ART treatment. A number of studies assessed mortality in Ethiopia and found a magnitude of 2-25.9%[101-104 310-313]. Most of these studies also found high death rates in the early period of ART treatment.

HIV mortality in the era of HAART in Africa is markedly declining. For example, according to the research from South Africa, 12-month corrected mortality ratio was 4%, 5% and 3.7% among patients who started treatment in calendar years 2007, 2008 and 2009 respectively[226]. Likewise, the HIV-attributable mortality in Tanzania showed a reduction from more than 50% in 2000 to around 35% in 2010 [314]. In general, studies reported a low death rate and these deaths occurred in the initial period following initiation of ART care.

2.6.2 Predisposing factors for HIV related mortality

Predictors of mortality among adults have been identified in many studies. They include age[315], gender[101 103 315-319], education[101 103], baseline WHO clinical stage[102 103 313 320], baseline CD4 count[103 313 321], adherence[322-324] and functional status. Additional child related factors affecting mortality included developmental milestone[325] and nutritional status[281].

Death rate was high among older, male and less educated patients with HIV. In one study, showed that mortality among older adult HIV patients aged above 35 was two times higher than among young adult patients[315]. This supports findings reported in sections 2.3.2, 2.4.2, 2.5.2, reporting high LP, discontinuation and immunologic failure among older adults. Mortality rates were also found higher among men than women. For example, one study found a death rate of 9% in women compared with 13.5% in men[316]. As described above, there were few programs that targeted men, and adherence rates for men were lower than for women[255 256]. Furthermore, alcohol consumption is high among men and this could contribute to the high rates of death among men than women[326]. People who completed secondary school or above were 65% less likely to die compared with those who did not attend school[101 103]. This could be linked with the level of awareness needed to seek the ART care.

Not surprisingly, risk of mortality was increased among patients with baseline CD4 count below 100 cells/mm^3, WHO stages 3 and 4, bedridden functional status and and those who were non-adherent to ART[236 313 315 320 322-324 327 328]. For example, patients who had baseline WHO clinical stage of 3 or 4 were four times more likely to die than those who had stage 1 or 2[102]. Similarly, the risk of death was 60% less in patients with higher baseline CD4 count[320]. Patients with poor baseline performance scale compared with normal activity were at four times higher risk of death [321]. Tb/HIV co-infected patients were also at higher risk of death than patients with HIV only[103 313]. In one hospital-based study in Ethiopia, patients with poor adherence to ART were 28 times at higher risk to death than their comparator[322]. The presence of low immunologic and clinical gain, comorbidities such as TB/HIV, being debilitated at the start of the treatment and poor compliance to the treatment lead to fast progression to AIDS stage and subsequently death [70].

In addition to being younger, having low CD4 count and advance WHO clinical stage[281 325 329], delayed developmental stage and under nutrition were the predictors of mortality among children. If children were delayed or regressed developmental milestone at initiation of ART, there was six times increased risk of mortality [325]. Children who were moderately (ten times) and severely underweight (47 times) had also high risk of dying than normally nourished children [281]. Such delayed growth and malnutrition impeded ART adherence, exposed to other comorbidities, and hasten progression to advanced AIDS stage and finally death.

Therefore, demographic and clinical predictors were the factors mostly reported as associated with death. This review showed that there were many factors correlated with HIV mortality among children and adults. Inconsistencies among factors affecting mortality were noticed, and these factors were assessed in relation to the overall mortality.

2.6.3 Summary

The literature review showed that there were numerous studies that assessed the overall trend, cumulative incidence and cumulative density of mortality. The vast majority of these studies reported that death rates were lower but the absolute number was higher than the previous years, becuase the number of people diagnosed with HIV in recent periods has increased significantly[227]. Most deaths happened in the early follow up period of ART care (below 24 months after ART initiation). Despite this fact, most studies assessed the predictors of overall mortality, as such, predictors of early mortality have not yet been assessed very well. No studies in Ethiopia considered the effect of LTFU on mortality. Very few studies were conducted on older people, and most studies have been in developed countries despite the growing number

of older adults on ART in developing countries. On a global scale, the number of older adults with HIV is rising, but because they are diagnosed late, substantial numbers of them come with poorer clinical outcomes and subsequently may die [330] [331]. Mortality was predicted by demographic and clinical factors, even though there were conflicting associations between some predictors and mortality. However, predictors for early mortality were not assessed much, particularly in studies from Ethiopia.

2.7 UNAIDS 90-90-90 treatment targets

2.7.1 Targets and measurements

In Melbourne, Australia, in 2014, UNAIDS[332] and partners proposed three targets for management of HIV infection[32]. These targets included (i) diagnosing 90% of people living with HIV, (ii) providing ART for 90% of those diagnosed patients, and (iii) achieving viral suppression for 90% of patients receiving treatment. The targets aimed at eliminating the AIDS epidemic through improving access to HIV testing and ART care [32] [333] [334] and measures for transmission prevention [335-337]. The plan was to achieve these targets in 2020 to laying the foundation to end the AIDS epidemic by 2030.

There are ideal surrogate measures for assessing the performance of each target. To measure the UNAIDS target one (first 90, HIV diagnosis), the number of people infected with HIV in the population is used[73] [338-340]. To measure the UNAIDS target two (second 90, ART treatment), the number of people infected with HIV who are receiving ART is used[338] [340]. To measure the UNAIDS target three (third 90, virological suppression), the number of patients with undetected viral count is used[338] [340]. Furthermore, the number of patients with immunological, clinical and treatment success are also used as a surrogate measure[275].

2.7.2 UNAIDS target 1- HIV diagnosis

There are performance estimates of progress since the inception of these UNAIDS targets. Levi et al. conducted complete assessment (three targets) for 32 countries and partial assessment for 37 countries[108]. This report showed that the global performance for target one was 54% in 2016[108], illustrating that an additional 13.4 million people needed to be diagnosed. For this target, Sweden was reported to have achieved 90%[107], followed by Netherlands with 87%, while Yemen achieved least performing at 11%[108]. A few studies estimated target performance within specific groups. For example, a study from San Francisco assessed the target for MSM, and found 97% achievement[341]. In Africa, Botswana was found to be the best performing country reporting 83.3%[342] while SSA achieved 45%[4] in the general population. A time series analysis to forecast UNAIDS target in Ethiopia found 67% achievement[110]. This study is the

only study that assessed the target performance in addition to the 2017 UNAIDS update that assessed the target performance of 67%[111].

There are several reasons for differences in performance on the HIV diagnosis target. The diagnosis target depends on[108 343 344]: (i) HIV testing technology, (ii) HIV testing uptake, (iii) methods (quality) for data collection, (iv) HIV epidemic status of the country for modelling and estimation, (v) the modelling type, and (vi) lack of uniform measurements. Difference in any of these factors could lead to performance differences. Studies showed various interventions to improve HIV testing services and uptake, and were discussed in section 2.3.4.

2.7.3 UNAIDS target 2- ART treatment

Globally, the performance of treatment target was 76% in 2016[108], reflecting that the current number of patients on ART has to at least be doubled. For this target, Sweden attained 97.1% followed by Switzerland (71%) while Yemen and Afghanistan attained 3% each[108]. The San Francisco study on MSM found 93% performance[341].

In SSA, an estimated of 86% of these diagnosed received ART[4]. Botswana's target performance was 87.4%, one of the highest in Africa[342]. The time series analysis in Ethiopia showed an 88% performance[110], and the 2017 UNAIDS update reported 59%[111].

Reasons for performance difference included[244 343 345 346]: (i) cultural and structural barriers of ART uptake, (ii) ART availability and associated costs, (iii) capacity of healthcare facility, and (iv) lack of consistent measurements or criteria for ART. Interventions to improve performance were described in section 2.4.4.

2.7.4 UNAIDS target 3- Virological suppression

The global performance of virological suppression was 78%. Sweden[107] followed by Switzerland [347] attained the highest performance with 95% and 68% respectively, whereas China had the lowest results, reporting 7% virological suppression[108]. According to the study in San Francisco, rate of virological suppression in MSM was 64%[341].

In Sub-Saharan Africa (SSA), an estimated 76% of those on ART achieved virological suppression[4]. Botswana found a target achievement of 95%, the only country from Africa that achieved this target[342]. Ethiopia's achievement based on the time series estimation analysis and 2017 UNAIDS update showed an 86% [110] and 61%[111] performance.

Similar to the above two targets, there are differences in performance for the third 90 due to[343 348]: (i) difference in definitions for undetectable viral load, (ii) demographic and structural barriers, (iii) poor retention, and (iv) availability of drugs in stock. The interventions described in sections 2.4.4 and 2.5.4 could help to meet the virological suppression.

2.7.5 Summary

In conclusion, the literature review found there had been progress towards achieving UNAIDS targets in developed countries, but there was less evidence of this in African countries. The available evidence showed that most countries in the world, except Sweden, were a long way from achieving the ambitious targets, and this signalled the need for further research. The review revealed that countries from Europe were among the better performers while countries from Africa and the Middle East were among the worst.

Of the three targets, the lowest level of achievement globally was for the first 90 (diagnosis). Data on achievement were not reported in sufficient detail by age (children and adults) or gender (male and female), risk behaviours (IDUs, homosexual and heterosexual contacts), epidemic of HIV (low, moderate and high) and other at-risk population groups (commercial sex workers and long-distance truck drivers). In Ethiopia, only one study was found, and it was a forecasting study based on retrospective data.

2.8 Overall summary

In this chapter, I have reviewed definitions, magnitude, predisposing factors and interventions for each stage of HCC outcomes. Except for mortality, the definitions for LP, discontinuation and immunologic failure outcomes were inconsistent. Overall, most studies found LP and discontinuation to be increasing, immunologic failure to be emerging and HIV mortality to be declining. In Ethiopia, these outcomes were reported to be a significant burden although most of the studies were geographically skewed to the north and northwest parts of the nation. The current literature about these outcomes for children and older patients with HIV remained poor.

The literature review also showed that there were several determinants of these outcomes including sociodemographic, economic, behavioural, clinical, structural and cultural barriers. There were conflicting findings between studies on the associations between variables and outcomes of interest. Retrospective cohort studies were overrepresented in the literature and some studies relied on small sample sizes and short follow-up periods. Baseline clinical and non-clinical characteristics were reported frequently across the literature. This illustrates that most studies assessed links between patient-related factors and outcomes. Some qualitative studies reported cultural barriers such as stigma and traditional healing, and behavioural barriers such as alcohol consumption and having contact with commercial sex workers; however, the effects of policy or health worker factors on outcomes were explored inadequately. There was very little evidence from mixed methods studies on links between

patient characteristics and barriers and either one or all outcomes of HCT. No study assessed the whole HCC.

The literature review highlighted that the UNAIDS targets were ambitious, and most countries of the world have not achieved the targets. The existing global evidence showed that reaching the first 90 was more challenging than achieving the other two. Studies assessing the targets were scanty, and none using ideal measures had been carried out in Ethiopia. Despite poor achievement of the three targets and assessing several factors of LP, discontinuation, immunologic failure and mortality, evidence on interventions to improve each stage of the continuum of care was insufficient.

Most interventions were facility-based, a few were community-based and self-administered interventions were rare. Interventions for LP included VCT, community-based HIV testing, HIV self-testing, decentralization, task shifting, POC CD4 measurement and peer educator-based HIV testing. Interventions for discontinuation included the *seek-test-treat-succeed* model, service integration, peer educator-based lost patient tracing or use of patient tracers, POC CD4 testing and community-supported programs. For immunologic failure, the interventions were HIV care support from peer health workers, DOT for ART, use of treatment partner-assisted therapy and home-based ART care.

From reviewing the literature on the ways to improve HCT, there were limited data that showed interventions to address each stage in the HCC. There was no exhaustive listing of possible interventions and no prioritization of available solutions was performed using consensus methods. No assessment of combinations of interventions was observed. For example, there were no studies investigating questions such as … "*what happens if facility-based HIV testing and HIV-self testing are implemented in combination?*" The evidence from the literature review also showed there were sparse data on children, homosexuals, and developing countries for all aspects of the problem.

Overall, the literature review in Ethiopia showed that there was no systematic review that comprehensively assessed ART discontinuation. Additionally, the different stages of HCC outcomes were studied inadequately, and the whole sequence of HCC was not assessed completely. Existing studies had conflicting findings in relation to the association of some factors and HCC outcomes, and most only used clinical and non-clinical characteristics of patients when discussing LP, discontinuation, immunologic failure and mortality. While negative HIV outcomes are determined by multiple ecologic level factors, the literature review found that factors affecting negative HCC outcomes beyond patient-level factors, such as institutional, community and policy level factors, were not explored. The literature review also

confirmed that potential interventions for LP, and ART attrition were assessed insufficiently. Furthermore, no consensus study has been published that attempts to prioritize interventions based on their relevance, feasibility and acceptability. Finally, the literature review found no studies that used mixed methods to research the complex nature of the care continuum.

2.9 Theoretical model

The research reported in this thesis was guided by a model called the social–ecological model (SEM). Investigation of the HCC pathway needs multi-level involvement and interaction[33]. Previous work attempted to explain HIV care needs has lacked multifaceted characterization incorporating several levels or sites of action, namely individual, community, institution, and policy levels[349-351]. When using the SEM[352] to investigate HCT challenges, the relationships that exist between an individual and the environment – interpersonal, community, organizational and policy levels – are assessed[353]. The SEM was established from the Ecological Systems Theory of Bronfenbrenner (1989)[354], Ecological Model of Health Behaviors of Leroy (1988)[355], and SEM of Health Promotion of Stokols (1996)[356]. The works of these and other researchers have been applied, modified, and developed into what is currently coined the SEM. There are several versions of the SEM that use slightly dissimilar grouping of levels[353 357]. For the present study, the enablers, barriers and possible solutions for HCT were explored at four levels with reference to Bronfenbrenner (1989)[354]. These are the individual, healthcare, community, and policy levels. The SEM is shown in Figure 2.1. In the model, the overlapping circles demonstrate how factors at a level affect factors at another level.

The first level, individual level, pinpoints biological and personal exposures that intensify the risk of becoming vulnerable to the the topic of interest[355] such as negative HIV care outcomes. Given that the SEM demonstrates the complex interaction at multiple levels, the knowledge and behaviour of an individual are constructed from social interactions such as morals, symbols, and beliefs at these levels[358]. These social interactions are imperative in determining how individuals describe meaning under the face of culture and language. In this project, the individual related perspectives comprised the demographic, socio-economic, knowledge, experience, expectations, attitudes, disclosure and beliefs of patients with HIV.

The second level, health care or *microsystem* level, focuses on the interactions with health workers, and access and availability of the healthcare service itself. Availability and access to healthcare particularly HIV care is a vital element of health development for patients with HIV patients. In addition, a warm welcome, courteous interactions and attention to patients' concerns have a substantial impact on the efficacy of services provided

in a health care facility[353]. In this project, the health care level comprised the interaction with HIV health care providers, distance, logistics and availability.

The third level, community or *mesosystem* level, targets on the institution of a community. The characterization of who and what institutes a 'community' is commonly described as involved networking, interactions between groups and organizations, and geographical settings[355]. Additionally, communities may be bound via religious, economic, cultural or geographic links, or any combination of these. Such interaction influences the promotion of wellbeing or could be a source of isolation or stigma. Therefore, interpretation of these community norms could enhance or deprive the HIV care services within a community[359]. For instance, interventions targeted at norms of simultaneous use of traditional and modern medicine could demonstrate efficacy in ART care. In this project, the community level factors comprised care and support, stigma, traditional healing, and social networks.

The fourth level, policy or *macrosystem* level, focuses on the policies and programs related with HCT. It is evident that *policies* of a state give a general framework of service provision for the generalized population and marginalized groups[360]. The planning, implementation and evaluation of these policies and programs can intensify or lessen the community's ability to use the available health care services[359]. Policies determine allocation of services to various settings or groups within the population, logistics or capacity building, development assistance and other services. These play a significant role in influencing structural contexts of HIV care services[361]. In this project, the policy or program level contained health policy, HIV/AIDS policy, distribution and referral systems, capacity building, guidelines and standards.

The SEM guided the data collection and analyses (methods), and interpretation of findings. The '*individual level*' of the model helps to explain the predictors of negative HCC outcomes. The methods that guide this are presented in sections 3.4 and 3.5 of Chapter three, and the findings are presented and interpreted in Chapters four and five. The *micro-* and *mesosystem levels* of the model help in exploration of additional barriers and respective interventions of negative HCC outcomes. The method to guide this is presented in section 3.6 of Chapter three, and the findings are presented and interpreted in Chapter six. Finally, the *macrosystem level* of the model helps to prioritize the possible interventions that were explored at the micro- and mesosystem level. The method to guide this is presented in sections 3.7 of Chapter three, and the findings are presented and interpreted in Chapter seven.

In summary, based on the designed conceptual framework, HIV diagnosis, ART care linkage and retention in care services of patients on ART depend on individual, community, organization, and policy level factors.

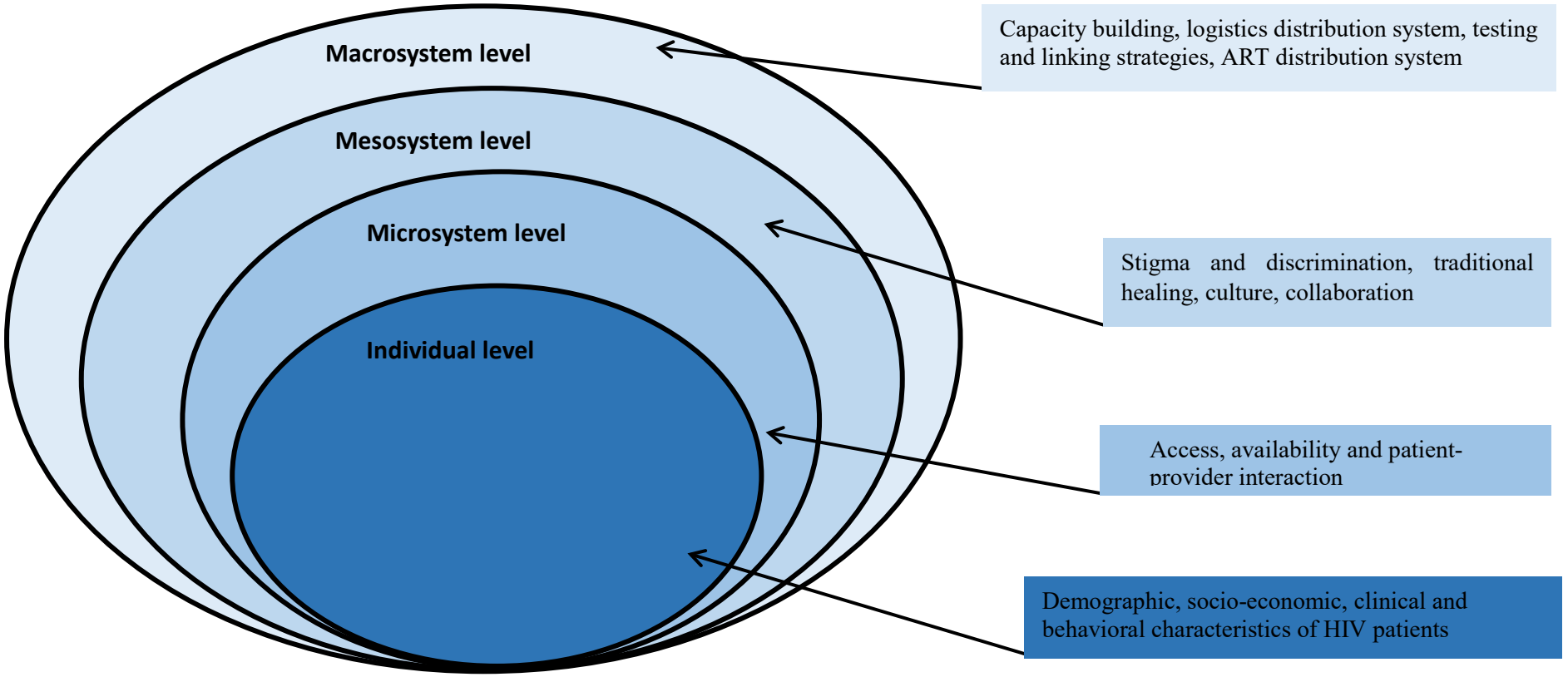

Figure 2-1: Factors influencing negative HIV care continuum outcomes, adapted from the social-ecological systems theory (Bronfenbrenner, 1989)[354]

This figure shows the application of SEM in the HCC framework. *Individual level* refers to patient level factors, *Microsystem level* refers to health care related factors, *Mesosystem level* refers to community related factors, and *Macrosystem level* refers to policy level factors. The overlapping circles in the model shows how factors at one level affect factors at another level[2].

[2] This figure needs to be viewed in colour but the colour intensity is only used to separate one level from the other not to demonstrate the rank of importance of the levels.

Chapter 3

Methodology and Methods

CHAPTER 3 - METHODOLOGY AND METHODS

3.1 Introduction

This chapter presents the methodological approaches and methods used for the project to explore the continuum of HIV care in Ethiopia. The project used a mixed methods approach comprising four studies: (i) systematic review and meta-analysis study, (ii) quantitative study using a retrospective cohort study design, (iii) qualitative study design, and (iv) consensus method study using the Nominal Group Technique. The chapter has nine sections. The first section describes the study setting and period. The second section provides the epistemological and methodological assumptions of mixed methods, and rationale of the approach applied in the project. Section three to six detail the studies and study designs described above, and section seven describes dissemination of the findings. Section eight presents the ethical considerations undertaken during the project processes. Finally, the section is concluded by summary of the study methods in the project by their respective objectives.

3.2 Study setting and period

The main studies were conducted in Jimma, Southwest Ethiopia. Jimma is located 357 km southwest of Addis Ababa and has a total area of 4,623 hectares. It is the capital city of Jimma zone and one of the 18 zones (councils) in Oromia region. The zone has a projected total population of 3 million, of which 89.69% are rural inhabitants [7 362]. Jimma town is bounded by Kersa *woreda* (district) in the east, Manna *woreda* in the west, Manna and Kersa *woreda* in the north and Seka *woreda* in the south. The town is divided into three *woreda* and 13 *Kebeles* (lowest administrative units in Ethiopia). It is sited at an altitude of 1750–2000m above sea level, the temperature ranges from 20–30^{o} C, and average annual rainfall is 800–2500mm[3]. A map of Jimma is shown in Figure 3.1.

Jimma town is located in Oromia region, a region that has the highest number of people infected with HIV in Ethiopia and one of the regions with least ART coverage[363]. It is near Gambela region, which had the highest prevalence rate of HIV in Ethiopia[363]. There is a refugee camp near the zone where refugees from different African countries (mostly from South Sudan) live. The presence of high migration from and to the city creates the risk of high HIV transmission. Jimma town has three public hospitals, JUTH, Shenen Gibie Hospital and Jimma Military Hospital, and three health centres with ART care services, Jimma, Higher 2 and Seto Semero health centres. Of these, JUTH is the biggest hospital in the town and zone and it provides services for people from Jimma zone and other surrounding areas including Gambela. It is plausible to hypothesize that regional states with higher prevalence of HIV could have

different predictors for negative HIV care outcomes.

JUTH, Shenen Gibie and the military hospital started to provide ART since 2003, 2016-17 and 1981 respectively[364]. Of the health canters, JHC started ART services provision since 2005[365] and the other health centres started ART after 2016. The current project was carried out in JUTH and JHC. These institutions have been providing ART services for a long period of time, have many patients on ART and their data are computerized. The hospital serves a catchment area of three million people, and the health centre serves nearly 25,000 people who come from rural, urban and semi-urban settings. As of 2015, a total of 8,170 and 1,600 patients with HIV were enrolled in HIV chronic care in the hospital and health centre, of which 5,299 and 800 respectively were on ART.

In all settings, VCT, PMTCT, ART and OIs treatment services are available. Once the patient confirmed his/her HIV status, an intake form is filled after the exhaustive counselling, and appointment made for further testing at six-months interval until the patient fulfils the criteria for ART. The criteria for ART initiation in Ethiopia is described in section 2.2. This procedure was functional until the at the beginning of 2016. However, since mid-2016, every person who tests positive for HIV can start ART irrespective of baseline CD4 count or WHO clinical stage. Patients who start ART have follow-up appointments every three months, and CD4 will be monitored every six months for the first year and yearly thereafter. CD4 cell count machines are available in both institutions.

The ART care facilities have an ART clinic with a minimum of one trained clinician who manages patients, a data clerk who ensures data management including electronic data update, a case manager and two peer educators (adherence supporters) to trace clients who miss appointments or are LTFU from care. Every health professional working at ART clinics undertakes comprehensive and refresher training about ART before commencing work. In addition to routine government support, the institutions are supplied by the International Center for AIDS Care and Treatment Programs (ICAP). ICAP, based at Colombia University in New York is an NGO established in 2004 that provides family centred HIV services at 3,300 sites across 21 countries. ICAP is known for developing capacity building and providing innovative and effective programs in the most challenging and resource meagre areas. ICAP mainly supports hospitals.

Data were collected between 2016 and 2018. For the retrospective cohort study, data were extracted from JUTH and JHC in 2016. Primary data for the qualitative inquiry and NGT were gathered from October 2017 to January 2018.

Figure 3-1: Map of Jimma, Southwest Ethiopia[3]

[3] This figure needs to be viewed in color.

3.3 Definitions and rationale of mixed methods

3.3.1 Mixed methods: epistemological and methodological assumptions

Mixed methods– alternatively termed as integrated, synthesis, qualitative and quantitative methods, multimethod, and mixed methodology– is a design that integrates or combines epistemological and methodological assumptions[366 367]. Epistemology refers to what the acceptable knowledge is (or should be) and has two distinct positions, namely positivism and interpretivism[367]. Positivism, essence of explanation, is an assumption based on objectivity, generalization and testing of theories[366 367]. Whereas, interpretivism, essence of understanding, is an assumption that is based on subjectivity, exploration and generating of theories[366 367]. Epistemology originates from ontology, a scientific inquiry on what things are or views about the nature of reality[368].

The choice of epistemological position is a bases to choosing a methodology– a framework and assumption of the research –, and methods– a technique of collection and analysis[368]. Thus, positivist epistemology follows a quantitative methodological approach whereas interpretivist epistemology follows a qualitative approach. In brief, quantitative methodology is an approach that emphasizes on quantification of a given problem using a deductive approach, whereas qualitative methodology is an approach that emphasizes exploration and understanding of ideas using an inductive approach[368].

Introduced in the 1980s and early 1990s, mixed methods design has been applied in multiple fields including health although their use has been accompanied by many philosophical debates[366 367]. There are different perspectives on the application of mixed methods, particularly on what and how researchers mix. The components may be dependent or interdependent on each other and the output may be different[369]. The extent to which approaches and outputs are combined may be explained using a '*salad'* and '*cake'* cookbook approach. The *'salad'* approach involves simply adding methods together but the output is not discernibly different from using each of them individually. In the '*cake'* approach, all ingredients are mixed together to give the flavour of each ingredient and produce a new output with value added.

The core principle of mixed methods is that using qualitative and quantitative methods together gives better understanding of problems than either method can do alone, by providing strengths that offset the drawbacks of each method[366 367]. When we mix the epistemologies and methodologies, the approaches may be purist (*the salad*) or pragmatic (*the cake*)[370]. Purists argue that methods cannot be mixed as the paradigms or philosophical assumptions are

incompatible rather doing variety things with different methods[370]. In opposition, pragmatists argue that multiple paradigms can be applied to assess research problems by integrating, sequencing, triangulating or combining data[370]. Mixed methods designs are classified as basic and advanced[366] and basic mixed methods design include convergent parallel, explanatory sequential and exploratory sequential mixed methods[366]. The advanced mixed methods design includes embedded, transformative and multiphase mixed methods. Detailed descriptors of these study designs can be found in John Creswell's work (2014)[366]. The current project was guided by multiphase mixed methods as described next.

3.3.2 The rationale of mixed methods and the current project

The rationale for the choice of mixed methods in the present project has general, practical and procedural perspectives. At a general perspective, it minimizes the limitations of both qualitative and quantitative approaches and draws adequate information from both methods to address the research problem in the project. At a practical perspective, it allows application of a sophisticated and complex innovative method. Due to the complex nature of the problem of study, the project required deep explanation and understanding of multiple aspects of the HCC (HIV diagnosis, ART linkage and retention) from multiple stakeholders (HIV patients, HIV care providers, community advocates and HIV program managers) to obtain multiple entities (facilitators, barriers and solutions) for better care. At a procedural perspective, this provided an option to obtain a more complete understanding of the research. This could be achieved through comparing different perspectives from both methods and explaining quantitative findings of the project with the qualitative component.

With the above underpinning epistemology in mind, multiphase mixed methods were applied to design different studies in this project. Four phases with four different study designs were implemented sequentially. In phase one, existing evidence on ART discontinuation was reviewed through systematic review and meta-analysis. In phase two, following the findings and implications obtained from phase one, the HCC was assessed through retrospective cohort studies. In phase three, a qualitative inquiry was applied to further explore the facilitators, barriers and solutions of HCT and this builds on the second phase of the project. In phase four, discussion with important stakeholders was performed to explore using a NGT based on the findings from phase three. Figure 3.2 describes the scientific inquiry to guide the project along with the four different study designs applied in four phases. The project methods and study designs are described in detail in the next four sections.

Application of mixed methods on the continuum of HIV care

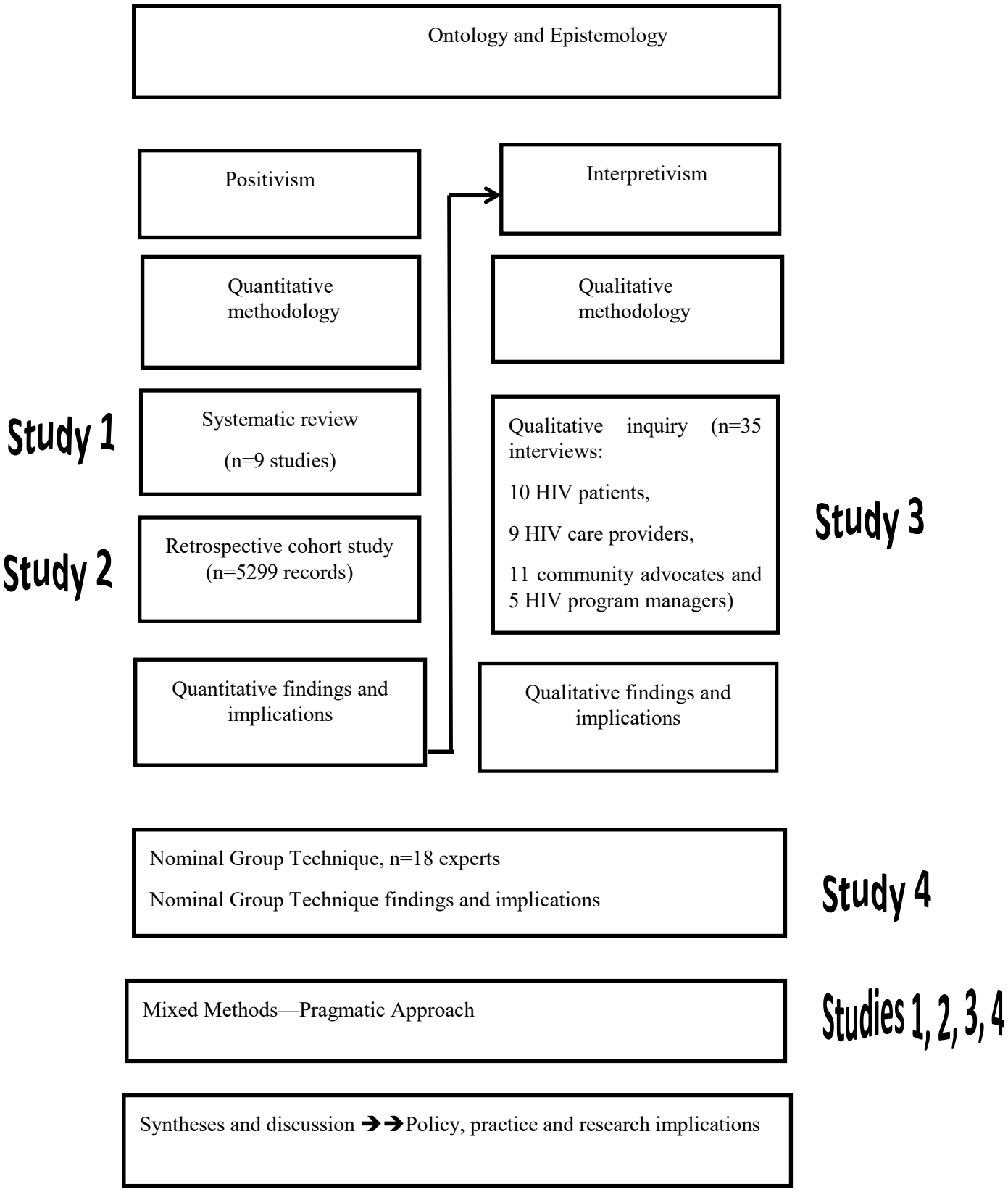

Figure 3-2: Methodological structure of scientific inquiry of HIV care continuum

3.4 Study one: Systematic Review and Meta-analysis Study

3.4.1 Introduction

This section describes the methods used to address the first research question and is presented in six parts. The study design and protocol, study participants and type of studies, and variables and measurement are presented in parts one to three respectively. Parts four and five present the search strategy, and selection of studies and assessment of methodological quality respectively. Finally, part six deals with data extraction and synthesis. This paper has been published in PLOS ONE[130] (Annex 3.1) and this section is an expanded version of the paper.

3.4.2 Study design and protocol development

A systematic review and meta-analyses were carried out to obtain the available evidence. A systematic review[371] is a literature review that critically appraises, synthesises and summarizes previous study findings to provide a high level of evidence on the risk factors or effectiveness of interventions. This review was conducted to explore current evidence relevant to the question about associated factors for discontinuation from ART among adult patients with HIV in Ethiopia. The review was undertaken using all quantitative studies on the exposure and outcome of interest published in Ethiopia in English language in the period between 2002 and 2015. The year 2002 corresponded with the introduction of ART in Ethiopia. A protocol initially published in *Joanna Briggs Institute* (JBI) was used to guide the systematic review (Annex 3.2) [372]. The evidence from this review identified problems with the current healthcare programs in Ethiopia and provided recommendations for future research on the identified problems. After the review of literature, the effect was estimated using a quantitative technique known as a meta-analysis[373]. The meta-analysis[373] provided a pooled estimate from the individual studies, a process of consolidating evidence from a large, complex and sometimes conflicting estimates. When conducted rigorously, systematic review and meta-analyses are valuable tools in the evidence-based medicine in informing policies and practices[373].

3.4.3 Study participants, variables and measurements

In this review, studies reporting on HIV-positive participants aged 15 years and older and starting ART were included. All analytical and descriptive epidemiological studies including cohort studies, case control studies, and cross-sectional studies were included for review. Studies that included the outcome 'ART discontinuation' were considered for review. ART discontinuation refers to LTFU, defaulting, or permanent stopping of medication. LTFU refers to patients missing at least three clinical appointments but who had not yet been classified as "dead" or "transferred out" (TO) while remaining in ART care. Defaulting refers to patients

missing fewer than three clinical appointments but who had not yet been classified as “dead” or “transferred out”. Stopping medication refers to patients who stop ART for any reason while remaining in care. Transferred out is the process of officially transferring a patient to another ART clinic within or outside a catchment area. Thus, in this review, ‘discontinuation’ includes all patients on ART who had missed at least one monthly clinical appointment but who had not yet been classified as “dead” or “transferred out”, and those who stopped ART for any reason.

The exposure variables included in this review were demographic, behavioural, clinical and institutional factors. Demographic factors include age, sex, educational status, place of residence and marital status. Behavioural factors include disclosure, partner's HIV status, smoking tobacco, mental status and drinking alcohol. Clinical factors include Tb/HIV co-infection, isoniazid (INH) prophylaxis provision, cotrimoxazole or OI prophylaxis provision, presence of side effects, baseline CD4 counts, baseline WHO clinical stage, baseline functional status, baseline body mass index (BMI) level, baseline haemoglobin level and regimen substitution. Finally, institutional factors included distance from the facility and facility type.

3.4.4 Systematic search strategy

Aiming to find both published and unpublished studies, a three-step search strategy was performed. Firstly, an initial limited search through Google Scholar, MEDLINE, CINAHL and SCOPUS was undertaken. This was followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe articles. This helped to construct the full search strategies for the respective databases. Secondly, a full search using all identified keywords and index terms across all included databases was done. Thirdly, a manual search of bibliographies of relevant articles for additional studies was conducted.

The following databases were included: Medline (PubMed interface), EMBASE, CINHAL and SCOPUS. In addition, resources to search unpublished studies included hand searches of studies and different sources of grey literatures from ProQuest Dissertations and Theses (PQDT), google scholar and Med Nar. The general keywords for the search were ‘ART, antiretroviral, HAART defaulting, dropout, attrition, lost to follow up, retention, linkage, discontinuation, engagement, Ethiopia’. The detail searching strategy is appended in Annex 3.3.

3.4.5 Selection of studies and assessment of methodological quality

Papers selected for retrieval were assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardized critical appraisal instruments from the *JBI Meta-Analysis of Statistics Assessment and Review Instrument* (JBI-MAStARI) (Annex

3.4). An article is retained if at least one search term for the outcome concept i.e. LTFU, defaulting or total stoppage was found. Articles that did not meet all eligibility criteria were excluded and reasons were noted. HAG and GTF[4] performed the review, and any disagreements between them were resolved through discussion. Where there was unclear or missing data, the authors of primary studies were consulted.

To assess the methodological quality of the included studies, a 9-item appraisal form developed by JBI was used. Each item in the critical appraisal instrument has four values: Yes, No, Unclear and Not applicable. For cohort studies, appraisal based on "has bias been minimized in relation to selection of cases and of controls" was interpreted as "has bias been minimized in relation to selection of exposed and of unexposed adults living with HIV/AIDS". The risk of bias was assessed using Agency for Healthcare Research and Quality (AHRQ) criteria (Annex 3.5) [374]. AHRQ develop a tool to assess the methodological quality of studies for inclusion for systematic review[375]. The tool allows researchers to evaluate unequivocally the following type of biases: (i) selection bias, (ii) performance bias, (iii) detection bias, (iv) attrition bias, and (v) reporting bias[375]. The tool has a separate judgement criterion to assess the risk of bias for each included study design, and the judgement criteria include four values: high, moderate, low or unclear risk of bias[376]. If the bias is significant (error in study design, data analysis and reporting) and this invalidates the findings, a study is judged as a '*high risk of bias*'. If there is or susceptibility of a bias but not enough to make the study invalid (missing data that make difficult to assess the limitations of the study) it is judged as at '*moderate risk of bias*'. If the bias is minimal and results are valid (valid patient allocation to comparator groups, low attrition rate, and with appropriate outcome measurement, data analysis and reporting) the study is judged as having '*low risk of bias*'. If studies are reported poorly, they are judged as '*unclear risk of bias*'.

3.4.6 Data extraction and synthesis

Data were extracted from papers included in the review using the standardized data extraction tool from JBI-MAStARI (Annex 3.6). The data included specific details about study design, outcome and their measurement, sample size, number of participants with and without the event by the exposures of interest and summary of the study. A narrative synthesis of outcomes along with the exposure variables of selected studies were demonstrated in the final review. The factors for the outcome ART discontinuation were summarized into themes, and summary findings of each study included in the review were presented in table.

[4] HAG=Hailay Abrha Gesesew, the PhD student of this project; GTF= Garumma Tolu Feyisa, research colleague

Quantitative data were pooled in statistical meta-analysis using Review Manager (RevMan)[371]. Clinical and statistical heterogeneity were assessed to check if each outcome and exposure were acceptable to add to the meta-analysis. The authorship team checked the clinical heterogeneity. The standard Chi-square and I^2 tests (below 85%) was used to assess the statistical heterogeneity, with significant heterogeneity detected at the P value < 0.05[377].

Meta-analysis was carried out for discontinuation and each exposure of interest separately. The Mantel Haenszel statistical method was used to calculate effect sizes. As described in detail in the methods section, the effect size was calculated using random or fixed effect meta-analysis based on the degree of heterogeneity[377 378]. The effect size was expressed as odds ratio and their 95% confidence intervals. If at least two studies assessed the outcome and the exposure of interest, then pooling would be considered. Publication bias was assessed using funnel plots.

3.5 Study two: Retrospective Cohort Study

3.5.1 Introduction

This section presents the methods used to answer the second research question. Historical data from a cohort of patients in JUTH were used to specifically assess LP[131], discontinuation from ART[132], immunologic failure[133], HIV mortalities[134] and the UNAIDS 90-90-90 targets. These studies have been published in different journals (Annexes 3.7-3.10) and the section is the expanded version of those papers. The same retrospective cohort study was used across the papers for different outcomes. Where necessary, the specific technique is described by mentioning the type of outcome. The section has five sub-sections. The first sub-section is about study design, and the second sub-section is about population and eligibility criteria. Sub-section three deals with data sources, procedures and quality assurance, and sub-section four deals with study variables and measurements. The data management and analyses is presented in the final sub-section.

3.5.2 Study design

A retrospective cohort study designs was applied to assess the aforementioned outcomes using 12-years of data from 21 June 2003 to 15 March 2015. Retrospective cohort study design, also termed as historical or non-concurrent cohort study, is a design in which association between exposure and outcome is determined using historically or retrospectively collected data. A retrospective cohort study is an observational epidemiological study design in which a researcher assessed whether the risk of expected outcome was different by the exposure of interest using existing data[379].

A retrospective cohort study is commenced after the exposure and outcome of interest have occurred. Hence, researchers design two groups who are known to be either exposed or not exposed to the factor of interest in a specific time frame and compare both groups on the outcome of interest. Odds ratio or hazard risk are used as measures of estimation of the relative risk in a retrospective cohort study[380]. This study design typically has the following characteristics. It requires fewer resource (time and money) to collect data on a large sample over a period of time, helps to address rare outcomes, and most importantly, better for assessing multiple outcomes. The current project has four outcomes: LP, discontinuation from ART, immunologic failure and HIV related mortality. Therefore, considering cost and multiple outcomes, a 12-year cohort was used to address our research question.

3.5.3 Population and eligibility criteria

The study population in this project were all patients with HIV, children (under 15 years old) and adults (15 years and older) enrolled in ART care in the selected hospital. If a patient's outcome status (death, discontinuation, transferred out or alive/on care) was not recorded, the patient was excluded from analyses. Specifically, for the assessment of LP, all ART patients with baseline CD4 and WHO clinical stages were eligible. For the assessment of ART discontinuation and mortality, patients enrolled to ART clinic with a minimum of one follow-up visit were eligible. For the assessment of immunologic failure, patients must have had at least six months' follow-up after ART initiation. Furthermore, there should be records of patients' CD4 count at least at two points, when beginning ART and after six months of treatment. For the assessment of mortality, the date of ART initiation and outcome status of last follow-up date should be recorded. Data were extracted from JUTH and Jimma health centre in 2016.

3.5.4 Data sources, procedures and quality assurance

ART data were recorded manually in both institutions at first. Later, a database called Electronic Medical Records or EMR was designed. This system is a Comprehensive Care Centre Patient Application Database (C-PAD) prepared in Structured Query Language (SQL) format. In JUTH, with the help of ICAP, data were retrospectively copied to the new database in 2007. Thereafter, patient information was recorded by clinicians on paper forms followed by data entry to EMR by two data clerks on the same or next day as each clinic visit.

Patient information includes clinical and non-clinical characteristics of each patient. If all patient information is available, data entry takes about 10 minutes for new patients and about 5 minutes for returning patients. Data clerks communicate immediately with clinicians

when any data are missing, and weekly EMR-generated patient summary reports help to identify patients with conditions requiring follow-up. ICAP provides technical assistance on the management of EMR and conducts random checks of data completeness. This ensures the accuracy and reliability of the EMR data.

3.5.5 Study variables and measurements

As described above, four outcome variables were assessed in this study. *Outcome 1: Time to present for HIV care (late, early):* The first outcome is time to present for HIV care presentation, dichotomized as late and early. Definitions of LP are shown in Table 3.1, and early presentation is the opposite of LP. The independent variables for LP among adults were age, sex, religion, education, marital status, Tb/HIV co-infection, baseline functional status, disclosure, history of HIV testing and HIV care enrolment period. Exposure variables for LP among children were age, sex, religion, Tb/HIV co-infection, history of HIV testing, HIV care enrolment period, baseline nutritional status and developmental milestones.

Outcome 2: ART discontinuation (discontinued, not discontinued): The second outcome is ART discontinuation, dichotomized as discontinued or not discontinued. Discontinuation from ART is defined in sub-section 3.2.4. The independent variables for discontinuation among adults included all clinical and non-clinical exposure variables assessed for LP, plus baseline WHO stage, baseline CD4 count, LP, immunologic failure, clinical failure, treatment failure, ART shift and adherence. The exposure variables for discontinuation among children included all clinical and non-clinical exposure variables assessed for LP plus baseline WHO stage, baseline CD4 count, LP, immunologic failure, clinical failure, treatment failure, ART shift and adherence.

Outcome 3: Immunologic status (failure, success): The third outcome is immunologic status dichotomized as immunologic failure or success. The definition of immunologic failure is shown in Table 3.1. The independent variables for immunologic failure among adults included all clinical and non-clinical exposure variables assessed for ART discontinuation plus ART discontinuation. Similarly, the exposure variables for immunologic failure among children included all clinical and non-clinical exposure variables assessed for ART discontinuation and the ART discontinuation itself.

Outcome 4: Early HIV related mortality (dead, alive): The fourth outcome is early HIV mortality, dichotomized as dead or alive. Mortality (all-cause mortality) is the death of a person on ART in the reporting period. Early mortality is death occurring in the 24 months following the start of ART. The independent variables for mortality among adults included all clinical and non-clinical exposure variables assessed for LP, discontinuation and immunologic failure.

Educational status was recorded as no education (could not read and write), primary (grades 1–8), and secondary and above (grades ≥9). Functional status was recorded as work (able to perform usual work), ambulatory (able to perform activities of daily living), and bedridden (not able to perform activities of daily living). Similarly, developmental milestone was grouped into appropriate (no negative developmental milestone), delayed (failure to attain milestone for age), and regressed (loss of what has been attained for age). History of previous HIV testing refers to testing (one or more times) for HIV before diagnosis. ART shift refers to change from first-line ART to second-line ART or second-line ART to third-line. HIV care enrolment period was dichotomized as enrolled for HIV care in 2003–11 or 2012 and after. Baseline variables refers to variables registered nearest to ART commencement date. To assess the baseline nutritional status of children, weight for age (WFA), height for age (HFA) and weight for height (WFH) were calculated and interpreted using WHO guidelines.

Table 3-1: Measurements for LP, immunological, clinical and treatment failure, and adherence

Late presentation for HIV care for adults[552 53 381]				
Enrolled in 2003-11		**Enrolled in 2012-15**		
CD4 lymphocyte count of <200 cells/ µl irrespective of WHO clinical stage at the time of first presentation to the HIV care		CD4 lymphocyte count of <350 cells/ µl irrespective of WHO clinical stage at the time of first presentation to the HIV care		
WHO clinical stage 3[6] or 4 irrespective of CD4 count at the time of first presentation to the HIV care		WHO clinical stage 3 or 4 irrespective of CD4 count at the time of first presentation to the HIV care		
Late presentation for HIV care for children[7]				
Age	**Moderate immunosuppression (damage) if CD4 count between**	**Severe immunosuppression (damage) if CD4 count between**		
0-12 months	750-1500 cells/ µl	<750 cells/ µl		
1-5 years	500-1000 cells/ µl	<500 cells/ µl		
≥ 6 years	200-500 cells/ µl (enrolled in 2003-2011)	<200 cells/ µl (enrolled in 2003-11)		
≥ 6 years	350-500 cells/ µl (enrolled in 2012-2015)	<350 cells/ µl (enrolled in 2012-2015)		
Adherence status[8382]				
Status	**Percentage of prescribed ART intake**	**Number of missing doses out of 30**	**Number of missing doses out of 60**	
Good	≥ 95%	<3	<4	
Fair	85-95%	3-5	4-9	
Poor	< 85	≥6	≥9	
Immunological and clinical failure[93]				
Clinical failure		**Immunological failure**		**Treatment failure**
New clinical condition indicating severe immunodeficiency (with the exception of Tb and WHO (World Health Organization) clinical stage 4[9]) after 6 months on ART		CD4 count falling to the baseline (or below) persistent CD4 levels below 100 cells/mm^3 after 6 months for two consecutive follow-up times		Having either clinical or immunological failures

[5] The definition for LP among Tb/HIV co-infected population was only based on the CD4 criteria.
[6] **WHO clinical Stage 3** is if one of the following is present in an HIV diagnosed patient: weight loss of >10% body weight, chronic diarrhoea for > 1 month, fever for >1 month, oral candidiasis, oral hairy leukoplakia, or pulmonary Tb within the previous year, or severe bacterial infections
[7] LP is also defined if WHO clinical stage 3 or 4 at first visit to the ART clinics
[8] Clinicians and pharmacists ask patients and check the pill container to collect the number of missing doses or day
[9] **WHO clinical Stage 4** was defined if one of the following is present in an HIV diagnosed patient: HIV wasting syndrome, PCP, toxoplasmosis of the brain, isosporiasis with diarrhoea for >1 month, cytomegalovirus disease of an organ other than liver, spleen or lymph node, herpes simplex virus infection, progressive multifocal leukoencephalopathy, candidiasis, extra-pulmonary Tb, lymphoma, kaposi's sarcoma, HIV encephalopathy

Using the outcomes described above, complex surrogate measures were used to assess performance of Southwest Ethiopia against the UNAIDS 90-90-90 goals. This equates with 90% of all HIV knowing their status, 81% of all HIV positive people receiving treatment and 73% of all HIV positive people attaining viral suppression[108]. However, the 90-90-90 goals are easy and direct to interpret than the 90-81-73, and most existing literature discussed using the three 90s interpretation. Therefore, the performance calculation and interpretation in this study was based on the 90-90-90 targets. In Table 3.2, the complex surrogate markers/indicators used to assess HCC outcomes are shown together with an overall proxy surrogate for UNAIDS targets. For measuring diagnosis target, number of people on ART who were diagnosed or presented to care early (early HIV care presentation, Table 3.1) was used as a surrogate marker. For measuring treatment target, number of people on ART out of those diagnosed was used as a surrogate marker. In addition, to assess whether the treatment intake was sustainable or not, number of people who had discontinued or transferred out, and number of people who had fair or poor adherence (Table 3.1) was considered. For measuring the viral suppression target, treatment success (combination of immunologic and clinical success) was used as a surrogate measure to increase the probability of estimating viral suppression.

Table 3-2: Ideal measure and surrogate markers for UNAIDS 90-90-90 targets, 2016

UNAIDS Target[10]	**Ideal measure**[338 340]	**Surrogate measures**
1	Rate of HIV infected population	Rate of patients with early HIV care presentation
2	Rate of HIV infected population receiving antiretroviral therapy (ART)	Rate of HIV patients on ART, and good adherence
3	Rate of patients with undetected viral count copies/mL)	Rate of patients with immunological, clinical and treatment success

3.5.6 Data management and analysis

Data were exported from SQL format to excel and then to SPSS version 22 for Macintosh for cleaning and analyses. The analyses of descriptive and inferential statistics were conducted after cleaning the data. Descriptive statistics[383] was done to describe study population characteristics, inconsistencies and missed values. Summary statistics were produced for categorical and continuous variables. Proportions and bar graphs were used to describe the

[10] **Target** 1 (HIV diagnosis): 90% of patients knowing their status; **Target 2** (HIV treatment): 90% of diagnosed patients receiving treatment; and **Target 3** (virological suppression): 90% of patients on ART achieving viral suppression.

categorical variables. In addition, cumulative incidence (CI) and incidence rate (IR) were used to describe a categorical data as presented in Table 3.3. Mean, median, standard deviation and range were used to describe the continuous variables. WFA, HFA and WFH were calculated to describe nutritional status of children using STATA[384]. To address incomplete data, missing data was treated using multiple imputations (n=5) assuming missing at random (MAR) pattern[385] and the model was reported with pooled imputed values[386]. The assumption of MAR was assessed graphically and fulfilled randomness of the missing values. The trend line was described by line graph (spaghetti plot)[383].

Table 3-3: Measurements of cumulative incidence, incidence rate and death rate, 2016

Variable	Definition	Numerator	Denominator
Cumulative incidence	The number of deaths among patients enrolled on ART during the follow-up	Number of deaths during the entire ART follow-up period (2003-15)	Number of patients during the entire follow up period (2003-15)
Incidence rate	Number of deaths among patients enrolled on ART in a person-time observations	Number of deaths during the entire follow up period	Time each person was observed, totaled for all persons (total person-years observations)
Annual death rate	The death rate in a specific calendar year among patients enrolled on ART during that calendar year	Number of deaths in a specific calendar year	Number of patients died plus alive and on ART plus discontinued plus transferred out during the specific calendar year
Calendar year	The year which the death rate is calculated	Not applicable (NA)	NA

ART: antiretroviral therapy; NA: not applicable

Binary logistic regression analyses were performed to determine the predictors for LP, ART discontinuation and immunologic failure, and cox regression analysis for mortality. LP was measured using baseline data of WHO clinical staging and CD4 count. Based on the definitions in Table 3.1, LP was dichotomized as *early* and *late*. Similarly, immunologic failure was measured by comparing baseline CD4 count and CD4 count measured at six months of ART follow up. In case CD4 count is not available at six months of ART follow up, the CD4 count recorded in the nearest month would be considered. Based on the definitions in Table 3.1, the immunological status was dichotomized into *immunological failure* and *immunological success*.

Binary logistic regression[380] was used to investigate the association of several variables upon a dichotomized response variable where the outcome was not measured at different points of time. In the present study, the outcome LP of all eligible study participants was measured at similar point of time i.e. at baseline. Similarly, the outcome immunologic failure of all eligible study participants was measured based on similar points of time i.e. at baseline and six months

of ART follow up. Therefore, binary logistic regression analysis was used. As to the ART discontinuation, it was observed that a single patient may discontinue one or more times at different points of time. Therefore, the status of ART discontinuation was only based on the outcome status recorded at the end of follow up date. The outcome ART discontinuation was dichotomized in to *alive* and *on ART* and *discontinued*. Hence, binary logistic regression was used to assess the factors affecting ART discontinuation.

During the analysis of binary logistic regression, both bivariate and multiple logistic regression were performed to identify the independently associated factors[380]. Bivariate logistic regression analysis was conducted to determine the presence of crude association and nominate the candidate variables (P<0.25 was considered significant) to multiple logistic regression. P ≤ 0.05 was considered as a cut off value for statistical significance in the final multiple logistic regression model. Odds ratio and 95% confidence interval was reported to summarize the data.

Cox proportional hazards regression[383], using a stepwise variable selection procedure, was used to identify the independent predictors for early HIV mortality among adults[11]. This is because patients died at different points of time and the time to occurrence of death (event) is important. The follow up time for HIV mortality was defined from ART initiation date to death and censoring where the censoring can be LTFU or dropout, transfer out or alive and on ART upon the last date of recording of the study. To estimate survival time and compare the time to event among the different groups of patients, a Kaplan Meir curve was used. To check any significant differences in survival among different levels of the categorical variables measured in the study, the log-rank test was used. The estimated survival time in months is calculated using the time between date of treatment initiation and date of death or censoring. The assumption for proportional hazard is checked graphically. Bivariate cox regression analysis is carried out to see the existence of crude association and select candidate variables (with *P* value below 0.25) to multiple cox regression. *P*-value of ≤5 % was considered significant in the final model.

Three models were constructed from the cox proportional hazards regression analysis. Model I shows the predictors of early mortality among HIV-infected patients attending short-term (<24 months) ART follow-ups. Death recorded before two years was considered the event, and discontinuation or alive and on ART were considered as censored. Model II shows the predictors of an overall mortality (cumulative) among patients with HIV attending ART in the real case assumption. This assumption considered death as an event whereas

[11] Event (death) among children was occurred only in 26 participants, and this does not allow to conduct further inferential statistics.

discontinuation and alive and on ART as censored. Model III shows the predictors of an overall mortality (cumulative) among HIV-infected patients attending ART in the worst-case assumption or intention-to-treat analysis. Under this assumption, discontinuation is considered an event (death) in addition to the real event, and alive and on ART as censored.

Goodness of fit of models, interaction and potential multi-collinearity were also assessed. The goodness of fit of the final models was checked using Hosmer–Lemeshow chi-squared test and were found fit. In addition, the presence of two-way interaction between variables was tested. Multi-collinearity was excluded using Spearman's correlation coefficient with a cut off at 0.7 and then variance inflation factor (VIF) of 10. The conclusion was through pseudo R-squared[387]. Each potential independent variable was regressed on the others and pseudo R-squared value was calculated, obtaining similar VIFs to OLS (ordinary least squares). Data were analysed using SPSS version 22.0 and STATA version 14.

3.6 Study three: Qualitative Study

3.6.1 Introduction

This section presents the methods used to answer the third research question. It is presented in four parts. The study design and participants' recruitment procedure are presented in parts one and two. Part three presents the data sources, instruments and data collection processes, and the data management and analyses is presented in part four.

3.6.2 Study design

A qualitative method was employed to explore the facilitators, barriers and solutions for HCT. The qualitative method is an approach that enables us to explore or understand the meaning of a social or human problem through the words of individuals or groups[366 368]. Although different, qualitative studies follow similar procedures to quantitative studies: defining research question, recruiting population, deciding the number of participants, choosing data collection and analysis methods, and structure of written report. However, qualitative research methods have their own peculiar characteristics[366 367]: (i) involves emerging questions and procedures; (ii) participant recruitment is flexible and the number of participants is small; (iii) data analysis involves inductive and deductive procedures; (iv) the researcher serves as a key instrument in interpreting the meaning of the data; and (v) the final report has a flexible structure. Qualitative study can be used to explore complex problems from the perspectives of multiple stakeholders to provide thick information about the given health problem of interest. John Creswell in his book[366] said,

"Qualitative researchers try to develop a complex picture of the problem or issue under study. This involves reporting multiple perspectives, identifying the many factors involved in a situation, and generally sketching the larger picture that emerges."

Qualitative study can be conducted on its own or used with quantitative study before, during or after the quantitative study, as described in section 3.1. In the present study, a comprehensive and complex problem was explored from the perspective of different groups based on the outcomes of the quantitative study. Therefore, a qualitative inquiry using in-depth interviews was employed to explore the facilitators, barriers and possible ways to improve HCT. Interviews were undertaken among the following study participants:

a) Patients with HIV who visit JUTH and JHC,
b) HIV- care providers working in ART clinic in JUTH and JHC,
c) Advocates/ members of communities living in Jimma, and
d) HIV-care system administrators from governmental organizations- Jimma Zone Health Department, Jimma HAPCO and Jimma Town Health Office, and NGOs- Organization Service for Social Aid (OSSA), Family Guidance Association Confidential, Marie Stopes International, and ICAP- working in Southwest Ethiopia.

3.6.3 Participants recruitment procedure

The basis for recruitment, population pool, number of participants approached and approximated sample size are summarised in the sampling matrix Table 3.4 below. Adult patients with HIV on ART program (had history of discontinuation, had history of good ART adherence throughout ART care) who visited health facility for regular care were the potential study participants for the interview. Patients were purposively sampled after they visit the clinic, which was the only opportunity available for the researcher to meet and interview the potential study participants who travelled from far distances from these clinics.

After patients received treatment, the ART nurse or physician provided information about the study for them to read through and decide whether they were willing to be potential participants for research on HIV care. This was the only way to reach eligible study participants because: i) the researcher could not access records of potential study participants; ii) it was not feasible for the researcher to screen potential participants while they were sitting in the waiting room; and iii) there would be less pressure or coercion felt by patients because the nurse or physician would not know whether they were willing to participate. The interviewer introduced himself through the letter of introduction (Annex 3.11). He provided study information through the information sheet (Annex 3.12) and asked participants to sign a consent form (Annex 3.13).

Participants gave informed consent. If participants had limited levels of literacy, the PhD student (interviewer) sought verbal consent (and a thumb print) after explaining the project and its aims in local languages, Amharic or Afan Oromo. The introduction letter, information sheet, consent form and interview guide were translated into these local languages.

For the HIV health care providers, community representatives and HIV care system administrators, recruitment was also purposive. An invitation letter was delivered to these target audiences through the following options (in order): a) posting on the office noticeboard and all potential departments; b) distributing in a staff meeting once the head gave permission for this to be an agenda item during the meeting; or c) requesting the department head to distribute letters to potential study participants. The invitation letter included the researcher's telephone number and participants were requested to send SMS text or report to a temporary office for interview if they were willing to participate. Then, the interviewer introduced himself through a letter of introduction, provided the study information through an information sheet, and asked study participants to sign a consent form before proceeding with the interview.

Table 3-4: Matrix for sampling in in-depth interview

Participant category	Basis for Recruitment	Population pool	Number of participants to be approached	Sample size (approximated)
Adult (age≥18) patients with HIV enrolled in ART program	Adult patients with HIV enrolled in ART program, and had history of ART discontinuation or good ART adherence in JUTH and JHC	Approximately 5700	100 patients	10-20 or until saturation is reached
HIV-care providers working in the ART clinic	HIV-care providers working in the ART clinic at JUTH and JHC	Approximately 33	All 33 health care providers	10-20 or until saturation is reached
Advocate or members of community age≥18 (associations of patients with HIV, religious groups, *Idirs* (local association established by small group of people), women's groups, HEWs)	Community representatives (age≥18) involved in patients with HIV association, religious groups, '*Idir',* women association and HEWs. In Ethiopia, these groups are involved in HIV advocacy activities in the community and experience of factors facilitating or hindering HIV care program.	Approximately 60	All 60 members	10-20 or until saturation is reached
HIV-care system administrators (Zonal Health Department, Zonal HAPCO, Town Health Office, local and global NGOs working on HIV/AIDS care and support in Southwest Ethiopia)	HIV-care system administrators from governmental and NGOs who are involved in HIV care programs planning, policy development & enforcement of policy implementation.	Approximately 40	All 40 administrators	10-20 or until saturation is reached

3.6.4 Data sources, instruments and data collection processes

Primary data were obtained by interviewing patients with HIV, HIV care service providers, advocates or community representatives, and HIV care administrators using a prepared interview guide (Annex 3.14). Primary data for the qualitative inquiry and NGT were gathered from October 2017 to January 2018. The PhD student carried out interviews using the interview guide. He translated documents from English to Amharic, and other professional interpreter(s) and researcher(s) translated the documents to Afan Oromo. Another professional interpreter checked the accuracy of translation by assessing de-identified transcripts (two from each language). Two additional co-researchers were recruited to interview patients who spoke Afan Oromo but were not able to speak Amharic. Interviews were recorded using a voice recorder once participants gave their consent.

Interviews took between 38 and 120 minutes and this was clearly conveyed in the letter of introduction and information sheet. Participants were interviewed in a quiet, secure and confidential area. Patients with HIV and health care providers were interviewed in a quiet area provided by the hospital and health centre administrators. Community interviews were held in quiet *kebele* offices provided by the *kebele* administrator. Interviews with HIV care system administrators were held in their offices, which were deemed to be quiet and private. Study participants were told the room and block number where the interviewing was held while signing the consent form. To assure anonymity, the rooms were not labelled. All study participants were asked to nominate another place within the hospital or health centre or work setting.

The interview guide had the following constructs: individual related perspectives (socio-economic, knowledge, experience, expectations, attitudes, beliefs, disclosure), institution related perspectives (access, distance, quality of care, interaction with HIV health care providers, referral and linkage, logistics, availability, administration, capacity building, guidelines and protocols, and new HIV care programs), community related perspectives (care and support, stigma and discrimination, traditional healing, and social networks), and policy related perspectives (health policy, HIV/AIDS policy, health care financing, guidelines and standards, new programs, and integration with NGOs). Pilot interviews were conducted to test the interview guide and the translation and transcription processes and necessary modifications were accommodated.

3.6.5 Data management and analyses

Audio-recorded semi-structured interviews were carried out and hand-written field notes were

taken immediately. Each interview was transcribed verbatim. The following notations were used within the transcripts: 1) *(health facility)* – Parenthesized words were possible statements that were hard to hear; 2) *NO NO* – Capitals, except at the beginning of lines or as acronyms, indicated loud voice relative to the surrounding talk; 3) *Yeah (.2)* – Numbers in parentheses showed elapsed time of silence in tenths of seconds; 4) *You know what they do?* – Punctuation indicates speaker's intonation; and 5) '*Tsebel'*– Words under single quotation are in the local language. Data analysis was started during data collection. Shortly after conducting each interview, the researcher read the full verbatim transcript several times. In order to help in writing the qualitative results, main ideas (memos) were written analytically during and after data collection. The resulting data were analysed according to thematic framework analysis approach for qualitative data analysis[388-390] using NVivo for Mac 11.4.1 (QSR International, Doncaster, VIC, Australia)[391].

The thematic framework analysis approach included the following steps. Firstly, there was familiarization with each interview and then transcriptions were carried out from the audiotaped interviews. Significant statements were identified by reading and re-reading the transcripts. Canvassing the data set generated initial codes. In order not to lose relevant themes, repeatedly stated codes of text were identified, coded to several key categories and sub-headings were then identified from the thematic analysis. The analyses were both deductive and inductive so categories that were known *a priori* and those that emerged from the data were established. By grouping together and synthesizing illustrative quotes, the PI and another researcher independently conducted open coding of each transcript manually using NVivo. Next, other researchers involved in the study checked the coding. The next step was developing a working analytical framework. Charting data into the framework matrix and interpreting the data subsequently were the last steps. The different narratives of findings from individuals, health workers, community representatives and administrators were finally triangulated. This helped to establish validity of the data and showed conflicting views.

To ensure issues of trustworthiness—credibility, transferability, dependability and reliability—, the following techniques were used. Credibility is the objectivity and candour of a qualitative data[392]. It is about getting 'believability' based on coherence, insight and trustworthiness through the data verification process. In this study, credibility was addressed through: i) establishing and building rapport and trust by outlining the PhD student's (interviewer's) clinical research experience in HIV care; ii) the use of multiple data sources from patients with HIV, health care providers, community advocates and HIV care system administrators; and iii) preparing a consultative meeting (debriefing) to discuss the main

findings. Thus, the main ideas were verified in the presentation, not by disclosing who said what but by demonstrating that speakers knew what they were talking about when the researcher displayed selected quotes and main ideas. Transferability is concerned with the extent to which the findings of a study can be applied or transferred to other situations[393]. Although the present study focused on care for individuals living with HIV, the results of the study may be transferable to other individuals with HIV or patients with other chronic diseases experiencing barriers to care. The common themes from the perspectives and unique lived experiences of the target audience about HIV care may add insight to the phenomena in other chronic illnesses.

Dependability or reliability is a process of establishing findings as consistent and repeatable[392]. In the present study, dependability or reliability was ensured by: i) pilot interviewing to maintain the consistency of the tools and interview process; ii) triangulation i.e. use of multiple data sources so that findings from the different target audiences were replicated; iii) maintaining an audit trial by keeping all raw data, field notes, records and excerpts; iv) stepwise replication i.e. analysing or evaluating the data and comparing the results—the PhD student, another researcher and the supervisors evaluated the coding and thematization process; iv) code–recode strategy in which the PhD student coded the data again for most transcripts after an interval of two months to see if the results were similar or dissimilar); and (v) inter-coder agreement, level of concordance between coders based on a codebook, was conducted by the PhD student and another researcher with similar experiences to produce consistent coding. The codebook was developed by the PhD student and another coder independently by reading three transcripts and developing codes. This was followed by both coders discussing the major codes, their definitions and examples until agreement. The same procedure was undertaken to develop themes.

3.7 Study four: Nominal Group Technique

3.7.1 Introduction

This section reports the methods used to answer the fourth research question. NGT was used to evaluate suggestions for improving HCT obtained from the qualitative study. This section has five parts. The first describes the study design, and the second outlines the number and selection of the NGT experts. The third, fourth and five parts describe the NGT processes.

3.7.2 Design— Nominal Group Technique

The present study used the NGT to rank the solutions for HCT obtained from the qualitative study. The NGT is a design for consensus development [394-396]. Developed by Delbecq and Van

de Ven, it has been widely used in health systems research in problem solving and deciding priorities including in HIV interventions [396-399]. Jones and Hunter[395] defined the NGT as

> *"The nominal group technique uses a highly structured meeting to gather information from relevant experts (usually 9-12 in number) about a given issue. It consists of two rounds in which panellists rate, discuss and then rerate a series of items or questions."*

The NGT involves a face-to-face group discussion in a highly structured meeting to collect views from relevant experts[396].The NGT process is tightly controlled by the facilitator/s to minimize the risk of a dominant participant unduly influencing the discussion. Delbecq and Van de Ven[399] explained that the NGT involves four main steps: i) silent generation of ideas—a process in which the participants silently develop their ideas at the beginning of the meeting; ii) round robin—a process in which the facilitator collects each participant's ideas in turn (round robin fashion) until no new ideas are forthcoming; iii) clarification—a process of including, excluding and altering ideas, and generating themes through group discussion; and iv) voting, ranking or rating—a process in which participants write their score or rating.

There are modifications to or variations on the NGT for many reasons such as the availability of research and participant time, level of clarification of solutions to be prioritized, and need or process of consensus for the research question. For example, ideas can initially be generated from a literature review or exploratory study instead of 'silent generation' [400 401]. Ranking can be performed by rating on a Likert scale or providing a score[401 402]. Furthermore, while re-rating, nominees can revise their original rating by re-rating in the original NGT meeting, or validation can be obtained by distributing a survey of nominal group results to other participants[401 403]. Box 1 presents the summary of the NGT process.

Box 1— The Nominal Group Technique process

Definition of Problem →→ which suggested solutions in the qualitative study are relevant, feasible and acceptable?

Selection of experts →→ e-mail sent to potential experts that involve HIV care providers from hospital and health centre, HIV program coordinators from local and global non-governmental organizations, town health office and zonal health departments, and researchers from university.

First round of nominal group →→ The facilitators unveiled lists of solutions and participants rated each suggested solution using three criteria of importance—relevance, feasibility and acceptability— on scale namely 1 "agree", 2 "neutral" and 3"disagree". Participants also asked to list additional solutions for HIV diagnosis, ART linkage and retention. The facilitators summarized the results and calculate a score.

Second round of nominal group →→ the participants discussed and re-rated the solutions that were initially rated in the first round.

Results analyzed for agreement using predefined rules →→ the facilitators summarized the final statement of consensus including the minority suggestions.

Adapted from Jones & Hunter, 1995)

3.7.3 NGT experts—Size and selection of participants

A purposely selected group of experts was invited via e-mail to attend the NGT (Annex 3.15). The definition of 'expert' was that they were professionals who had been involved in clinical or research practices in the HIV area. Experts were selected based on the following criteria: willingness to participate, position held in relation to HCT, years of experience in and contribution made to HCT. Guided by Chitu et al[404], five steps were applied to select the experts: 1) preparing a knowledge resource nomination worksheet to categorize the experts and identify relevant disciplines and organizations before nominating names of experts; 2) writing lists of potential experts from the identified disciplines and organizations; 3) contacting experts listed in step two and asking them to nominate other experts; 4) ranking experts listed in step two and three according to their disciplines and organization; and 5) inviting experts in order of their ranking until achieving the targeted sample size.

Twenty-five (25) participants including HIV program managers, researchers and service providers from Jimma University, JUTH, JHC, Jimma Town Health Office, Jimma Zonal Health Department, ICAP at Colombia University (a global NGO working on HIV care in Southwest Ethiopia) and OSSA (local NGO working on HIV care in Southwest Ethiopia) were invited to the NGT. Of the 25 invited, 18 participated in the NGT.

3.7.4 Description of NGT process—idea generation

The 'silent generation' step of the NGT was modified to use ideas from the qualitative study conducted in phase three. The qualitative study identified the following suggestions: SHT, H2H, assigning peer educators with HEWs in a teach, test, link and trace strategy (TTLT), ART in health post (ART_{HP}), ART in private clinics (ART_{PC}), community ART groups (CAGs), and filling gaps in laws (law). The process of generating ideas through the previous study is viewed as a technique to attain greater consultation. Participants were also asked to suggest their own solutions before the start of the NGT in addition to the aforementioned solutions. The question devised by the researchers was "*What new programs do you suggest for improving HIV diagnosis, ART linkage or ART retention, apart from the suggested solutions identified through the exploratory study?*"

3.7.5 Description of NGT process—Discussion and ranking of solutions

Seven solutions were obtained from the qualitative study, and the PhD student who was a facilitator provided lists of suggested solutions to participants before the NGT. In addition, when the facilitator asked participants to list additional ways of improving HCT, participants identified three additional solutions. However, after discussion, all of these were merged with

the seven suggested solutions. Facilitators asked participants to rate or evaluate each suggested solution based on a criterion of importance, by considering relevance, feasibility and acceptability. A self-administered questionnaire was used to rate each solution (Annex 3.16). The self-administered questionnaire had a three-point Likert scale, agree (1), neutral (2) and disagree (3), and space for remarks about justifications. Experts completed the rating before discussion started (Round 1 rating).

The facilitators then presented the qualitative findings about the major barriers, facilitators and solutions of HCT. The presentation was accompanied by detailed discussion. The discussion process was stopped once a predefined stop point, achievement of consensus, was reached. The discussion was audio-recorded with the consent of study participants to provide a record of the proceedings. Finally, the participants were asked to re-rate, and give their justification for not agreeing with or differing significantly from the group opinion after the discussion (Round 2 rating). The facilitators presented the final statement of group consensus with overall ratings and minimum, maximum and average ratings.

3.7.6 NGT process— Data management and analysis

Data analyses involved both quantitative and qualitative components. For the quantitative component of the NGT, descriptive and inferential statistical were applied. Data were described using median, individual and score of the criteria, and were presented in a table. Wilcoxon signed-rank test was used to examine the statistical difference between the ratings in rounds 1 and 2. This test is a non-parametric test that does not require assumption of normality in the data[405]. This test was chosen for the following reasons. The response variables (suggested solutions) were measured at ordinal level i.e. agree (1), neutral (2) and disagree (3) for all three criteria (relevance, feasibility and acceptability). The independent variables consisted of two categorical and related groups, rounds one and two ratings. The distribution of differences between the values of rounds one and two was symmetrical in shape. Thus, 21 hypotheses (7*3 i.e. seven suggested solutions and three criteria for each) were tested. *P* value<0.05 was used to denote statistical significance. The hypothesis, for each suggested solution and criterion, was

Ho (null hypothesis): There was no difference between round one and two.

H_A (alternative hypothesis): There was a difference between round one and two.

Content analysis was used for the qualitative component of the NGT, the justifications for rankings in the two rounds and ideas from the discussion session. A main feature of content analysis is having *a priori* domains (the seven suggested solutions) originating from the qualitative inquiry. The following steps were conducted to carry out the content analysis[406]: i) record the ideas of each discussant and take field notes side by side; ii) transcribe the records

and hand-written field notes; iii) read through the transcripts and list notes (codes) and tally the codes; iv) go through the list of codes and classify them; v) read through the classification, find if there is a link, and name a theme for each; and vi) review the steps from i–v to confirm that all codes that need to be categorised have been included (i.e. categories are exhaustive), check that no code is classified more than once (i.e. categories are mutually exclusive), and to see whether there are minor or interrelated themes that can be merged (i.e. categories are independent).

The criteria suggested by Lincoln and Guba (1985) were used to ensure trustworthiness of the process[392]. Credibility of the data and processes was verified by the expert panel's positive comments. Exemplars of feedback included:

> *First of all, I would like to thank you for bringing this important issue, and some of the findings are shocking for me. After 30 years of HIV introduction, hearing these issues are very shocking. It is a wakeup alarm for the government and every stakeholder working in the area of HIV (Dean/Public Health, Associate Professor, Reproductive Health, University)*.

> *I would like to appreciate you and the ways you went through to discover these findings because I found most of them very interesting, so that anyone who wants to further prevent AIDS epidemic expansion can work on these important findings (Assistant Professor, Epidemiology, University).*

In addition, credibility was addressed through obtaining information from multiple types of study participants—HIV care providers, government and non-government HIV program managers, and higher institution researchers. Reliability was ensured via triangulation and audit trial as described in sub-section 3.7.5.

3.8 Ethical considerations

In this project, apart from study one (systematic review and analysis), ethics approval was applied and obtained for each study separately. Ethics approval was not required for study one because it was a review of available studies. For study two, the retrospective cohort study, the study proposal was submitted to and received approvals from the Social and Behavioural Research Ethics Committee of Flinders University (Approval Notice project number: 7086, Annex 3.17) and Institutional Review Board (IRB) of Institute of Health at Jimma University (Ref No: RPGC/386/2016, Annex 3.18). Information gathered was treated as confidential and accessible only to the PhD student. No participants were directly involved in the study with

only anonymised data being extracted from the electronic medical system. No information about the project was published in any form that allowed any individual person in the participating organizations to be identified. All data and collected information were kept in a locked filing cabinet only accessible to the PhD student and computer files were protected with passwords that only the PhD student knew.

For study three, the qualitative study, ethics approval was obtained from the Social and Behavioural Research Ethics Committee of Flinders University (Project No: 7698, Annex 3.19) and the IRB of Jimma University (Ref. No: IHRPG/878/2017, Annex 3.20). Permission was received from their respective institutions to approach study participants (Annex 3.21). Written consent was sought prior to interview. Study participants were assured that the information they gave would be treated with the strictest confidence and no identifying information would be published. It would remain confidential and would not be shared with any party without their knowledge or consent. However, complete anonymity could not be guaranteed given the involvement of the ART nurse/physician.

Individual participants were informed about the voluntary nature of participation in the study, so that they were free to withdraw from the study at any time or decline to answer some questions. Their decision would never affect access to services, their relationship with the HIV health care providers or the clinic in general. Data collection instruments would not contain respondents' names. All study participants were assured that the information they gave would remain confidential and anonymous and would not be shared with any party or in any report, publication, or presentation without their knowledge or consent. The co-researcher(s) who would be involved in translation, interview and transcription of the interviews knew the ethical issues—respect for persons (autonomy, volunteer participation and confidentiality), beneficence (benefits, risks and its assessment) and justice. The PhD student would also strictly inform the researcher about the basic principles of ethics, particularly anonymity, confidentiality, benefits and risks, and obtain a signed confidentiality agreement. The information was kept and locked in a filing cabinet with the key only accessible to PI and the computer files were protected with passwords that only the PhD student knew.

Although this research project may not have a direct benefit for the study participants, the study findings will benefit the discipline of public health by providing multi-dimension critiques of the nexus of patients with HIV in care of public hospitals and health centres. The study will benefit individuals newly infected with HIV indirectly, to remain in care, improve their immunity and subsequently enhance their survival ensuring their quality of life. The study will help health workers to prioritize groups of people at risk of discontinuation from treatment,

prone to treatment failure and death. Policy makers will also get insights enabling them to revise policies for interventions for people with HIV including best time to commence treatment.

There were no risks for people participating in the study or for the researcher during the interview processes. However, participants might feel burdened by the amount of time spent in the interview, negative concerns (such as service denial) of being identified as having been involved in the study, and stress while talking about HIV. The following measures were taken to manage any anticipated risks that happened: i) participants were informed that their participation was entirely voluntary and at any level of the interview they could discontinue the interview; ii) participants would be referred to a counselling service within the respective hospitals if they felt stressed during the discussion about HIV; iii) participants were reimbursed ($35 each) for costs incurred because of their participation in the interview—the information and payment process was performed after the interview to manage information bias; iv) participants were interviewed in a quiet, secure and confidential area, and they were asked to nominate another place in the hospital or health centre or work setting if they preferred; and v) although not expected to happen, if a participant preferred the interview to be conducted in his/her own home and their home is inside the town, the researcher would notify a colleague about the location and time of the interview.

The following strategies were used to avoid any real or perceived coercion felt by potential participants during the direct recruitment process. Firstly, the interviewer informed the study participants about the purpose of the interview as part of a research study, his position as a PhD student and the absence of any association with the clinic. He wore a badge that showed him as a researcher. Secondly, the participants were informed that their decision would never affect access to services, their relationship with the HIV health care providers or clinic in general. Thirdly, the participants were informed that their participation was exclusively for research purposes and that they may not get direct benefit from participation in the study.

For study four, the NGT, ethics approval was secured from the Social and Behavioural Research Ethics Committee of the Flinders University (Project No: 7698) (Annex 3.19) and the IRB of Jimma University (Ref. No: IHRPG/878/2017) (Annex 3.20). Because this study emerged after receiving ethics approval for study three, an ethics modification was applied for and received from both offices. Oral consent was sought from participants prior to recording the discussion. All panellists were assured that the information they gave would be treated with confidence and no identifying background would be published. In addition, respondents were asked not to identify their backgrounds in the self-administered questionnaire and audio-record

discussion to ensure their anonymity. The panel of experts was informed about the voluntary nature of participation in the discussion. There was no risk for members in taking part in the meeting or for the researcher during the discussion processes. Nonetheless, members might have felt burdened by the amount of time spent in the discussion, and stress during discussion about HIV. The participants would be informed that their participation was entirely voluntary, and can choose to discontinue the meeting. The experts were provided with light refreshments and lunch and reimbursed for transport expenses.

3.9 Communication of findings

As a part of dissertation chapters, the project report was submitted to the following offices: Research Higher Degree, College of Medicine and Public Health, and Discipline of Public Health at Flinders University. The research findings of this project have been disseminated through publications and workshops. The list of published original papers related to the thesis[130-134] [372]and the conference presentations [407-418]were listed in pages xx-xxi. A paper reporting the findings from the systematic review and meta-analysis that was presented at the 2016 SA Population Health Conference received the Most Popular Session award at the conference (Annex 3.22). In addition to the publications, a media release, entitled as *Ethiopia suffers from HIV treatment fears*, (Annex 3.23) by Flinders University communication office was released on 19th June 2018[419]. Findings from the qualitative study and NGT were contained in a summary report distributed to other responsible bodies and organizations. Manuscripts are on preparation for publication in a reputable journal. To recognize his contribution to public health, the PhD student received *The 2018 Fran Baum Equity Scholarship Award* at the 2018 SA Population Health Conference on 01 December 2018 (Annex 3.24).

3.10 Summary

This project used a multi-phase mixed methods study to address four complex research questions. In phase one, a systematic review and meta-analysis was used to review the existing evidence on discontinuation from ART in Ethiopia. In Phase two, a retrospective cohort studies were used to assess the magnitude and predictors of the whole HCC. In phase three, a qualitative study was used to explore the facilitators, barriers and ways to improve the HCC from the opinion of multiple stakeholders. Finally, in phase four, a nominal group technique was applied to evaluate and rank the suggested solutions in phase three by discussing with panel of experts in HIV. Table 3.5 describes the summary of methods for each objective.

Table 3-5: Summary of methods used in studies in the project, Ethiopia, 2018

Study	Objective/s	Design	Population	Sample size	Data analysis (software)	Dissemination
1	1.1 To identify the best available evidence on predictors of HIV treatment discontinuation among patients with HIV aged >= 15 years in Ethiopia	Systematic review	Adult patients with HIV on ART	9 studies, 62156 patients	Synthesis, Meta-analysis (RevMan)	Published in PLOS ONE Oral presentation in Australia
2	2.1 To assess LP among patients with HIV enrolled in ART clinics of JUTH and JHC from 2003-15	Retrospective cohort	All patients with HIV on ART	5299 (Children=399, Adults=4900)	Descriptive analysis, Logistic regression analysis, Multiple imputation (SPSS, STATA)	Published in BMC Infect Dis Oral presentation in Japan e-Poster presentation in Brazil
	2.2 To assess ART discontinuation among patients with HIV enrolled in ART clinics of JUTH and JHC from 2003-15				Descriptive analysis, Logistic regression analysis, Multiple imputation (SPSS, STATA)	Published in PLOS ONE Oral presentation in Japan e-Poster presentation in Brazil
	2.3 To assess immunologic failure among patients with HIV enrolled in ART clinics of JUTH and JHC from 2003-15				Descriptive analysis, Logistic regression analysis, Multiple imputation (SPSS, STATA)	Published in BMJ Open Oral presentation in Japan e-Poster presentation in Brazil
	2.4 To assess HIV related mortality among patients with HIV enrolled in ART clinics of JUTH and JHC from 2003-15				Descriptive analysis, Cox regression analysis, (SPSS, STATA)	Published in PLOS ONE Media release on 19 June 2018
	2.5 To estimate Southwest Ethiopia's performance to the UNAIDS 90-90-90 targets				Descriptive analysis (SPSS, STATA)	Oral Presentation in Ethiopia Oral presentation in Japan e-Poster presentation in Brazil e-Poster presentation in France
3	3.1 To explore facilitators, barriers and solutions for HIV diagnosis, ART linkage and retention in care from the perspectives of patients with HIV, HIV care providers, community advocates and HIV care system administrators in Southwest Ethiopia	In-depth Interviews	Patients with HIV, HIV care providers, Community advocates, and HIV program managers	11 HIV patients, 9 HIV care providers, 10 community advocates, 5 HIV program managers	Thematic framework analysis (NVivo)	Oral Presentation in Ethiopia Oral Presentation in Australia Oral Presentation in Thailand Media release on 19 June 2018
4	4.1 To recommend relevant, feasible & applicable solutions for HIV diagnosis, ART linkage, retention	Nominal Group Technique	HIV experts	18 experts	Wilcoxon Signed Rank test, Content analysis (SPSS, manual)	Oral Presentation in Ethiopia Oral Presentation in Australia Oral Presentation in Thailand

Chapter 4

Systematic review and Meta-analysis

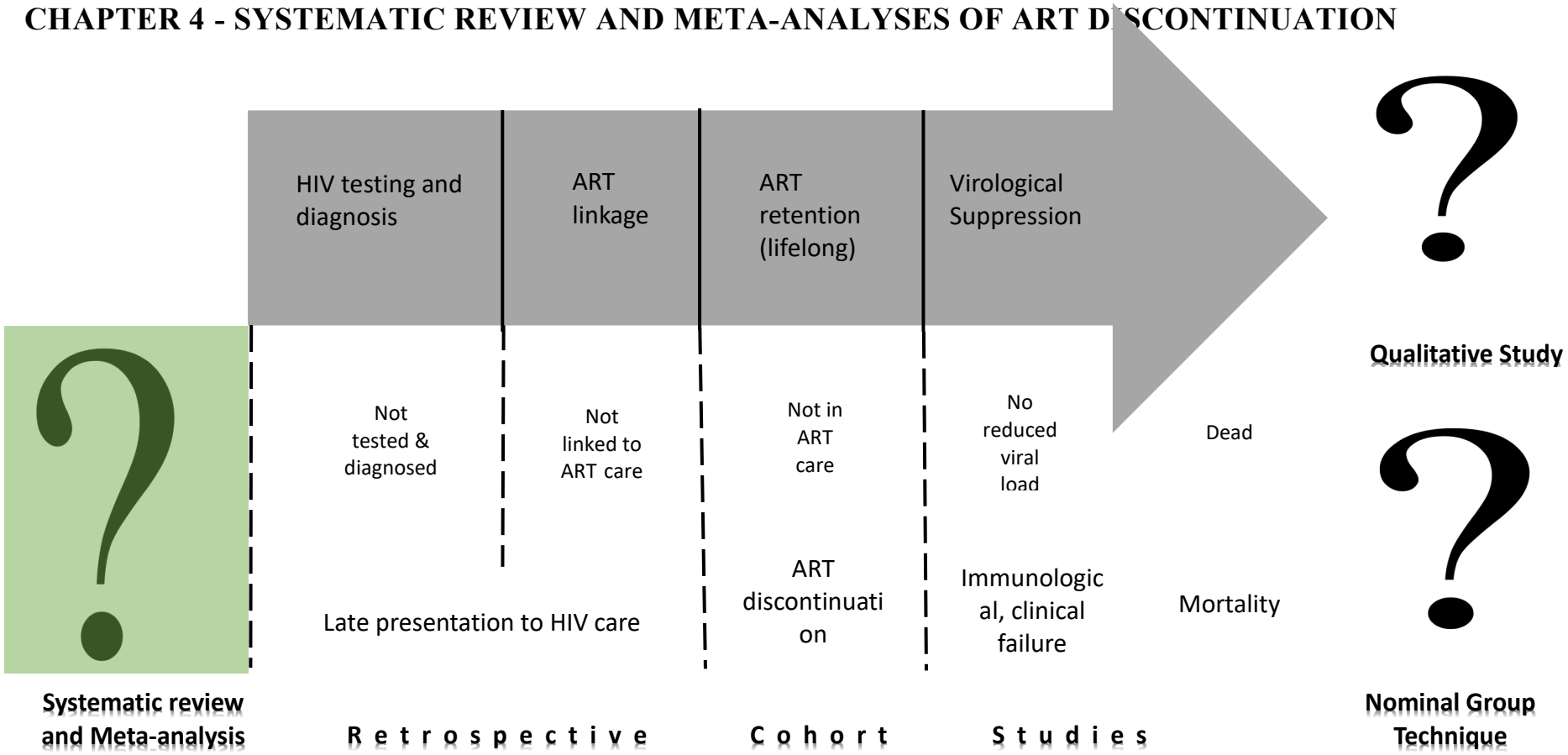

Figure 4-1: A systematic review of ART discontinuation among adults in Ethiopia

4.1 Introduction

This chapter describes the findings from the systematic review and meta-analyses which was published in PLOS ONE (Annex 3.2)[130]. The chapter is an extension of the paper and is based on the *Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols* (PRISMA-P) (Annex 4.1). The study was conducted to review the available evidence on status and predictors of ART discontinuation in Ethiopia from 2002 to 2015. The methods used to review the literature have been described in detail in the methodology chapter. The description of available evidence on ART attrition in relation to discontinuation informed the subsequent retrospective cohort analysis presented in Chapter 5, where the HCT are assessed. This chapter has the following sections: description of articles, methodological quality and measurements, review of factors associated with ART discontinuation, meta-analyses of factors associated with ART discontinuation, discussion, and conclusions and recommendations. This chapter presents the individual level of the theoretical model, SEM.

4.2 Description of articles

In this review, a total of 1219 potential studies were identified of which 1216 were from literature search and three (3) were from reference list of relevant articles. Forty-one (41) duplicated records and 1150 abstracts were excluded after screening. Full texts were obtained for 28 articles, of which 19 were excluded upon further screening due to the following reasons: 11 articles did not report on the desired outcome, four were qualitative study designs, two did not involve adults, one did not report on the desired exposures of interest, and one did not use objective measurement of outcomes. Finally, nine (9) studies were included to assess the association between the outcome and at least one of the aforementioned exposures of interest. Figure 4.2 presents the selection of studies.

Table 4.1 presents the design, setting, sample size, outcome, measurement and main findings of the reviewed studies[80 82-84 86 106 218-220]. Of the nine studies conducted from across the nation, four studies were from the northern part of Ethiopia, and three studies were from the southern part. The studies had relatively high sample sizes and together included 62,156 patients with HIV. All included studies were analytical study designs, of which three were case control studies[82 83 86], five were retrospective cohort studies[80 84 106 219 220] and one was a prospective cohort study[218]. All studies assessed at

least one component of the outcomes: seven studies[80 83 84 106 218-220] assessed factors associated with LTFU, two studies[82 86] assessed factors associated with defaulting, and one study that assessed LTFU[218] also assessed 'stopped treatment'.

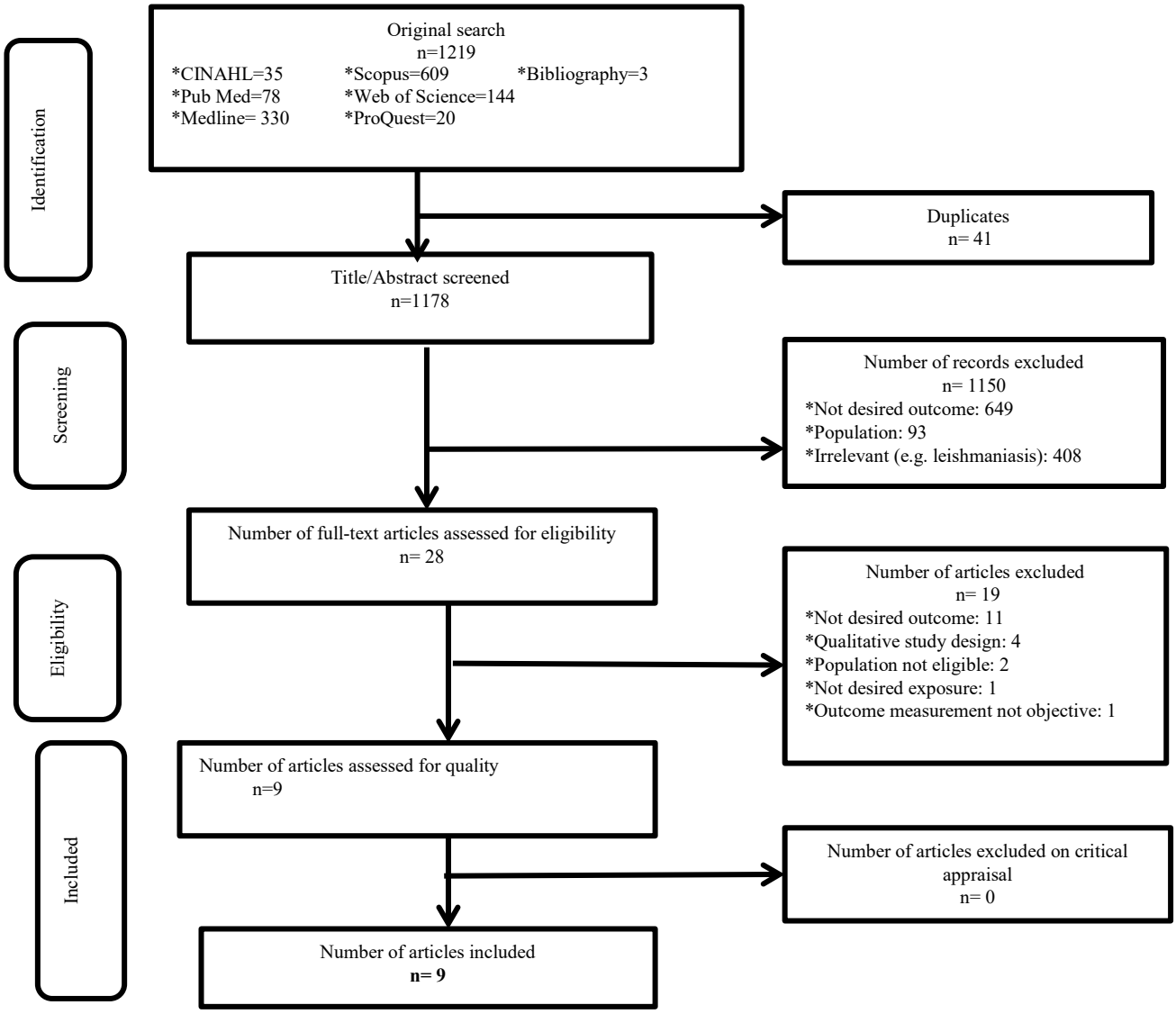

Figure 4-2: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart detailing identification and selection of studies for inclusion in the review

Table 4-1: Characteristics of included articles

Author	Year	Sample size (n)	Study design	Outcome of interest	Measurement	Setting	Summary
Deribe et al.[86]	2008	1094	Case control	Defaulting	Individuals who had missed two or more clinical appointments (i.e. had not been seen for the last two months)	Jimma, South west Ethiopia	Not taking hard drugs (cocaine, cannabis and IV drugs) (AOR=0.02, 95% CI: 0.003-0.17), excessive alcohol consumption (AOR=6, 95% CI: 3.3-11.1), being bedridden (AOR=5.7, 95% CI: 1.6-20.2), living outside Jimma town (AOR=2.2, 95% CI: 1.4-3.5) and having an HIV negative (AOR=3.5, 95% CI: 1.1-11.1) or unknown (AOR=1.7, 95% CI: 1.02-2.9) HIV status partner were associated with defaulting ART.
Asefa et al.[82]	2013	236	Case control	Defaulting	Cases were individuals who had missed two or more clinical appointments (i.e. had not been seen for the last two months)	Nekemtie, South west Ethiopia	Living far from the facility (AOR=4.1, 95% CI: 1.86-9.42), being dependent for source of food (AOR=13.9, 95% CI: 4.23-45.99), not being mentally at ease (AOR=4.7, 95% CI: 1.65-13.35), having HIV negative partner (AOR=5.1, 95% CI: 1.59-16.63), having a partner who hadn't been tested for HIV or unknown (AOR=2.8, 95% CI: 1.23-6.50] and fear of stigma (AOR=8.3, 95% CI: 2.88-23.83) had statistically significant associations with LTFU compared with their counterparts.

Author	Year	Sample size (n)	Study design	Outcome of interest	Measurement	Setting	Summary
Wubshet et al.[106]	2013	2461	Retrospective cohort	LTFU	Adult patients who were three months late for their appointment to pick-up their antiretroviral drugs	Gondar, Northwest Ethiopia	Reasons for non-deaths losses include: stopping antiretroviral treatment due to different reasons, 135(53.36%), and relocation to another antiretroviral treatment program by self- transfer, 118(46.64%).
Berheto et al.[84]	2014	2133	Retrospective cohort	LTFU	Not taking ART refill for a period of three months or longer from the last attendance and not yet classified as 'dead' or 'transferred-out'	Mizan, Southwest Ethiopia	Patients with regimen substitution (HR=5.2, 95% CI: 3.6-7.3), non-isoniazid (INH) prophylaxis (HR=3.7, 95% CI: 2.3-6.2), adolescent (HR=2.1, 95% CI: 1.3-3.4), and had a baseline CD4 count < 200 cells/mm^3 (HR=1.7, 95% CI: 1.3-2.2) were at higher risk of LTFU. WHO clinical stage 3 (HR=0.6, 95% CI: 0.4-0.9) and 4 (HR=0.8, 95% CI: 0.6-1.0) patients at entry were less likely to be LTFU than clinical stage 1 patients.
Tadesse et al.[80]	2014	520	Retrospective cohort	LTFU	Patients who had missed one or more clinical appointments	Axum, Northern Ethiopia	The independent predictors of LTFU of patient were being smear positive pulmonary Tb (AHR=2.05, 95% CI: 1.02, 4.12), male gender (AHR=2.73, 95% CI: 1.31, 5.66), regimen AZT-3TC-NVP (AHR=3.47, 95% CI: 1.02-11.83) and weight ≥60kg (AHR= 0.24, 95% CI: 0.06-0.96).

Author	Year	Sample size (n)	Study design	Outcome of interest	Measurement	Setting	Summary
Bucciardini et al.[218]	2015	512	Prospective cohort	LTFU[1], Stopped treatment[2]	[1]Patients who missed scheduled visit to the same health facility more than three months after the last visit; [2]patients known to have discontinued ART for any reasons	South Tigray, North Ethiopia	Active Tb (HR=1.72, 95% CI: 1.23–2.41) and gender (HR=1.64, 95% CI: 1.10–2.56) were also significantly associated with attrition.
Dessalegn et al.[83]	2015	727	Case control	LTFU	Patients who had missed two or more clinical appointments	Wukro, Northern Ethiopia	Presence of bereavement concern (AOR=0.1, 95% CI: 0.01-0.3), not being provided with isoniazide prophylaxis (AOR=3.04, 95% CI: 1.3-7.3), and presence of side effects (AOR=12.3, 95% CI: 4.9-31.4) were found to be associated with increased odds for being lost to follow up.
Melaku et al.[219]	2015	53,300[a]	Retrospective longitudinal	LTFU	If patients were not recorded as dead, transferred, or initiating ART, and if they did not have a recorded visit for 12 months or more with no subsequent visit	Ethiopia	Younger age, female gender, never being married, no formal education, low CD4+ cell count, and advanced WHO clinical stage were associated with increased LTFU

Author	Year	Sample size (n)	Study design	Outcome of interest	Measurement	Setting	Summary
Teshome et al.[220]	2015	1173	Retrospective cohort	LTFU	If he or she failed to visit the health facility for more than 3 months after the last appointment date.	Southern, Nations, Nationalities and Peoples Region, South Ethiopia	The competing-risk regression model showed that body mass index >=18.5 vs <18.5(AHR=0.6, 95% CI: 0.4-0.9), WHO clinical stage late vs early (AHR=1.4, 95% CI: 1.02-1.9), isoniazid prophylaxis no vs yes (AHR=1.9, 95% CI=1.1-3.2), age 26-39 vs 15-25 years (AHR=0.6, 95% CI: 0.4-0.8), facility type health centre vs hospital (AHR=0.7, 95% CI: 0.5-0.9), and educational status 2^{0+} vs no (AHR=0.6, 95% CI: 0.4-0.7) were independently associated with LTFU.

4.3 Methodological quality and measurements of reviewed studies

Of the nine studies, three studies[82 83 86], all case control by design, were included for the methodological quality assessment and met seven out of nine JBI critical appraisal criteria (Annex 3.4 & 4.2). Eligibility criteria were clearly defined on these articles. The study sample sizes were representative of all respective adult (similar in course of their condition/illness) populations living with HIV/AIDS. Outcome was measured reliably and assessed using objective criteria. Confounding factors were identified and strategies to deal with them were stated. Comparisons were made among groups, and appropriate methods of analysis and statistics were used in the study. However, because these studies were case controlled, appraisal based on adequate follow-up and analyses of withdrawals were not applicable.

Six of the nine studies[80 84 106 218-220], all cohort studies by design, were included for the methodological quality assessment and met eight out of the nine JBI critical appraisal criteria (Annex 3.4 & 4.2). Eligibility criteria were also clearly defined. The study sample sizes were representative (similar in course of their condition/illness) of all adults living with HIV/AIDS. The follow-up of adults living with HIV/AIDS was carried out over a sufficient time period. The outcome was measured reliably and assessed using objective criteria. Confounding factors were identified and strategies to deal with them were stated. Comparisons were made among groups and appropriate statistics were used in the study. However, because included studies were cohort design, appraisal based on "has bias been minimized in relation to selection of cases and of controls" was interpreted as "has bias been minimized in relation to selection of exposed and of unexposed adults living with HIV/AIDS".

Furthermore, a summary of risk of bias of the included studies was assessed using the Agency for Healthcare Research and Quality (AHRQ) criteria (Annex 3.5 & 4.3). 'Low risk' bias was found in the majority of areas. However, because of inapplicability of design nature of the studies, they had 'unclear risk' judgment in a few of the criteria for assessing bias. Quality scores are reported in Annexes 4.2 and 4.3.

As discussed in Chapter three, the measures of discontinuation were based on LTFU, defaulting or stopping medication. As a result, LTFU was measured as missing more than one[80], two[83] or three[84 106 218 220] monthly clinical appointments and not yet been classified as "dead" or "transferring out" in six of the studies that assessed discontinuation attributed to LTFU. One other study[219] that assessed LTFU defined it if there was no record of patient visits for 12 months or if there were no more subsequent visits. Two studies[82 86] assessed factors affecting defaulting, and both considered defaulting if individuals missed two or more clinical appointments. One study[218] assessed discontinuation attributed to 'stopped treatment'. The

study measured stoppage treatment when HIV positive patients on ART have stopped the treatment due to any reason while they remained in care.

4.4 Review of factors associated with ART discontinuation

4.4.1 Socio-demographic determinants

In this review, four themes emerged while synthesizing the factors affecting ART discontinuation in Ethiopia. One theme was sociodemographic and economic determinants, and under this theme, the following factors were analysed to assess their relationship with LTFU, defaulting or stopping ART treatment: age, sex, place of residence, marital status and educational status.

The association of age with discontinuation was assessed in all nine studies. Of these, three studies[84 106 219], found that patients' age had a significant association with discontinuation. Melaku and colleagues[219] reported that youths 15–24 years of age had the highest rates of LTFU (AHR (50+ vs. 15–24) = 0.67, 95% CI: 0.54-–0.81; (40–49 vs. 15–24)= 0.67, 95% CI: 0.60–0.75; (25–39 vs. 15–24)= 0.77, 95% CI: 0.72–0.83). In their study, Wubshet and colleagues reported that the probability of LTFU decreased with increasing age[106].

All studies assessed the relationship between sex and discontinuation. Four studies [80 106 218 219] found a significant association between sex and discontinuation. Bucciardini and colleagues reported that males were at high risk of attrition (AHR=1.6, 95% CI: 1.1–2.6) compared with their female counterparts[218]. In addition, Melaku and colleagues (AHR (females vs males) = 0.73, 95% CI: 0.7–0.8) [219], Tadesse and colleagues (AHR (males vs females) = 2.7, 95% CI: 1.3-–5.7)[80] and Wubshet and colleagues (AHR (males vs females) = 1.7, 95% CI: 1.3–2.3)[106] also supported findings of Bucciardini and colleagues[218].

Four studies[82 83 86 106] assessed the association of place of residence and discontinuation. Of these, two studies[86 106] reported significant association, finding that patients living in rural settings were more likely to discontinue than those living in urban areas. Six studies[80 82 83 86 219 220] assessed the association of marital status and discontinuation, and only Melaku and colleagues [219] reported a statistically significant association. This study reported that married individuals had the lowest rates of LTFU (AHR (widowed vs never married) = 0.8, 95% CI: 0.7–0.9; (separated/divorced): 0.9, 95% CI: 0.8–0.96; (married/living together vs never married) = 0.67, 95% CI: 0.63–0.7).

Seven studies[80 82 83 86 218-220] assessed the association between educational status and discontinuation, for which only Melaku and colleagues [219] found statistical association. Melaku and colleagues revealed that patients reporting no formal education had higher LTFU rates.

4.4.2 Behavioural determinants

'Behavioural determinants' was another theme in the synthesis of factors correlated with discontinuation. In this theme, the following factors were analysed to assess their correlation with LTFU, defaulting or stopping ART treatment: HIV status disclosure, partner's HIV status, smoking tobacco and drinking alcohol. Two studies[82 86] assessed the relationship between tobacco use and discontinuation. Both studies reported that their odds were non-significant. In addition, these two studies[82 86] also assessed the association of alcohol intake with discontinuation. Deribe and colleagues showed that heavy drinkers had higher rates (AHR=3.6, 95% CI: 1.8–7.1) of LTFU than those who did not drink[86].

Three studies[82 83 86] assessed the relationship between partner's HIV status and discontinuation, and two of them observed a statistically significant association[82 86]. Asefa and colleagues indicated that individuals with a HIV positive partner had lower rates of LTFU than those with negative or unknown status (AOR (HIV negative vs positive) = 5.1, 95% CI: 1.6–16.6); (not known/tested vs positive) = 2.8, 95% CI: 1.2–6.5)[82]. Similarly, Deribe and colleagues reported that having a HIV positive partner was a lower risk for defaulting than having a partner with negative or unknown HIV status[86]. Two studies[83 220] discussed the correlation of HIV disclosure status with discontinuation, and both reported non-statistically significant associations.

4.4.3 Clinical determinants

The third theme that emerged during the synthesis of factors affecting ART discontinuation was clinical determinants. The theme included the following codes: mental health, Tb/HIV co-infection, isoniazid (INH) prophylaxis provision, cotrimoxazole or OIs prophylaxis provision, presence of side effects, baseline CD4 counts, baseline WHO clinical stage, baseline functional status, baseline BMI level, baseline haemoglobin level and regimen substitution.

Two studies[82 86] assessed the link between mental health problems and discontinuation attributed to defaulting, and both reported the presence of a statistically significant association. Asefa and colleagues showed that people with a mental illness were at almost five times greater risk of discontinuing from ART compared with their counterparts[82]. Similarly, Deribe and colleagues revealed that those who had mental illness were at three times higher risk of ART discontinuation compared with those who had no illness[86].

Three studies [82 83 220] assessed the association of ART side effects with discontinuation. Dessalegn and colleagues reported that there was a statistically significant association between ART side effects and discontinuation[83]. This study revealed that those who developed ART

side effects were at 12 times (AOR=12.3, 95% CI: 4.9–31.4) higher risk of LTFU compared with those who did not develop side effects[83].

Seven studies[80 82-84 86 106 220] measured the association between baseline functional status and discontinuation, and two[84 86] reported statistical significance. Deribe and colleagues showed a higher probability (AOR=7.4, 95% CI: 1.9–28.6) of LTFU among bedridden study participants than among those who were working[86]. However, Berheto and colleagues reported the reverse, (AHR (ambulatory vs working) = 0.4, 95% CI: 0.3–0.6; (bedridden vs working) = 0.7, 95% CI: 0.5–0.9[84].

Seven studies[80 82 84 86 106 218 220] assessed the correlation between Tb status or being on Tb treatment and discontinuation. Of these, three studies[80 106 218] reported a statistically significant correlation. Bucciardini and colleagues found that patients with HIV who were Tb smear positive were about two times (AHR=1.7, 95% CI: 1.2–2.4) more likely to be LTFU than those who were Tb smear negative[218]. Similarly, Tadesse and colleagues reported that Tb smear positive participants had higher risk of LTFU (AOR=2.05, 95% CI: 1.02–4.12) than their counterparts[80]. Contrary to this, Wubshet and colleagues reported that development of Tb at ART initiation was a protective factor for LTFU (AHR=0.7, 95% CI: 0.5–0.9)[106]. Four studies[80 82 84 86] assessed the association between OI treatment or cotrimoxazole prophylaxis and discontinuation but none of them reported statistical significance.

All studies assessed the relationship between baseline CD4 counts and discontinuation, and two studies[84 219] found a statistical difference. Berheto and colleagues revealed the risk of LTFU was higher in patients with baseline CD4 cell counts <200 cells/mm^3 (HR 1.7; 95% CI 1.3–2.2) compared with patients with counts >200 cells/mm^3[84]. Melaku and colleagues also reported that fewer patients initiating ART with baseline CD4 cell counts <100 cells/mm^3 experienced LTFU compared with patients with counts of >350 cells/mm^3 (AHR=1.4, 95% CI: 1.2–1.7)[219].

Six studies[83 84 106 218-220] assessed the correlation of WHO clinical stage and discontinuation. Of these, three studies[84 220 240] found a statistically significant difference. Berheto and colleagues[84] showed that patients who were diagnosed as WHO clinical stages 3 (AHR=0.6; 95% CI: 0.44–0.9) and 4 (AHR=0.8; 95% CI: 0.6–1.0) at entry had lower LTFU rates than patients at WHO clinical stage 1. Nevertheless, Melaku and colleagues[219] (AHR (Stage 4 vs 1) =1.6, 95% CI: 1.4–1.9; (stage 3 vs 1) =1.2, 95% CI: 1.1–1.3) and Teshome and colleagues[220] (AHR (late vs early WHO clinical stage) =1.4, 95% CI: 1.03–1.9) reported the reverse.

Three studies[83 84 240] assessed the association between INH prophylaxis and discontinuation, and all of them reported a statistically significant difference. Berheto and colleagues[84] revealed that patients who were not on INH prophylaxis were at about four times higher risk of LTFU (AHR= 3.7, 95% CI: 2.3–6.1) than their counterparts. Similarly, Dessalegn and colleagues[83] and Tadesse and colleagues[80] revealed that, compared with their counterparts, patients who were not on INH prophylaxis were at three (AOR=3, 95% CI: 1.3–7.3) or two (AHR=1.9, 95% CI: 1.1–3.2) times higher risk of LTFU respectively.

Finally, two studies[83 84] assessed the correlation between ART shift and discontinuation. Of the two, Berheto and colleagues reported significant association between these variables, reporting that patients on regimen substitution were at five times greater risk of being lost from ART care in comparison to their counterparts[84].

4.4.4 Institutional determinants

Institutional determinants were found as an emerging theme for correlates of ART discontinuation. In this theme, distance to the health care facility and the facility type were the factors reported to affect discontinuation. Two studies[82 83] assessed whether distance from patients' residence to the health care facility was a factor for discontinuation. Asefa and colleagues reported significant association, stating that long distance has a direct correlation with discontinuation[82]. Two studies[218 220] investigated the relationship between facility type and discontinuation, and both reported significant association. According to Teshome and colleagues, patients attending health centres were 30% less likely (AHR=0.7, 95% CI: 0.5–0.9) to discontinue treatment than those attending hospitals[220]. On the contrary, Bucciardini and colleagues reported that attending HIV care at health centres carried higher risk of discontinuation than attending hospitals[218].

4.5 Meta-analyses of factors affecting ART discontinuation

In this review, studies with sufficient data were included in the meta-analyses that identified factors affecting ART discontinuation among patients with HIV. The meta-analyses were conducted using proportions, not specific estimates, of the exposure variables for the dependent variable assessed in primary studies[80 82-84 86 106 218-220] to estimate the pooled effect size.

If studies had moderate heterogeneity when combined, a random effects meta-analysis model was considered[377], while for studies with low or no heterogeneity, a fixed effect model was considered[377]. Nevertheless, irrespective of the level of heterogeneity, if the number of studies reporting the exposure of interest was small (n<5), a fixed effect meta-analysis model was considered[420 421]. Studies with high heterogeneity (I^2 >85%) were not included in the meta-

analyses[377]. In the meta-analyses, ART side effects was not included as a variable because studies[82 86] reporting it displayed severe heterogeneity (I^2=90%). A Mantel–Haenszel statistical method was used to calculate effect sizes. Individual and pooled ORs were presented using forest plots for the meta-analyses of sociodemographic, behavioural, clinical and institutional factors as shown in Figures 4.3–4.14.

The following sociodemographic variables were included in the meta-analysis: age, sex, place of residence, educational status and marital status. Meta-analyses showed that age and sex did not have significant statistical associations with discontinuation (Fig. 4.3; OR=1.2, 95% CI: 0.9–1.5) and (Fig. 4.4; OR=0.9, 95% CI: 0.7–1.1). The meta-analyses showed that patients who were from rural dwellings (Fig. 4.5; OR=2.1, 95% CI: 1.5–2.7, I^2=60%) and those who had low literacy status (Fig. 4.6; OR=1.5, 95% CI: 1.1–2.1) had higher odds of discontinuation than their counterparts.

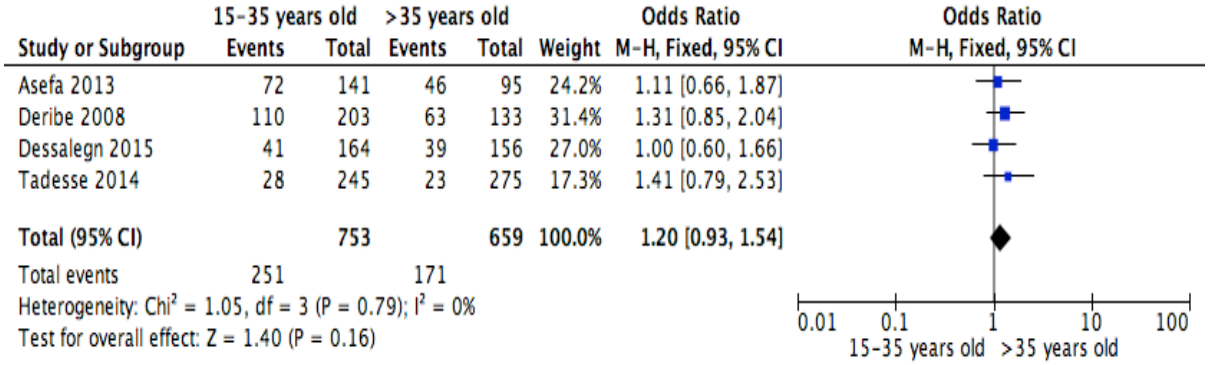

Figure 4-3: Forest plot of meta-analytic association between age and ART discontinuation, 2016

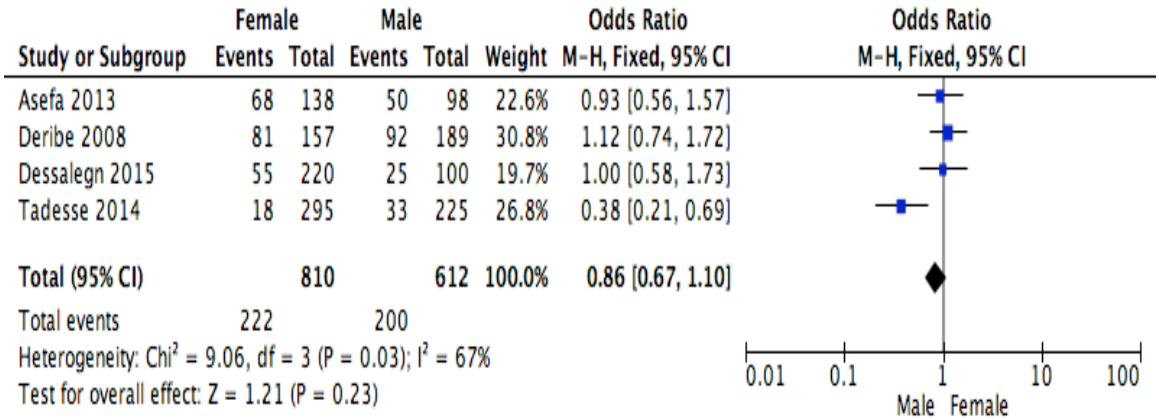

Figure 4-4: Forest plot of meta-analytic association between sex and ART discontinuation, 2016

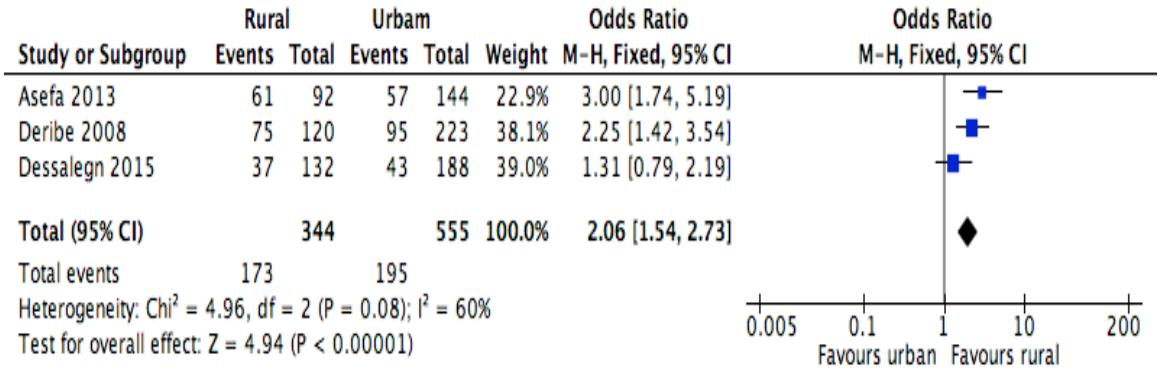

Figure 4-5: Forest plot of meta-analytic association between residence and ART discontinuation, 2016

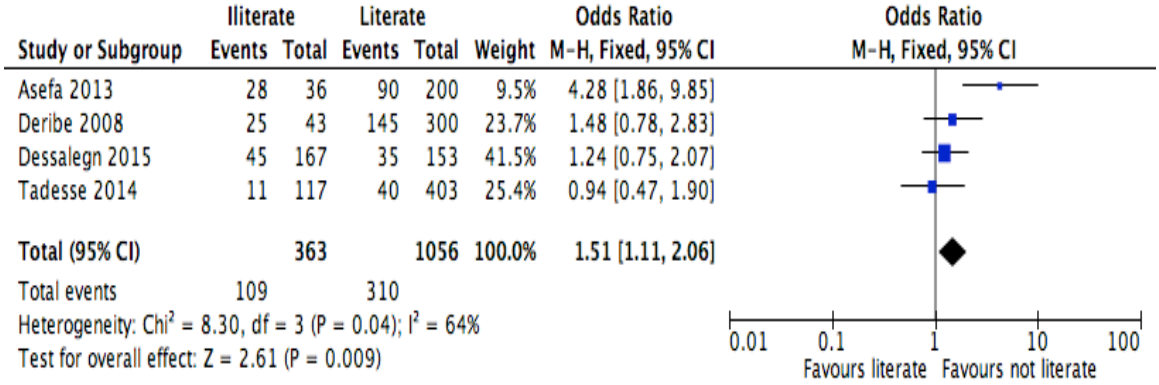

Figure 4-6: Forest plot of meta-analytic association between level of education and ART discontinuation, 2016

Being not married (Fig. 4.7; OR=1.4, 95%CI: 1.1-1.8) in comparison with being married was also another risk factor for discontinuation.

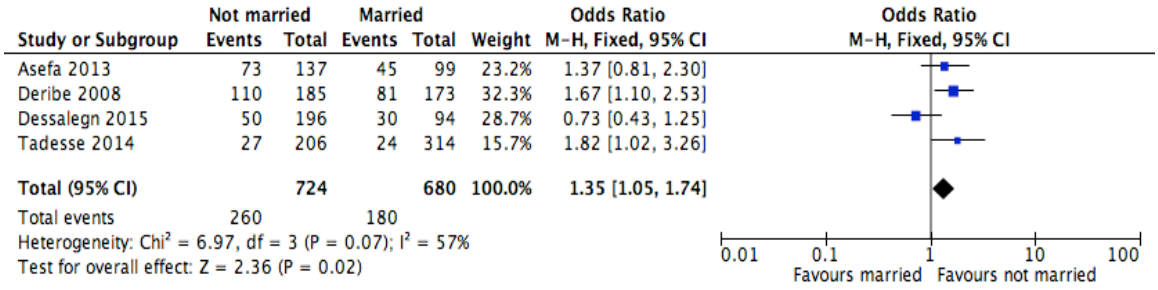

Figure 4-7: Forest plot of meta-analytic association between marital status and ART discontinuation, 2016

Of the behavioural factors influencing discontinuation, HIV disclosure, partners' HIV status, tobacco smoking and alcohol drinking were included in the meta-analyses. Partners' positive HIV status was associated with lower odds of discontinuation (Fig. 4.8; OR=0.4, 95%

CI: 0.3–0.6, I^2=69%) while a significant association was found between alcohol drinking and discontinuation (Fig. 4.9; OR=2.9, 95% CI: 1.9–4.4, I^2=39%). Similarly, tobacco smoking was correlated with discontinuation (Fig. 10; OR=2.6, 95% CI: 1.6–4.3, I^2=74%).

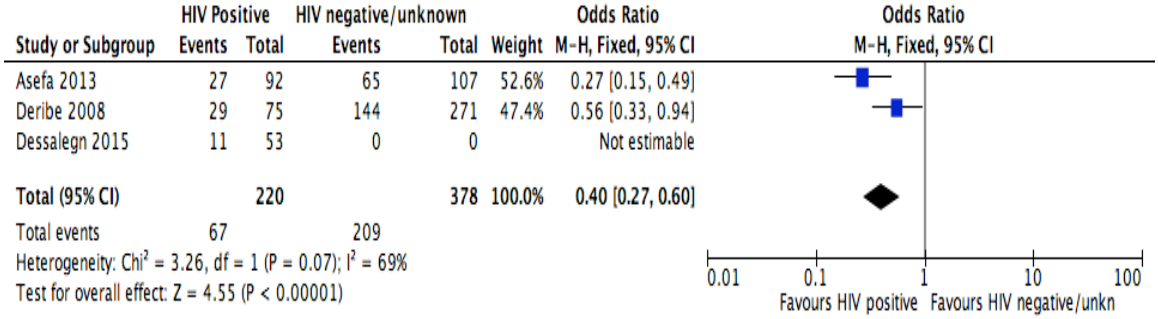

Figure 4-8: Forest plot of meta-analytic association between partners' HIV status and ART discontinuation, 2016

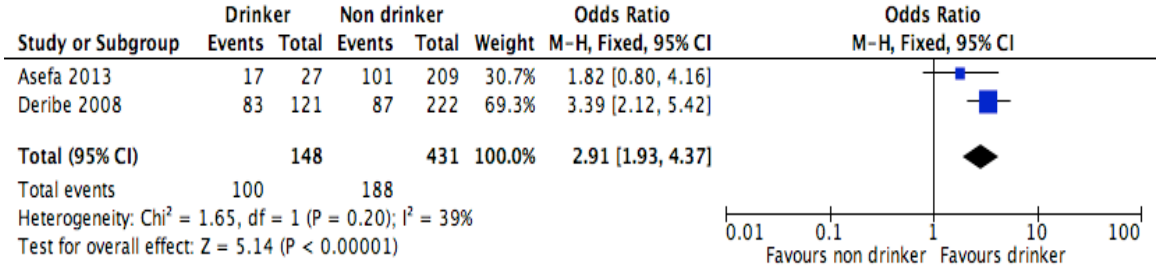

Figure 4-9: Forest plot of meta-analytic association between alcohol drinking and ART discontinuation, 2016

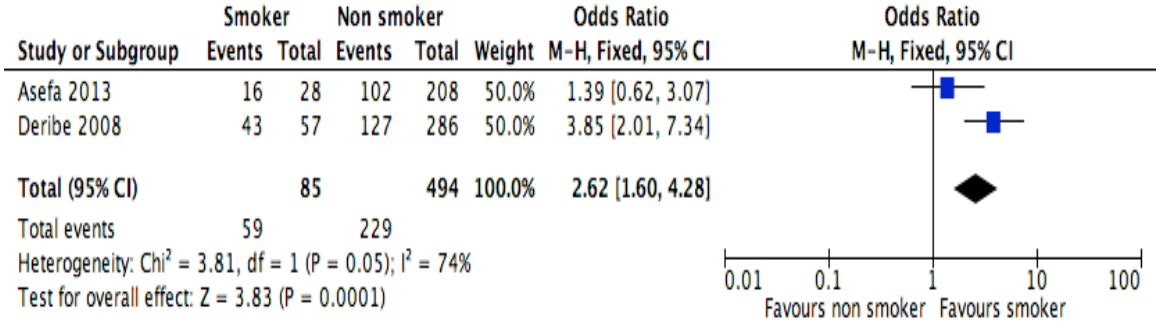

Figure 4-10: Forest plot of meta-analytic association between tobacco smoking and ART discontinuation, 2016

Clinical variables included in the meta-analysis were Tb/HIV co-infection, INH prophylaxis, cotrimoxazole or OIs prophylaxis, ART side effects or toxicity, baseline CD4 count level, baseline WHO clinical stage, baseline functional status, mental status, baseline body mass index (BMI), baseline haemoglobin and ART regimen substitution. According to the meta-analyses, Tb/HIV co-infection was associated with lower odds of discontinuation

(Fig. 4.11; OR=0.6, 95% CI: 0.4–0.9, I^2=0%). As shown in fig 4.10, the article by Tadesse and colleagues[80] was removed from the meta-analyses to prevent the introduction of significant heterogeneity. Having bedridden functional status at entry had higher probability of discontinuation than having either work or ambulatory functional status (Fig. 4.12; OR=2.3, 95% CI: 1.5–3.4, I^2=37%). Patients with HIV who also had mental illness were at about three times higher risk (Fig. 4.13; OR=2.7, 95% CI: 1.6–4.6, I^2=0%) of defaulting than their comparators. Conversely, cotrimoxazole or opportunistic infections prophylaxis was not associated with discontinuation (Fig. 4.14; OR=0.6, 95% CI: 0.4–1.1).

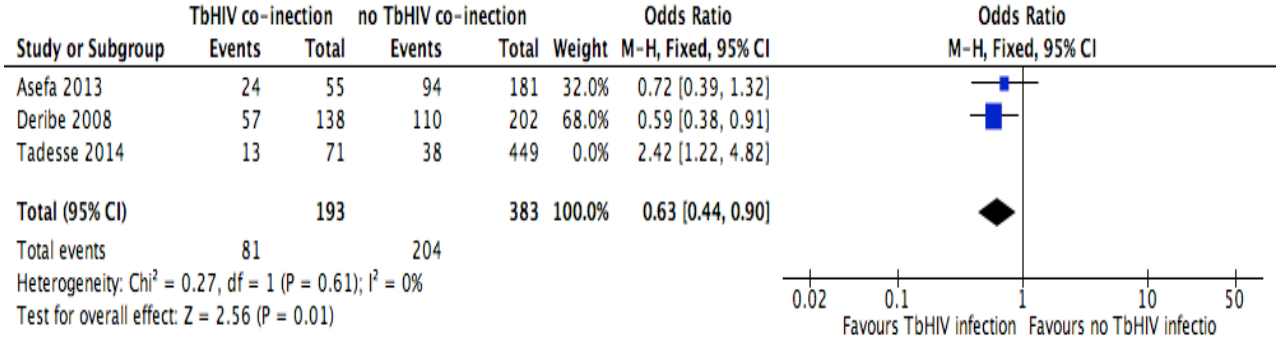

Figure 4-11: Forest plot of meta-analytic association between Tb/HIV co-infection and ART discontinuation, 2016

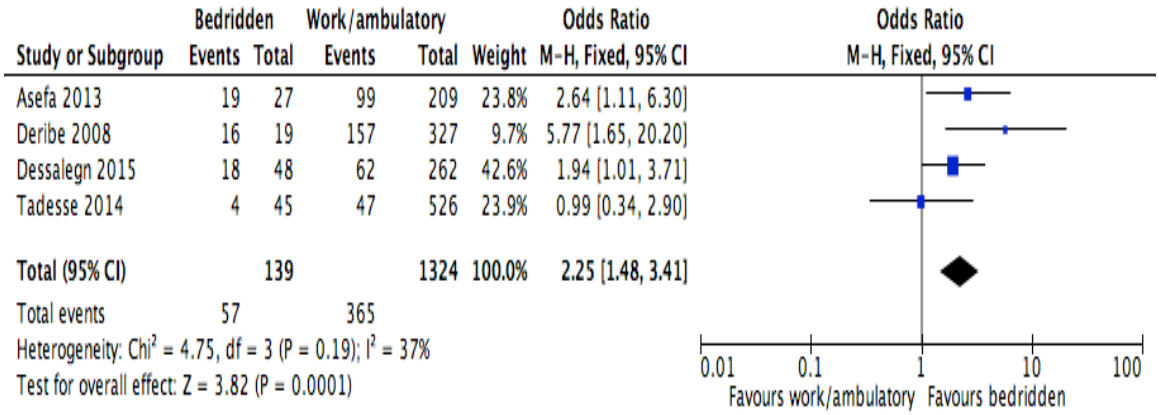

Figure 4-12: Forest plot of meta-analytic association between functional status and ART discontinuation, 2016

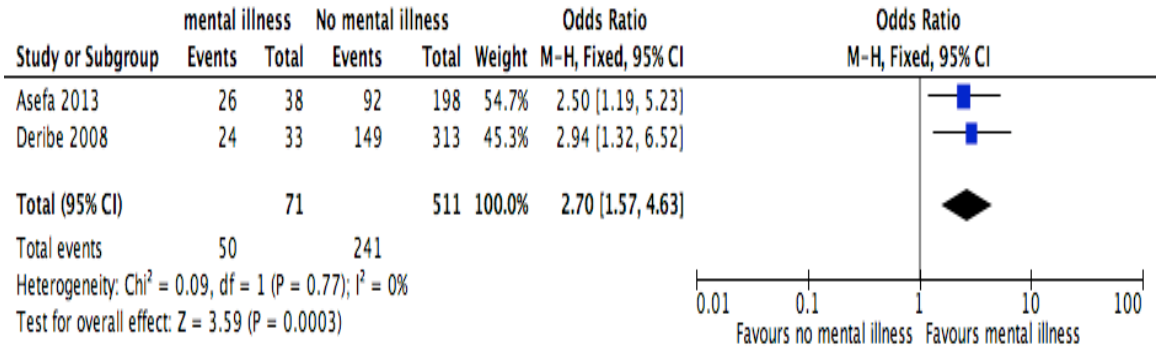

Figure 4-13: Forest plot of meta-analytic association between mental status and ART discontinuation, 2016

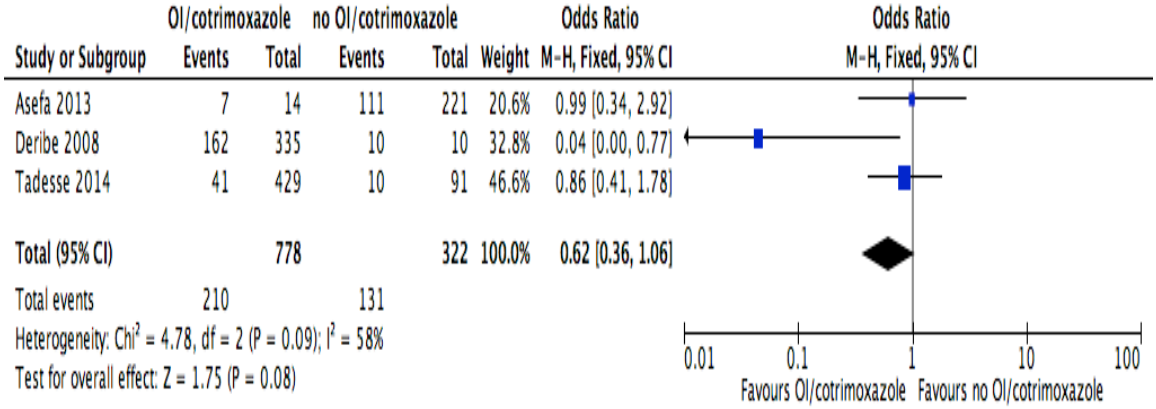

Figure 4-14: Forest plot of meta-analytic association between cotrimoxazole or opportunistic infections prophylaxis and ART discontinuation, 2016

4.6 Discussion

Globally, ART discontinuation has been identified as a key challenge for patient retention and favourable ART treatment outcome[77 79 217 422]. The available evidence in Ethiopia showed that discontinuation was a barrier for ART linkage and ART retention[68 69 306].

In the current systematic review and meta-analyses, several determinants of discontinuation were identified[80 82-84 86 106 218-220]. The studies reported that a large number of patients discontinued. Nevertheless, there were only nine studies of this over 13 years, which implied that little evidence is available despite the high rate of discontinuation. In addition, as far as is known, there have been no previous systematic reviews or meta-analyses that examined and prioritized determinants affecting discontinuation of HIV care in Ethiopia. The present study identified studies conducted in three regional states of Ethiopia and reported the following factors: being a rural dweller, being illiterate, being not married, being alcohol

drinker, being tobacco smoker, having mental illness, having bedridden functional status, having HIV positive partner and being co-infected with Tb/HIV.

In the meta-analyses, demographic factors such as place of residence and educational status affected discontinuation of ART. The study found that patients with HIV from rural settings were more likely to discontinue ART than patients from urban settings, and this was supported by a systematic review conducted in sub-Saharan Africa[33]. Given that infrastructure is poor and with low availability and accessibility of health care services in rural settings[423 424], this finding might not be surprising. Thus, HIV care services should be decentralized and integrated with other services delivered by community health workers[425]. Such decentralization should go down to the level of community engagement so as to remove ART inequity between rural and urban areas[426]. A comprehensive framework called *seek-test-treat-succeed* model for HIV care has been promoted globally[268], and this should be implemented in Ethiopia. This model entails reaching out to individuals who are at risk but do not know their HIV status (*seek*), screening their HIV status (*test*), linking people who test positive for HIV to ART treatment services (*treat*) and enabling uninterrupted lifelong service utilization (*succeed*)[35 427]. A systematic review in sub-Saharan Africa also revealed that community supported programs were effective in improving ART linkage and retention in care[272].

Educational status was significantly associated with ART discontinuation in the meta-analyses. Patients with HIV who had not attended school had a greater risk of discontinuation than those who had. The association of low educational level and discontinuation could be explained by the fact that most patients could be from rural settings. Schools may be physically inaccessible in rural areas, which in turn could lead to a knowledge gap about HIV care. This knowledge gap has been associated with low educational levels which are prevalent among rural residents. In addition to 'knowledge effect', education has also an 'income effect'—the more that a person is educated is the more that the person has good income and this helps to acquire health enhancing goods and services including the ability to pay transportation. Although there is no systematic review study that reported the association of educational status and discontinuation, one study reported that patient education is effective for improving compliance to ART[428].

Of the clinical factors considered for meta-analyses in this study, baseline functional status, Tb/HIV co-infection and mental health status were found to be significant predictors. Patients with HIV with bedridden functional status had twice the risk of discontinuation when compared with patients with working or ambulatory functional status. There were no systematic review studies that assessed the correlation between functional status and ART

discontinuation. However, a primary study from Nigeria supported the finding of the current meta-analysis[236]. This poor baseline performance scale might be due to LP[429].

Patients with Tb/HIV co-infection had lower odds of discontinuation than patients with HIV alone in this meta-analysis. The combined fear of consequence of both diseases may encourage patients not to interrupt their HIV treatment. A systematic review conducted in sub-Saharan Africa also revealed that patients who were co-infected with Tb had higher pre-ART care retention than those with HIV alone; however, this was supported by limited evidence and needs further exploration[430].

Being mentally ill was another determinant factor for discontinuing ART care. In this meta-analysis, patients with mental illness were at about three times higher risk of discontinuing than those patients with HIV without mental illness. HIV worsens the risk of mental illness and mental illness exposes people to the risk of HIV infection, causing a severe bidirectional and synergistic combination of diseases[262]. In addition, mentally ill patients with HIV face double stigma from both diseases and this can deter them even more from HIV care seeking[262 263]. A recent systematic review and meta-analysis also showed that having mental illness or symptoms thereof was found to be a barrier to HIV care retention[431]. This implies that HIV care and mental health services should be integrated because the services are provided separately at present. It is evident that treating mental illness for patients with HIV improves their CD4 count and reduces the overall mortality of patients with HIV[432].

Of the behavioural factors included in the current meta-analyses, smoking tobacco and HIV status of the partner were the predictors of ART discontinuation. Patients who currently smoked or had history of smoking were at three times higher risk of ART discontinuation than patients with HIV who had never smoked. It is evident that smoking may have a number of toxic effects and this may induce inflammation and lead to patients becoming immunocompromised. This leads to failure to thrive and prevents patients from attending ART care services continuously[433]. Although there is no proven evidence about the favourable effects of smoking cessation on HIV treatment outcomes[434 435], it an issue that needs further examination. It is important to consider the integration of smoking cessation strategies such as Medication-Assisted Therapies [436] and group behaviour therapy programs[437] with routine HIV care services.

Having a partner who was HIV positive was found to be a protective factor for ART discontinuation in the current meta-analysis, which showed that patients whose partner was HIV positive were at 60% less risk of discontinuation than their comparator. If both partners were positive, the probability of disclosing one's HIV status to one's partner may be higher

than for someone whose partner was HIV negative. This was supported by a systematic review conducted in low- and middle-income countries that reported that partner notification was the strongest factor in disclosure[438]. The sero-status discloser helps a person to obtain support from their partner to remain in care[121 439]. On the other hand, health professionals may give less attention to counselling HIV negative partners about supporting their HIV positive partner[430]. It is therefore necessary to invite and counsel the partners of all patients with HIV because they play a key role in supporting their partner.

Several gaps were noted in the studies reviewed in this systematic review and meta-analyses. First, studies used different instruments to define LTFU and defaulting. This limitation reflects the absence of a 'gold standard' definition for discontinuation attributed to LTFU or defaulting[440]. Second, all the studies included in the meta-analyses were from three major regional states of Ethiopia, namely Tigray, Amhara and Oromiya. The prevalence of HIV in these regions is 2% compared with other regions such as Gambela with higher prevalence of 4.8%[10]. Determinants of discontinuation for patients from regions with high HIV prevalence may also be different to those in regions with low HIV prevalence.

Third, the outcome status of patients whose discontinuation was attributed to LTFU, default or stopping treatment was only reported in one study[106]. Tracing studies in Kenya[105] and Zambia[441] revealed that more than 40% of discontinued patients failed to re-engage with HIV care, and those patients who did re-start only accessed the care after their condition deteriorated. This implies the need for future tracing studies, such as developing the role of tracers and establishing the benefits of a community tracking system[442]. Finally, because the majority of articles included in the meta-analyses were retrospective cohort studies, it was not possible to assess the impact of potential causes of discontinuation such as HIV related stigma. Thus, further primary studies that include qualitative inquiry are needed.

Generally, the systematic review and meta-analyses findings have the following limitations: (i) the meta-analytic findings may not be causally related because all except one of the studies were retrospective studies; (ii) there may be a reporting bias because the search strategy was limited to studies published in English[443]; (iii) a funnel plot was not reported to detect publication bias because the number of studies per each exposure was limited ($n<10$)[443]; (iv) the generalizability or inferences of the findings is limited because the reviewed studies were skewed geographically, being from only three of the nine regions and two chartered cities of Ethiopia; (v) the exclusion of transferred out cases may bias the finding and these patients may not be engaged in care in another institution as opposed to our assumption; (vi) this study did not assess the effect of WHO clinical stage of HIV, CD4 level, regimen substitution,

haemoglobin level, isoniazid (INH) prophylaxis and facility type on ART discontinuation although they were considered for the meta-analyses calculation. This was because some authors did not explicitly report the numbers of discontinued patients by the abovementioned exposures of interest. The researcher has tried to contact the authors and none of them replied; and (vi) due to the nature of the design and its analysis, reverse causation was not managed.

4.7 Conclusions and recommendations

Nine primary studies, published in English language, addressed LTFU and defaulting in Ethiopia between 2002 and 2015. All included studies reported the desired outcomes and at least one of the exposures of interest. In summary, patients with HIV who came from rural settings, did not attend school, did not get married, drank alcohol, smoked tobacco, had mental illness, and had bedridden functional status at baseline presentation were at higher risk of discontinuing ART. Conversely, patients with HIV who had a HIV positive partner and Tb/HIV co-infection were at lower risk of discontinuing treatment. Therefore, retention strategies should target these population groups with HIV.

The following recommendations could be considered to improve ART attrition attributed to ART discontinuation: (i) awareness of ART care and inequity has to be improved for people who live in remote areas and have low literacy status, (ii) support strategies could be developed to help people who never been married to take ART regularly, (iii) behavioural therapies such as smoking and drinking cessation strategies could be integrated into the HCC, (iv) early HIV care presentation strategies could be promoted to improve functional status of patients at entry, and (v) integration of mental health care into routine HCT program. Further research is also recommended to: (i) review the determinants of ART discontinuation among children, because the focus of current study was only adults, and (ii) conduct similar work for patients on second-line ART regimen because the current study was of discontinuation from first-line ART regimen. Evidence shows that the number of patients on second-line ART regimen is increasing[444 445]. Given that this review included patients with HIV attending HIV clinics from only three regions in Ethiopia, the problem has to be assessed in a setting where patients with HIV attend HIV clinics in other regional states. This study has also implied that late presentation could be the major reason for discontinuation and this has to be assessed contextually. Furthermore, outcomes for these discontinued and other patients were not known and this also needs further research. Hence, in order to address the gap in the whole HCC, a retrospective cohort study was conducted using data from JUTH. The findings of the cohort are presented in the next Chapter (Chapter five).

Chapter 5

Cohort study

CHAPTER 5 - RETROSPECTIVE COHORT STUDY OF HIV CARE AND TREATMENT

5.1 Introduction

Chapter five presents the findings of the retrospective cohort study and discussion of them. The findings and implications in Chapter four led to this chapter, where the whole HCC is assessed using a 12 year (2003–15) retrospective cohort study. The discussion of available evidence on the HCC in this chapter informs the subsequent qualitative study presented in chapter six, where HCT is explored beyond the individual level barriers, by investigating the influence of factors such as health care professionals, community members and policy makers, and suggested possible solutions identified by consulting these stakeholders.

Chapter five is organized in relation to the sequential series of continuum of HIV care and has eight sub-sections. Sub-sections one and two comprise the introduction to the chapter and description of the overall cohort respectively. Sub-section three contains data on patients who present late for HIV care and is followed by sub-sections four, five and six that focus on discontinuation from ART, immunologic failure and HIV related mortality respectively. The seventh sub-section deals with the performance of UNAIDS 90-90-90 treatment targets using surrogate measures described in sub-sections three to five. The last sub-section presents the overall conclusions, strengths, limitations and implications for future studies. This chapter presents the individual level of the SEM.

5.2 Description of Cohort

It was intended to extract data for the present cohort study from ART clinics at JUTH and JHC. However, there was inadequate information on the main outcome variables and exposure variables in the health centre. Therefore, the cohort study was based on data from JUTH, which had 8172 patients in the HIV care program from 21 June 2003 to 15 March 2015. Of these, 5299 (64.8%) patients with HIV had been documented as commencing ART. The remainder included 34.9% on pre-ART, 0.2% eligible for ART and 0.1% eligible and ready for ART. Figure 5.1 shows the status of all patients with HIV, by age, in the cohort. Of the 5299 patients on ART, 4900 (92.5%) were adults with HIV and 399 (7.5%) were children aged below 15 years old.

Stratified by age, the clinical and non-clinical characteristics of the study participants on ART is presented in Table 5.1. Among the 4900 adult patients with HIV on ART, 80% were aged 25–<50 years, 60% were female, 43% were married, 59% were Christian, and 34% had

completed primary education. The median baseline CD4 count was 156 (0–1313) cells/mm^3, and about one-third (33%) of participants had baseline WHO clinical stage 3 or 4. Of the 399 children, three-fifths were aged 5–<15 years, more than half were males, and one-third were from Christian families. The prevalence of Tb/HIV co-infection in children was 29%.

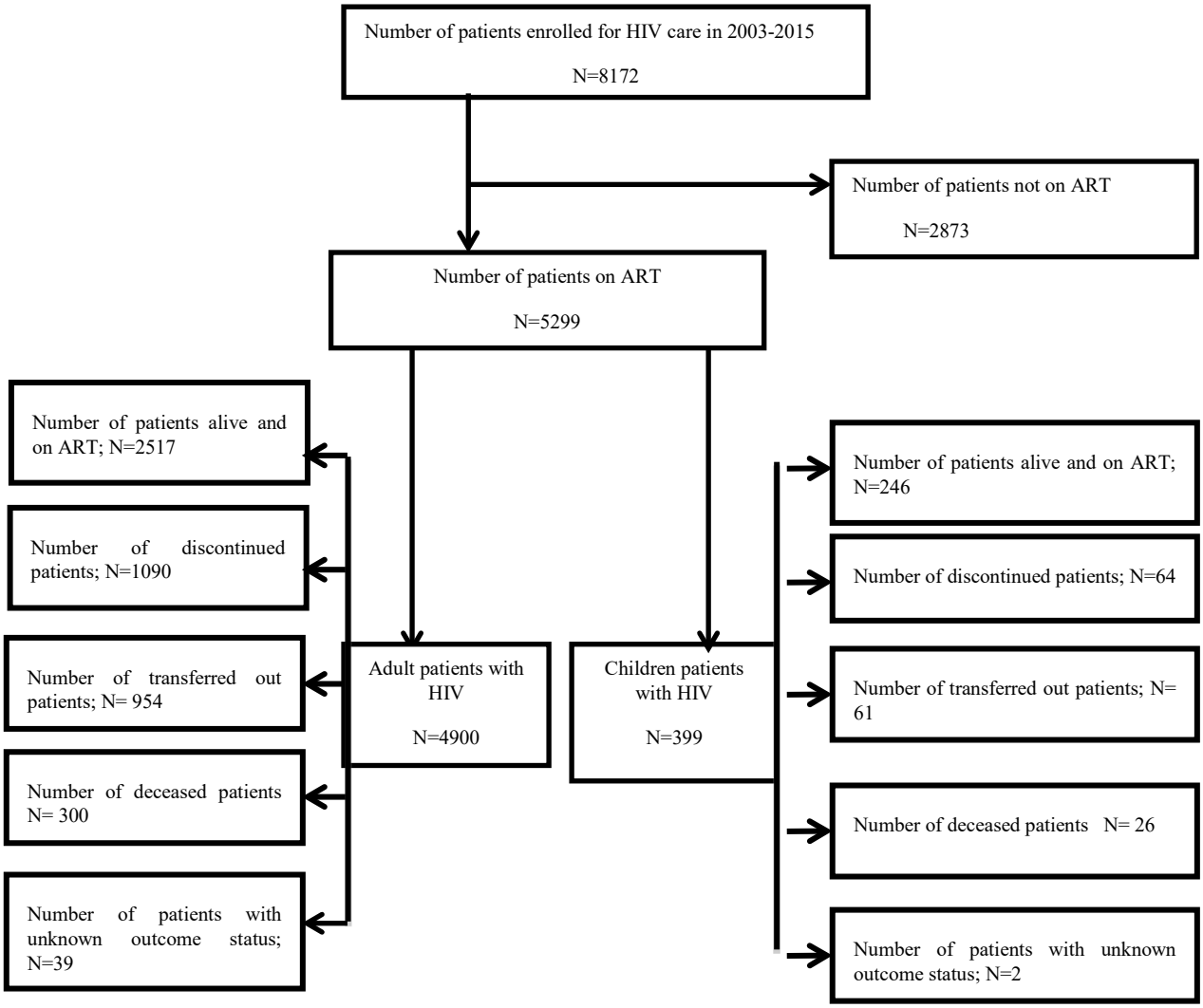

Figure 5-1: Schematic presentation of data extraction of patients with HIV on ART in 2003-15 in Jimma University Teaching Hospital, Southwest Ethiopia

Table 5-1: Characteristics of patients with HIV in ART care, Southwest Ethiopia, 2003-15

Variable		**Children (N=399),** N (%)	**Adult (N=4900),** N (%)
Age in years	<1	21 (5.3)	----------
	1-<5	146 (36.6)	----------
	5-<15	232 (58.1)	----------
	15-<25	----------	711 (14.5)
	25-<50	----------	3937 (80.3)
	50+	----------	252 (5.2)
	Median (range) age in years	6 (<1-14)	30 (15-81)
Sex	Male	209 (52.4)	1971 (40.2)
	Female	190 (47.6)	2929 (59.8)
Marital status	Never married	-----	897 (18.3)
	Married	-----	2094 (42.7)
	Separated/divorced/widowed	-----	1311 (26.8)
	Missing	-----	598 (12.2)
Education	No education	-----	945 (19.3)
	Primary	-----	1687 (34.4)
	Secondary and above	-----	1685 (34.4)
	Missing	-----	583 (11.9)
Religion	Muslim	47 (11.8)	1402 (28.6)
	Christian[12]	133 (33.3)	2893 (59)
	Missing	219 (54.9)	605 (12.3)
Baseline WHO classification	1 or 2	108 (27.1)	1355 (27.7)
	3 or 4	110 (27.6)	1608 (32.8)
	Missing	181 (45.3)	1937 (39.5)
Baseline CD4 count category[13]	No damage	72 (20.6)	---------
	Moderate or severe damage	277 (79.4)	---------
	Median (range) CD4 count	282 (0-2250)	----------
Baseline CD4 count (cells/mm3)	<200	156 (39.1)	3275 (66.8)
	≥ 200	193 (48.4)	1174 (24)
	Missing	50 (12.5)	451 (9.2)
	Median (range)	282(0-2250)	156 (0-1313)
History of Tb/HIV co-infection	No	285 (71.4)	3533 (72.1)
	Yes	114 (28.6)	1367 (27.9)
ARV adherence	Good	319 (79.9)	4064 (82.9)
	Fair or poor	80 (20.1)	836 (17.1)
Cotrimoxazole adherence	Good	315 (78.9)	4119 (84)
	Fair or poor	84 (21.1)	762 (15.6)
	Missing	----	19 (0.4)
History of HIV testing	Yes	399 (100)	2860 (58.4)
	No	0 (0)	2040 (41.6)
ART shift	No	214 (97.7)	3190 (65.1)
	Yes	5 (2.3)	29 (0.6)
	Missing	180 (45.1)	1681 (34.3)
Baseline functional status	Appropriate	170 (42.6)	----
	Delay or regression	229 (57.4)	----
Baseline functional status	Work or ambulatory	----	3064 (62.5)
	Bedridden	----	1437 (29.3)
	Missing	----	399 (8.1)
Timing to HIV care presentation	Early	162 (40.6)	894 (18.2)
	Late	215 (53.9)	1788 (36.5)
	Missing	22 (5.5)	2218 (45.3)
Baseline CD4 count in cells/mm3 by enrolment period (median (range))	enrolled in 2003-11	273 (0-2000)	119 (0-1641)
	enrolled in 2012 and after	368 (3-2247)	178 (0-1638)
ART follow up time in months, median (range)		40 (0-116)	49 (0-137)
Estimated survival time in months, median (95% CI)		104.2 (99.8-108.5)	121.9 (120.3-123.5)

Tb=tuberculosis, ---- = Not applicable or not available

[12]Orthodox, Catholic, Protestant

[13] 0 CD4 count refers to undetectable CD4 count

5.3 Late presentation for HIV care

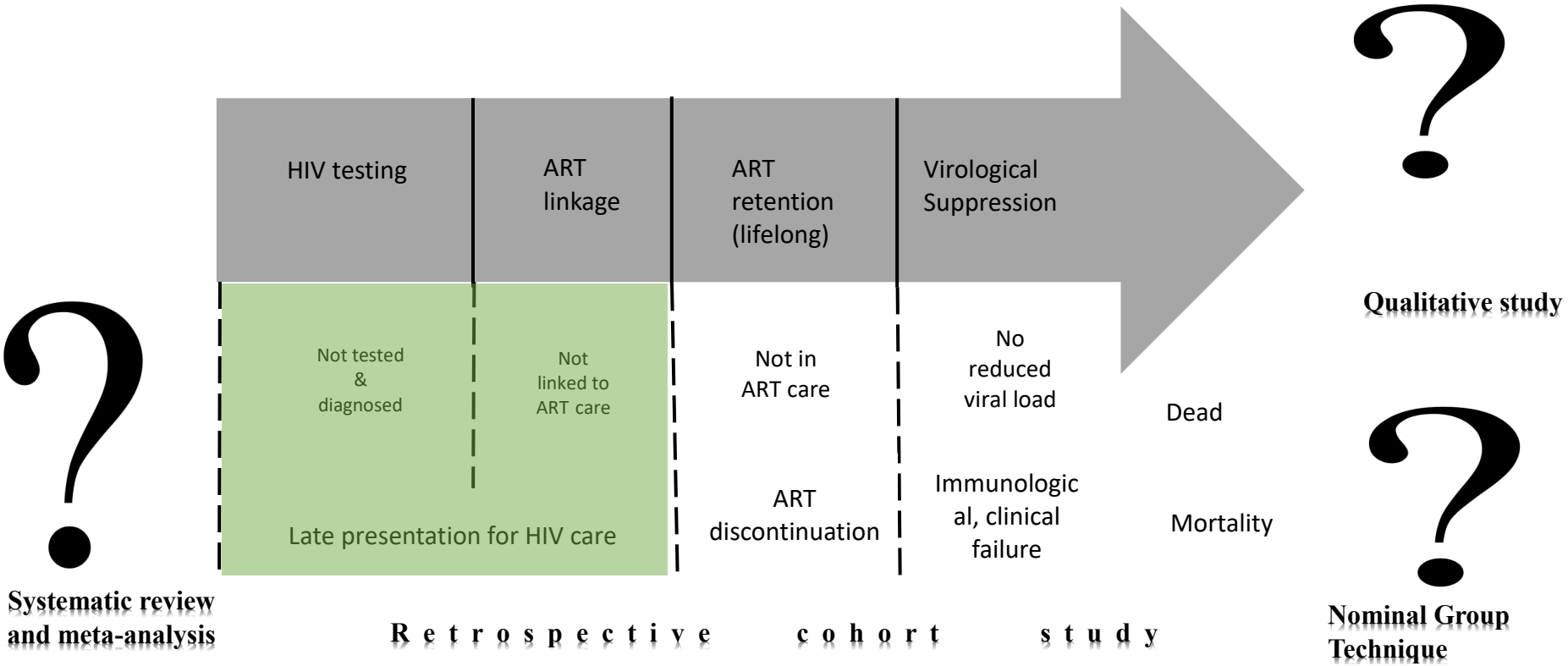

Figure 5-2: HIV care continuum- Late presentation for HIV care in Southwest Ethiopia[14]

[14] This figure needs to be viewed in colour

5.3.1 Introduction

This sub-section presents the initial stage of HCC, figure 5.2 shaded in green, namely LP among children and adults. As described in section 3.5.5 of Chapter three, LP was defined if the baseline CD4 count of a patient was low irrespective of WHO clinical stage, or advanced WHO clinical stage irrespective of CD4 count. The findings from section 5.3 have been published in *BMC Infectious Diseases*[131] (Annex 3.7), and this sub-section is an extended version of that paper. The prevalence, trend, outcomes and predictors of LP are presented in the sub-section. Lastly, the discussion and conclusions of the findings, and recommendations are also presented at the end of the sub-sections.

5.3.2 Prevalence, trend and outcomes of late presentation for HIV care

A total of 215 (57%) children and 1788 (66.7%) adult patients were late presenters for HIV care, and the overall prevalence of LP was 65.5%. The annual percentage change in new HIV care enrolment and trend in LP among people newly infected with HIV and on ART are presented in Table 5.2. There was a significant increase in new enrolments in the period between 2004 and 2006 but a decline in later years. In the period between 2004 and 2014, the proportion of LP was significant although it showed signs of declining over the years. LP reached a peak (83%) in 2004 and subsequently declined to 62% in 2014.

Table 5-2: Annual number of new HIV care enrolment and the percentage distribution of late presentation for HIV care among people newly infected with HIV on ART at enrolment, Southwest Ethiopia, 2004–14

Year	Annual new enrollment of HIV patients[15]			
	Total (A)	Annual change in percentage (B)	Eligible for LP assessment	
			Total (C)	LP, n(%) (D)
2003[16]	---	---	---	---
2004	62	0[17]	31	26 (83)
2005	484	681	280	206 (74)
2006	973	101	575	389 (68)
2007	622	-36	353	229 (65)
2008	555	-11	336	237 (71)
2009	566	2	343	240 (70)
2010	481	-15	290	175 (60)
2011	461	-4	269	146 (54)
2012	383	-17	229	141 (62)
2013	324	-15	177	106 (60)
2014	320	-1	174	108 (62)
2015[18]	---	---	---	---

[15] The annual change in percentage, (B), is calculated: $B= \{(A_i - A_{i-1})/A_i\}*100$ where i is the number of new enrolment in the year.
[16] Data from 2003 were not from complete number of months and were excluded when describing the LP trend.
[17] As this is the baseline, the value for the percentage change is '0'.
[18] Data from years 2015 were not from complete number of months and were excluded while describing the LP trend.

The negative outcomes of LP in both children and adults are presented in Table 5.3. Of the children, 57.1% died, 32.3% discontinued care, and 96.9% of children with immunologic failure presented late for HIV care. Chi-squared tests showed that there was a statistically significant difference between LP and immunologic failure (p=0.005) and ART discontinuation (P=0.020). Similarly, of adults, 64.7% died, 65.3% discontinued care, and 78.7% of adults who had immunologic failure presented late for the HIV care. The chi-squared test found a statistically significant difference between LP and immunologic failure (p<0.001) but not between LP and mortality or discontinuation.

Table 5-3: Outcomes of late presentation for HIV care among patients with HIV enrolled in HIV care, Southwest Ethiopia, 2003-15

Age	Variable	Mortality		Discontinuation		Immunological status	
		Alive, n (%)	Death, n (%)	Retained, n (%)	Discontinued, n (%)	Immunologic Success, n (%)	Immunologic Failure, n (%)
Children	EP	64 (44.8)	3 (42.9)	64 (44.8%)	21 (67.7)	40 (25.3)	1 (3.1)
	LP	79 (55.2)	4 (57.1)	79 (55.2%)	10 (32.3)	118 (74.7)	31 (96.9)
	Total	143 (100)	7 (100)	143 (100)	31 (100)	158(100)	32 (100)
	P-value (of X^2)	0.921		0.020		0.005	
Adults	EP	459 (33.1)	65 (35.3)	459 (33.1)	184 (34.7)	682 (36.5)	99 (21.3)
	LP	927 (66.9)	119 (64.7)	927 (66.9)	347 (65.3)	1187 (63.5)	365 (78.7)
	Total	1386 (100)	184 (100)	1386 (100)	531 (100)	1869 (100)	464 (100)
	P-value (of X^2)	0.550		0.524		<0.001	

EP: early presentation for HIV care; LP: late presentation for HIV care presentation; X^2: Chi-square

5.3.3 Predictors of late presentation for HIV care

Baseline clinical and non-clinical characteristics such as age, sex, Tb/HIV co-infection, previous history of HIV testing before diagnosis and HIV care enrolment period were found to be predictors of LP among adult patients with HIV. The output of multiple logistic regression analysis is presented in Table 5.4.

The risk of LP among patients with HIV aged between 25–<50 years (AOR=0.4, 95% CI: 0.3–0.6) and 50+ years (AOR=0.4, 95% CI: 0.2–0.6) was 60% less than for patients aged between 15–<25 years. Females were at a 20% higher risk (AOR=1.2, 95% CI: 1.03-–1.5) than males to present late for HIV care. Patients with HIV with Tb/HIV co-infection were 60% more likely (AOR=1.6, 95% CI: 1.09–2.1) to present late to HIV care than patients with HIV alone. In addition, patients who had never been screened for HIV before diagnosis were 20% more likely (AOR=1.2, 95% CI: 1.1–1.4) to present late than patients who had been tested for HIV before diagnosis at least once. Finally, the risk of LP among patients with HIV enrolled for HIV care in 2012 and after was 20% less (AOR=0.8, 95% CI: 0.7–0.9) than for patients

enrolled before 2012. For children, no statistically significant predictors were observed for LP and this reflects the presence of false negativity.

Multiple imputation using five imputed data sets was conducted to treat the missing data (Table 5.4). Except for variables Tb/HIV co-infection and previous history of HIV testing, which were marginally statistically significant in the multiple imputation analyses, the outputs in multiple imputations and complete case analyses were similar among adults.

Table 5-4: Logistic regression findings of factors linked with late presentation for HIV care in people with HIV, Southwest Ethiopia, 2003-15

Variable		Children				Adults				
		Time at presentation for HIV care*		COR (95% CI)	AOR (95% CI)	Time at presentation for HIV care		COR (95% CI)	AOR (95% CI): Complete cases	AOR (95% CI): Multiple imputations
		Early, n (%)	Late, n (%)			Early, n (%)	Late, n (%)			
Age	<1	7 (36.8)	12 (63.2)	1	1	----	----	----	----	----
	1-<5	56 (42.1)	77 (57.9)	0.8 (0.3-2.2)	0.5 (0.1-2.6)	----	----	----	----	----
	5-<15	99 (44)	126 (56)	0.7 (0.3-1.9)	0.4 (0.1-2.2)	----	----	----	----	----
	15-<25	----	----	----	----	96 (73.8)	340 (26.2)	1	1	1
	25-<50	----	----	----	----	739 (35.2)	1362 (64.8)	0.5 (0.4-0.7) [a]	0.4 (0.3-0.6) [a]	0.5 (0.4-0.7)[a]
	50+	----	----	----	----	59 (40.7)	86 (59.3)	0.4 (0.3-0.7) [a]	0.4 (0.2-0.6) [a]	0.4 (0.3-0.6)[a]
Sex	Male	91 (46.2)	106 (53.8)	1	----	359 (37.1)	609 (62.9)	1	1	1
	Female	71 (39.4)	109 (60.4)	1.4 (0.9-1.9)	----	535 (31.2)	1179 (68.8)	1.3 (1.1-1.5) [a]	1.2 (1.03-1.5) [a]	1.2 (1.003-1.4)[a]
Marital status	Never married	----	----	----	----	151 (30.2)	349 (69.8)	1	1	1
	Married	----	----	----	----	391 (33.6)	772 (66.4)	0.9 (0.7-1.1)	0.8 (0.7-1.07)	0.8 (0.7-1.05)
	Separated or divorced or widowed	----	----	----	----	238 (31.9)	509 (68.1)	0.9 (0.7-1.2)	0.9 (0.6-1.1)	0.9 (0.7-1.2)
Educational status	No education	----	----	----	----	149 (32.5)	309 (67.5)	1	----	----
	Primary	----	----	----	----	320 (34.8)	599 (65.2)	0.9 (0.7-1.2)	----	----
	Secondary and above	----	----	----	----	313 (30.2)	722 (69.8)	1.1 (0.9-1.4)	----	----
Religion	Muslim	16 (37.2)	27 (62.8)	1		245 (33.1)	496 (66.9)	1	----	1
	Christian [b]	52 (40.9)	75 (59.1)	0.9 (0.4-1.7)	0.9 (0.4-1.9)	535 (32.3)	1123 (67.7)	1.1 (0.9-1.3)	----	1.02 (0.9-1.2)
Tb/HIV co-infection	No	120 (45.5)	144 (54.5)	1	1	656 (34.5)	1244 (65.5)	1	1	1
	Yes	42 (37.2)	71 (62.8)	1.4 (0.9-2.2)	1.3 (0.7-2.7)	238 (30.4)	544 (69.6)	1.2 (1.01-1.4) [a]	1.6 (1.09-2.1) [a]	1.2 (1.00-1.4) [a]
Baseline functional status	Appropriate	66 (42.6)	89 (57.4)	1	1	----	----	----	----	----
	Delay or regression	96 (43.2)	126 (56.8)	1.03 (0.7-1.6)	1.1 (0.5-1.9)	----	----	----	----	----
Baseline functional status	Working/ambulatory	----	----	----	----	542 (32)	1150 (68)	1	1	1
	Bedridden	----	----	----	----	293 (36.9)	500 (63.1)	0.8 (0.7-1.1)	0.8 (0.6-1.002)	0.8(0.7-1.001)
Previous HIV testing before diagnosis	Yes	162 (43)	215 (57)	----	----	529 (34.4)	1008 65.6)	1	1	1
	No	0	0	----	----	365 (31.9)	780 (68.1)	1.1 (0.9-1.3)	1.2 (1.1-1.4) [a]	1.1 (1.00-1.3) [a]
HIV care enrollment period	enrolled in 2003-11	128 (42.2)	175 (57.8)	1	----	698 (32.1)	1478 (67.9)	1	1	1
	enrolled in 2012 and after	34 (45.9)	40 (54.1)	0.9 (0.5-1.4)	----	196 (38.7)	310 (61.3)	0.7 (0.6-0.9)[a]	0.8 (0.7-0.9)[a]	0.7(0.5-0.9) [a]

COR: crude odds ratio; AOR: adjusted odds ratio; CI: confidence interval; Tb/HIV: tuberculosis/HIV; ART: antiretroviral therapy; [a] statistically significant at P-value=0.05; [b] orthodox, protestant, catholic; ---- = Not applicable or not available

*The category totals in the 'time at presentation for HIV care' may not add up to the actual sample due to missingness.

5.3.4 Discussion

Evidence shows that LP is a significant challenge to attaining the first 90 of the UNAIDS treatment target directly, and the second and third targets indirectly[57]. Furthermore, evidence[37] showed that LP is also a major challenge to achieving the revised UNAIDS targets of 95-95-95[19]. The present study has contributed to the LP literature, and next I discuss the prevalence, trend, outcomes and predictors.

The present study found that the overall magnitude of LP is very high, showing that two-thirds of patients with HIV presented late for HIV care. The magnitude of LP in the current study (65.5%) was greater than the prevalence found in other studies, such as 23% in Kenya[446]. This may be due to the high prevalence of HIV related stigma in Southwest Ethiopia, reported as 31–66%[447] compared with a reported prevalence of (23%) in Kenya[448]. Furthermore, the presence of a diverse population of people with HIV in Southwest Ethiopia, including people from refugee camps and those with nomadic and agrarian lifestyles[449]—compared to the Kenyan study setting may mean that not all patients have equitable access to treatment. This could lead to patients developing advanced HIV disease quickly with symptoms of delayed HIV diagnosis.

The prevalence of LP, however, in the present study is lower than that seen in Asia (72–83.3%)[38 144]. The number of people from groups with high risk behaviours for HIV, such as MSM, male and female sex workers and IDU, is significantly higher in Asia than in Ethiopia in particular and Africa in general[450]. It is therefore plausible to hypothesize that these groups suffer from double stigma, HIV and their sexuality or risk behaviours, and such stigma may deter them from presenting early to care.

Observing the trends in the present study, LP was highest (83%) in 2004 and this might be because: (i) ART was not freely available[68], (ii) ART was only available in selected hospitals[68], and (iii) HIV was widely perceived as sinful and patients with HIV were perceived as cursed[451]. All these reasons would inhibit patients from pursuing timely care. It was also noted in the present study that prevalence was persistently elevated (54–83%) throughout the eleven years of the study although a declining trend was observed. This finding implies that there is significant LP in Ethiopia even in the era of free ART. This could be explained by: i) poor awareness of HIV and care[53], ii) high levels of HIV stigma[54 65], iii) perceptions of being at low risk of HIV[53 65 452], and iv) phasing out of NGOs[145]. The presence of poor access to HIV services could also contribute to the high magnitude of LP[145 179]. For example, about 20% of

[19] 95-95-95: diagnosing 95% of people living with HIV, providing 95% of those diagnosed antiretroviral therapy, and achieving viral suppression for 95% of patients receiving treatment

all health facilities in Ethiopia were not delivering HIV counselling and testing services at the time of data collection (2016)[453].

In the present study, the negative outcomes of LP included death, ART discontinuation and immunologic failure. Consistent with findings from other studies carried out elsewhere[150 151], death rates were higher in the vast majority of delayed presenters compared with early presenters. The LP causes patients to become immunocompromised and show poor response to ART, which, in turn, leads to a rapid progression to the final stages of AIDS and ultimately death[54]. Similarly, ART discontinuation and immunologic failure were observed more in delayed presenters than in early presenters. This finding was consistent with the findings of studies undertaken elsewhere[152 162]. As has been described above, delayed presenters progressed rapidly to the final stage of AIDS that were characterized by a marked reduction of CD4 counts and manifold comorbidities[258 260], and this could interrupt taking treatment regularly[259]. Comparing adults and children, LP was higher among adults. The 'opt out' screening programs for women and their children may have a positive impact for children to start their treatment early[144].

Among adults, being young, female, Tb/HIV co-infected, having no history of HIV testing, and getting enrolled in HIV care before 2012 were associated with high risk of LP. Compared with young patients, older adult patients presented early to HIV care. Given that there is a progression to AIDS related to ageing and long periods of HIV infection, this finding was surprising, and not consistent with the results of other studies in Africa[454 455]. Nonetheless, HIV related stigma is high in young adults and this fear hinders them from knowing their status and seeking timely care[456]. Furthermore, the desire and culture that adult persons are responsible for looking after their family might also encourage them to commence their treatment early.

LP was higher among females than males in this study, in contrast to other findings[162 455]. This may be because 62% of females in the current study had not been screened for HIV before diagnosis. This may lead women to feel healthy, and such subjective views of being healthy could have an impact on presenting late. In addition, females have lower knowledge of HIV and its care[54], and have lower general health seeking behaviours[457] than males in Ethiopia.

LP was observed more in patients co-infected with Tb/HIV than in patients with HIV alone, which replicates another study[50]. The synergistic combination and intricate linkage of Tb and HIV enhance progression of HIV disease to an advanced stage. In so doing, this dissuades patients from engaging in timely HIV care[449]. Additionally, while there has been significant efforts to reduce Tb and integrate Tb services into routine HIV care[458], these efforts

must be consistent and sustainable to reduce Tb/HIV co-infection because Tb is still the highest cause of mortality among patients with HIV[4].

Previous history of HIV testing is also related with LP. Patients with HIV who had never been tested before HIV diagnosis were more likely to present late than those who had been tested for HIV before diagnosis. This may be associated with lack of knowledge of HIV care[54], lack of access to HIV counselling and testing and ART care[453], stigma[253], fear of HIV diagnosis[459], and perceiving low risk and feeling healthy[169]. Lastly, LP was high in the period before 2012 and the decline may be linked to improved knowledge, access and availability of HIV care services.

The study has its limitations. First, LP was not analysed across VCT, PITC and outreach or 'opt out' programs. Evidence shows that timely HIV care presentation differs depending on the type of HIV testing program. For example, there was no additional benefit of early HIV diagnosis from PITC over targeted HIV counselling[37]. Second, it was not possible to discern whether the LP occurred before HIV diagnosis, between HIV diagnosis and initial entry to HIV care, or between initial entry to HIV care and commencing ART. Third, no predictor was identified for LP among children, which may be due to the small sample size. Nevertheless, despite these limitations, the study has provided a comprehensive description of the problem, magnitude, trends, predictors and outcomes.

5.3.5 Conclusions and recommendations

In conclusion, LP was observed in about two-thirds of study participants with high and persistent annual proportions over the eleven years studied. Additionally, significant numbers of delayed presenters, both children and adults, discontinued from ART, transferred to other ART sites or developed immunologic failure. Adult patients with HIV who were younger, female, Tb/HIV co-infected, with no history of previous HIV testing before diagnosis and enrolled to HIV care before 2012 were much more likely to present late than their comparators.

To enhance coverage of testing and timely HIV diagnosis, adoption of different strategies that have been found effective elsewhere is recommended. For example, Malawi has been using drones to transport laboratory specimens to reduce delays in infant diagnosis[460]. The following programs also contribute to addressing the challenge of HIV testing coverage: repeat HIV testing[346], community-based HIV testing[461 462], and HIV screening by community workers[31].

HIV related stigma should also be tackled contextually because it continues to be a lingering issue among people infected with HIV. Further exploration is needed as to why

different studies show contradictory findings with regard to the association of gender and LP. Additional research is also recommended to set a contextual measurement and gold standard definition for LP in the era of test and treat strategies. Lastly, to identify predictors of LP among children, further studies with a larger cohort and bigger sample size should be conducted.

5.4 Discontinuation from antiretroviral therapy

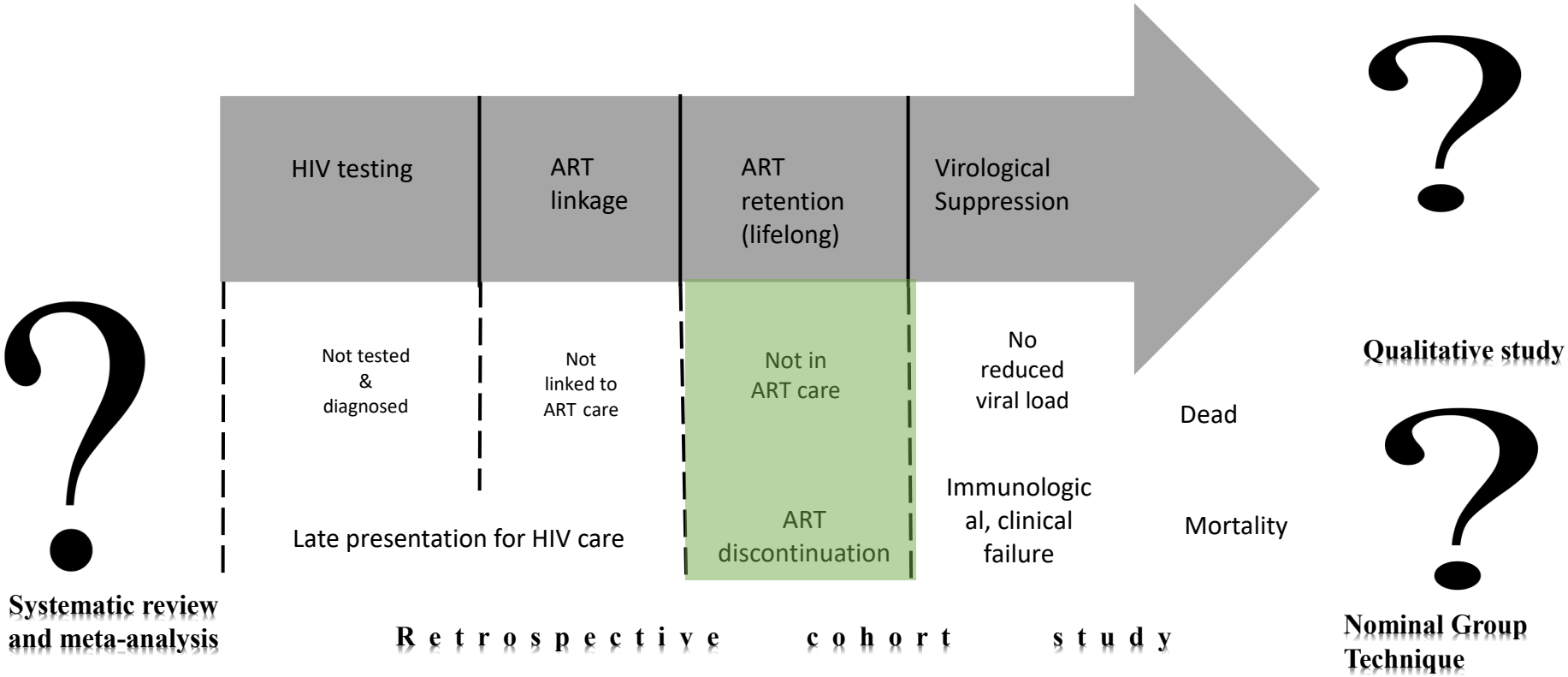

Figure 5-3: HIV care continuum– Discontinuation from antiretroviral therapy in Southwest Ethiopia[20]

[20] This figure needs to be viewed in colour.

5.4.1 Introduction

This sub-section presents the HCC stage that occurs after LP, namely discontinuation of ART among children and adults (figure 5.3 shaded in green). As described in section 3.5.5 of Chapter three, discontinuation was defined as LTFU, defaulting or permanently stopping ART. This section 5.4 has been published in *PLOS ONE*[132], and the expanded version of the published paper (Annex 3.8) is presented in the present sub-section. The sub-section has four components. The first component presents the prevalence, trend and risk factors of ART discontinuation. The second component presents the predictors, and third component presents discussion of the major findings. Finally, the fourth component summarizes the sub-section and suggests the possible recommendations to reduce discontinuation of ART.

5.4.2 Prevalence and trend of ART discontinuation

In total, 64 (16.1%) of 399 children and 1090 (22.3%) of 4900 adults had discontinued. Most children who discontinued (84.4%) were '*defaulter'* and the remainder were LTFU. Similarly, 83% of adults who discontinued were '*defaulter'* followed by 13.3% LTFU and 3.6% *'total stoppage'*. Table 5.5 shows the annual numbers (trend) and overall outcome status of patients with HIV on ART in the cohort.

The trend of ART discontinuation in both children and adults showed a mixed pattern. For children, the magnitude of discontinuation remained consistent (1%–2%) except for the years 2007, 2010 and 2014 where it reached a peak (5%–6%). For adults, the proportion of discontinuation showed a decreasing trend from 2004 to 2007. However, from 2008 to 2011, the trend showed a sharp decline from 6% to 2% between 2008 and 2009, a sharp rise from 2% to 6% between 2009 and 2010, and a decline to 3% in 2011. In both age groups, the proportion of discontinuation has increased recently.

5.4.3 Predictors of ART discontinuation

Table 5.6 shows the predictors of ART discontinuation among children and adult patients with HIV from the analyses of multiple logistic regression. Of the children, patients with HIV who were aged 1–5 years old and presented late for HIV care were at higher risk of discontinuation than their comparator. Children between 1–<5 years old, compared with those under 1 year old, had lower risk (AOR=0.1, 95% CI: 0.02–0.7) of discontinuation. The risk of discontinuation increased among late presenters (AOR=4.8, 95% CI: 1.8–28.3) compared with early presenters.

Among adults, females, Tb/HIV co-infected, those who had developed immunologic failure and those who had never been tested for HIV before diagnosis were more likely to

discontinue treatment. ART discontinuation among females (AOR=2.1, 95% CI: 1.7–2.8) was twice as high as among males. The risk of ART discontinuation among patients co-infected Tb/HIV was 50% higher (AOR=1.5, 95% CI: 1.1–2.1) than for patients with HIV alone. Similarly, ART discontinuation in patients with HIV with no previous history of HIV testing before diagnosis was almost twice as high (AOR=1.8, 95% CI: 1.4–2.9) as in those patients who had been tested at least once. Finally, patients with HIV who developed immunologic failure were at double the risk of discontinuation (AOR=2.3, 95% CI: 1.9–8.2) than those with immunologic success. To address missing values, multiple imputations was carried out using five imputed data sets, and the model with pooled imputed values is reported in Table 5.6. With the exception of ART adherence and history of HIV testing before diagnosis, the results of multiple imputations and complete case analyses were similar.

Table 5-5: Annual number of patients with HIV on ART care and their outcomes, Southwest Ethiopia, 2003-15

Year	New enrollment A		Death B, n(%)		Discontinuation C, n(%)		Transferred out D, n(%)		Alive & on ART E, n(%)		Total in Cohort F	
	Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults
2003[a]	---	8	---	0 (0)	---	1 (13)	---	0 (0)	---	7 (88)	---	8
2004	---	62	---	1 (1)	---	7 (10)	---	1 (1)	---	60 (87)	---	69
2005	16	468	1 (6)	27 (5)	0 (0)	51 (10)	1 (6)	8 (2)	14 (88)	442 (84)	16	528
2006	68	905	3 (4)	63 (5)	2 (2)	88 (7)	0 (0)	71 (5)	77 (94)	1125 (84)	82	1347
2007	48	574	3 (2)	50 (3)	7 (6)	148 (9)	5 (4)	132 (8)	110 (88)	1369 (81)	125	1699
2008	59	496	4 (2)	41 (2)	7 (4)	105 (6)	4 (2)	93 (5)	154 (91)	1626 (87)	169	1865
2009	58	508	3 (1)	39 (2)	4 (2)	50 (2)	6 (3)	103 (5)	199 (94)	1942 (91)	212	2134
2010	29	452	3 (1)	20 (1)	13 (6)	139 (6)	7 (3)	74 (3)	205 (90)	2161(90)	228	2394
2011	41	420	3 (1)	26 (1)	5 (2)	88 (3)	12 (5)	100 (4)	226 (92)	2367 (92)	246	2581
2012	31	352	1 (0)	10 (0)	5 (2)	96 (4)	7 (3)	96 (4)	244 (95)	2517 (93)	257	2719
2013	24	300	3 (1)	14 (0)	5 (2)	112 (4)	5 (2)	102 (4)	255 (95)	2589 (92)	268	2817
2014	24	296	2 (1)	7 (0)	13 (5)	166 (6)	11 (4)	147 (5)	253 (91)	2565 (89)	279	2885
2015[a]	1	59	0 (0)	2 (0)	3 (1)	39 (1)	3 (1)	27 (1)	246 (98)[b]	2556 (97)[c]	254[b]	2624[c]
Overall			26 (6.6%)	300 (6.1%)	64 (16.1%)	1090 (22.3%)	61 (15.4%)	954 (19.5%)	246 (61.9%)	2517 (51.4%)	399[d]	4900[c]

[a] data from years 2003 and 2015 were not from complete number of months and were excluded while describing the outcomes by trend.

[b] excluded two patients with unknown outcome status to calculate the overall percentage for discontinuation.

[c] included 39 patients with unknown outcome status.

[d] included two patients with unknown outcome status and were not included in calculation of percentage for the overall proportion of all outcomes.

E = F-B-C-D; where F = E (previous year) + A (current year); B, n(%)= (B/F)*100%; C, n(%)= (C/F)*100%; D, n(%)= (D/F)*100%; E, n(%)= (E/F)*100%.

Table 5-6: Logistic regression findings of factors affecting for ART discontinuation in HIV infected patients, Southwest Ethiopia, 2003-15

Variable		Children				Adults				
		Discontinued, n (%)	Retained, n (%)	COR (95% CI)	AOR (95% CI)	Retained, n (%)	Discontinued, n (%)	COR (95%CI)	AOR (95%CI): Complete cases	AOR (95%CI): Multiple imputations
Age	<1	13 (5.3)	5 (7.8)	1	1	----	----	----	----	----
	1-<5	92 (37.4)	20 (31.3)	0.6 (0.2-1.8)	0.1 (0.02-0.7) [a]	----	----	----	----	----
	5-<15	141 (57.3)	39 (60.9)	0.7 (0.2-2.1)	0.3 (0.05-1.8)	----	----	----	----	----
	15-<25	----	----	----	----	380 (15.1)	174 (16)	1	1	
	25-<50	----	----	----	----	2004 (79.6)	855 (78.4)	0.9 (0.8-1.1)	0.8 (0.6-1.3)	0.9 (0.7-1.1)
	50+	----	----	----	----	133 (5.3)	61 (5.6)	0.9 (0.7-1.4)	0.9 (0.5-1.1.4)	0.8 (0.5-1.2)
	Median (range), years					30	30			
Sex	Male	40 (62.5)	127 (51.6)	1	----	482 (44.2)	903 (35.9)	1	1	1
	Female	24 (37.5)	119 (48.4)	1.6 (0.9-2.8)	----	608 (55.8)	1614 (64.1)	1.4 (1.2-1.6) [a]	2.1 (1.7-2.8) [a]	1.7 (1.4-2.0) [a]
Marital status	Never married	----	----	----	----	188 (25.5)	397 (25.1)	1	----	1
	Married	----	----	----	----	356 (48.2)	731 (46.2)	0.9 (0.8-1.2)	----	0.8 (0.4-1.6)
	Separated or divorced or widowed	----	----	----	----	194 (26.3)	453 (28.7)	1.1 (0.9-1.4)	----	1.1 (0.9-1.3)
Educational status	No education	----	----	----	----	169 (23)	315 (19.6)	1	1	1
	Primary	----	----	----	----	301 (40.9)	656 (40.8)	1.2 (0.9-1.4)	1.1 (0.6-8.3)	1.9 (0.5-5.4)
	Secondary and above	----	----	----	----	266 (36.1)	635 (39.5)	1.3(1.0-1.6)	1.8 (0.7-11.2)	1.7 (0.6-9.9)
Religion	Muslim	8 (21.6)	35 (28.5)	1	----	251 (34.2)	506 (31.7)	1	----	----
	Christian [b]	29 (78.4)	88 (71.5)	0.7 (0.3-1.7)	----	482 (65.8)	1091 (68.3)	1.1 (0.9-1.4)	----	----
Baseline WHO clinical stage	Stage 1 or 2	21 (67.7)	64 (44.8)	1	1	276 (43.5)	706 (48)	1	1	1
	Stage 3 or 4	10 (32.3)	79 (55.2)	3.3 (1.4-5.9) [a]	1.3 (0.2-1.9)	359 (56.5)	764 (52)	0.8 (0.7-1.0)	0.5 (0.2-1.8)	0.8 (0.3-2.1)
Baseline CD4 count	<200	20 (40.8)	104 (45.6)	1	----	731 (78.9)	1657 (69.9)	1	1	----
	>=200	29 (59.2)	124 (54.4)	1.2 (0.4-1.5)	----	195 (21.1)	712 (30.1)	1.6 (1.3-1.9) [a]	1.8 (0.9-2.1)	----
Clinical failure	No	23 (74.2)	111 (77.6)	1	----	495 (80.1)	1157 (81.4)	1	----	1
	Yes	8 (25.8)	32 (22.4)	0.8 (0.4-2.02)	----	123 (19.9)	265 (18.6)	0.9 (0.7-1.2)	----	0.8 (0.6-1.8)
Immunologic failure	No	47 (97.9)	185 (81.1)	1	----	726 (87.8)	1808 (77.8)	1	1	
	Yes	1 (2.1)	43 (18.9)	10.9 (1.5-81.4) [a]	----	101 (12.2)	516 (22.2)	2.05 (1.6-2.6)	2.3 (1.9-8.2) [a]	1.5 (1.3-1.9) [a]
Time to present HIV care	Early	8 (36.4)	25 (18.8)	1	1	459 (33.1)	184 (34.7)	1	1	----
	Late	14 (63.6)	108 (81.2)	2.5 (0.9-6.5)	4.8 (1.8-28.3) [a]	927 (66.9)	347 (65.3)	0.9 (0.7-1.3)	0.8 (0.6-1.8)	----
Tb/HIV co-infection	No	44 (68.8)	174 (70.2)	1	----	636 (71.7)	1305 (69)	1	1	
	Yes	20 (31.3)	72 (29.3)	0.9 (0.5-1.7)	----	251 (28.3)	587 (31)	1.1 (0.9-1.4)	1.5 (1.1-2.1) [a]	1.4 (1.2-1.8) [a]
ART adherence	Good	51 (79.7)	180 (73.2)	1	1	727 (82)	1520 (80.3)	1	1	1
	Fair or poor	13 (20.3)	66 (26.8)	1.4 (0.8-2.8)	1.3 (0.3-2.4)	160 (18)	372 (19.7)	1.1 (0.9-1.4)	1.3 (0.8-1.7)	1.6 (1.2-2.3) [a]
Cotrimoxazole adherence	Good	53 (82.8)	197 (80.4)	1	----	737 (83.1)	1541 (81.8)	1	----	----
	Fair or poor	11 (17.2)	48 (19.6)	1.2 (0.6-2.4)	----	148 (16.7)	342 (18.2)	1.1 (0.9-1.4)	----	----
Baseline functional status	Appropriate	16 (25)	101 (41.1)	1	----	----	----	----	----	----
	Delay/regression	48 (75)	145 (58.9)	0.5 (0.3-0.8)	----	----	----	----	----	----

Variable		Children				Adults				
		Discontinued, n (%)	Retained, n (%)	COR (95% CI)	AOR (95% CI)	Retained, n (%)	Discontinued, n (%)	COR (95%CI)	AOR (95%CI): Complete cases	AOR (95%CI): Multiple imputations
Baseline functional status	Working/ambulatory	----	----	----	----	32 (3.8)	82 (4.7)	1	1	----
	Bedridden	----	----	----	----	801 (96.2)	1664 (95.3)	0.8 (0.5-1.2)	0.9 (0.7-2.8)	----
History of HIV testing	Yes	64 (100)	246 (100)	----	----	643 (59)	1436 (57.1)	1	1	1
	No	0	0	----	----	447 (41)	1081 (42.9)	1.1 (0.9-1.2)	1.8 (1.4-2.9) [a]	1.1 (0.9-1.3)
HIV care enrolment period	enrolled in 2003-11	184 (74.8)	53 (82.8)	1	1	2059 (74.5)	951 (82.4)	1	1	----
	enrolled in 2012-15	62 (25.2)	11 (17.2)	0.6 (0.3-1.3)	0.7 (0.5-1.4)	704 (25.5)	203 (17.6)	0.6 (0.5-0.7)	0.9 (0.7-1.3)	----
ART shift	Yes	39 (100)	125 (96.2)	----	----	703 (100)	1599 (98.2)	----	----	----
	No	0	5 (3.8)	----	----	0	29 (1.8)	----	----	----

COR: crude odds ratio; AOR: adjusted odds ratio; CI: confidence interval; Tb/HIV: tuberculosis/HIV; ART: antiretroviral therapy; [a] statistically significant at P-value=0.05; [b] orthodox, protestant, catholic; ----= not applicable or not available

[a] statistically significant at p-value ≤0.05; [b] Orthodox, Protestant or Catholic

5.4.4 Discussion

Discontinuation from ART is a challenge to the success of ART treatment and virological suppression goals[4]. In the present study, the magnitude of ART discontinuation in adult and children patients with HIV was 22% and 16% respectively. The magnitude of discontinuation from ART among adults in the present study was higher than a finding from Tigray[80] and lower than a finding from Amhara in Ethiopia[81]. Furthermore, the magnitude was lower than findings from other studies in Africa, such as 51.1% in Guinea-Bissau[463], 28% in Nigeria[464], and 83% in a multi-site study in Republic of Congo, Cameron and Burundi[241]. Reasons for the dissimilarity could include differences in definitions[440] and implementing existing and innovative strategies for ART retention[465 466]. In addition, access and availability of ART care services[467] could also be additional reasons for differences in the magnitude of the problem.

Among children, the magnitude in the current study was higher than that found in South Africa (7.3%)[266], but lower than findings from Mozambique (39%)[88] and West Africa (21.2%)[468]. This magnitude was also lower than a finding from a study conducted in another part of the country (34%)[469]. The differences could be attributed to the strength of the program to prevent mother-to-child HIV transmission (PMTCT) [39] and the implementation of effective programs to improve treatment outcomes in children[465 466].

Even though a number of clinic-based programs have been implemented, the present study shows that the number of patients with HIV who discontinued HIV care was significant and the trend had increased recently. Therefore, consideration must be given to designing community-based strategies that involve patients with HIV[470]. For example, community-based ART distribution was found to be very effective in retaining patients with HIV[57 471]. Improving adherence strategies such as adherence clubs[472] and home-based nursing interventions[473] could also enhance regular ART retention in care.

The present study revealed the following to be predictors for ART discontinuation among adult patients with HIV: being female, Tb/HIV co-infected, having immunologic failure and no history of HIV testing before diagnosis. Studies reported contradictory findings with regard to the association between gender and ART discontinuation. There were studies that showed no difference between males and females[84 474], while other studies showed that males were at higher risk than females[475-477], and this and other studies revealed that females were at higher risk than males[232 251]. Evidence shows that there is higher perception of HIV related stigma[120 122 252 253] and usage of traditional healers[124 126 478] in females than males, and both these barriers, stigma[120-122] and traditional healing[121 124 126], have been regularly observed to

interrupt ART uptake. Patients with HIV who developed immunologic failure were more likely to discontinue treatment than those who had immunologic success. This finding was similar to other work [479 480]. It is documented that patients with HIV who develop immunologic failure are highly vulnerable to several comorbidities and this hastens the progression to advanced stages of HIV and AIDS[258 260], which may interrupt the consistent use of ART[259].

ART discontinuation was found to be higher in Tb/HIV co-infected patients than their comparator, and this finding is consistent with other studies[243 257 481]. This finding was not surprising because the intimate and complex linkage of both diseases leads to a rapid progression to AIDS and thereby makes it difficult for patients to maintain regular ART intake[261]. The effect of pill burden from both diseases could be another reason for patients with Tb/HIV not to continue their treatment. Additionally, patients with Tb/HIV face double stigma and this could contribute to ART discontinuation. Given that Tb is a prevalent disease and the major cause of mortality in patients with HIV, it is necessary to give special attention to patients co-infected with Tb/HIV[4]. Patients with HIV who had never been tested for HIV before diagnosis were more likely to discontinue than those patients who had ever been tested. This could be associated with fear of HIV diagnosis, poor awareness about HIV testing facilities[54 70] and feeling healthy[169]. Evidence shows that being screened repeatedly for HIV provides an opportunity to familiarize oneself with HIV care services and builds trust in health professionals[482]. A multi-centre qualitative study in Zimbabwe, Malawi, Tanzania, South Africa, Kenya and Uganda also revealed that repeat testing has positive implications for patients remaining in care[482].

Despite the above data, the present study did not conduct a tracing study or identify outcome status of patients who discontinued. In Ethiopia, two previous studies showed that more than half of lost patients subsequently died[70 106]. Another study from Kenya also reported that 9% of transferred out and 40–86% of lost patients did not re-engage with care[105].

5.4.5 Conclusions and recommendations

In conclusion, ART discontinuation was recorded in one in six children and one in five adult patients with HIV on ART. Children who discontinued were more likely to be young and with delayed presentation. In addition, adults who discontinued were more likely to be female, co-infected with Tb, had developed immunologic failure and with no previous history of HIV testing.

To ensure regular ART uptake, the focus of strategies targeting ART discontinuation must be on the above groups of patients with HIV. Previous studies have recommended a new

program called linkage-case-management[483] which was found to be effective in enhancing ART retention in care. Additionally, strengthening adherence strategies also helps patients with HIV to improve their immunologic success thereby facilitating regular uptake of ART. It would be interesting to encourage repeated HIV testing[346 484] not only to improve patients' retention in care through familiarity of HIV services but also through early diagnosis, another facilitator for ART retention.

5.5 HIV related immunologic failure

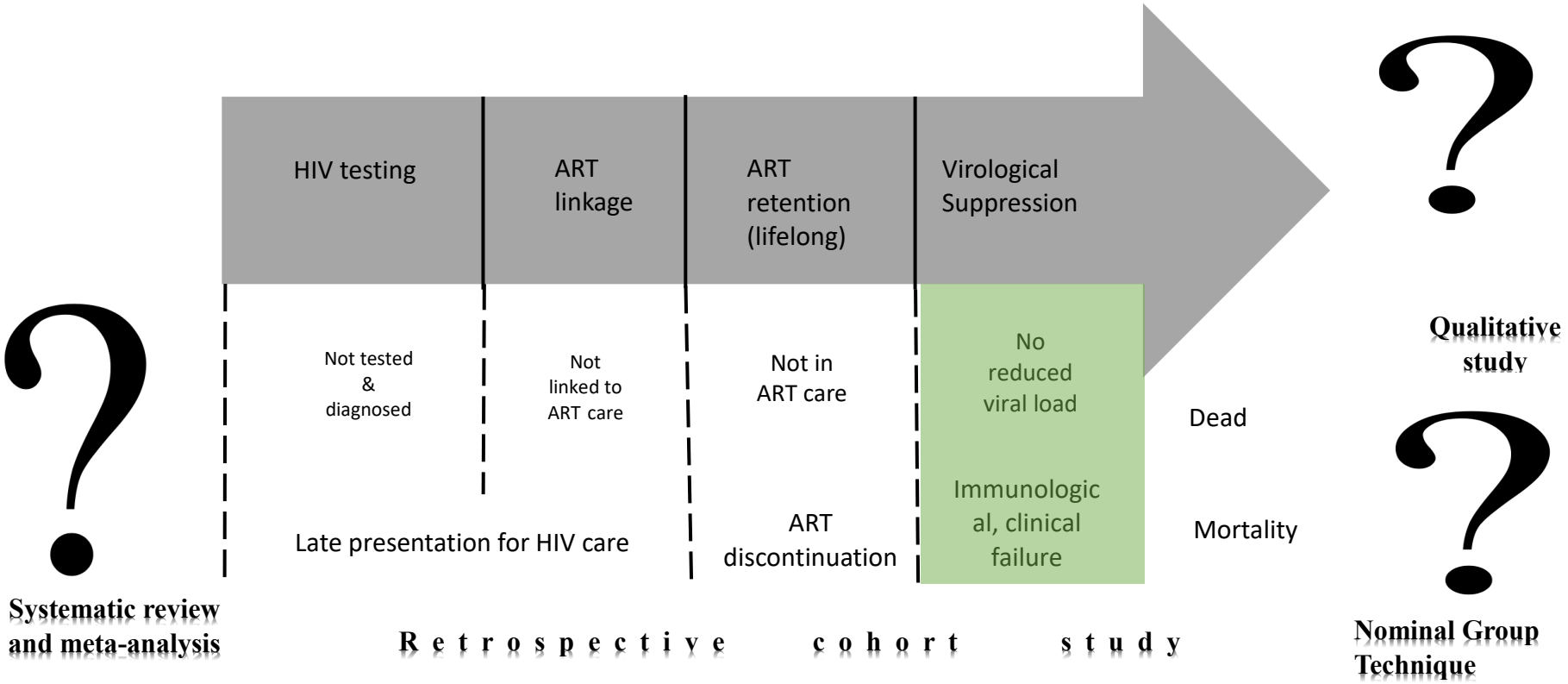

Figure 5-4: HIV care continuum– Immunologic failure among patients with HIV in Southwest Ethiopia[21]

[21] This figure needs to be viewed in colour.

5.5.1 Introduction

This sub-section presents the final component of HCC, namely immunologic failure among children and adult patients with HIV (figure 5.4 shaded in green). As described in section 3.5.5 of Chapter three, immunologic failure was defined if CD4 count after six months fell to baseline level (or below) or was persistently below 100 cells/mm^3 after two consecutive follow-up measurements. This section 5.5 has been published in *BMJ Open*[133] (Annex 3.9), and the extended version of the paper is presented here. It has four parts. Part one describes the magnitude and outcomes of immunologic failure, and part two presents the predictors of immunologic failure. The discussion of magnitude, outcomes and predictors of immunologic failure is presented in part three. Lastly, part four concludes the sub-section and describes some recommendations.

5.5.2 Magnitude and outcomes of immunologic failure

Of the 399 children enrolled on ART between 2004 and 2015, 14 children received ART for less than six months, and CD4 counts at baseline and six months were not recorded for 37 children. A total of 348 children were included in the analysis, of which 53 (15.2%) had developed immunologic failure. Of these, 7 (13.2%), 9 (16.9%) and 37 (69.8%) children were followed for 6-<12, 12-<24 and ≥24 months respectively. Among the children with immunologic failure, one child died, one child discontinued, seven children were transferred out and 43 (81.1%) were alive and on ART (Figure 5.5). Five children were switched to second-line ART drugs.

Eighty percent (3939/4900) of adult patients with HIV who enrolled on ART in 2003–15 received ART for more than six months, and CD4 counts for these patients were recorded at least at baseline and after six months, the eligibility criteria for immunologic failure. A total of 961 patients with HIV on ART were excluded from the analysis of immunologic failure: 217 patients received ART for less than six months, and 744 patients had no record of CD4 level at baseline and six months. Of the 3939, 775 (19.7%) patients developed immunologic failure. Of these, 83 (10.7%) patients were followed for 6-<12 months, 88 (11.3%) patients were followed for 12-<24 months and 604 (77.9%) patients were followed for ≥24 months. Two-thirds (516, 66.6%) of the patients who developed immunologic failure were alive and on ART, 33 (4.3%) had died, 101 (13%) had discontinued, 118 (15.2%) had been transferred to other clinics and 7 (0.9%) had unknown outcome status (Figure 5.5). Twenty-nine (0.9%) patients were changed onto second-line ART drugs.

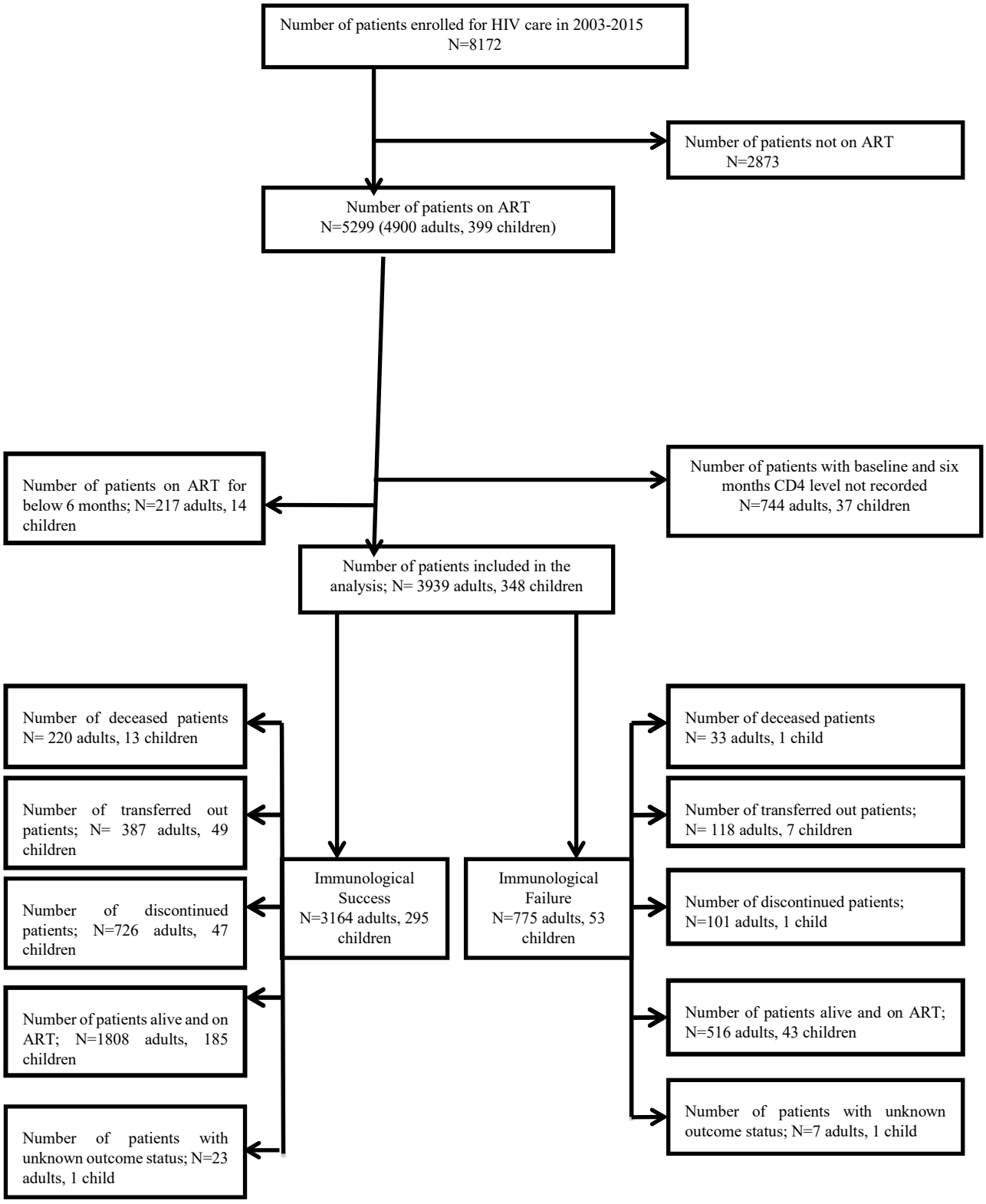

Figure 5-5: Immunological status and their outcomes of HIV-infected patients in Jimma University Teaching Hospital in Southwest Ethiopia, 2003-2015

5.5.3 Predictors of immunologic failure

The predictors of immunologic failure among adults and children are presented in Table 5.7. Among children, being female, LP, poor or fair cotrimoxazole adherence and having clinical failure were the predictors for immunologic failure. Females had higher risk (AOR=4.8, 95% CI: 1.7–13.2) of immunologic failure than their male comparator. Children who presented late for HIV care had a greater risk of immunologic failure (AOR=10.5, 95% CI: 1.4–79.5) than early presenters. The risk of immunologic failure among children who developed clinical failure was two times (AOR=2.1, 95% CI: 1.1–5.8) higher than in children without clinical failure. Immunologic failure among children was also higher in children with poor or fair cotrimoxazole adherence.

The complete case analysis shows that adult patients with HIV who were aged between 25<50 years, females, late presenters to HIV care, those with low baseline CD4 count or who had been previously tested for HIV before diagnosis had higher risk of immunologic failure than their comparator. The risk of immunologic failure in older adult patients with HIV (25-<50 years) was 50% (AOR=1.5, 95% CI: 1.2–2.4) higher than in young adults (15<25 years). Females had double (AOR=1.8, 95% CI: 1.3–1.9) the risk of immunologic failure than males. Late presenters were at twice the risk (AOR=2.2, 95% CI: 1.6–2.7) of immunologic failure than early presenters. The risk of immunologic failure among patients with HIV with baseline CD4 counts of <200 cells/mm^3 was very high (AOR=5.5, 95% CI: 4.1–7.4) when compared with those who had 200 cells/mm^3 and above. Finally, patients who were not screened for HIV before diagnosis were 30% less likely (AOR=0.7, 95% CI: 0.5–0.9) to have immunologic failure than those who were screened before diagnosis at least once.

With the exception of baseline CD4 count, variables that were statistically significant in the complete case analysis were also found to be statistically significant in the multiple imputations analysis. Furthermore, Tb/HIV co-infection was found to have a statistically significant difference in the multiple imputations analysis unlike in the complete case analysis.

Table 5-7: Logistic regression findings of factors affecting immunologic failure in HIV patients, 2003-15

Variable		Children				Adults				
		IS*, n (%)	IF*, n (%)	COR (95% CI)	AOR (95% CI)	IS, n (%)	IF, n (%)	COR (95% CI)	AOR (95% CI): Complete cases	AOR (95% CI): Multiple imputations
Age	<1	11 (3.7)	5 (9.4)	1	1	----	----	----	----	----
	1-<5	96 (32.5)	24 (45.3)	0.6 (0.2-1.7)	0.7 (0.5-1.9)	----	----	----	----	----
	5-<15	188 (63.7)	24 (45.3)	0.3 (0.08-0.9)	0.4 (0.1-0.8)	----	----	----	----	----
	15-<25	----	----	----	----	488 (15.4)	74 (9.5)	1	1	1
	25-<50	----	----	----	----	2560 (80.9)	674 (87)	1.7 (1.3-2.3) [a]	1.5 (1.2-2.4) [a]	1.8 (1.7-2.1) [a]
	50+	----	----	----	----	116 (3.7)	27 (3.5)	1.5 (0.9-2.5)	1.3 (0.7-2.9)	2.3 (1.9-2.7) [a]
	Median (range), years									
Sex	Male	162 (54.9)	18 (34)	1	1	1488 (47)	274 (35.4)	1	1	1
	Female	133 (45.1)	35 (66)	2.4 (1.3-4.4) [a]	4.8 (1.7-13.2) [a]	1676 (53)	501 (64.6)	1.6 (1.4-1.9) [a]	1.8 (1.3-1.9) [a]	1.7 (1.6-1.8) [a]
Marital status	Never married	----	----	----	----	632 (23.3)	152 (21.7)	1	----	1
	Married	----	----	----	----	1316 (48.5)	357 (51.1)	1.1 (0.9-1.4)	----	1.04 (0.0-1.1)
	Separated or divorced or widowed	----	----	----	----	766 (28.2)	190 (27.2)	1.03 (0.8-1.3)	----	1.9 (0.7-2.1)
Educational status	No education	----	----	----	----	559 (20.5)	145 (20.8)	1	1	1
	Primary	----	----	----	----	1089 (39.9)	287 (41.1)	1.01 (0.8-1.3)	1.3 (0.7-2.9)	1.03 (0.9-1.1)
	Secondary and above	----	----	----	----	1084 (39.7)	266 (38.1)	0.9 (0.8 -1.2)	0.7 (0.4-3.7)	0.9 (0.8-1.1)
Religion	Muslim	32 (26)	7 (20)	1	----	871 (32)	239 (34.5)	1	----	1
	Christian [b]	91 (74)	28 (80)	1.4 (0.6-3.5)	----	1849 (68)	453 (65.5)	0.9 (0.8-1.06)	----	0.8 (0.7-1.9)
Baseline WHO clinical stage	Stage 1 or 2	79 (50)	11 (34.4)	1	1	842 (45.1)	216 (46.6)	1	1	----
	Stage 3 or 4	79 (50)	21 (65.6)	1.9 (0.9-4.2)	1.7 (0.8-3.9)	1027 (54.9)	248 (53.4)	0.9 (0.8-1.2)	1.7 (0.8-3.9)	----
Baseline CD4 count	>=200 cells/ul	148 (50.2)	8 (15.1)	----	----	2558 (80.8)	350 (45.2)	1	1	1
	<200 cells/ul	147 (49.8)	45 (84.9)	----	----	606 (19.2)	425 (54.8)	5.1 (4.3-6.06) [a]	5.5 (4.1-7.4) [a]	1.8 (0.9-3.01)
Clinical failure	No	126 (81.3)	22 (68.8)	1	1	1493 (81.3)	352 (80.5)	1	1	1
	Yes	29 (18.7)	10 (31.3)	1.9 (0.8-4.6)	2.1 (1.1-5.8) [a]	343 (18.7)	85 (19.5)	1.1 (0.8-1.4)	1.3 (0.9-1.8)	2.8 (0.7-4.9)
Time to present HIV care	Early	40 (25.3)	1 (3.1)	1	1	682 (36.5)	99 (21.3)	1	1	1
	Late	118 (74.7)	31 (96.9)	9.5 (2.4-69.5) [a]	10.5 (1.4-79.5) [a]	1187 (63.5)	365 (78.7)	2.1 (1.7-2.7) [a]	2.2 (1.6-2.7) [a]	1.1 (1.01-1.2) [a]
Tb/HIV co-infection	No	203 (68.8)	37 (69.8)	1	1	2229 (70.4)	536 (69.2)	1	1	1
	Yes	92 (31.2)	16 (30.2)	0.9 (0.5-1.8)	0.4 (0.3-2.1)	935 (29.6)	239 (30.8)	1.06 (0.9-1.3)	1.8 (0.7-4.9)	1.08 (1.01-1.2) [a]
ART adherence	Good	231 (78.3)	44 (83)	1	1	2595 (82)	648 (83.6)	1	----	1
	Fair or poor	64 (21.7)	9 (17)	0.7(0.3-1.6)	0.09 (0.01-1.9)	569 (18)	127 (16.4)	0.9 (0.7-1.1)	----	0.9 (0.8-1.9)
Cotrimoxazole adherence	Good	231 (78.3)	39 (73.6)	1	1	2632 (83.5)	639 (82.5)	1	----	----
	Fair or poor	64 (21.7)	14 (26.4)	1.3 (0.7-22.5)	10.7 (1.9-58.3) [a]	521 (16.5)	136 (17.5)	0.9 (0.8-1.2)	----	----
Baseline functional status	Appropriate	114 (38.6)	29 (54.7)	1	1	----	----	----	----	----
	Delay/regression	181 (61.4)	24 (45.3)	1.8 (0.6-2.9)	1.9 (0.7-3.1)	----	----	----	----	----
Baseline functional status	Working/ambulatory	----	----	----	----	1992 (68.1)	549 (74.7)	1	1	----
	Bedridden	----	----	----	----	933 (31.9)	186 (25.3)	0.7 (0.6-0.9) [a]	0.8 (0.6-1.02)	----
History of HIV testing	Yes	295 (100)	53 (100)	----	----	1793 (56.7)	468 (60.4)	1	1	1
	No	0	0	----	----	1371 (43.3)	307 (39.6)	0.9 (0.7-1.0)	0.7 (0.5-0.9) [a]	0.8 (0.7-0.9) [a]
	enrolled in 2003-11	250 (84.7)	38 (71.7)	1	1	2537 (80.2)	621 (50.1)	1	----	----

Variable		Children				Adults				
		IS*, n (%)	**IF*, n (%)**	**COR (95% CI)**	**AOR (95% CI)**	**IS, n (%)**	**IF, n (%)**	**COR (95% CI)**	**AOR (95% CI): Complete cases**	**AOR (95% CI): Multiple imputations**
HIV care enrolment period	enrolled in 2012-15	45 (15.3)	15 (28.3)	2.2 (1.1-4.3)	1.8 (0.8-3.8)	627 (19.8)	154 (19.9)	1.003 (0.8-1.2)	----	----
ART shift	Yes	159 (97.5)	25 (96.2)	1	----	2086 (98.9)	500 (99.2)	1	----	1
	No	4 (2.5)	1 (3.8)	1.6 (0.2-14.8)	----	24 (1.1)	4 (0.8)	0.7 (0.2-2.01)	----	0.8 (0.6-1.03)

IS= immunologic success; IF= immunologic failure; COR: crude odds ratio; AOR: adjusted odds ratio; CI: confidence interval; Tb/HIV: tuberculosis/HIV; ART: antiretroviral therapy; [a] statistically significant at P-value=0.05; [b] orthodox, protestant, catholic; ---- = not applicable or not available

[a] statistically significant at p-value ≤0.05; [b] Orthodox, Protestant or Catholic; * the category subtotal values may vary due to missing values

5.5.4 Discussion

The present study adds information on the magnitude, trend and predictors of immunologic failure to the global literature. The magnitude of immunologic failure among children was 15% and this finding is higher than the findings of studies conducted in other parts of the nation, where it was reported to be 6.7%[284] and 11.5%[100]. The findings show the magnitude is significant particularly for this age group. The following reasons could partly explain this: i) children depend almost entirely on their caregivers to give them ART consistently and this makes it difficult for children to retain and gain their immunity[49]; ii) if the ART schedules of children and their caregivers are not aligned, the caregivers may not visit the ART clinic again to collect drugs for the children which could lead to children not being able to take their medicines regularly, further exposing them to risk of immunologic failure[49]; and iii) palatability, size, storage, and formulations of medications could affect treatment adherence and immunologic failure[485]. In this study, children who had poor or fair adherence to cotrimoxazole were more likely to develop immunologic failure than those who had good adherence. Furthermore, children who presented late and developed clinical failure had higher risk of immunologic failure than their comparator.

Consistent with the work of Melsew and colleagues[486], the present study reported that one in five adult patients with HIV developed immunologic failure. However, this finding is higher compared with findings from other parts of the country (6.7–17.6%)[92 487 488]. This failure could lead us to hypothesize that patients who come from or attend their care in settings with high prevalence of HIV could be more at risk of immunologic failure than patients in settings with low HIV prevalence. The fact that immunologic failure was common in areas with high HIV prevalence could be explained by the following reasons. First, there may be different strains of the virus among patients with HIV in HIV prevalent settings and this may reduce the immunologic benefit obtained from ART[489 490]. Second, the prevalence of drug resistance related to ART is higher in high HIV prevalence settings compared with settings with low HIV prevalence, and this reduces the immunologic benefit of ART[491]. Thirdly, the level of awareness about HIV and its care may be low in patients with HIV who come from high HIV prevalence areas[492], and this could have a negative influence on gaining the immunologic benefit[10]. The EDHS 2016 revealed that women in urban settings such as Addis Ababa have increased HIV knowledge compared with women in rural areas and this may be reflected in reduced levels of immunologic failure in their children [10].

The present study revealed that most patients (78%) with immunologic failure attended ART care for more than two years. Similar to other studies, this implies that the risk of immunologic failure increases as the follow-up time increases[46 486]. When patients are on ART for long periods, challenges such as drug resistance, drug–drug interaction and non-compliance may occur, and all these may diminish the immunologic gain from ART[46 47]. Plasma HIV-1 RNA is not available for routine viral load monitoring in resource limited countries such as Ethiopia[285].

In the present study, immunologic failure was linked with older age, being female, LP, low baseline CD4 counts and history of HIV testing before diagnosis. It was shown that older adults (25-<50 years) were at higher risk of developing immunologic failure than young adults (15-<25 years) and this is consistent with studies conducted elsewhere[217 288]. This could be associated with LP because 65% of patients with HIV aged 25-<50 years old presented late compared with 26% of patients aged 15-<25 years (Table 5.3). It was also shown that immunologic failure was one of the outcomes of LP in the present study (Table 5.2). Furthermore, age related immunologic impairment may be another reason because thymic function and other regenerative mechanisms are reduced during older age[288].

The role a child's sex in immunologic failure was found to be intriguing. Some studies reported no association[299 493 494], others indicated that female children had a better immunologic response[495 496], and the current study revealed that females were at a greater risk of immunologic failure. It has been noted that the reduction rate of viral counts for females compared with male children over time is greater even if they have higher viral loads[299]. However, the role of a child's sex in immunologic failure should be explored in depth. Similarly, among adults, the risk of immunologic failure was higher in females than in males in the present study, unlike the findings of most other studies [296-298] although a study from Africa supported the finding[98]. This could be associated with LP and ART discontinuation because females were more likely than males to present late to HIV care (Table 5.3) and discontinue ART (Table 5.6) [478].

Immunologic failure was also associated with low baseline CD4 count and delayed HIV care presentation, a finding consistent with others[98 292 497 498]. As described above, patients with HIV who presented at an advanced stage were at a high risk of OIs and multiple comorbidities and these challenges the immunologic success of ART[258 259]. Finally, it is surprising that patients with HIV who had a previous history of HIV testing before diagnosis had less risk of immunologic failure than those who had not ever been tested before diagnosis. This needs further exploration, but it might be explained by the fact that those who had been tested before

diagnosis and found to be HIV negative could feel healthy. These people may not be tested until they become seriously ill, which could limit the immunologic benefit from treatment[259]. Although significant numbers of patients with HIV had developed immunologic and clinical failure, very few (5 children, 29 adults) patients switched their regimen to second-line ART drugs. This implies that most patients who developed treatment failure attributed to immunologic failure and clinical failure were not switched to second-line therapy. It has been shown that delayed ART regimen shift leads to drug resistance and challenges the long-term outcomes of patients with HIV receiving ART. However, this implication should be interpreted cautiously. Research has shown that immunologic and clinical failure are less sensitive and specific to treatment failure[275 499].

5.5.5 Conclusions and recommendations

To conclude, immunologic failure was found to be marginally higher (20%) in or near settings with high HIV prevalence than settings with low HIV prevalence in Ethiopia (7%–18%). The present study, however, replicated prior research on most of the predictors for immunologic failure: age, sex, time to present for HIV care, baseline CD4 count and history of HIV testing before diagnosis.

In addition to targeting the above groups, existing programs need to respond to gender disparity and increase gender equity in HIV care activities and services. To allow regular monitoring of virological suppression in patients on ART, access to plasma HIV viral load testing should be improved. Given that the HIV RNA plasma viral load testing is limited, GenXpert and other alternative options should be considered for HIV viral load testing[57]. For example, the GenXpert was found effective in other African countries.

The following recommendations could improve the immunologic response of a children: i) providing better education and support groups for caregivers[500] and using adherence aids[501]; ii) arranging same day appointments for caregivers and children[485]; iii) preparing palatable ARV formulations[49]; and iv) tracing defaulters and lost children[49].

5.6HIV related mortality

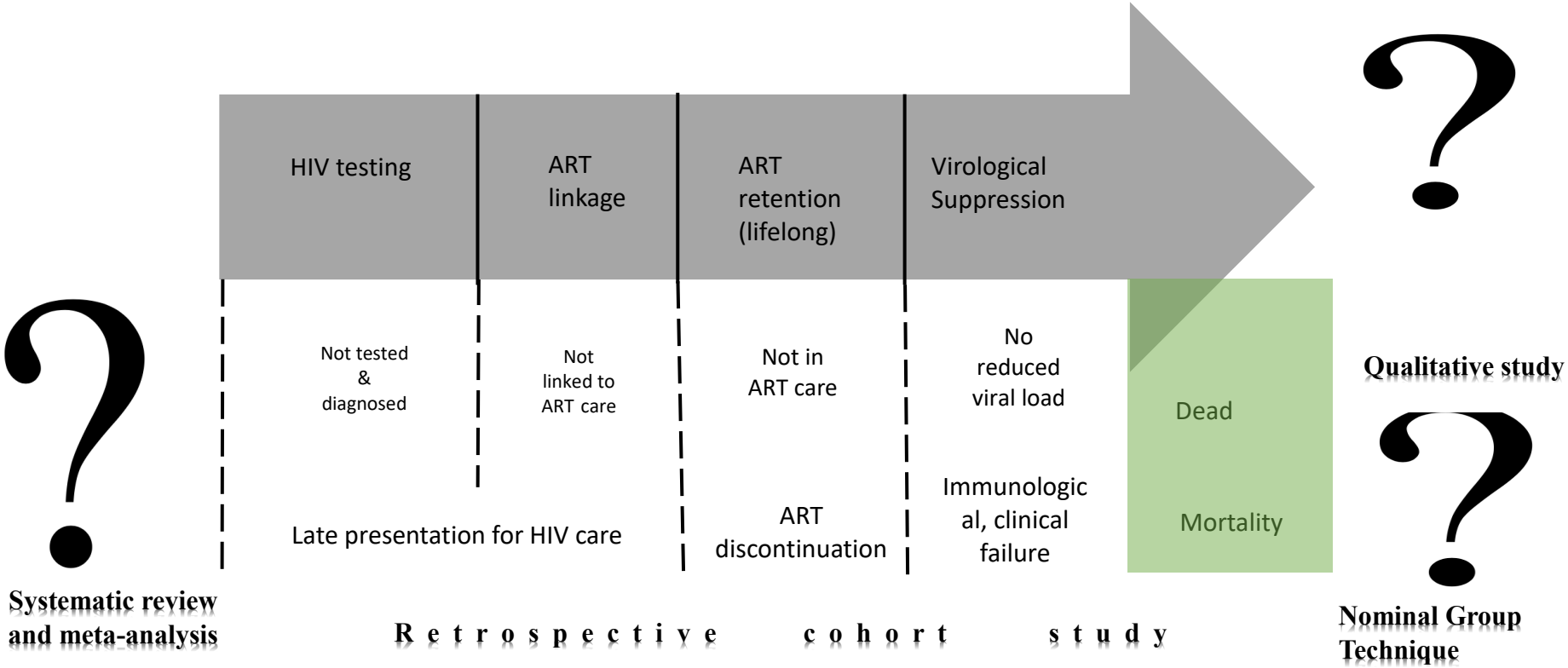

Figure 5-6: HIV care continuum– Mortality among patients with HIV on antiretroviral therapy in Southwest Ethiopia[22]

[22] This figure needs to be viewed in colour.

5.6.1 Introduction

This sub-section demonstrates HIV-related mortality among children and adults, shown in figure 5.6 shaded in green. Mortality was defined as the death of a person on ART due to any cause in the reporting period. The section has four parts. Part one presents the mortality rate in the cohort and part two presents predictors of HIV related mortality in adults. The third and fourth parts deal with discussion of the findings, and conclusions and recommendations. As this analysis has been published in *PLOS ONE*[134] (Annex 3.10), the present sub-section presents the extended version of the paper.

5.6.2 Cumulative incidence and incidence rate of mortality

Table 5.5 demonstrates the annual and overall mortality rate of patients with HIV in the cohort. About 6% (326/5299) of patients with HIV died in the period of 2003–15. The cumulative incidence in children was 6.5% (26/399) and that of adults was 6.1% (300/4900). Of the 326 patients who died, 220 (67.5%) died in the first six months of ART follow-up, 37 (11.3%) died between 6-<12 months, 32 (9.8%) died between 12-<24 months and 37 (11.3%) died in ≥24 months.

The extent of follow-up was 15,051 person-years observations, with an estimated survival time of 121.9 (95% CI: 120.3-–123.5) months. The overall incidence rate was 21.7 deaths per 1000 person-years observations. Stratified by age, the incidence rate among children was 22.2 deaths per 1000 person-years and that of adults 21.6 deaths per 1000 person-years. As shown in Table 5.5, the number of deaths peaked in 2006 and reduced in subsequent years. Log rank tests were used to identify the existence of significant differences in hazard by baseline CD4 count (p=0.007), immunologic failure (p=0.069), history of Tb/HIV co-infection (p=0.016) and baseline functional status (p=<0.001). The Kaplan–Meier analyses shown in Figures 5.7–5.10 revealed that there were statistically significant differences in the categories of baseline CD4 count, history of Tb/HIV co-infection and baseline functional status.

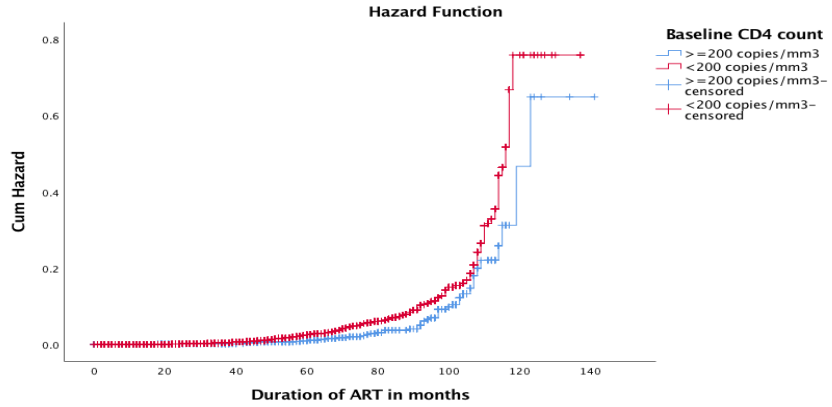

Figure 5-7: Kaplan-Meier plot of hazard function stratified according to baseline CD4 count among a cohort of ART patients, Southwest Ethiopia, 2016

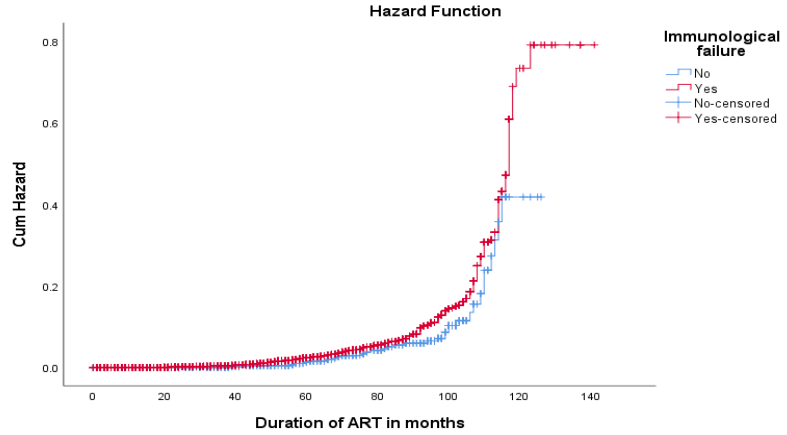

Figure 5-8: Kaplan-Meier plot of hazard function stratified according to immunologic failure among a cohort of ART patients, Southwest Ethiopia, 2016

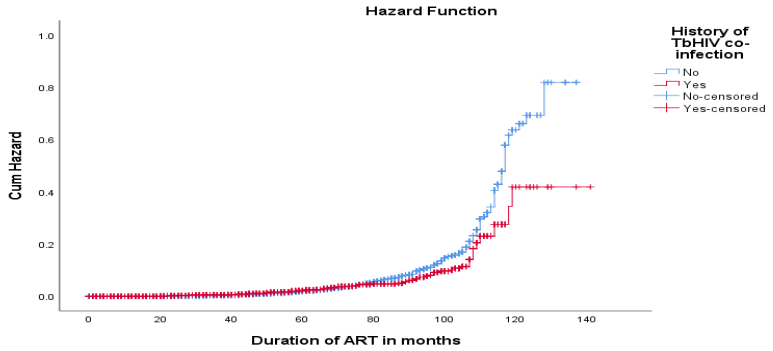

Figure 5-9: Kaplan-Meier plot of hazard function stratified according to history of Tb/HIV co-infection among a cohort of ART clients, Southwest Ethiopia, 2016

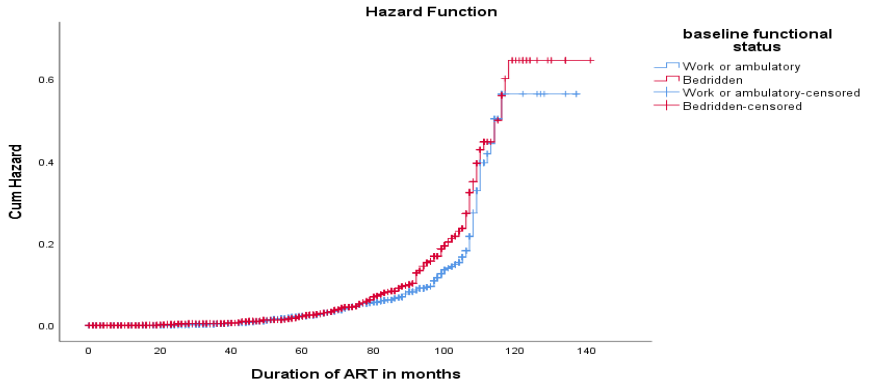

Figure 5-10: Kaplan-Meier plot of hazard function stratified according to functional status among a cohort of ART clients, Southwest Ethiopia, 2016

5.6.3 Predictors of mortality

Three models were produced using Cox regression analysis and are shown in Table 5.8. Model-I describes findings about factors that affect early HIV mortality. Model-II describes findings about factors that affect the overall mortality assuming discontinued patients as alive but deleted from the study. Finally, model-III describes the predictors of overall mortality assuming discontinued patients as dead.

Model-I presents the predictors of early HIV mortality among adult patients with HIV who attended ART follow-up for 24 months. Early mortality was higher among patients who had never been married, had bedridden functional status, low baseline CD4 count, advanced baseline WHO clinical stage, who developed immunologic failure, had fair or poor ART compliance and no history of HIV testing. The risk of early mortality was 50% less (AHR=0.5, 95% CI: 0.3–0.8) in separated, divorced, or widowed patients compared with not married patients. The risk of early mortality was 60% higher (AHR=1.6, 95% CI: 1.05–2.01) among patients with baseline CD4 count <200 cells/μL than their comparator. Similarly, the risk of early mortality was 50% higher (AHR=1.5, 95% CI: 1.05–2.5) among patients with baseline WHO stage 1 or 2 than patients with stage 3 or 4. The risk of early mortality in patients with immunologic failure was double (AHR=2.1, 95% CI: 1.4–3.01) compared with those with no immunologic failure. Interestingly, patients with HIV whose ART compliance was poor or fair were 40% (AHR=0.4, 95% CI: 0.2–0.7) less likely to die early than patients with good ART compliance. The risk of early mortality among bedridden patients was three times higher (AOR=2.9, 95% CI: 2.02–4.07) than for working or ambulatory patients. The risk of early mortality was also higher among patients with no history of HIV testing before diagnosis (AHR=2.7, 95% CI: 1.9–3.7) than those who had a history of HIV testing.

Model-II demonstrates the predictors of overall mortality using a real case assumption. This model assumes death as event. In this model, the predictors included being separated or widowed or divorced, having low baseline CD4 count, short ART duration, being bedridden and having no history of HIV testing before diagnosis. The risk of death among separated, divorced or widowed patients was 50% less (AHR=0.5, 95% CI: 0.2–0.9) than for patients who never married. The risk of death was double (AOR=2.01, 95% CI: 1.5–3.5) in patients with baseline CD4 count <200 cells/μL compared with those with baseline CD4 count 200 cells/μL and above. Longer ART duration compared with short duration was found to be a protective factor (AHR=0.08, 95% CI: 0.05–0.1) for overall mortality. Patients with bedridden functional status had an elevated risk of death (AHR=2.2, 95% CI: 1.4–3.9) compared with those with working or ambulatory status. Lastly, patients with HIV who had no history of HIV testing

before diagnosis were at a higher risk (AHR=2.7, 95% CI: 1.9–3.8) than those who had been tested.

Model-III shows the predictors of overall mortality using a worst-case assumption or intention-to-treat approach. This model assumes discontinuation and death as events. In this model, the predictors included being older adult, having immunologic failure, bedridden functional status and no history of HIV testing before diagnosis. The risk of death in older adults was 20% less than in younger adults (AHR= 0.8, 95% CI: 0.6–0.9). Compared with patients with HIV who did not develop immunologic failure, patients with immunologic failure had 40% higher risk (AHR= 1.4, 95% CI: 1.09–1.8) of death. The risk of death was also higher in patients with HIV who presented with bedridden baseline functional status (AHR=3.00, 95% CI: 2.3–4.0) than in the working or ambulatory patients. Lastly, the risk of death was two times higher (AHR=1.9, 95% CI: 1.6–2.4) in patients with no history of HIV testing before diagnosis than in those with a history of HIV testing.

Table 5-8: Predictors of HIV-associated mortality among patients with HIV in Southwest Ethiopia, 2003-15

Variable		Status* (Short-term follow up)		Model I: <24 months of follow-up (Short-term follow up)		Model II: Cumulative (0-140 months of follow-up) (Real case assumption)		Model III: Cumulative (0-140 months of follow-up) (Worst case assumption)	
		Censored, n(%)	Event, n(%)	CHR (95% CI)	AHR (95% CI)	CHR (95% CI)	AHR (95% CI)	CHR (95% CI)	AHR (95% CI)
Age	15-<25 years)	554 (95.2)	28 (4.8)	1	1	1	1	1	1
	25-<50 years	2859 (92)	249 (8)	0.9 (0.7-1.00)	0.8 (0.6-1.2)	1.3 (0.9-1.9)	1.3 (0.9-1.9)	0.8 (0.7-0.98) [a]	0.8 (0.6-0.9) [a]
	50+ years	194 (89.4)	23 (10.6)	1.2 (0.9-1.6)	1.1 (0.7-1.8)	2.5 (1.4-4.3) [a]	1.9 (0.4-3.3)	1.2 (0.9-1.6)	0.8 (0.4-1.5)
Sex	Male	1385 (91.2)	134 (8.8)	1	-------	1	-------	1	-------
	Female	2222 (93)	166 (7)	1.02 (0.9-1.1)	-------	1.06 (0.84-1.3)	-------	1.02 (0.9-1.1)	-------
Marital status	Never married	686 (90.7)	70 (9.3)	1	1	1	1	1	1
	Married	1503 (91)	149 (9)	1.4 (1.2-1.6) [a]	0.8 (0.5-1.1)	0.99 (0.7-1.3)	0.7 (0.5-1.05)	1.4 (1.2-1.6) [a]	1.3 (0.9-1.7)
	Other [b]	896 (93.6)	6.4	1.2 (1.06-1.5) [a]	0.5 (0.3-0.8) [a]	0.7 (0.5-1.02)	0.5 (0.2-0.9) [a]	1.2 (1.06-1.5) [a]	1.09 (0.9-1.5)
Educational status	No education	679 (94.4)	40 (5.6)	1	-------	1	-------	1	1
	Primary	1227 (91.8)	109 (8.2)	1.00 (0.8-1.1)	-------	1.6 (0.97-2.2)	-------	0.9(0.8-1.2)	1.00 (0.7-1.4)
	Secondary & above	1197 (89.9)	135 (10.1)	1.2 (1.01-1.4) [a]	-------	1.9 (0.8-2.7)	-------	1.2 (1.01-1.4) [a]	1.3 (0.9-1.8)
Religion	Muslim	1026 (92.3)	85 (7.7)	1	-------	1	-------	1	-------
	Christian [c]	2060 (91.3)	197 (8.7)	1.01 (0.9-1.1)	-------	1.2 (0.9-1.5)	-------	1.009 (0.9-1.1)	-------
Baseline WHO status	1 or 2	982 (91.5)	91 (8.5)	1	1	1	1	1	1
	3 or 4	1123 (90.6)	116 (9.4)	1.07 (0.9-1.2)	1.5 (1.05-2.01) [a]	1.0 (-1.4)	1.1 (0.6-1.5)	1.07 (0.9-1.2)	1.1 (0.9-1.2)
Baseline CD4 count	>=200 cells/µL	907 (95.3)	45 (4.7)	1	1	1	1	1	1
	<200 cells/µL	2388 (91.6)	218 (8.4)	1.3 (1.1-1.5) [a]	1.6 (1.05-2.5) [a]	1.6 (1.1-2.1) [a]	2.01 (1.5-3.5) [a]	1.3 (1.1-1.5) [a]	1.1 (1.07-1.3)
Clinical failure	No	1652 (91.6)	151 (8.4)	1	-------	1	-------	-------	-------
	Yes	388 (88.6)	50 (11.4)	0.8 (0.7-1.0)	-------	1.03 (0.7-1.4)	-------	-------	-------
Immunologic failure	No	617 (94.9)	33 (5.1)	1	1	1	1	1	1
	Yes	2534 (92)	220 (8)	1.5 (1.3-1.8) [a]	2.1 (1.4-3.01) [a]	1.4 (0.9-2.02)	1.2 (0.5-2.4)	1.5 (1.3-1.8) [a]	1.4 (1.09-1.8) [a]
HIV care presentation	Early	643 (90.8)	65 (9.2)	1	-------	1	-------	1	
	Late	1274 (91.2)	119 (8.5)	1.00 (0.8-1.1)	-------	1.01 (0.7-1.2)	-------	1.00 (0.8-1.1)	
ART duration	Short	-------	-------	-------	-------	1	1	-------	-------
	Long	-------	-------	-------	-------	0.07 (0.05-0.11) [a]	0.08 (0.05-0.1) [a]	-------	-------
Tb/HIV co-infection	No	2546 (91.5)	238 (8.5)	1	1	1	1	1	1
	Yes	1061 (94.5)	62 (5.5)	0.85 (0.75-0.97) [a]	0.7 (0.6-0.9)	0.7 (0.5-0.9) [a]	0.9 (0.6-1.3)	0.85 (0.76-0.97) [a]	1.1 (0.9-1.4)
ART adherence	Good	2938 (91.8)	264 (8.2)	1	1	1	-------	1	1
	Fair or poor	667 (94.9)	36 (5.1)	0.7 (0.6-0.8) [a]	0.4 (0.2-0.7) [a]	0.6 (0.5-0.8) [a]	-------	0.7 (0.6-0.8) [a]	0.9 (0.7-1.1.3)
Cotrimoxazole adherence	Good	2983 (91.7)	269 (8.3)	1	1	1	-------	1	1
	Fair or poor	609 (95.3)	30 (4.7)	0.8 (0.7-0.9) [a]	0.7 (0.4-1.09)	0.6 (0.4-0.9) [a]	-------	0.8 (0.7-0.9) [a]	0.8 (0.6-1.3)
Functional status	Working/Ambulatory	3103 (94.8)	171 (5.2)	1	1	1	1	1	1
	Bedridden	442 (81.1)	103 (18.9)	2.5 (2.3-2.8) [a]	2.9 (2.02-4.07) [a]	2.8 (2.1-3.6) [a]	2.2 (1.4-3.9) [a]	2.5 (2.3-2.9) [a]	3.00 (2.3-4.0) [a]
History of HIV testing	Yes	2079 (93.2)	152 (6.8)	1	1	1	1	1	1
	No	1528 (91.2)	148 (8.8)	1.9 (1.7-2.1) [a]	2.7 (1.9-3.7) [a]	2.9 (2.3-3.6) [a]	2.7 (1.9-3.8) [a]	1.9 (1.7-2.1) [a]	1.9 (1.6-2.4) [a]
HIV care enrollment	enrolled in 2003-11	2773 (76.9)	289 (96.3)	-------	-------	-------	-------	-------	-------
	enrolled in 2012-15	834 (23.1)	11 (3.7)	-------	-------	-------	-------	-------	-------
ART shift	Yes	2302 (91)	228 (9)	-------	-------	-------	-------	-------	-------
	No	29 (100)	0 (0)	-------	-------	-------	-------	-------	-------

[a] statistically significant at p-value ≤0.05; [b] Separated/divorced/widowed; [c] Orthodox, Protestant or Catholic; ------- = not applicable ; * the category subtotal values may vary due to missing values

5.6.4 Discussion

The introduction of ART has had a significant effect on reducing HIV mortality. Nevertheless, early HIV mortality is still an issue in developing countries such as Ethiopia. In the current study, a 6% cumulative incidence of HIV mortality was reported. This is lower than the findings from other parts of Ethiopia, such as 9% in Tigray[101], 10% in Southern Nations, Nationalities and Peoples Region (SNNPR)[313] and 41% in Amhara[62]. The difference could be associated with the level of LP, ART adherence and Tb/HIV co–infection. For example, the magnitude of delayed HIV care presentation in the current study is slightly lower than in Tigray (65% vs 69%)[65]. The level of fair or poor adherence in the present study is also lower, 20%, when compared with 26% in the SNNPR[502]. In addition, the prevalence of Tb/HIV co-infection in the present study is 28% compared with 44% in Amhara[503].

Consistent with the findings of others[70 313], the majority of deaths in the present study were within the first six months of ART commencement. This finding has an implication for the criteria for ART initiation. Until the end of 2016, Ethiopia has been using CD4 count and/or WHO clinical staging to initiate ART[138 139]. As of the end of 2016, the country launched the test and treat strategy in which diagnosed patients are able to start ART immediately. Nevertheless, this program has not been implemented in all HIV care facilities in the nation; therefore, it should be implemented throughout the country because the outcome is a striking improvement in mortality.

As to the trend of mortality, death rates peaked in 2005-07. This could be due to the following reasons. Firstly, ART was introduced without charge in 2005-06 in Ethiopia. However, there was no intensive preparation to monitor the service[70]. Secondly, the magnitude of LP was high during this period (70-74%) as shown in Table 5.2. Thirdly, the trust in and awareness of modern medicine was poor, and conversely high in traditional medicine which patients could consider as an alternative option[504 505]. Fourthly, the availability and accessibility of ART was poor during this period compared with recent times. Similar to other studies[506-508], the mortality related to HIV has markedly declined since 2008. In the present study, the overall mortality rate decreased by 40% in 2007, 85% in 2011 and 100% in 2014 since 2005. This could be because of the profound improvement in health infrastructure and expansion of ART programs to primary health care facilities by the government[24 141 509].

In this study, death rates were higher among patients with HIV who had low baseline CD4 count, advanced baseline WHO clinical stage, and who developed immunologic failure than among their counterparts. These findings supported other studies[70 227 230 313 510]. As has been described throughout the chapter, these groups of patients with HIV are vulnerable to

having an advanced stage of disease accompanied by multiple comorbidities, poor prognosis and subsequent death. Similarly, the present findings, similar to other findings, revealed that having no previous history of HIV testing before diagnosis [511] and being bedridden [70 313] were risk factors for early HIV mortality. As shown in Table 5.4, patients who had no previous history of HIV testing before diagnosis could be at a higher risk of LP, and this could accelerate rapid progress to AIDS and subsequent death[511]. Lastly, we need further studies to explore why those with fair or poor adherence are at a lower risk of death than those with good adherence to ART.

The present study should be interpreted with consideration of the following limitations. First, outcome status of 30 patients was unknown and this could slightly affect the cumulative incidence of HIV mortality in the study. Second, while analysing the real (model-II) and worst (model-III) case assumptions, deaths among discontinued patients may have been misclassified. Third, the survival functions may be underestimated in the intention-to-treat analysis because all patients who discontinued from treatment were assumed dead. Fourth, the findings from this analysis do not date back to 2015, the *'test and treat'* strategy period. Fifth, it was not possible to conduct an inferential statistical analysis to determine the predictors of HIV mortality among children because the number of children with the event was very small (26).

5.6.5 Conclusions and recommendations

In conclusion, the incidence of HIV mortality was 22 deaths per 1000 person-years, and most deaths (89%) occurred within two years of ART follow-up. Attrition attributed to death was associated with late presenters, patients with bedridden functional status, immunologic failure and those who do did not have HIV testing history before diagnosis.

Possible recommendations to address LP and immunologic failure were suggested in sub-sections 5.3.5 and 5.5.5 respectively. In the present study, the factors affecting early HIV mortality were also found to affect the overall mortality even in the intention-to-treat analysis where discontinuation from ART was assumed as death. This suggests that applying interventions targeting at the aforementioned predictors of mortality could reduce attrition attributed to death and discontinuation.

5.7 Performance on UNAIDS 90-90-90 treatment targets

5.7.1 Introduction

This sub-section deals with the performance of Southwest Ethiopia in achieving the UNAIDS 90-90-90 treatment targets, using surrogate measures. The cohort included 8172 patients with

HIV, of which 5299 patients had ever started ART. About 59% of these patients on ART were female. Of the 4900 adult patients with HIV on ART, 61% did not attend school or had only completed primary school. In this sub-section, the performance on the first, second and third criteria is presented in three parts. This subsection also includes discussion, conclusions and recommendations components. Figure 5.11 presents the Southwest Ethiopian continuum performance on the UNAIDS 90-90-90 targets in summary, and they are reported in detail as follows.

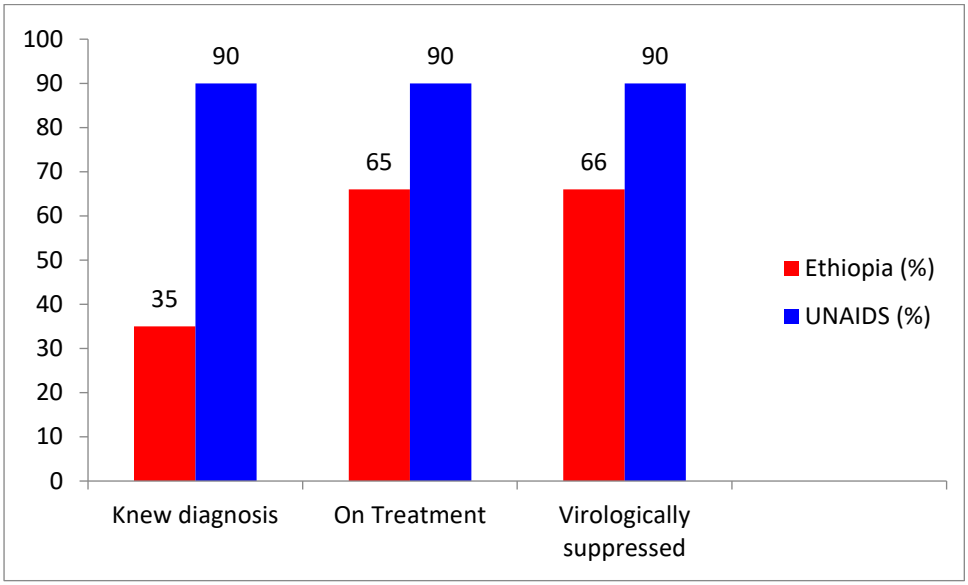

Figure 5-11: Jimma, Southwest Ethiopia cascade of the UNAIDS 90-90-90 targets, 2016[23]

5.7.2 UNAIDS target 1- HIV diagnosis

Target 1 of the UNAIDS 90-90-90 goals aims at diagnosing and knowing HIV status for 90% of people living with HIV. In order to assess target 1, the proportion of early HIV diagnosis was considered as a surrogate measure. Overall, 34.5% of patients were deemed to have received early HIV diagnosis, with females accounting for 35.7% of these. This indicates that 34.5% of patients knew their status in timely manner. When analysed by age, the prevalence of early HIV diagnosis was 43% among children and 33.3% among adults.

5.7.3 UNAIDS target 2- ART treatment

Target 2 of the UNAIDS 90-90-90 goals aims at providing sustainable HIV treatment for 90% of people diagnosed with HIV. In order to assess target 2, the proportion of patients with HIV on ART was considered as a surrogate measure. In the present study, 5299 (65%) of the 8172 patients with HIV received ART. Of those enrolled in ART, 1154 (21.9%) patients

[23] This bar graph needs to be viewed in colour.

discontinued from treatment (54.8% were female). Additionally, 1015 (19.3%) patients transferred out to other sites and of these, 54.6% were female. Totals of 228 (4%) and 688 (13%) patients had fair and poor adherence respectively. The significant rates of ART discontinuation, transferred out and ART non-adherence indicate that the treatment was not provided sustainably.

5.7.4 UNAIDS target 3- Virological suppression

Target 3 of the UNAIDS 90-90-90 goals aims at achieving virological suppression for 90% of the people on ART. In order to assess the performance of virological suppression, the proportion of immunologic, clinical and treatment success was used as a surrogate measure. In total, 80.7%, 80.3% and 65.8% of patients had immunologic, clinical and treatment success respectively. This shows that at least an estimated 65.8% of patients achieved viral suppression.

5.7.5 Discussion

This study provided important insights about the progress of the UNAIDS 90-90-90 targets in Jimma, southwest Ethiopia. There were high prevalence rates of delayed HIV diagnosis, ART discontinuation, non-adherence, and immunologic, clinical and treatment failure rates, implying low achievement of UNAIDS targets.

In the present study, over half (59%) of patients with HIV who received ART were female. This reflects a disproportionate HIV prevalence by gender, with females being more affected by the HIV epidemic than males. This is also supported by the current national data (2016) in which the prevalence of HIV infection in females was two times higher than in males (1.2% vs 0.6%) in Ethiopia[10]. Data from most African countries also supported this finding. For example, the female to male prevalence of HIV infection was 6.5% to 4.7% in Kenya in 2015[512] and 7.5% to 4.3% in Uganda in 2016[513]. In Southern Africa, young females were infected with HIV about 10 years earlier than their male comparator[514]. Despite significant efforts to implement female-based HIV programs and other approaches to halt the HIV epidemic in women, there are a multitude of barriers that increase women's vulnerability to HIV infection and its negative outcomes. These include socioeconomic, cultural, behavioural, structural and biological risks[514]. Therefore, the package of HIV prevention should also address these factors.

In terms of literacy status, 61% of adult patients with HIV who received ART were either not able to read and write or had only completed primary education and most of these were from rural settings. The fact that this group of patients with HIV, being women and having low education levels, were at a higher risk of the infection has important implications for equity

in HIV care. The gender gap remains high because of higher HIV infection rates in women, and access to HIV care services is mainly urban-based. It is therefore important to identify potential population groups who could be underserved by HIV care services.

High prevalence rates of delayed HIV diagnosis in the study implies that many people did not know their HIV status early. In the current study, only 35% of patients knew their status in timely manner, a very low performance compared with the UNAIDS target and the 45% performance in SSA[4]. Additionally, about 40% (3225/8172) of participants in the current study did not have a history of HIV testing. Therefore, strategies that were found effective elsewhere to enhance testing coverage[461 462 515] should be implemented in the country.

As reflected in the findings, only 65% of people diagnosed with HIV infection received ART. Even among those who received ART, 22% of patients had discontinued treatment, 19% of patients had been transferred out to other ART sites, and 17% of patients had fair or poor ART adherence. These figures indicate that a considerable number of patients were not receiving ART sustainably. This is lower than the target set by UNAIDS and findings from SSA[4] which reported 86% achievement. Hence, effective strategies linking patients to care, revised eligibility criteria for ART and retention of patients in care will help the transition from diagnosis to successful treatment[516 517]. For example, immediate or same day ART initiation after diagnosis was found to be an effective linking strategy in resource-limited settings[518]. For countries with civil unrest or other humanitarian disasters, MSF introduced a new approach called “runaway packs” that enabled individuals to collect sufficient medications for use over long periods of time[519].

Given that the access to Plasma HIV-1 RNA (viral load) monitoring is very limited and not available for routine services in Ethiopia, treatment successes (a combination of immunologic and clinical successes) was used as a surrogate marker for virological suppression. Accordingly, 66% of patients on ART showed treatment success reflecting that an estimated 66% of patients achieved viral suppression. This performance is also lower than the UNAIDS target, and the 76% achievement by SSA[4]. Previous studies[95 96 520] have shown that the CD4 count determines virological failure or suppression, while others have reported the reverse[275 499]. Strategies that heighten treatment effectiveness such as adherence clubs[108], treatment simplification to single dose combinations[521] and access to viral load testing[57] should also be considered.

Overall, the UNAIDS goal of 90-90-90 targets for diagnosis, treatment and viral suppression is ambitious when compared with the current performance respectively of 35-65-66 in this nation and the 2017 UNAIDS update that reported a 67-59-51 performance[111]. This

performance seems too low to meet the expected UNAIDS targets for Ethiopia during the prescribed timeframe to 2020. This performance underscores the need for concentrated efforts to implement innovative strategies and effective programs. In addition, it has been noted that the actual outcomes also depend on the commitment of funding organizations[522] and political stakeholders[191 461 522]. The lack of sufficient funds and human resources to deliver ART for people infected with HIV , together with rising ART drug resistance, will make achievement of the goal to halt AIDS by 2030 very difficult[3]. However, Ethiopia has committed to a plan that would use health extension workers as potential human resources to achieve 90-90-90 targets.

This retrospective cohort study has the following limitations. The real number of individuals infected with HIV or persons who have been diagnosed with HIV cannot be obtained from routinely collected programmatic data. Immunologic, clinical and treatment successes might not match actual viral suppression, as stated by Rutherford and colleagues[275], but this could be a valid surrogate for resource-constrained countries with high burdens of HIV where Plasma HIV-1 RNA testing is not routine, such as Jimma, Southwest Ethiopia. Measuring the achievement of UNAIDS 90-90-90 targets has its own limitations. Comparisons over time and space may be misleading because of the introduction of a variety of HIV programs such as "treat all", testing and linkage and *seek-test-treat-succeed* model[268]. Patients infected with HIV who present for care with lower viral counts are much less likely to commence ART than patients presenting with higher viral counts despite being eligible, and this may have led to selection bias[523]. The UNAIDS 90-90-90 targets was not assessed by some demographic variables such as gender and residence and this could be an area for further research.

5.7.6 Conclusions and recommendations

In summary, of the 90-90-90 goal set by the UNAIDS, Southwest Ethiopia achieved an estimated percentage of 35-65-66 meaning that an estimated 35% of patients knew their status in timely manner, 65% of diagnosed patients received treatment and 66% of patients on ART achieved viral suppression. A primary study is recommended to assess performance towards the UNAIDS 90-90-90 targets. Furthermore, the performance target has to be estimated for different populations such as military groups, commercial sex workers and other most at-risk population groups. Even though the report is based on surrogate measures, performance is very low and setting targeted interventions for each goal is mandatory. Solutions have been recommended in sub-sections 5.3.5, 5.4.5 and 5.5.5 to improve delayed HIV care, ART

retention and immunologic failure respectively. A further study is recommended to explore the best solutions for each treatment target.

5.8 Summary, strengths, limitations and implications

Over the 12-year period, it was observed that poor HCT outcomes were prevalent. Overall, 66% of patients with HIV presented late for HIV care, 22% of patients discontinued ART, 19% of patients developed immunologic failure and 6% of patients died from any cause. Southwest Ethiopia performed at 35-65-66 compared with the 90-90-90 UNAIDS treatment targets. Nevertheless, negative outcomes have decreased since ART has been provided free of charge and treatment decentralized to health centres in remote villages. This carries the strong implication that continuous improvement of ART decentralization would have favourable outcomes.

Patients with HIV who had low baseline CD4 count, presented late for HIV care, developed immunologic failure and had no past history of HIV screening before diagnosis were at a higher risk of negative HIV outcomes. Another particular concern is that LP, discontinuation from ART, and immunologic, clinical and treatment failures rates were higher for females, a finding that requires special attention at each stage of the HCC. The current program must acknowledge and respond to the gender disparity. In general, this shows that there are sub-groups of patients with HIV who require priority attention when designing and implementing HCT programs. When examining the association of gender and poor HIV treatment outcomes, no consistent finding was obtained, and this triggers a research question for further exploration.

The present study was a 12-year retrospective cohort study that assessed the whole HCC. Furthermore, the sample included children and adults in a large cohort (5299). The present study also reported an estimated performance on the UNAIDS 90-90-90 treatment targets by Southwest Ethiopia. In spite of the above strengths, the present study has several limitations. First, data were collected from a single referral hospital, a hospital that also caters for patients referred with advanced stages of HIV infection, and the findings may not be generalized to health centres or private clinics. Second, because of the retrospective nature of the design, some data were incomplete and this could cause bias in the precision of estimates, but this deficiency was managed using multiple imputation. Third, the exclusion of patients with unknown outcome from the analyses may lead to selection bias. Fourth, the relationships of some important variables such as HIV related stigma, traditional healing, mental illness and others with negative HIV care outcomes were not established. Fifth, this study is a retrospective

cohort which can establish an association but is unable to impute causality. Sixth, the wide confidence intervals in the inferential analysis of factors in children could be due to the small sample size. Seventh, as the percentage of CD4 was not available, CD4 count was used to measure immunologic failure for children aged under five years. There were studies which showed that, as CD4 count in children is high and variable, CD4 percentage is preferred for immunologic monitoring in children under five years old[524].

Evidence on the influence of gender on ART discontinuation from the cohort study provided mixed findings. Generally, the predictors of all outcomes reported in the present study were only elucidated from baseline clinical and non-clinical characteristics of individual patients with HIV. The findings implied that factors affecting these outcomes should be assessed beyond the individual level. Additionally, further exploration was recommended to illuminate possible solutions to improve each step of the continuum from multiple levels. Additional further studies were also recommended to explore the contribution of HIV related stigma and traditional healing to ART discontinuation. Based upon these findings, a qualitative study was conducted to explore barriers to and solutions for LP and ART attrition by interviewing patients with HIV, HIV care professionals, community advocates and program managers. The next chapter, Chapter six, presents the findings from the qualitative study.

Chapter 6

Qualitative study

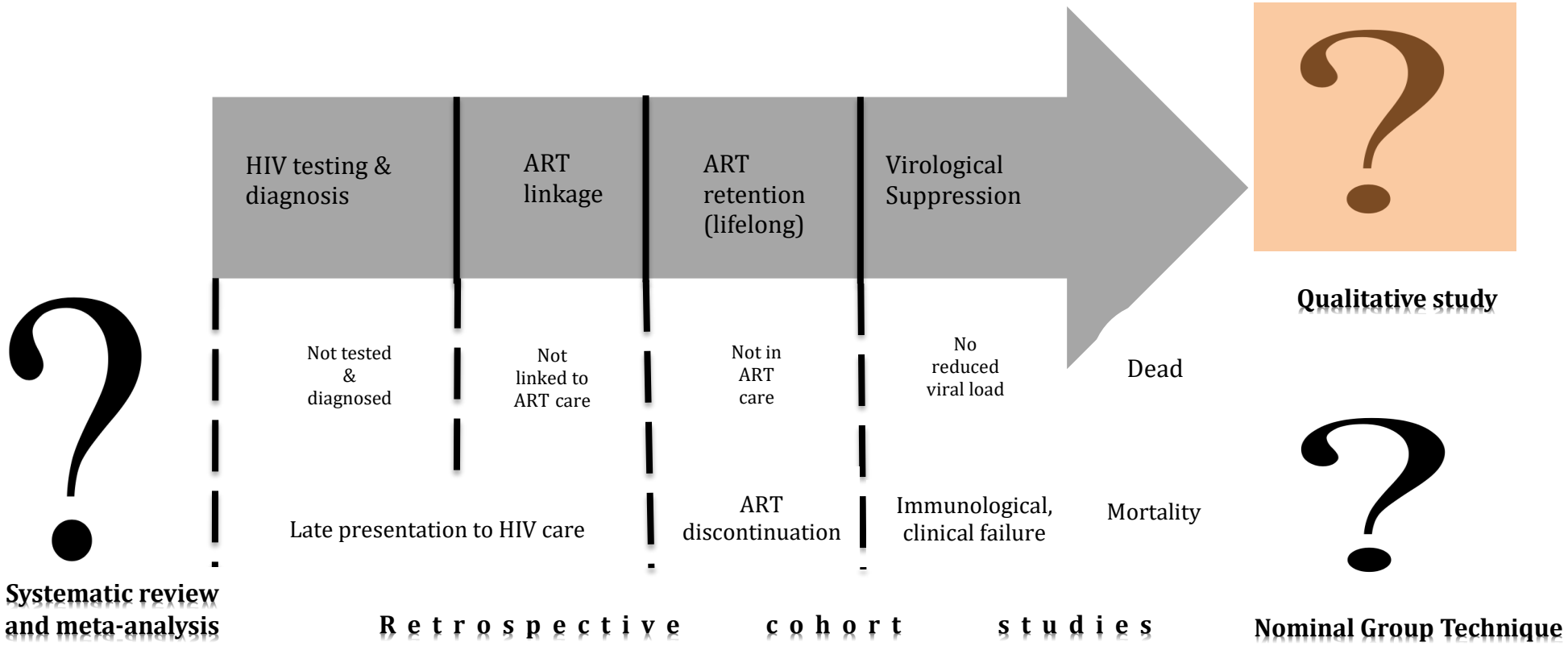

Figure 6-1: HIV Care Continuum- Qualitative study

6.1 Introduction

Chapter six presents the key findings from and discussion of the qualitative study in the PhD project, shown in Figure 6.1, shaded in green. The qualitative study explored the facilitators, barriers and solutions for HCT through in-depth interviews with 35 participants. Data were collected from multiple groups, comprising patients with HIV, health workers, community members and program managers. Nearly all interviewees from all groups showed similar opinions; hence, the reporting of findings is integrated. Where necessary, the similarities and variations across participant groups are highlighted. The findings are organized according to emerging themes and their illustrative quotes from the respondents' group. While presenting sources of the illustrative quotes, codes were assigned for the study participants based on the group they belonged to. The following codes were used throughout the quotes: (i) PHo: a patient participant from a hospital, (ii) PHC: a patient participant from a health centre, (iii) HWHo: a health worker participant from a hospital, (iv) HWHC: a health worker participant from a health centre, (v) C: a participant from a community group, and (vi) Admin: a participant from HIV program manager group. This chapter presents the micro- and mesosystem levels of the SEM.

In this chapter, the results and discussions are integrated to reduce repetition of the lengthy findings. Furthermore, the study requires in-depth understanding and discussion of the facilitators and barriers before discussing solutions. The chapter has five sections. Section one presents the descriptive characteristics of the study participants. Sections two to four demonstrate the key facilitators, barriers and solutions for HCT respectively. The last section describes limitations, conclusions and recommendations of the study. Subsequently, the chapter introduces the NGT study reported in chapter seven that ranks the suggested solutions in this chapter from the perspectives of researchers, government and non-government HIV program managers and HIV health care providers.

6.2 Demographic characteristics of study participants

Table 6.1 presents the demographic characteristics of all respondents included in the in-depth interviews. A total of 35 participants was interviewed, and these represented a variety of organizations and positions throughout Jimma, Southwest Ethiopia. Eleven patients with HIV, nine HIV care providers, 10 community advocates and five HIV care system administrators participated in interviews. Of the 11 patients with HIV, nine were female, eight were orthodox Christian followers, four each had completed primary or secondary school, five were married, four were from rural areas and five had a history of ART discontinuation. The median time that

the patients had been on ART care was nine years (range 2–16). For patients who travelled on foot to the clinic, most of them lived inside Jimma town and it took a median time of 27 minutes (range 15–45) for them to reach the ART clinic. Most of participants living outside of Jimma town travelled using public transportation and it took a median time about 30 minutes (range 5 minutes–4 hours) to reach the ART clinic.

Of the nine HIV care providers, five were female, five were orthodox Christian followers and all had completed a college diploma and above with nursing qualifications. The median time of total work experience for the health care workers was 20 years (range 6-32), and of their work experience in HIV clinic 6 years (range 2-12). Of the 10 community advocates, seven were female, six were orthodox Christian followers, and seven had completed college or above. Three HIV volunteers, three Religious leaders, and four HEWs were included in the community advocates group for interviews. The median time of work experiences in HIV care program for the community advocates was 8 years (range 3-12). Of the five HIV care system administrators, three were male, three were orthodox Christian followers, and all held college degrees or above. Participants' positions included program managers at NGO level, chief HIV expert at district and zonal level, and service provision supervisor at NGO level. The median time of total work experience for the administrators was 17 years (range 7-26), and their work experience in HIV care programs was 3 years (range 2-12).

Table 6-1: Demographic characteristics of respondents

Characteristics, N=35		Patients with HIV, N=11 (31.4%)	HIV care providers, N=9 (25.7%)	Community advocates, N=10 (28.6%)	HIV care administrators, N=5(14.3%)
Age	Median (range), years	33 (21-42)	40 (27-50)	32 (28-48)	35 (27-42)
Sex	Male	2	4	3	3
	Female	9	5	7	2
Religion	Orthodox	8	5	6	3
	Muslim	1	1	3	2
	Protestant	2	3	1	0
Ethnicity	Oromo	2	5	9	2
	Amhara	4	3	1	3
	Debub[a]	5	1	0	0
Education	Not read and write	1	---	0	---
	Primary	4	---	1	---
	Secondary	4	---	2	---
	College and above	2	9	7	5
Marital status	Never married	2	---	2	1
	Married	5	---	8	4
	Separated or divorced	4	---	0	0
Residence	Urban	7	---	5	5
	Rural	4	---	5	0
Status	Lost	5	---	---	---
	Retained	6	---	---	---
Position	HIV volunteer	---	---	3	---
	Religious leaders	---	---	3	---
	Coordinator or expert	---	7 [b1]	4 [b2]	2[b3]
	Program manager	---	2	---	3
Total work experience [c]	Median (range), years	---	20 (6-32)	8 (3-28)	19 (7-26)
Work experience [d]	Median (range), years	---	6 (2-12)	8 (3-12)	3 (2-12)
Time since on ART	Median (range), years	9 (2-16)	---	---	---
Average time to reach ART clinic	Median (range), minutes	30 (5-240) by transportation or 27(15-45) on foot	---	---	---

[a] Debub refers to people who come from Gguragie, Wollayta and Keffa ethnic groups
[b1] All were ART nurses from hospital or health centre;
[b2] Two were urban health extension professionals (UHEPs) and two were rural health extension workers (HEWs) from health posts;
[b3] Both were coordinators and counsellors from non-governmental organizations;
[c] Total work experience in carreer;
[d] Work experience in the current institution;
--- refers to *Not Applicable or No information*.

6.3 Key facilitators for HIV care and treatment

Three key themes emerged as facilitators for HCT:

6.3.1 New programs,

6.3.2 Knowing and trusting ART, and

6.3.3 Support

6.3.1 New programs

Ethiopia has been launching new programs to intensify HIV detection, ART linkage and retention rates in care. These programs are still at a pilot project level at hospitals or scaled up to selected health centres. In this theme, Index Family Testing, test and treat strategy, and Appointment Spacing Model were the new programs that enabled HCT. The participants noted that the new HIV testing, treatment and care programs had paramount advantages in timely diagnosis, ART linkage and lifelong retention. The approaches and their implementation helped to enhance awareness and improve decision making to seek and use HIV care services. Furthermore, these programs facilitated the use of HIV care services by reducing common barriers.

Index Family Testing, a program run by a local NGO called OSSA, was one facilitating factor for HIV testing that emerged from the qualitative data analysis. Index Family Testing is an HIV testing program for household members of an index case. An index case is a known HIV patient registered in HIV care who reported having a household member not tested for HIV. A household member is a person, child, spouse, sexual partner, sibling or parent, residing in a nearby compound of the index case at the time of screening. The HIV testing program for household members of index cases can be either facility-based testing or house-to-house. If the index case chooses facility-based HIV testing, they are told to bring the household members to a health facility to receive HIV testing and counselling services upon arrival. The HIV testing procedure follows national guidelines[139]. If the index case chooses house-to-house HIV testing, a trained peer educator, HEW or other health worker visits their home at the convenience of the household members. Their consent is obtained before visiting the home, and which household members and how they are visited is discussed before home visits. This optional availability of the HIV testing program with facility-based or home-based HIV testing encourages people to seek or improve their use of the program. For example, a volunteer working in OSSA (local NGO) said that,

> *I am one of the volunteer members working with OSSA groups, and we were doing house-to-house HIV testing for people who had contact with known HIV patient or have HIV+ person in their family. It is really becoming effective. (C—01, HIV volunteer, 39 years old, female, kebele)*

In the above quote, it shows that the program was designed to be provided through home-based HIV testing i.e. peer educators screen the index families in their house. While the peers providing an enhanced counselling about HIV testing and treatment services to the family members, this helps the index families to improve understanding and facilitate decision making to utilize the services timely. The timely utilization of HIV care services enables people to early know their HIV status and link them to ART care. Further, the peer educators visit consenting HIV diagnosed patients till they are engaged to health services and continue to visit or follow up until they officially enrol on the ART care. The counselling also encourages patients to facilitate their HIV status disclosure to obtain support from families, peers and other volunteer community-based organizations. The health workers involved in the in-depth interview discussed that the program helps to identify HIV positive individuals early, and further encourages to be linked to ART care. For example, an ART nurse from hospital stated:

> *We have a family matrix in the ART follow up form. We update it every time and check whether members of HIV+ family are tested or not. We test our index case's family either in their house or tell to bring here (health facility). (HWHo—8, BSc nurse, 36, male, hospital)*

From the above quote, index family testing program also systematically targets high risk groups i.e. people who have or potentially have contact with HIV. This was supported by a local NGO manager working in the area:

> *I believe this targeted HIV testing (index family testing) is more effective. We test, refer to his/her choice of clinic, send to the referral institution either by our transportation or paying transportation cost, and confirming engagement into the referral clinic. That's why our referral system is designed to be 100%, not writing the referral in a piece of paper and give to the patient. We found this also reduces stigma as the testing is also conducted in every household. (Admin 03, NGO manager, 45, male, local NGO)*

The above quote also depicts that the availability of the service at household level by itself is a facilitating factor for patients who have lack of access to the service because of distance, transportation, or other reasons. Other studies have also showed that index case testing primarily helps to achieve the first 90 of the UNAIDS program. In Malawi, a total of 25,572 people from families living with HIV were tested through index family testing, and 22% of them were HIV positive[525]. It has also been shown in Tanzania that similar program was a key intervention in early HIV diagnosis and ART engagement [526].

Test and treat strategy is another program mentioned as enabling factor for ART linkage and retention. Test and treat strategy is a program that allows people diagnosed with HIV to start ART immediately or within five days of HIV diagnosis. This program acknowledges "*treat all*" strategy irrespective of WHO clinical stage or CD4 count. According to the participants, this program improves patients to link early, which, in turn, also encourages them

to stay long as they get the benefit timely. A retained patient witnessed this in the following quote.

> *Now is really good. You see everybody starts ART immediately, and you don't need to stay till declining your CD4 count. I wish I could get this chance. I have a scar (due to zoster infection) on my breast and this wouldn't have happened if I were on ART immediately. By the way this program also reduces stigma—no scar, no weight loss, you work as normal, look after your children, can marry and begot a child ... no body suspects you and no body isolates you. (PHo—11, retained patient, 36, female, hospital)*

From the above quote, it is possible to understand that the program enables patients to start ART immediately. This avoids multiple clinical visits for CD4 check-up for ART eligibility. Before the initiation of this program, patients used to wait until their CD4 count declined to 200 or 350 or below for the CD4 based ART eligibility, and they should have to come every 3-6 months for CD4 count check-ups. Avoiding multiple appointments at the health facilities connotes reducing exposure to people, which in turn, results in reducing stigma and discrimination. On the other hand, immediate ART initiation reduces complications associated with OIs and side effects of the drugs such as scars, significant weight loss and repeated illness due to lack of immunity. If these symptoms are shown frequently in a person, people may perceive that the person is infected with HIV and may start to isolate him/her from any social activities. Therefore, the program could facilitate service utilization via reducing common barriers such as stigma. For example, a health care provider from hospital said,

> *We let them (patients) start the medication within 5 days. Yeah (.2), once we check that they are willing and compliant, and our peer educators provide additional counselling, we give them for 6 months. By the way, patients better share their secrets and listen to peer educators than us. (HWHo—09, Diploma nurse, 27 years old, female, hospital)*

It can be seen from the above quote that the program significantly reduces LTFU during the pre-ART period. Patients with HIV used to disengage from the pre-ART care program when they were told to stay on it for months until their CD4 count fell to the criteria required to start ART[527 528]. The importance of peer educators was also noted in the quote above and is described in sub-section 6.3.3. Studies in other countries supported the positive impact of the program. For instance, immediate or same day ART initiation after diagnosis was found to be an effective linking strategy in resource-limited settings[518]. A randomized trial that assessed the RapIT (rapid initiation of ART) program in South Africa, in which ART initiation occurred at a single visit, reported a 25% improvement in ART initiation and 10% improvement in virological suppression at 10 months compared with standard ART care[529]. Even though the context is different, a test and treat strategy in Los Angeles County it was found to reduces HIV infection by one-third, new AIDS cases by two-thirds and deaths by one-third[530]. WHO recently

recommended ART initiation irrespective of CD4 count, and this has been reported to reduce new HIV diagnoses[31].

Another program enhancing ART retention mentioned by participants was the Appointment Spacing Model, in which patients were given enough pills for six months of ART. Previously, stable patients with HIV had to visit a clinic at least 4–6 times a year to collect their pills and have check-ups. As of October 2016, under the leadership of Federal Ministry of Health of Ethiopia, ICAP introduced a pilot model called Appointment Spacing Model[531], which is a facility-based differentiated care model in which patients with HIV have appointments only twice a year for clinical assessments and refill, as opposed to 4–6 times[531]. This model results in patients worrying less about frequent appointments, which, in turn, reduces exposure to HIV related stigma and transportation costs. This model was initially started in six hospitals—Zewditu Memorial, Nekemte, Dessie, Hawasa, Mekele and Hiwot Fana hospitals— in Ethiopia and further scaled up to hundreds of other hospitals and health centres[531]. This program was mentioned by the majority of study participants in interviews. A program manager from Zonal Health Department said:

> *To prevent lost to follow up due to distance or other reasons, we have started a new program called appointment spacing model since last year—patients will collect their drugs every 6 months if they are single, and every three months if they are couple. (Admin—2, HIV administrator, 35, male, Zonal Health Department)*

According to the above speaker, the approach benefits both patients and the health system[34]. For patients, it reduces direct and indirect costs associated with transport and long waiting times in the facility. For the health system, prescribing ART for six months means reducing the daily flow of patients, and this reduces the workload of nurses and pharmacists in the clinic. WHO recently found that the Appointment Spacing Model helps to maintain and improve health care by improving retention and self-management of patients[34]. The establishment of a six-monthly appointment program in Chiradzulu district, Malawi, through the help of MSF improved retention in care[190]. For countries with civil unrest or other humanitarian disasters, MSF introduced a new approach called “runaway packs” that enables individuals to pick up enough medications for use over a long period[519]. In Conakry–Guinea, the six-monthly appointment system was found to be very effective in reducing staff workload and patient attrition rates from ART care[532]. Therefore, it is important that this program is scaled up to remote areas where it has not commenced.

6.3.1 Knowing and trusting ART

Participants from all categories described that issues related to knowledge and trust facilitated the timeliness of HCT. In this theme, the following codes were included: feeling ill, feeling at risk, fear of HIV complications, awareness about the benefits of ART, perceived ART benefits, observing HIV-free babies from HIV positive partners, trusting ART care and 'hope' for innovation of new ART that can cure HIV. In the present study, it was found that participants had varying levels of knowledge about ART. It must be noted that the vast majority of people know methods of HIV transmission and check their HIV status and link to care when they feel ill or at risk. Fear of risks of HIV and its complications is a contributing factor to wanting to know more about HIV and care:

> *We see people are living long once they start to take the medication. There was a very slim and paralysed lady when she came here for the first time … but months after she started ART, she became amazing and now she is told to lose her weight (laughing...). Don't you get tested if you see this? (PHo—11, retained patient, 36, female, hospital)*

The above quote shows that HIV can progress to an advanced stage with serious complications like loss of weight and paralysis if it is not treated in a timely manner, and this fear pushes patients to enter HIV care. Meanwhile, quick recovery, regaining health and strength, and the ability to accomplish daily routine activities after starting ART encourage people to seek and remain in HIV care. A young patient from the health centre witnessed the benefit of ART to the extent of having a baby free of HIV born into a family that was HIV positive:

> *Glory to God, we have got an HIV free baby—he is 6 years old now and is free (from HIV). So, every HIV+ person should start the medication including pregnant women. (PHC—04, lost patient, 21 years old, female, health centre)*

On a similar experience, a patient from a health centre appreciated the benefit of ART through the following quote.

> *What I have observed is, you know the advantage (of ART) when you start to use. If you never use, you will never understand …. You won't understand until you do it. So, people shouldn't fear to take it. It really saves (life); most people die because of not using it in a timely manner. (PHC—06, retained patient, 43, female, health centre)*

The speaker reveals that patients are dying because of not using ART, and are surviving because of the use of ART. In addition, the use of ART by itself improves knowledge about it. This recognition enables other people to seek HIV care early and sustainably. Furthermore, such recognition improves trust in the ART care system. This was supported by a health professional working in a hospital.

> *Those who believe in ART do never stop the medication. Yeah…if they have good information about the benefits of medication, they won't stop it. They even know the time matters. For example, they worry*

much if they take at 8.00 am that should have been taken at 7.30 am. (HWHo—09, Diploma nurse, 27 years old, female, hospital)

The above statement is similar to other reports from Africa[121 249 533-535], showing that improving awareness about the disease and its treatment helps patients to decide whether to trust the ART care system. If patients with HIV know and believe that ART improves their quality of life and survival, a decision to use the medication will be made. It is, therefore, plausible to argue that familiarity with and knowledge about ART builds trust in utilization of the ART care system and even inspires hope. Furthermore, improvements in the dosage and number of pills required each day encourages people to take ART consistently with hope. The standard ART prescription has fallen from more than 10 pills three times a day to a single pill once a day. People also have hope that treatment comprising a single injection twice or thrice a year might be developed, or even treatment leading to total cure. A health worker from a hospital said,

*Sometimes, they (the patients) challenge us when they hear something new or rumour about ART in the media. They asked us to bring an injection (ART drugs in the form of injection) that is provided once in six months. (HWHo—*08, *BSc nurse, 36, male, hospital)*

A patient from hospital corroborated the above statement:

... ART drugs were too many like about 14 pills per day, but now is coming down to one pill a day and who knows for the future? You can see HIV+ people who counselled me 10 years ago are still here ...living more than 10 years... so, much improvement is there and people now are knowing this. Seeing this hope and experience, why don't you start the treatment if you are positive? (PHC—11, retained patient, 36, female, hospital)

The above quote shows that the institutional trust—trust in the ART care system— is improving through the journey of HIV care. Key informants in a study conducted in Mekele, North Ethiopia, revealed that belief in the efficacy of ART and particularly its benefit in regaining strength to perform routine activities gave patients hope and motivation to remain in care[121]. Furthermore, another study reported that the new treatments for HIV are relatively safe, have less resistance profile and simplify the treatment with less frequent doses, and this encourages patients with HIV to remain in care[536].

6.3.2 Support

In this sub-theme, the following codes were included: family support, person/s with HIV within the family, family responsibility, HIV status disclosure, having children, patient–provider interaction, after hours services and counselling. The study revealed that support for people who are HIV positive at several levels—partner, family, health care providers, volunteers and HIV program coordinators— has an important role in the whole continuum of care:

My first job is disclosing myself, then sharing my lived experiences, and then counselling patients accordingly. I always encourage them not to stop their medication. Some of them don't believe that I am HIV+. I tell them that I live more than nine years with the virus and feel nothing … I am looking great. Hearing this, some of them take my phone number for consultation. (C—01, HIV volunteer, 39, female, kebele)

From the above quote it can be seen that HIV volunteers, patients who provide support to others, — were willing to share their lived experiences and this significantly helps other patients with HIV to seek the benefit of the treatment sustainably. When patients with HIV perceive that the volunteers have a good quality of life, looking like they are HIV negative, feeling well and staying on ART for nine years and more, they will be empowered to access the care. In addition, the presence of a family member with HIV also encourages others to make use of care, as described elsewhere[121]. The quote also illustrates how much trust patients with HIV show in the volunteers, for example by seeking consultations with them, and this improves HIV care service utilization. Seeking consultation and being willing to disclose their HIV status to these HIV volunteers helps patients with HIV to obtain support in addition that from HIV care providers. Thus, it is logical to believe that disclosing one's HIV status could be a key to get social support. For example, a manager working in a local NGO said,

As a local NGO, if they (HIV patients) come to us, we offer variety supports—treatment, financial, and spiritual. We also fix their house as you see these women. We supply hygienic materials. We aid orphaned children like school associated costs, health care costs, and food and other psycho-social support. This motivates patients to remain in care. (HIV program manager, 47 years old male, local NGO)

Similarly, a patient from health centre who had discontinued said,

Thanks to God, I have got a very lovely husband—he rings every time to remind me to take the medications when he is away to work. He never forgets his medication too. By the way, no body suspects us that we are HIV positive- I am slim from the very beginning, and my husband is very huge even after acquiring the virus. (PHC—04, lost patient, 21 years old, female, health centre)

The above two quotes describe how disclosing one's HIV status helps a person to obtain clinical, financial and spiritual or emotional support. This significantly helps them to develop a power within and not to hide themselves from seeking and using care. In addition, disclosure helps patients with HIV to establish their own community, in which they can share the benefits and challenges together and help others who have not accessed care. Nonetheless, the above quote also reveals a misconception about HIV, that being slim is a sign of being HIV positive while being large signifies HIV negative status. This misconception with its connotation is described in sub-section 6.4.2. In the present study, study participants showed that there are a number of people who become motivated to engage in HCT for sake of their children or family. For example, a mother who had never discontinued from ART said,

I told to my child that I am taking anti-cardiac pills but always tell him to use his own blade or other sharp things to cut his nail or remove dental plaque from his teeth. I never kiss him. I fear not to infect him in any way. But you see … he always reminds me to take my pills. Also some husbands remind their wives by telling that the radio or TV program starts …. Like, they say VoA (Voice of America) starts now or … the drama is on or etc. … which means that it is time to take the pills. (PHo—11, retained patient, 36, female, hospital)

On a similar note, another mother revealed,

Some patients take the medication because they are responsible for their children, and they become hopeful when they see their family encourage them… I am really happy that I have two children and they are both HIV negative. Who would take care of them at this age if I were not compliant? No body. (PHC—05, retained patient, 35 years old, female, health centre)

The quotes demonstrate: i) the contribution of partners and children in encouraging patients to remain in long-term care and comply with treatment; ii) the commitment to remain in care to support family, and this acts as an indirect enabling factor for having a good quality of life; and iii) the awareness of HIV transmission methods and taking maximum care not to transmit the virus to others.

There is still a fear of disclosure of HIV status and poor open communication about HIV, and this is described in the stigma related barrier to HCT in sub-section 6.4.1. As seen in the previous quotes, most women, as per Ethiopian culture, accept responsibility for caring for children and handling household activities. This tradition also helps women to stay in HIV care. For example,

Once females disclose and start medications, they don't want to stop, because they really take the responsibility to look after the family. Their big problem is, either they may not disclose their status or they start late. (PHC—06, retained patient, female, health centre)

This speaker shows how the culture in Ethiopia places an imposition on women to develop their internal motivation to stay in HIV care for the sake of their family although they struggle with non-disclosure and LP. Such non-disclosure, fear of stigma and LP in women exposes them attrition. The retrospective cohort analyses reported in phase two of the project showed that women were more likely to delay HIV care presentation[131] and discontinue treatment[132]. The reasons why women face difficulty in disclosing their status, present late to HIV care and discontinue treatment are described in sub-sections 6.4.1 and 6.4.5. A qualitative study in Uganda reported that support from partner, peer or family motivated patients with HIV to access ART uptake and remain in care[439]. Similarly, in studies conducted elsewhere[121 537], patient–provider interaction and counselling have had a remarkable impact on HCT. The above-mentioned drivers for HCT were mentioned by all target audiences in the current study.

6.3.3 Summary of facilitating factors for HIV care

In summary, the facilitators for HCT in the present study included: new programs such as Appointment Spacing Model, Family Index Testing and test and treat strategy, improved knowledge and trust in ART care, and support from partner, family health workers or other organizations.

6.4 Key barriers to HIV care and treatment

Several key themes emerged from the analysis about the barriers to components of HCT, namely HIV diagnosis, ART linkage and ART retention. An additional level of analysis, cross analysis, was carried out to explore which factors affected which components of HCT, and which factors are common to both or all components of the treatment continuum. This is displayed in Figure 6.2. These barriers are grouped into key themes as key barriers to HCT and are presented based on the themes. Where necessary, we will refer to the figure to show the significance of the factor/s as intersecting barrier/s and with implications for the solutions described in sub-section 6.5. A similar font colour is chosen to show which factors belong to which theme. The key barriers, demonstrated in Figure 6.2, include:

6.3.2 Fear of being seen by others
6.3.3 Knowing and trusting ART
6.3.4 Availability
6.3.5 Free ART as expensive
6.3.6 The role of tradition/culture
6.3.7 Fragmented health care system

6.4.1 Fear of being seen by others

All groups of study participants mentioned fear of their status becoming known to others as a cross-cutting barrier throughout the continuum of HIV care (Figure 6.2). Fear of stigma, fear of HIV diagnosis, visiting private clinics, non-disclosure and HIV fear factors were the codes under this theme. When HIV was first made known to people, it had a very bad image and people have developed excessive fear of HIV compared with other lifelong and potentially fatal diseases. Such fear results in people being stigmatized, discourages them from seeking HIV care services and even causes worries about what will happen after death. For example, a patient from a health centre said,

> *I can tell you that nobody will care for my dead body except those HIV+ people. Who else will do that? You can imagine that it (the HIV related stigma) worries me even after death. So, there should be a miracle to stop this stigma. (PHC—02, lost patient, 42, male, health centre)*

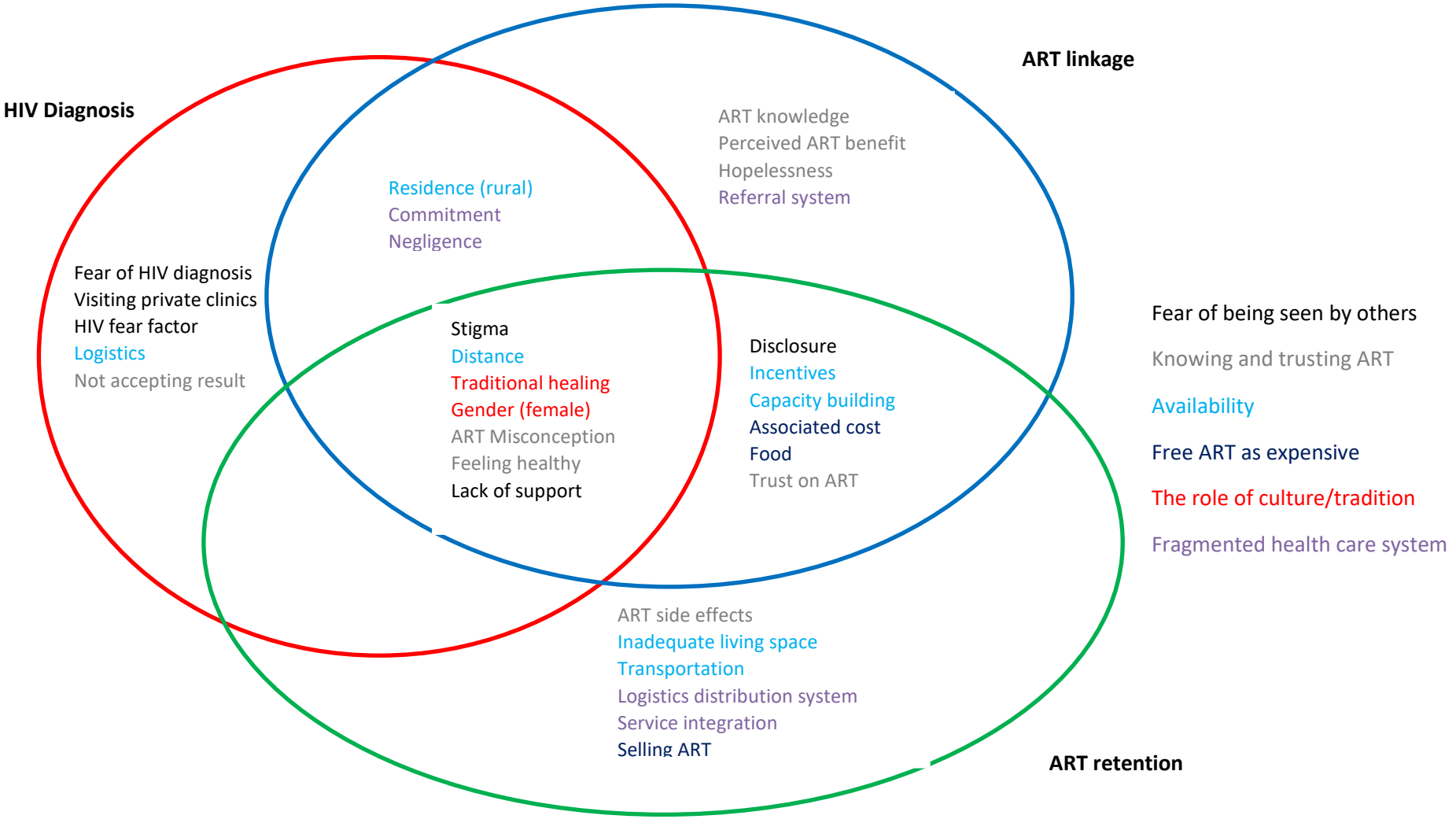

Figure 6-2: Barriers to HIV care and treatment in Southwest Ethiopia, 2017/18[24]

[24] This figure needs to be viewed in colour

On the same note, another participant described how stigma is still a challenge:

> *It (HIV related stigma) is still there. When neighbours quarrel each other, those HIV free people insult HIV+ people mentioning the disease (HIV) and that they are the cursed ones. Especially, the women …. Allah! … They never keep the secret. They insult HIV+ positive people by mentioning the disease even in front of many people. This significantly affects people not to be tested for HIV. You can imagine, people make a long queue to check their blood pressure but you can't see this for HIV. (C—05, rural health extension worker, 28, female, kebele)*

The above quotes reveal that HIV related stigma is still an important barrier to the HCC. In Ethiopia's tradition, seeing many people at a funeral shows pride and how much that deceased person (and the family) was respected. On the other hand, if very few people attend one's funeral, society understands that the person was regarded as having low status in the community and the family members will be similarly regarded. If family members perceive that society labels them in this class, they feel isolated and may not participate in day-to-day social gatherings. Likewise, the community may also not want to perform social activities with these family members. They may not want them to eat with them and may not allow their children to be engaged with these poorly regarded family members. This phenomenon is very difficult to cope with, especially when living in a very communal society like Ethiopia. Being HIV positive is one of the reasons for this kind of misconception. As the speaker above explained, people reveal a person's HIV positive status when quarrelling because they know that this is an embarrassing issue. Therefore, because people understand this, patients with HIV may prefer not to disclose their HIV status in order to get many people attending their funeral so that the remaining family members would not be treated differently. For example, a 30 years old patient said,

> *People don't want to be recognized as HIV+ in their workplaces or other social gatherings. I remember one ridiculous scenario. There was one HIV+ woman in a group of people eating porridge. One of them (from the HIV negative persons) pierced the container hiddenly and the cheese floating on top flew down so that the virus would flow down together. Seeing this, why should one go to get tested, and disclose his/her HIV status? (PHo—09, retained patient, 30 years old, female, hospital)*

The quotes illustrate an intertwined connecting of stigma and misconception. Unlike patients with other illnesses, people isolate patients with HIV because of the assumption that they are cursed. Such fear of stigma and HIV diagnosis results in people going to private clinics to seek treatments for OIs instead of being screened for HIV and receiving treatment. Patients may also choose to collect their medicine from ART clinics that are located far from their catchment area in order not to be recognized by their neighbours. For example,

> *People who come from distant places such as Gambela (450 kms far from Jimma, the study setting) were complaining to take ART for 4 or 5 months because they don't have money for transportation. They*

sometimes even use plane if it is not safe to use bus. If they don't have that transportation cost, the option is to stop… so they are suffering.... but this doesn't mean that there is no ART service in Gambela. Some others don't want people to talk about them, about their taking ART regimens…NEVER. (HWHo—08, BSc nurse, 36 years old, male, hospital)

A myriad of studies reported that HIV stigma continues to undermine the positive outcomes of the HCC[120-122].

Unlike the attitudes reported by most patient groups, HIV care providers, community advocates and HIV program managers revealed a decline in the HIV fear factor, particularly in urban settings. This is a result, participants said, of complacency and a reduction in the community's attention to HIV, which in turn has contributed to an increasing number of new HIV infections (sub-section 6.4.6). A manager from an NGO reported:

People nowadays believe that there are other more fatal lifelong diseases (e.g. diabetes mellitus) than HIV. This concept is misinterpreted and reduces the HIV fear factor. Because, you don't see HIV patients suffering from different symptoms or lesions, and being bed ridden. This deceives people to consider HIV as other normal disease, and even to forget in some instances. You remember HIV in the earlier times was seen as a horror, and people stop accompanying during funeral ceremonies. (Admin—03, HIV program manager, 47, male, local NGO)

According to the above quote, when responsible bodies become silent about HIV, people may assume that the virus has been eliminated and subsequently the fear of HIV diminishes. This has also been seen in other countries. For example, in their book[127], Sophie Harman demonstrates this by mentioning governments of South Africa and Uganda. The silence and denial of Thabo Mbeki's government in South Africa is a typical example in which the country is home to the world's largest HIV epidemic. On the other hand, the acknowledgement of HIV problems in Yoweri Museveni's Uganda has been heralded a success story in comparison to neighbouring countries. Furthermore, in their analysis of HIV news published in *The Sydney Morning Herald* in the year 2000-2005, Newman and colleagues revealed that there was complacency and a dearth of concern about HIV, and this had resulted in increased HIV risk environments in Australia[128]. Therefore, it is crucial to re-motivate responsible stakeholders to deliver HIV information consistently and strengthen existing programs sustainably, as described in sub-section 6.5.1.

6.4.2 Knowing about and trusting ART

In this qualitative study, it was found that people did not seek HIV care unless they showed signs and symptoms, a condition which may be related to low health literacy status. In addition, fear of ART side effects, reduced trust in ART care, undermining of the perceived benefit of ART and ART being a lifelong prescription were other barriers to the HCC mentioned by

participants in the present study. In sub-section 6.3.2, it was reported that the levels of knowledge and trust in ART care vary among participant groups. The presence (and advantages) of ART are yet to be appreciated by some people who are HIV positive and sections of the wider community. The study found that there were people who resisted accepting their HIV result, did not start ART unless they showed signs and symptoms, and stopped when they felt healthy or developed serious side effects. A restarter who had discontinued ART to try *Holy Water* said,

> *Did I know before (HIV treatment)? No, I did not. Only the ones in the urban and few literate people from rural know the presence of treatment for HIV. How many people are in the village? And how many of them went to school? So many people have no awareness. It is clear … go to the cause they assume—it is the curse, the punishment of God. So, the assumed solution is from Him …. going to religious places and pray. (PHC—02, lost patient, 42, male, health centre)*

The above quote vividly depicts that there are people who do not know what services are available for HIV and where these can be accessed. The quote also demonstrates that there are people who assume HIV is the result of a curse and consider substitute treatment including traditional healing (sub-section 6.4.4). People may believe that ART is not effective, or not comparable with the religious treatment they receive. This misconception could result from the lack of ART services, because it was high among rural dwellers and they are the people with disproportionately less benefit from the availability of ART, as described in the next sub-section. This suggests that increasing the availability of ART could improve knowledge of ART, as discussed in 6.3.2. Another problem is that even if they know about HIV treatment, as described in sub-section 6.4.4, they have a belief that HIV medicine needs to be accompanied by highly valuable foods like meat, milk, eggs or others:

> *…. There is a false but defaulted information in most HIV patients mind that you have to eat good food (highly valuable food in the culture such as meat, milk and egg) to take the medication. They won't take it (ART) if we don't give them a 'Plumpy' nut[25]. (HWHo—06, reproductive health specialist, 49, male, hospital)*

In addition, side effects of drugs were another barrier challenging retention in care. For example, a female patient from a hospital said,

> *I lost all my teeth; my nails were removed and my appearance is changed after starting the medication. If I were not strong (morally and psychologically), I would stop the drugs. Yes, so it (side effect) will challenge. (PHo—10, retained patient, 30 years old, female, hospital)*

[25] 'Plumpy' Nut is a peanut-based paste in a plastic wrapper specifically formulated for nutritional rehabilitation in treatment of severe acute malnutrition, manufactured for children from six months of age and adults. It is made for home based or outpatient treatment. HIV patients are provided 'Plumpy' Nut if they are diagnosed with severe malnutrition.

The lack of knowledge that ART may have minor or major side effects but that these are temporary and manageable leads to an inadequate trust in ART care. In addition, people may expect total cure from the virus, and when they find that ART is not a one-off cure but requires lifelong prescription, they might lose trust and hope, and stop the drug. This was supported by a patient from a health centre.

> *Some people become hopeless and stop it when they think that it (ART) is life-long and see no change or cure. And then they start to take substances, drink beer or 'Tej' (honey wine), and stop the drugs. Finally, they store medications at home… (they) won't take it. (PHC—05, retained patient, 35, female, health centre)*

Previous studies indicated that a number of patients with HIV stopped ART medication through lack of knowledge or misconceptions, perceived health status and side effects of ART medication[121 248 538 539]. In general, the misconceptions or lack of knowledge about the presence (and advantages) of ART affects trust in ART care. Trust scholars note that knowledge improves trust, and trust improves choice and decisions to use health care services[540 541]. Thus, it is imperative to promote HIV care services consistently and improve the quality of HIV counselling programs.

6.4.3 Availability

Availability of health care services can be viewed in terms of total supply of services or personnel, and in terms of geographical distribution of the service. In the present study, residence, distance from ART, phasing out of NGOs, transportation, logistics, staff numbers, incentives and capacity building were identified in this theme. People with HIV, particularly rural residents, may not have HIV care services available because of long distances or lack of transportation. A discontinued patient said,

> *… HIV testing is conducted here around the cities. Health workers? They don't want to go to very remote areas on foot to do HIV screening…. People from remote areas took them hours on foot to reach main roads to catch a bus, and hours by bus to reach the HIV clinic. And this will be for those who can afford transportation cost. They can do this for one, two or three months but impossible for life long. Thus, they are obliged to stop the medication. (PHC—02, lost patient, male, 42, health centre)*

The quote may suggest a poor commitment from health workers. One reason why health workers are becoming reluctant to go to rural settings to conduct HIV testing is because of the lack of incentives, which, as described below, used to be paid by some local or global NGOs. In addition, the quote also reflects the presence of inequity in HIV care, in which people living in rural areas cannot easily access HIV testing programs. The quote also implied that a lack of infrastructure and the unaffordability of transportation have a considerable impact on ART attrition. The unavailability of ART services as a barrier to HIV care seen in the current study

is also supported by the low ART coverage in the region (Oromia) and nation[27 542]. In other African countries, the coverage of ART is very low, which, in turn, affects successfully achieving the second and third 90s of the UNAIDS target[3 116 543]. In areas where services do not exist or are less available and accessible, particularly in rural areas, females suffer more than males:

> *If a woman who doesn't disclose her HIV status wants to go to health centre to collect drugs, she has no reason to tell her husband where she went, why she did not feed the children, why she didn't do the housework, etc…. All these are the responsibility of women in village. But if the health facility is near, she could quickly go to collect the drugs and back to her children and cattle. But the transport (and its cost) still matters. (PHC—03, lost patient, 30, female, health centre)*

Gender inequity, particularly women's vulnerability to poor availability of HIV services, is well displayed in the above quote. The negative impact of male dominance on women's HIV care practices is also challenging, as depicted in the quote. Monitoring of family money by husbands in rural areas means that women may not get enough money for the cost of transportation to use a service even where transportation is available. A finding from the retrospective cohort study also confirmed that females were more likely to have started ART late[131] and be lost from ART follow up[132]. Rural areas have inadequate infrastructure including transportation (and its associated costs) and this was associated with low coverage of HIV diagnosis, ART linkage and ART retention[116-119].

NGOs initially facilitated HIV testing and diagnosis, ART engagement and promotion of ART retention. However, they are now phasing out these services and handing them over to local governments. To investigate whether this phasing out by NGOs has created a gap in sustaining the quality of the services, the analysis across groups (cross analyses) was used and it showed contradictory sentiments. Participants from NGOs, community advocates and most patients in the current study acknowledged a clear gap in sustaining HIV care services. For example, a program manager from an NGO said,

> *HIV communication was quick and targeted when NGOs hold HIV works, whereas not in the government houses. You can see that the government has poor monitoring and evaluation system, and we noticed increasing number of new HIV patients. (Admin—03, HIV program manager, 47, male, local NGO)*

On the other hand, some HIV care providers and the public HIV program managers believed that they ensured there was no gap in services. For example, a program manager from a Zonal Health Department reported that

> *..... we can't say that the job fails if no NGO or the job will be successful if it is done with NGO. Even though the presence of a partner is good, the reason why the prevalence of HIV is increasing is not because of phasing out of the majority of NGOs but because of the reluctance and carelessness of*

government officials. I have to be honest—NGOs usually have a problem of transferring skills to the immediate responsible bodies rather they want to do by themselves. (Admin—02, HIV program manager, 35, male, Zonal Health Department)

Such controversies need further exploration and there is blame shifting between the government and non-government officials[544]. Government officials blame NGOs for being inefficient, having non-targeted use of budgets, and limited skill transfer to local staff. On the other hand, NGOs blame government officials for their non-coordinated activities and lack of commitment. Despite these controversies, most participants, *en bloc*, reported that HIV testing kits and ART medications are not available in some clinics, including the current study setting, despite the physical presence of an ART clinic. For example,

Well, let alone in village, there is shortage of kits [545] here in the hospital… in city. There are times that we do not test people due to this. There are also times we make appointments for patients for another time when ART trained health workers are off duty. That's why, sometimes, we prescribe ART without training. For example, I was doing in tuberculosis clinic and just saw while my colleagues prescribe ART, and then started to prescribe …. which actually was not correct. (HWHo—09, Diploma nurse, female, 27, hospital)

The speaker in this quote shows that logistics problems are still a challenge in urban health institutions and more so in rural health care facilities. People who came for HIV testing were returning home without being tested because of lack of HIV testing equipment or personnel. Evidence shows that people who come for HIV testing by themselves could be those who felt at risk, and the odds that they will test positive may be high. Hence, if these people return home without receiving HIV counselling and testing services, they would be denied the early benefits of ART. In addition, the risk of HIV transmission to others is increased, a significant public health impact. The speaker in the quote also shows that if patients with HIV come to collect ART in the absence of ART trained personnel, then ART discontinuation may be triggered and attrition increased. This is consistent with reports from other African countries[112-115]. There were also participants who did not access ART programs or who travelled long distances intentionally to collect pills, sometimes paying up to 200 birr (average earnings for a day and a half) to do so, even when there was a clinic nearby. This was because of their fear of being recognised by people they knew, including patients with HIV, HIV care providers, case mangers or other people in the clinic as described in section 6.4.1.

6.4.4 Free ART as expensive

ART dramatically reduces HIV related mortality and other complications[546]. These advantages were remarkably recognized in the era of ART scale-up when the government started to provide ART free of charge. Ethiopia commenced free access to HIV treatment at the point of service

in 2005, like other countries in Africa such as Botswana in 2002, Tanzania in 2004 and Zambia in 2005[547]. Yet, the benefits of this are suboptimal because of a number of misconceptions. In the current study, selling ART drugs, fear of ART stock running out, lack of food and unaffordable associated costs were barriers to starting ART and remaining in care. For example, participants stated that people assumed the drug is very strong and people on it need adequate and diversified food. If they know they do not have this food, they will not start ART, or if already started they stop it. One speaker from a hospital has pointed this out:

> *Yes, people believe that when you start ART, your appetite will increase and you need to have adequate food; otherwise you will die if you take it on empty stomach. For this, some HIV patients prefer not to start ART if they feel they don't have enough money to buy adequate and diversified food. (PHo—08, retained patient, 35, female, hospital)*

The above quote reflects that there are people who perceive ART needs highly valuable foods (e.g. milk, meat, and egg) in the community. This assumption originates from the idea that ART is strong and requires these foods otherwise the drugs will not work. In Ethiopia, these foods are very expensive and are not affordable by everyone. Therefore, HIV positive people who cannot afford these food items prefer not to start treatment. Previous studies have also shown that having insufficient food to accompany ART limited people from engaging with or remaining in HIV care [119 246]. A study from Nigeria revealed that inability to afford to purchase meat by farmers with HIV affected retention in care[119]. In addition, people stopped ART because they could not afford the associated costs, such as costs for OI drugs, drugs for other comorbidities and laboratory investigations. These misconceptions and associated costs were also mentioned as common barriers to HCT in other studies[121 246 548].

In the present study, despite the fact that ART is free of charge, participants revealed that pills were sold secretly on a black market, and this happened for numerous reasons. Patients travelled more than 355 kms (to the capital city, Addis Ababa) to purchase ART from private clinics located in the capital city which sell ART covertly. In addition, there were patients with HIV who enrolled at (and collected from) more than one ART clinic, and these patients also sold ART drugs. A patient from a health centre explained how ART is sold in illicit places:

> *You are letting me speak what I don't want to speak (smiling …). Let's talk frankly. You know that there is a civil conflict in some places in Oromia, Gambela…… Many HIV+ people have fear, and I myself have a great fear. There is a fear that the Pharmacy may be robbed or the medications may be taken away to other places. So, if you have money and such fear, why wouldn't you buy? I know I will get them in a black market either from patients or private clinics in Addis (Addis Ababa, Capital city, Ethiopia).*

By the way, people used to buy ART drugs for treating kidney failure. (PHC—02, lost patient, 42, male, health centre)

Similarly, a health worker from the hospital spoke:

People on ART know that they can get the treatment services from any ART clinic for one month (as emergency medicine) reasoning out that they lost their drugs or left it at home. Plus, you know what they do? ... they are enrolled (and take the drugs) from here (hospital) for themselves. At the same time, they can be enrolled in another place and take the drugs so that they can sell to others who take the treatments secretly. Not only the drugs, they also sell the Plumpy'nut we give them to improve their nutritional status. (HWHo—03, BSc nurse, 49, female, hospital)

The notion that patients with HIV are registered with more than one ART clinic and may be taking non-prescribed drugs has a number of individual and public health implications: i) double reporting (or more) biases the incidence and prevalence of HIV in the nation; ii) if patients take drugs not prescribed for them, they may face serious acute and chronic side effects from ART; iii) taking non-prescribed drugs could also result in drug resistance and other drug–drug interaction problems, because there are different categories of ART drugs and these are prescribed based on a number of indications; and iv) the long-term prognosis of patients taking non-prescribed drugs may be very poor.

According to the participants, there are various reasons why patients buy ART drugs. There are people diagnosed with HIV who do not want to visit HIV clinics. This is mainly because of the fear of stigma and these people purchase the 'free ART' either from other patients with HIV or private clinics. Participants noted that people also buy ART drugs for HIV positive family members or friends living abroad. Fear of ART stock running out because of civil instability is another reason why patients buy the drugs. There were on-and-off internal conflicts and civil unrest during the data collection period in some places in the region (Oromia, Ethiopia) including Jimma, where data collection was carried out. Patients with HIV stated that they were worried about missing a single dose which was very important to them. In addition, they stated that the situation was made worse because ART drugs are only available in public health facilities, unlike all other types of drugs in the setting. To avoid running out, they want to buy the drugs. Participants also reported that people (either HIV positive or negative) buy ART drugs for treating other illnesses such as hepatitis or kidney failure. For example, a patient from health centre said,

Previously, the drugs were six pills and of these, one pill was assumed as a treatment for kidney failure. So, HIV+ people sell the pills for anybody who diagnosed kidney failure themselves whether they are HIV+ or not. But now, since it is single pill, I don't think there is (such issue). (PHC—02, lost patient, 42 years old, male, health centre)

The above quote reveals serious implications for health outcomes. The use of ART to treat kidney disease does not have a scientific basis. In fact, HIV infection could damage kidneys, lead to kidney disease and even kidney failure[549]. Some ART drugs can affect kidneys and health workers undertake careful consideration when prescribing the dose and type of ART for patients with kidney disease[549 550]. Therefore, there is no basis for the use of ART to treat kidney disease, rather its use has serious side effects and complications. Similarly, HIV and hepatitis B are globally known co-infections. The treatment of both illnesses should be coordinated to reduce the emergence of HIV/hepatitis B resistant strains. Furthermore, careful consideration should be undertaken while prescribing ART drugs with hepatitis B treatment. Therefore, using ART for hepatitis B treatment needs careful consideration and like other medicines, it should be prescribed by professionals. Cross analyses among the target audiences showed "known unknowns" i.e. although patients knew that ART is for sale, neither the HIV program managers nor most health workers and community advocates knew about the issue. For example, a HIV program manager stated,

> *ART for sale? This is my first time, and I will take a note—I am very happy for the information though. What I have observed is we have to have a check and balance system. We know patients sometimes don't give us their real name and address. This may open to the enrolment here and there you are saying. It also makes tracing of lost patients very complex. I wish there is a uniform software to reduce double reporting. (Admin—02, HIV program manager, 35, male, Zonal Health Department)*

In addition, very few HIV health care providers had noticed the issue, but they do not have checking mechanisms that could overcome the problem. HIV program managers from districts and zones were surprised by the issue and took a note to explore and solve it. Therefore, the issue of ART for sale is a hidden yet serious problem. The issue of selling ART in black markets is not limited to Ethiopia. For example, a study from South Florida revealed that ART drugs were for sale in illicit marketplaces, and reasons for buying the drugs off the street included having limited access to HIV care, to replace lost/ruined pills, and to have a backup stock[551]. This was also reported in South Africa[552].

6.4.5 The role of tradition

The role of tradition in challenging access to HCT has been recognized since the emergence of HIV. However, there has been conflicting information about the role of structural factors in enabling/hindering access to HCT[124 126 244 553]. In the current study, traditional healing, gender, male dominance and social pressure were explored as significant challenges to HIV care, treatment and support programs. The participants explained that most people in the country

consider traditional healing as an alternative medicine for treating illnesses including HIV. This leads people to delay HIV care, and discontinue ART either temporarily or permanently.

Our respondents mentioned that Orthodox Christian and Muslim followers go to '*Tsebel'* or Holy Water places and Protestant Christians go to their churches, and most of the attendants had low literacy status. According to the participants, some priests do not allow foreign material including drugs to be brought into the Holy Water places, because they believe that the foreign material will bring a curse on the Holy place. So, patients with HIV are not allowed to bring and use their pills while visiting those places. Apart from this, participants noted that there are priests who believe that the use of ART drugs is a demon's work and is testing or interrogating God. Thus, they preach to their followers to pray and not to use the drugs. Similarly, participants noted that pastors in the Protestant Christian churches assume that the virus can be eliminated by praying to God. When patients with HIV go to a Protestant church, the pastor prays for patients and tells them that they are blessed and the virus is gone, and orders them to discard the pills. For example, a patient who visited a Holy Water place seeking HIV cure said,

> *... while you drink the Holy Water, the virus will be removed in the form of diarrhoea once your sprit communicated with God. The Muslims come here too to share this blessing. The Protestants go to their pastor. Everybody wants to try and communicate with his creator. (PHC—03, lost patient, 30, female, health centre)*

On the same note, a HIV volunteer explained that medications are not allowed in some Holy places:

> *Most people go to 'Tsebele', and there, the priests or deacons check you up…. nobody is allowed to bring in pills. Then HIV patients stay there for one, two, three or more months without taking their medication. Sadly, they will either die or deteriorate—six people died last week from 'Arsema Tsebele' (a Holy Water place 70 km from Jimma town). Also, a number of people come on a stretcher from a new protestant church opened in Bishoftu (above 400 kms from Jimma town). I don't know what is better. (C—06, HIV volunteer supporter, 39, female, kebele)*

The quotes demonstrate that traditional healing such as Holy Water is perceived as alternative treatment for HIV irrespective of the religion people follow. Furthermore, the spiritual leaders prohibit people from bringing the medication into these religious places or tell them to discard their pills. As the participants noted, as patients who visited the Holy Places and Churches had low literacy status, they could not re-check or re-test their HIV status and decide to simultaneous use of the traditional and modern medicine. This facilitates the rapid progression of HIV infection to the AIDS stage. Even if patients could take traditional healing and modern medicine simultaneously, this has rarely been practiced until now for various reasons. Some of

the reasons[123] are that: i) there is lack of formal recognition of traditional healing, ii) the traditional healers do not agree to have the herbs or Holy Water they prescribe tested or their efficacy proved, iii) there is poor understanding of modern medicine by the traditional healers, and iv) traditional medicines are less costly and more available than modern medicine. The use of Holy Water and/or other religious treatment as an obstacle to the success of HCT has been explored in studies from Ethiopia[121] and other African countries[124-126]. The use of religious leaders in informing patients about simultaneous use of ART and religious treatments should be emphasized.

As with findings from other reports[478 554], the present study found that females used traditional healing more than males and thus they are more often the victims of HIV complications. The existing patriarchal society and social pressure leaves women vulnerable to poor HIV outcomes, as revealed in other studies[170-172]. One respondent health worker mentioned:

> *... Females are the ones who frequently go to traditional healings like Tsebel (Holly Water) and stop drugs then after. In addition, husband here is very dominant in the society; so, if he orders his wife not to go to health centres, she will stop. (HWHo—08, BSc nurse, 36 years old, male, hospital)*

In most rural communities in Ethiopia, the place of women is assumed to be in the kitchen; as a result, they have limited access to education[555]. Furthermore, they have limited access to modern health facilities whenever they seek these. In some instances, participants said, husbands allow wives to go to Holy Water places but not to health centres or hospitals. Thus, women, particularly those from rural settings, disproportionately suffer the burden of HIV complications[556].

6.4.6 Fragmented health care system

The numerous successes in the delivery of services to patients with HIV is overshadowed by a fragmented service provision. Despite the fact that there are good physical structures within and among service delivery organizations and donors, most activities are uncoordinated and produce suboptimal outcomes[129]. In the present study, referral procedures, patient handling, ART distribution systems, commitment, negligence and service integration were mentioned as barriers related to a fragmented health care system. Weak referral and patient handling systems have significant impact on timely linkage to, and retention in, care. There are few checking mechanisms to see whether a person diagnosed with HIV initiated treatment at the referral clinic.

Given the growing number of HIV care facilities and the introduction of the EMR system across the nation, it is feasible to develop an electronic referral system that can work

off/online among facilities. On another note, after arrival in the health institution, patients may not be seen if they do not come on the appointed date, because security staff may not let them in. They are told to go back home and come back for their next appointment. They do not want to tell the security staff that they are HIV positive and have come to collect ART drugs. The patients are obliged to stop taking their pills until next appointment or obtain a one-month emergency supply from another clinic. This problem was identified by a speaker from a hospital.

> *... patients may come before or after their appointment date, and the security may not let them in. Patients can't say that they are positive (HIV). They get disappointed and go back home. We have told this to our ART focal person and we are waiting for the solution. It is a difficult situation. The security asked us to give the lists of HIV patients to let them in but this is impossible. Yea so that's a very big problem. (HWHo—09, Diploma nurse, 27, female, hospital)*

There were many patients who came from distant places such as from Gambela (450 kms away) in the current study, and it is common for these patients to miss their appointment date. Yet, they face problems beginning with the security staff. Thus, the government should identify which bodies are responsible for maintaining contact with patients with HIV.

The current study showed that the programs which used to be carried out at the facility or community level were often interrupted, and the commitment from individuals, health workers and government to implement those programs was also diminishing. These contributed to increasing HIV transmission rates, declining ART linkage and retention rates[557] [558]. For example, a community health worker said,

> *Nowadays, the virus is increasing and the main reason for this is that everybody forgets it (talking about the virus)—school health programs are not functioning, no community awareness about HIV, no conversation in 'Idir' and no advertisements in the medias. The community conversation (CC) which was originally established for HIV conversation is now a forum on solid and liquid waste management or other issues. So, people assume that the virus is eliminated, and become careless. (C—05, HEW, 28, female, kebele)*

On a similar note, a nurse from hospital said,

> *I am seeing 2-3 new infections a day and so do my other colleagues. This shows that the number of new HIV infections is raising ... (HWHo—07, BSc nurse, 27, female, hospital)*

A health worker also reported how health workers are becoming negligent about providing consistent HIV information.

> *.... we are far from teaching (about HIV) the people consistently. There used to be frequent advertisements and information dissemination forums from different media. All these things are not present these days. We talk about HIV once a year when on November 29 (referring to World AIDS Day) approaches. (HWHo—08, BSc nurse, 36, male, hospital)*

The above quotes showed that it appears that the attention given to promote HIV prevention activities has declined over time, and as a result, the number of new HIV infections is rising. Even the community conversation (CC) which was a key forum to talk about HIV is now overlooked and it is used instead for other matters. Thus, multiple actors—patients with HIV, community, health workers, policy makers—must be committed to promoting HIV treatment, care and support activities consistently.

Participants in the present study also noted that the current distribution system of HIV materials such as HIV testing kits and ART drugs is very unreliable. PFSA's distribution system (the sole HIV care logistics distributor) does not run on time nor is it based on need. A study from Kisesa, Tanzania reported that challenges in the health care system affect ART retention in care[352]. Participants in the current study also showed that the management systems for comorbidities such as hypertension, diabetes mellitus or mental illnesses are not integrated into chronic HIV care. In particular, as stated elsewhere[548], patients with HIV who develop mental illness experience challenges because of the multiple appointments necessary for HIV and mental illness. This discourages people from consistently taking their medication, for example, a person may have an appointment for mental illness on one day, and for HIV on the next. Therefore, HIV care services for patients should be all-inclusive services.

6.4.7 Summary of barriers to HIV care

In summary, the barriers to HCT in this study included: fear of HIV related stigma, poor knowledge and trust in ART care, inadequate availability of ART care services, the cost of free ART, presence of patriarchal society, traditional healing and fragmented health care system.

6.5 Key solutions to improve HIV care and treatment

Four key themes emerged as solutions for HCT from the analysis. These include,

6.5.1 Strengthening existing programs,

6.5.2 Implementing new programs,

6.5.3 Decentralizing and integrating services, and

6.5.4 Filling gaps in legislation

6.5.1 Strengthening existing programs

The government of Ethiopia has designed a number of relevant programs for comprehensive HIV/AIDS prevention, treatment, care, and support services. Nonetheless, the study participants, with one voice, mentioned a lack of consistent commitment to implement these programs. There have been several community awareness programs, voluntary counselling and

testing campaigns, and other HIV prevention, care, treatment and support programs. All these programs are now insufficiently performed[27 68]. Therefore, participants in the present study suggested there is a need to strengthen those programs. The following codes were listed under this theme: strengthening previous programs, involving religious groups, and using '*toko-shenni'* or one-to-five networks.

Strengthening existing programs is fundamental to achieving the ambitious targets developed by UNAIDS. Like findings from other studies[559 560], in this study, the vast majority of participants suggested strengthening the already established systems for HIV prevention, community outreach, clinical services, and other care programs for HIV. For example, a health worker from hospital said,

> *What I suggest is the government should work hard like at the beginning. Every activity was taken seriously during HIV emergence—the awareness creation, the VCT campaign, the involvement of NGOs, etc. Such courage should comeback.… The commitment of every individual should be as it used to be. (HWHo—07, BSc nurse, 27, female, hospital)*

On a similar note, another health worker from hospital said,

> *It is good if different campaigns such as VCT continue as it used to be. And for this to be conducted consistently, the government should have to support logistics and other financial issues. There shouldn't be a lack of kits at all. We shouldn't return people who come for testing due to lack of kits. (HWHo—09, Diploma nurse, 27 years old, female, hospital)*

These quotes showed that there is a high-level need for underpinning the existing programs. There was perceived negligence at each level—community, health workers and the program managers. The first quote showed that a gap existed as a result of the phasing out of NGOs, as described in sub-section 6.4.6. The gap in availability of HCT logistics may also be associated with phasing out of NGOs. Therefore, according to participants, there is a need to strengthen existing activities and strategies at all levels. The participants also said that there is involvement of or linkage with religious leaders but support and regular follow-up is inadequate. Hence, this should be strengthened to reduce the number of patients who fail to commence or withdraw from ART when visiting traditional or religious healing places. The following quote demonstrates the importance of religious leaders in counselling patients to use modern and traditional healing simultaneously.

> *…the religious leaders themselves should do the counselling that patients can take their medication while they are visiting the religious places. Patients listen more to their religious leaders than the health workers. (PHC—03, lost patient, 30, female, health centre)*

This speaker implied that counselling traditional healers on the simultaneous use of ART and traditional healing for patients with HIV has a greater role to play in keeping patients in lifelong

care. Ethiopia is a country where culture and religion are mixed, and the use of traditional healing is high. As religious leaders are highly regarded in the country, they could be a vital means of improving HCT programs. Given this, the collaboration with religious leaders could begin by actions as simple as considering HIV counselling within their congregation. Nowadays, there are some promising activities involving religious leaders in HCC programs. For example, MSH[561] is piloting a program called Ethiopia Network for HIV/AIDS Treatment, Care and Support (ENHAT-CS) program, a pilot project in Tigray and Amhara in North Ethiopia[562]. The program supports patients with HIV from selected health centres and hospitals who visit traditional healing places, and it is conducted in partnership with Ethiopian HIV positive people and religious associations.

Structures that are available for other purposes can also be used to run HIV care programs. In Ethiopia, there is a new structure, model or network called "one to five, locally called *toko-shenni*"[563]. As described in Chapter one, this network involves a group of six individuals or households in which members choose a group leader called convenor. The convenor or leader organizes and calls for meetings, plans activities and facilitates discussion on various issues such as health, agriculture, education, security and other social issues that are organized as packages. Furthermore, the leader mobilizes, monitors, and trains five others or households on the issues. The participants in this study suggested that HIV counselling and testing can be included as one of the packages in this network.

For example, a patient from hospital said,

> *I would suggest integrating HIV testing program into the "toko-shenni" or (one-to-five network). Government is using this program for its politics, why not for health then ha …. (Laughing)? (PHo—08, retained patient, 35 years old, female, hospital)*

Such a system might allow people to exchange information about HIV and its care. In particular, the network would improve availability of HIV testing programs and could be cost-effective and efficient. Even though there are no studies supporting the use of one-to-five networks in HIV care, the networks have been used to improve immunization coverage in pastoral communities in Ethiopia[17]. Therefore, the program could be scaled up for use in the HIV care program. Nevertheless, there could also be limitations with the program as the members are from the same local areas and there may be an issue of confidentiality and reated problems.

6.5.2 Implementing new programs

In addition to strengthening existing programs, it is also necessary to implement new programs to meet the ambitious UNAIDS 90-90-90 treatment targets. The following new programs were

suggested by study participants: HIV self-testing, house-to-house HIV testing, community ART distribution, and *teach-test-treat-link* strategy. HIV self-testing (SHT) is a screening process whereby a person collects a specimen from him- or herself, performs a test, interprets the result in private and refers oneself to a health worker for confirmation of any positive result. This program was supported by more than half of the study participants. They mentioned advantages like preventing HIV transmission to others, linking to ART care early and reducing stigma. A young HIV patient explained how SHT is important:

> *... village merchants have the money but they are not educated and they can do whatever they like. If they ask a village girl for sex, none will say 'no'. In addition, those merchants can officially have 4 or 5 wives .... you can imagine what will happen if he got infected by HIV. So, if they are able to test themselves, at least, they know their status and they may not infect others. And if it is for free, this will be outstanding. It also helps to decrease the stigma. (PHC—04, lost patient, 21, female, health centre)*

The above quote suggests that SHT is significant for individuals through knowing one's HIV status early and seeking care in a timely manner. In addition, the program is also significant for the public through reducing HIV transmission. The quote also shows that SHT may be very effective for special groups in the population who are at risk of HIV, considering the cost of HIV testing kits. On the other hand, there were participants who opposed the implementation of this new program. Failing to cope with emotions (e.g. shock or committing suicide), fear leading to not linking to care, revenge, shortage of testing material and lack of technique when testing were the disadvantages and worries identified. Some African countries such as Kenya[204], Malawi[205] and Zimbabwe[206]are implementing the program.

House-to-house (H2H) testing was also suggested by more than half the participants. H2H is an approach whereby HIV testing is undertaken in every house by peer educators, HEWs or trained lay counsellors. Supporters of this program noted the following advantages: reducing stigma, availability of services particularly for those patients who may be bedridden at home, preventing HIV transmission to others, and timely linking to ART care. Particularly, participants emphasized that this program has a considerable impact in reducing HIV related stigma. Conversely, other participants raised the following as being challenges to the success of home-based HIV testing: difficulties in disclosure, family stigma, fear of confidentiality, failing to cope with emotions and shortage of HIV kits. For example, a quote from a program coordinator from one local NGO mentioned,

> *House to house HIV testing? Nope, people (who are diagnosed through House-to-House HIV testing) may not come to care or be compliant if they linked in to the care. If the testing is especially conducted by HEWs, there may be fear of stigma. By the way, HEWs lacks motivation and responsibility. (Admin—05, Program coordinator, 27, female, local NGO)*

Interpreting the above quote, home-based HIV testing may not be successful if HEWs are involved in the screening program. This may be because most community health workers in Ethiopia are drawn from their home locations and people fear lack of confidentiality regarding their HIV status. This leads to limited trust in these community health workers. H2H has been implemented and found to be very effective in some African countries[190 515].

Community ART groups (CAGs) was another new solution suggested by some participants. CAGs is a program in which people who are HIV positive and who disclose their HIV status to other patients nearby form a group and collect pills for the group in rotation or via their representatives. Like other new suggested programs, CAGs was supported by some study participants and opposed by others. For example,

> *Yes, we are doing this (CAGs) and it doesn't have a problem. We have three cases who come from a very far place and they don't want to take from the nearby clinics for the fear of isolation. So, they collect their pills in rotation. Husband takes his wife's medication and wife takes her husband's. But now because we have the 'appointment spacing model', I don't think we need it. (HWHC—05, BSc nurse, 40, female, health centre)*

Even participants who supported the Appointment Spacing Model thought that CAGs was also an important program. Participants who were in favour of this program identified the following benefits: stigma can be reduced, group members can establish their own community, and patients can save their energy, time and transportation costs particularly those from remote areas. On the other hand, participants who were against this program argued that drugs may be misused (lost, sold and exchanged), people may not be compliant and associated complications such as treatment failure may develop, and disclosure may be a challenge. This program has also been implemented in Mozambique, Malawi, South Africa and Democratic Republic of the Congo[190].

Another new program which emerged from the analyses was the *teach-test-link-trace* model (TTLT). Peer educators are trained patients with HIV who disclose their HIV status publicly. Study participants acknowledged that these peer educators encouraged other patients with HIV to link into and remain in HIV care. These peer educators convince most patients with HIV who are resistant to starting ART when counselled by health workers, and also trace patients who have been lost from HIV care. In addition, in Ethiopia, it is known that HEWs visit every house on a daily basis to implement their 16 packages. Therefore, in cooperation with HEWs, it is possible to assign peer educators to counsel about HIV (*teach*), perform HIV testing (*test*), link HIV positive patients to HIV care (*link*) and trace lost patients house-to-house (*trace*). A new term called the *teach-test-link-trace* model was coined for the approach.

Peer educators are HIV+ people and it is easy for them to share their story and experiences, so that other HIV+ people easily accept their lived experiences. When they give a witness how ART helps to be what they are now, people start to lose their fear of HIV testing or going to health facilities to get HIV treatment ….so, yeah, this will be an outstanding. You see, the benefit is also for them (peer educator) because they are getting a little monthly salary…. (C—03, UHEP, 31, female, kebele)

Although not comprehensive, a peer education program piloted in 2007–08 in Ethiopia is becoming very effective in HIV counselling and tracing lost patients with HIV[69]. A qualitative study conducted in Ethiopia revealed the crucial role of case managers or peer counsellors in sustaining patients on treatment[564]. In South Africa, community adherence clubs working through lay counsellors or peer educators significantly improved retention in care and decreased the number of those LTFU[190]. Different countries support the involvement of peer educators in HIV care to enhance testing coverage, ART linkage, ART retention, and subsequently virological suppression[57 471].

6.5.3 Decentralizing and integrating service

History has provided a witness to the success of decentralization and task shifting in the context of ART services in Ethiopia[27] and other countries[565 566]. ART was provided in selected public hospitals initially and it has now been decentralized to the level of health centres[27]. Similarly, ART was once prescribed only by specialized internists but diploma-level nurses can now do it. More recently, the involvement of peer educators has had a dramatic impact in reducing ART discontinuation. Participants in the present study suggested decentralizing services to private clinics and health posts, and shifting the task to HEWs. Decentralization of ART to the level of health centres or district level hospitals has been promoted by other scholars from Africa[565 566].

The participants in the current study noted that they saw HEWs had had a significant impact in reducing maternal and child health morbidity and mortality, and they predicted similar achievements in HIV. Thus, they recommended the expansion of services into every community by providing ART in health posts.

…. the service should go to the community or to the people out there. For sure, it will be started in the health post. It will not be a problem too if ART is started in the private clinic but the government should support a budget since they are organizations for profit. History tells that it is possible. Initially, ART was prescribed by specialists and then by general practitioners in hospital, then by health officers and nurses in health centre. So why not by HEWs in the health post? (HWHo—06, reproductive health specialist, 49, male, hospital)

On the other hand, there were participants who questioned the success of decentralization and task shifting. According to them, HEWs are overloaded, have less capacity and commitment

to manage HIV, and are not trusted to be confidential by the community. For example, a volunteer supporter said,

> *Let me tell you one case. One patient defaulted from ART care, and the nurses gave to trace the patient's address to a HEW. She (the HEW) met him (defaulted patient) in a market and she said …. "Hey, why don't you attend your ART clinic?". This is in a market where mass is gathered, and you can imagine how he feels ashamed and traumatized. Thus, there are people who don't accept and trust those HEWs. (C—01, HIV volunteer, 39 years old, female, kebele)*

A HEW who is in charge of a health post also supported that it was not feasible to provide ART in health posts:

> *ART in health post? Well, with this issue, one, we need to have a training. Second, 80% of our work is field work— we are in office once a week. So, people may not see us and default or likes may happen. The office arrangement does also not allow for ART drugs to store in a way it should be. Yeah… it needs a lot of resources. And the other is we are too busy—we are collecting taxes, organize microfinance, doing other non-health related activities. So, we couldn't provide ART in health post. (C—03, UHEP, 31, female, kebele)*

From the above quotes, the decentralizing of ART care services is very challenging from the perspectives of patients and the HEWs themselves. The HEWs who were in charge of health posts did not support the commencement of ART programs in them. Furthermore, trust in the HEWs was also described as a challenge by other study participants. There are countries, however, who use community health workers to distribute ART. In these countries, the community health workers are only responsible for ART distribution, not other health activities. In Ethiopia, HEWs are responsible for implementing 16 packages and it could be a significant challenge for them to provide ART care services as well[13 14]. With regard to ART in private clinics, there were study participants who opposed launching ART services in private clinics. They believed private clinics might lack the capacity to run programs and may misuse the drugs (e.g. selling) as described in sub-section 6.4.4. On the other hand, study participants who had observed the successful management of the tuberculosis program proposed the commencement of ART services in private clinics. One of the district town health office experts also supported this argument.

> *ART in private clinics is good. Because, there are rich people who don't need to see public clinics so we can get those patients through private clinics. By the way, we are having a plan to start ART in one private clinic. I have told you that we start HIV testing in selective private clinics, and we propose three private clinics for this year. (Admin—01, BSc Nurse, 32, male, Town Health Office)*

Furthermore, this has been achieved in private hospitals in Addis Ababa, capital city of Ethiopia[565]. Alternatively, it may be possible to introduce a public–private partnership in which health workers from private clinics can treat patients in public hospitals or health centres[567].

Integrating HIV and AIDS services with other health care services such as mental health and other chronic illnesses would enhance availability of and access to treatment and make programs more cost-effective. It is evident that the sophisticated combined highly active ART (HAART) has transformed HIV into a treatable chronic disease. However, the rise of non-communicable diseases (NCD) such as cardiac illnesses, cancer, mental illness and diabetes mellitus in most HIV affected countries has led to concerns that patients with HIV may be saved from AIDS related diseases only to develop these NCDs[568]. Thus, it seems natural that there is a high need to integrate NCD and HIV care. Most participants supported integrating the management of chronic illnesses. They were very confident because such integration has been shown to be successful in previous programs for sexually transmitted infection management, tuberculosis management and family planning. In Swaziland, as a pilot project in selected HIV clinics, screening for diabetes, hypertension and cervical cancer was been performed routinely for patients with HIV[569]. Similarly, a hospital in Malawi also piloted combining HIV and NCD care[570]. A systematic review on integrating NCD with HIV also found that it was feasible and effective to combine both services[571]. Furthermore, integration of services for HIV and other chronic illnesses to facilitate uptake and linkage in HIV services across the continuum of care has been supported by different studies[235 572 573]. Ethiopia has been using the experience of leveraging HIV care programs into other chronic illness care but it is yet to combine both services[574].

6.5.4 Filling gaps in legislation

The legislation of FDRE has laws related to HIV. The revised criminal code (2005)[26] provides for punishment up to and including the death penalty for the intentional spread of HIV. The legislation also guarantees the right to privacy (confidentiality) of HIV status except for children, bedridden or seriously ill patients, and mentally incapable patients[27]. Yet, there are gaps within the existing legislation. Participants in the study identified gaps in laws about disclosure and traditional healing and stated that these gaps were challenges to achieving the desired outcomes of ART. For example, the gap in disclosing partner's HIV status is one of the sensitive issues. A husband who does not disclose his HIV status to his pregnant wife prevents her and the baby receiving HIV care services. Similar problems occur if a mother who is HIV positive does not disclose her status to her husband. Thus, participants in the present

[26]Article 514, criminal code, FDRE constitution

[27]Articles 26 FDRE constitution

study suggested the need to develop legal provisions to mandate notification of HIV status to one's partner. For example,

> *If a husband for instance doesn't disclose his HIV status for his wife and if his wife got pregnancy, this is a crime and is not different from stabbing to death. He is infecting two lives at the same time. This is happening. We have to try our endeavour to counsel them to disclose their status and bring their partners to care. If this fails, the partner should be sued. I can't see this is clashing with confidentiality. They are husband and wife and this should be treated differently. (C—04, rural HEW, 33, female, kebele)*

The quote reflects that partners need to disclose their HIV status to each other for the sakes of themselves and their child/ren. There are inconsistent laws in countries and among states within a country with regard to mandatory HIV status disclosure to a partner. For example, in Australia, HIV positive people in Tasmania are required to disclose their status before sexual contact, and similarly before sexual intercourse in NSW but this is not required in Victoria[575]. In the US, the penalty for nondisclosure in North Carolina is stricter than in Alabama and supported by HIV criminalization by HIV care providers [576].

Another issue related to gaps in legislation covering HIV care provision is the importance of implementing a legal framework regarding traditional healers. In sub-section 6.4.5, it is noted that there are traditional health practitioners who declare HIV cured and obligate patients with HIV to stop their treatment. A pastor declaring that a person with HIV is cured and telling that person to discard their pills can be accused of killing or attempting to kill that person. Furthermore, the pastor is providing false witness if this person is not cured. Similar activities happen in the Orthodox religion. These scenarios are against the law in some countries, and yet they are the most difficult to overcome. For example,

> *There are religious fathers who prohibit pills while people visit the Holy place. If this happens, we may consider the law but teaching takes precedents. If you see the Protestants that broadcasted on a TV show (live TV show where pastors declare HIV cure), this is really serious. At least, let them tell the patients to go and re-check, or not to stop the drugs…. but I don't think they will. If not, there should be a law. (HWHo—08, BSc nurse, 36, male, hospital)*

Similarly, a religious leader backed up the establishment of a legal framework

> *As a pastor, I have told you earlier that my job is to pray for people, not to order to discard their pills. Recently, three people with HIV came to me to cure them from the virus. Then, I had to pray, pray and pray in front of God, and finally three of them cured by my service. They went to re-check and were negative. I am right to declare the cure (HIV) but I shouldn't order to throw pills. However, there are pastors who emotionally order people to discard pills, and they should be asked by law—they do this to get acceptance from the attendants. I support considering this to be included in the legislation. (C—10, Pastor, 28, male, Protestant Christian)*

These quotes demonstrate the role of traditional healers in modern HIV care management. Examples such as Orthodox priests not allowing patients to bring pills to Holy Water places, protestant Christian pastors broadcasting on live TV shows that they have cured HIV by praying, and religious fathers passing a rule for followers to discard pills led participants to consider the need for legal provision. Nevertheless, they pointed out the problems of filling these gaps systematically. In South Africa, it is against the law for traditional healers to treat undiagnosed patients with HIV, and they are obliged to refer people to a hospital if they visit their place before diagnosis[577].

6.5.5 Summary of solutions for HIV care

In summary, the following solutions were suggested for improvement of HCT: strengthening current HIV programs, implementing new programs such as SHT, home-based HIV testing and TTLT model, decentralizing services to health post and private clinics, integrating HIV care services with NCD care, addressing mandatory HIV status notification to partner, and fixing the gap between modern and traditional medicine.

6.6 Strengths, limitations, conclusions and recommendations

6.6.1 Strengths

This study was conducted following a quantitative study and it helps to contextualize the complex concept of HCC. A wide range of perspectives was collected from participants in the qualitative study, who represented many types of organization: health centre, hospital, private clinic, town and zonal district health office, and local and global NGOs. The study explored additional important barriers that were not identified in the retrospective cohort study. Above all, new barriers were found that were not known to program managers but revealed by the other study participants, and this could be of particular interest to policy makers. Furthermore, the study produced new solutions for each stage of the HCT continuum. Specifically, some of the solutions that emerged such as the TTLT model could be a holistic way to address the whole HCC. Lastly, the cross-analyses conducted to explore the barriers to HIV diagnosis, ART linkage and retention in care from multiple groups could give insight into modifications needed in the linearly constructed existing HCC.

6.6.2 Limitations

Along with the above strengths, the present study possesses some limitations. First, only a small number of study participants (n=5) were HIV care program managers. Nevertheless, the total number of interviewees (35) was within the acceptable range of sample size for qualitative studies. Additionally, most of the findings from the four target audiences, including from the

HIV program managers, complement each other. Second, because no participants from private health facilities were included, anyone other facilitators, obstacles and interventions may have been missed that affect patients attending private ART clinics, HIV health care providers working in private ART clinics and community advocates supporting patients with HIV from private ART clinics. However, the participants included in the present study highlighted possible factors or interventions for HCT related to ART in private clinics. Third, the study included only participants from Jimma, and females were overrepresented the study. Although we need multi-site studies and heterogeneous participants to explore more contextual entities, it is believed that data saturation was reached. Furthermore, most findings from qualitative studies cannot be generalized beyond the context of a study setting. Although it may have been possible to conduct interviews with participants in a different way, face to face was the only choice for collecting data because telephone interviews were not possible because of several factors: participants had limited access to mobile phones, the mobile phone network is unreliable and there is no consistent supply of electricity for charging mobile phones, particularly in the villages. Lastly, it is common for an interviewer and interviewee to be of the same sex for cultural sensitivity and to manage potential power imbalances, and failing to consider the gender sensitive approach to the qualitative data collection may be another limitation although point of saturation was attained.

6.6.3 Conclusions

In conclusion, the study findings highlight that implementing new programs, improving knowledge of and trust in ART care, and support from partners, families, HIV health care providers and other volunteers facilitated the HCC. Barriers that impeded the HCC included: the fear of being seen by others, poor availability of HIV care services, the role of traditional practices, the hidden costs of free ART, poor knowledge of and trust in ART, and a fragmented health care system. This qualitative study identified several programs for tailoring interventions to enhance HIV/AIDS treatment and care at each point of the continuum of care: strengthening existing programs, implementing new programs such as SHT, H2H, CAGs and TTLT model, decentralizing services to the level of health posts and private clinics, and filling gaps in legislation.

6.6.4 Recommendations

Based on the above conclusions, the following recommendations are proposed:

1. Some of the suggested facilitators identified in the current study, particularly the new programs for HCT, should be scaled up to other ART clinics. From the in-depth interviews,

it was observed that ART clinics outside Jimma town were yet to apply the test and treat strategy and Appointment Spacing Model. Hence, scaling up of these programs would improve the linkage to and retention in ART care throughout the country, and this, in turn, would enhance the achievement of the second and third 90 of the UNAIDS goals.

2. Knowledge of ART had improved over time but it was still low in certain groups such as rural residents and women. In particular, because of the cultural practices and presence of patriarchy in Ethiopia, women had less access to HIV care. This HIV care inequity has to be addressed, and the involvement of patients with HIV in the HCT particularly has to be encouraged.
3. Similarly, the present qualitative study revealed that trust in the HIV care system and HIV care providers has improved over time; nevertheless, the lack of trust in HEWs is frustrating. Given that the government of Ethiopia is involving HEWs in most of the primary health care activities including the continuum of HIV care, strategies have to be designed to build people's trust in these community workers.
4. In the present study, HIV related stigma was found to be a barrier to HIV diagnosis, ART linkage and lifelong retention. Hence, an innovative and contextual exploration and solution is required to halt it. Most of the available strategies to intervene in stigma are at the individual level, hence, interventions should be explored that work beyond the individual level such as community, health care provider and program level drivers.
5. ART for sale—the *known unknowns*—was found to be a unique barrier in the present study. This issue should first be assessed in other regions in the country, and then, strategies to manage it and its complications should be explored. There must be mechanisms developed to manage illicit selling of ART by some patients and private ART clinics. Further, the government has to develop a program that allows patients to enrol in one ART clinic only. Health workers ask to see identity cards (ID) of patients with HIV when they register them in the ART log book. Nevertheless, patients can illegally obtain more than one ID which means that they can be registered in more than one ART clinic. Thus, the *kebele*, the place where ID cards are issued, should also be responsible for this act and a unique system or software should be developed in the country.
6. The involvement of religious leaders in the continuum of HIV care and the integration of traditional healing services with modern HIV care must be a priority area. In countries like Ethiopia, where 80% of the people use traditional medicine or healing and the vast majority of people are strongly integrated with culture and religion[578], the involvement of traditional healers or religious ministers can offer a paramount advantage in HIV diagnosis, ART

linkage and retention in care. Further programs to extend those on pilot studies[562], are needed to examine the impact of traditional healers on the HCT.

7. Ethiopia has to clarify the issue of mandatory HIV notification in its legislation. This should also be discussed and clearly written in each of the regional states in the country. Additionally, the need for a legal framework should be discussed explicitly to manage circumstances where traditional healers treat undiagnosed patients with HIV and patients lost from ART follow up, declare HIV cured and preach to stop ART. Experiences of other neighbouring countries could also be contextualized to clarify this problem.
8. Further study is required to prioritize the suggested solutions for HIV diagnosis, (SHT, H2H and TTLT model), and ART linkage and retention (test and treat strategy, TTLT model and community ART groups). Similarly, additional study is also required to investigate whether ART in health posts and private clinics at Zone or district level is relevant, feasible and acceptable. The suggested solutions in the current study give a glimpse of possibilities for improving HCT in Ethiopia.

Chapter 7

Nominal Group Technique

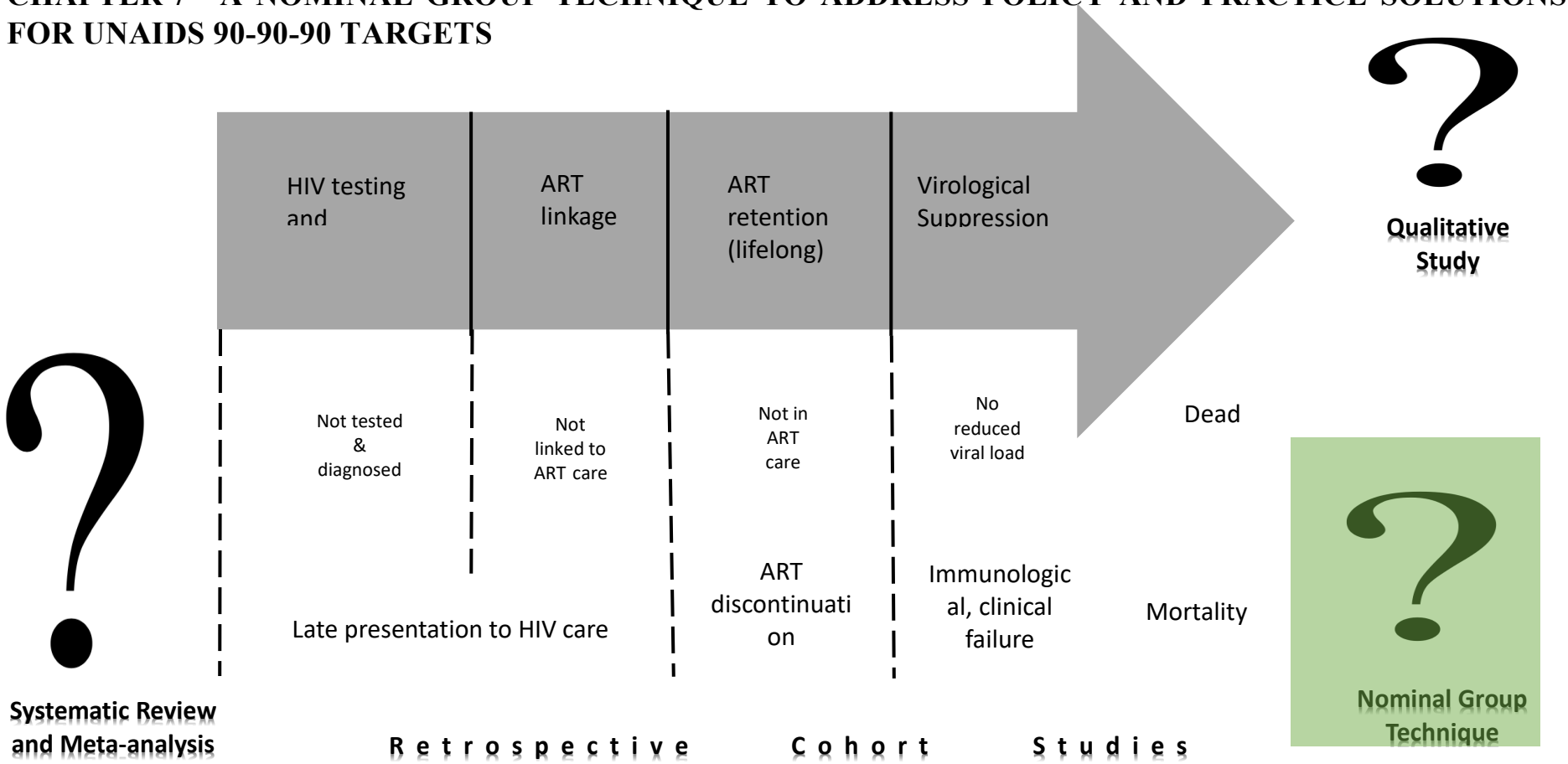

Figure 7-1: A nominal group technique method on policy and practice solutions for the UNAIDS 90-90-90 goals in Southwest Ethiopia[28]

[28] This figure needs to be viewed in colour

7.1 Introduction

Chapter seven discusses the findings of the NGT, shown in figure 7.1 shaded in green, to rank the relevance, feasibility and acceptability of solutions presented in chapter six, and seek expert advice from key stakeholders. This chapter has four sections. Section one presents demographic characteristics of the members of the expert panel. Section two presents the suggested solutions for HCT, and section three deals with discussion of these solutions. The last section presents conclusions and recommendations of the study. This chapter presents the macrosystem level of the SEM.

7.2 Characteristics of panel of experts

Eighteen (18) members of the 25 identified and invited panellists participated in the discussion, giving a 72% acceptance rate. The panel of experts comprised academics, service providers, and government and non-government officials. All except three were males, and median age of the participants was 39 (29-63) years. The academic experts were three full professors in public health, reproductive health and epidemiology and four assistant professors in epidemiology, reproductive health, health service management and mental health. All academic experts had backgrounds in public health and were engaged in teaching and research activities and HIV program management roles. Non-academic experts were involved in ART clinic, HIV care program management and program coordination. The expert panel represented a range of organizations involving Jimma University, JUTH, Jimma health centre, Jimma Town Health Office, Jimma Zonal Health Department, Southwest region of ICAP and Southwest region of OSSA.

7.3 Solutions for HIV care and treatment

In the qualitative chapter, the lists of suggested solutions to improve the access to, quality and equity of HCT were presented in section 6.5. In the present study, the expert panellists were asked to suggest additional solutions and prioritize the solutions explored in the qualitative chapter using a self-administered questionnaire (Annex 3.16). The researcher presented the suggested solutions before inviting the experts to discuss them. Based on the feasibility, acceptability and relevance criteria, the panel of experts ranked the solutions before (round 1) and after (round 2) the discussion.

All panel members took part in round 1 rating and the discussion, and 16 members participated in round 2 rating. Two experts, a clinician and a program coordinator, withdrew from the discussion because of unforeseen emergency commitments. Table 7.1 shows individual ratings for suggested solutions for HCT in round 1. SHT, filling gaps in legislation

(law) and H2H were rated highest with 14 members ticking them as relevant, while ART_{HP} was ranked lowest with 11 votes. In terms of feasibility, law and ART_{PC} were rated highest by 15 and 12 participants respectively. Only six (6) people agreed that H2H is a feasible solution and this was the least feasible solution. Asked which of the suggested solutions were most acceptable, law and ART_{PC} were rated highest with 13 members, while H2H was the least acceptable solution. Calculating the average score for relevance, feasibility and acceptability, the following solutions were recommended *in order* in the first round: law, ART_{PC}, SHT, TTLT model, CAGs, ART_{HP}, and H2H.

Tables 7.2 describes individual ratings for suggested solutions for HCT in round 2. SHT, law and TTLT were the top three solutions in round 2, while ART_{PC} was ranked least relevant by 9 panel members. In terms of feasibility, law and H2H were rated highest with 13 and 9 votes respectively, while only three (3) people agreed that ART_{HP} was a feasible solution. Asked to rate the acceptability of suggested solutions, law and SHT were rated highest with 13 and 9 members. However, H2H, ART_{PC} and ART_{HP} were the least acceptable solutions with fewer than half of the study participants identifying acceptability of these solutions. Calculating the average scores for relevance, feasibility and acceptability, the following solutions were recommended *in order* in the second round: law, SHT, TTLT model, H2H, CAGs, ART_{PC}, and ART_{HP}.

Table 7-1: Relevance, feasibility and acceptability of suggested solutions for improving HIV care and treatment (Round 1)

P	Sex	Age (years)	Profession of panel members	Round 1 (before discussion; 9:30 am) on 21 December 2017; Jimma Central Hotel, Jimma, Southwest Ethiopia P= participants R=relevant; F=feasible; A= acceptable; 1=Agree; 2=Neutral; 3=Disagree																			
				SHT			**H2H**			**TTLT**			**ART_{HP}**			**ART_{PC}**			**CAG**			**Law**		
				R	**F**	**A**	**R**	**F**	**A**	**R**	**F**	**A**	**R**	**F**	**A**	**R**	**F**	**A**	**R**	**F**	**A**	**R**	**F**	**A**
P1	---	--	--- missing	1	1	1	1	2	1	2	2	2	1	1	1	3	3	1	1	1	1	2	2	2
P2	M	39	MSc in Public Health	1	2	2	1	2	2	1	1	1	3	3	3	3	3	3	1	2	2	1	1	1
P3	M	30	MSc in Public Health	1	3	1	2	3	2	1	3	3	1	3	1	1	1	1	1	1	1	1	1	1
P4	F	53	Professor (Public Health)	1	3	2	1	3	2	1	3	2	1	1	3	1	1	1	1	1	2	1	2	2
P5	M	60	Professor (Epidemiology)	1	1	2	1	1	2	2	2	2	1	1	1	1	1	1	1	1	2	1	1	1
P6	M	48	MSc in Public Health	1	1	1	1	1	2	1	1	1	3	3	3	1	1	1	2	2	2	1	1	1
P7	M	58	BSc Nurse	3	3	3	1	1	1	2	2	2	3	3	1	1	1	1	2	2	2	2	1	2
P8	M	30	BSc Nurse	1	1	1	1	1	2	1	1	1	1	1	3	1	1	1	1	2	2	1	1	1
P9	F	48	BSc Nurse	1	1	1	2	2	2	1	1	1	2	2	2	1	1	1	3	3	3	1	1	1
P10	M	32	Associate Professor (HSM)	1	3	2	1	3	3	1	1	1	1	2	1	1	1	1	1	1	1	1	1	1
P11	M	63	Professor (Reproductive Health, RH)	1	1	2	1	2	1	1	1	3	1	1	1	1	2	1	1	1	1	1	1	1
P12	M	38	Assistant Professor (RH)	1	1	2	1	2	1	1	1	1	1	1	1	1	1	1	1	2	1	1	1	1
P13	M	31	Assistant Professor (Epidemiology)	3	3	3	2	2	2	1	1	1	3	3	3	2	2	2	1	1	1	1	1	1
P14	M	30	Assistant Professor (Epidemiology)	1	2	2	1	2	2	1	2	2	2	1	2	2	1	2	2	1	2	1	2	2
P15	F	45	Associate Professor (RH)	1	2	1	1	2	3	1	3	3	1	2	1	1	1	1	1	3	3	1	1	1
P16	M	45	Master of Business Administration	1	1	1	1	1	2	2	2	3	1	2	3	1	1	1	3	3	3	1	1	1
P17	M	33	Assistant Professor (Epidemiology)	1	1	1	1	1	1	1	1	1	3	3	3	3	3	3	1	1	1	1	1	1
P18	M	29	MSc in Public Health	1	3	2	1	3	1	1	1	1	1	1	2	1	3	2	1	3	1	1	3	3
Sum				**1**	**16**	**9**	**8**	**15**	6	6	**14**	**10**	**9**	**11**	**8**	**8**	**13**	**12**	**13**	**13**	**9**	**8**	**16**	**15**	**13**
				2	0	3	**8**	3	**8**	**10**	4	5	5	2	4	3	2	2	3	3	5	7	2	2	4
				3	1	6	2	0	4	2	0	3	4	5	6	7	3	4	2	2	4	3	0	1	1

SHT is a screening test whereby a person who wants to know their HIV status collects a specimen, performs a test and interprets the result in private. this.**H2H** refers to conducting HIV testing in every house by HEWs, trained lay counsellors or peer educators.This process includes collecting a specimen, performing a test, interpreting the result and referral for further follow-up test or linkage (if the result is positive). **TTLT** involves formally employing and assigning peer educators (29) with HEWs (health extension workers) to teach the community about HIV, conduct HIV testing, linking into ART care and tracing lost patients coined as *Teach–test–link–trace strategy* (TTLT). **ART_{HP}** is the provision of ART in health posts by HEWs. **ART_{PC}** is the provision of ART care in private health clinics by the health workers employed in the clinic. ART will be provided free by the government. **CAGs** is a process whereby stable HIV+ persons (who disclose publicly) living establish a group nearby and collect their medications in rotation. They choose a leader who arranges monthly meetings to count pills and check overall ART adherence. The people on ART are told to visit the clinic whenever they feel ill. **Law** refers the need for legislative changes to allow prosecution of HIV+ men who do not disclose their status to wife after repeated counselling (because this prevents the woman from timely engagement with HIV care, and prevent HIV transmission to children when pregnant. Another scenario is the need for legislation permitting prosecution of religious leaders or witch doctors who declare HIV has been cured because this is a false witness and against the law. In addition, if religious leaders or witch doctors tell patients to stop ART and if patients die or become seriously sick as a result of this, he/she is responsible for the death or attempt, and this is against law.

29 peer educators are volunteer HIV positive persons who disclosed themselves publicly

Table 7-2: Relevance, feasibility and acceptability of suggested solutions for improving HIV care and treatment (Round 2)

P	**Round 2** (after discussion; 2:30 pm) on 21 December 2017; Jimma Central Hotel, Jimma, Southwest Ethiopia																				
	P= Participants p=relevant; F=feasible; A=acceptable; 1=Agree; 2=Neutral; 3=Disagree																				
	SHT[30]			**H2H**[31]			**TTLT**[32]			**ART_{HP}**[33]			**ART_{PC}**[34]			**CAG**[35]			**Law**[36]		
	R	**F**	**A**	**R**	**F**	**A**	**R**	**F**	**A**	**R**	**F**	**A**	**R**	**F**	**A**	**R**	**F**	**A**	**R**	**F**	**A**
P1	1	2	3	3	2	3	1	1	1	3	3	3	3	2	3	1	1	1	1	1	1
P2	1	2	2	1	2	2	1	1	2	2	2	2	3	3	3	2	2	2	1	1	1
P3	1	1	1	1	1	1	2	2	2	2	2	2	3	3	3	2	2	2	1	1	1
P4	1	3	1	2	3	3	1	2	3	1	3	2	1	1	1	1	1	1	1	1	1
P5	1	1	2	1	1	2	1	2	3	1	1	1	2	2	2	1	2	2	2	1	2
P6	1	1	1	1	1	1	1	1	1	3	3	3	3	3	3	1	1	1	1	1	1
P7	1	2	1	1	1	1	2	2	1	1	2	1	1	1	2	2	1	2	1	1	1
P8	1	1	1	1	1	2	1	1	1	1	1	3	1	1	1	1	1	1	1	1	1
P9	2	2	2	2	2	2	1	1	1	1	2	2	1	1	2	1	2	2	1	1	1
P10	1	3	1	1	1	3	1	1	2	1	2	1	1	1	1	1	3	2	1	1	2
P11	1	1	1	1	1	1	1	2	2	1	2	2	1	2	2	1	2	2	1	2	2
P12	1	3	2	2	2	2	1	3	2	1	2	2	1	1	1	1	1	1	1	1	1
P13	1	3	2	1	1	2	1	1	3	1	1	1	2	1	1	1	1	1	1	2	1
P14	2	3	1	2	1	2	2	2	1	2	2	1	2	1	2	1	2	2	2	2	1
P15	1	1	1	2	2	2	1	1	1	2	2	2	3	3	3	2	2	2	1	1	1
P16	1	3	3	1	3	1	1	3	1	2	3	1	1	2	3	2	3	1	1	1	1
1	**14**	**6**	**9**	**10**	**9**	5	**13**	**8**	**7**	**9**	3	6	**8**	**8**	5	**11**	**7**	7	**14**	**13**	**13**
2	2	4	5	5	5	**8**	3	6	6	5	**9**	**7**	3	3	**7**	5	**7**	**9**	2	3	3
3	0	6	2	1	2	3	0	2	3	2	4	3	5	5	4	0	2	0	0	0	0

30 **SHT** is a screening test whereby a person who wants to know their HIV status collects a specimen, performs a test and interprets the result in private.

31 **H2H** refers to conducting HIV testing in every house by HEWs, trained lay counsellors or peer educators. This process includes collecting a specimen, performing a test, interpreting the result and referral for further follow-up test or linkage (if the result is positive).

32 **TTLT (***Teach–test–link–trace strategy* involves formally employing and assigning peer educators (32) with HEWs (health extension workers) to teach the community about HIV, conduct HIV testing, linking into ART care and tracing lost patients.

33 **ART_{HP}** (antiretroviral therapy in health post) is the provision of ART in health post by HEWs.

34 **ART_{PC}** (antiretroviral therapy in private clinic) is the provision of ART care in private health clinics by the health workers employed in the clinic. ART will be provided free by the government.

35 **CAG** is a process whereby stable HIV+ persons (who disclose publicly) living establish a group nearby and collect their medications in rotation. They choose a leader who arranges monthly meetings to count pills and check overall ART adherence. The people on ART are told to visit the clinic whenever they feel ill.

36 **Law** (filling gaps in law) refers the need for legislative changes to allow prosecution of HIV+ men who do not disclose their status to wife after repeated counselling (because this prevents the woman from timely engagement with HIV care, and prevent HIV transmission to children when pregnant. Another scenario is the need for legislation permitting prosecution of religious leaders or witch doctors who declare HIV has been cured because this is a false witness and against the law. In addition, if religious leaders or witch doctors tell patients to stop ART and if patients die or become seriously sick as a result of this, he/she is responsible for the death or attempt, and this is against law.

In both rounds, law and SHT were among the top three recommended solutions, and ART_{HP} was among the least recommended solutions. TTLT was ranked fourth before discussion but third after the discussion. As shown in Table 7.3, the Wilcoxon signed rank test showed no statistical difference between round 1 and round 2 for any suggested solutions. In the open discussion, all the suggested solutions were discussed, and expert panels forwarded directions on how these programs can be implemented. The summarized findings below are based on the rank of round 2 and discussion during the workshop.

7.3.1 Filling gaps in legislation (Law)

The constitution of FDRE has set laws related to HIV. The Revised Family Code of July 2000[37] sets the minimum age for marriage (18 years old), freedom of marriage, and equal rights of the partners before, during and after marriage, and the need for HIV testing before marriage. If implemented, this legislation carries a significant advantage for halting the transmission of HIV and reducing the vulnerability of women and girls[38]. The revised criminal code (2005)[39] allows for punishment up to and including the death penalty for the intentional spread of HIV. The constitution also guarantees the right to privacy (confidentiality) of HIV status except for children, bedridden or seriously ill patients, and mentally incapable patients[40].

However, gaps remain within the existing legislation. Husbands may choose not to disclose their HIV status to their wives, and this may affect women and unborn children, and the same applies to husbands if their wives do not disclose their HIV status. According to the participants in the NGT, failing to disclose to a partner equates to intentional transmission of HIV in terms of public health implications. Furthermore, the PMTCT program is ineffective if a mother is linked late to HIV care. The untimely disclosure of HIV can also be associated with poor HIV treatment outcomes. The expert panel suggested the inclusion of mandatory disclosure of one's HIV status to a partner, or a combination of legal framework and promotion of voluntary notification. An extended effort has to be made to enhance people's understanding of the benefits of disclosure so that patients with HIV will disclose their HIV status voluntarily. Meanwhile, developing this law would reduce HIV transmission to unborn babies, promote early presentation to HIV care and, finally, increase survival. An expert from the mental health department supported this.

[37]"The Revised Federal Family Code of Ethiopia", Federal Negarit Gazetta of the Federal Democratic Republic of Ethiopia (July 4, 2000) 6th Year Extra Ordinary Issue No.1, Addis Ababa
[38]Article 13(b), The Revised Family Code, FDRE constitution
[39]Article 514, criminal code, FDRE constitution
[40]Articles 26, FDRE constitution

Table 7-3: Wilcoxon Signed Rank Test output for HIV care and treatment solutions

Solution	Criteria	Round				Percentiles			Test [a] (P-value)
			N	Mean	SD	25th	50th	75th	
SHT	Relevance	Round 1	16	1.00	0.000	1	1	1	0.317
		Round 2	16	1.06	0.250	1	1	1	
	Feasibility	Round 1	16	1.63	0.719	1	1.5	2	0.194
		Round 2	16	1.94	0.929	1	2	3	
	Acceptability	Round 1	16	1.56	0.629	1	1.5	2	0.763
		Round 2	16	1.63	0.619	1	2	2	
H2H	Relevance	Round 1	16	1.27	0.594	1	1	1	1.000
		Round 2	16	1.27	0.458	1	1	1	
	Feasibility	Round 1	16	1.67	0.724	1	2	2	0.234
		Round 2	16	1.93	0.799	1	2	3	
	Acceptability	Round 1	16	1.67	0.816	1	1	2	0.305
		Round 2	16	1.93	0.704	1	2	2	
TTLT	Relevance	Round 1	16	1.13	0.342	1	1	1	1.000
		Round 2	16	1.13	0.342	1	1	1	
	Feasibility	Round 1	16	1.44	0.629	1	1	2	0.417
		Round 2	16	1.63	0.806	1	1	2	
	Acceptability	Round 1	16	1.69	0.793	1	1.5	2	1.000
		Round 2	16	1.69	0.793	1	1.5	2	
ART_{HP}	Relevance	Round 1	16	1.63	0.806	1	1	2	0.527
		Round 2	16	1.50	0.632	1	1	2	
	Feasibility	Round 1	16	1.81	0.834	1	2	2.75	0.608
		Round 2	16	1.94	0.680	1.25	2	2	
	Acceptability	Round 1	16	2.06	0.854	1	2	3	0.564
		Round 2	16	1.94	0.772	1	2	2.75	
ART_{PC}	Relevance	Round 1	16	1.56	0.892	1	1	2.75	0.180
		Round 2	16	1.75	0.931	1	1	3	
	Feasibility	Round 1	16	1.69	0.873	1	1	2.75	0.317
		Round 2	16	1.56	0.892	1	1	2.75	
	Acceptability	Round 1	16	1.75	0.856	1	1.5	2.75	0.480
		Round 2	16	1.63	0.885	1	1	2.75	
CAGs	Relevance	Round 1	16	1.31	0.602	1	1	1.75	0.480
		Round 2	16	1.19	0.403	1	1	1	
	Feasibility	Round 1	16	1.75	0.775	1	2	2	0.414
		Round 2	16	1.63	0.719	1	1.5	2	
	Acceptability	Round 1	16	1.56	0.629	1	1.5	2	0.564
		Round 2	16	1.50	0.632	1	1	2	
Law	Relevance	Round 1	16	1.00	0.000	1	1	1	0.083
		Round 2	16	1.19	0.403	1	1	1	
	Feasibility	Round 1	16	1.25	0.577	1	1	1	0.577
		Round 2	16	1.38	0.619	1	1	2	
	Acceptability	Round 1	16	1.31	0.602	1	1	1.75	0.739
		Round 2	16	1.38	0.500	1	1	2	

[a] Test refers to Wilcoxon Signed Rank Test; N= number of participants; SD =standard deviation; SHT= self-HIV testing; H2H= house to house HIV testing; TTLT= teach, test, link and trace strategy; ART_{HP}= antiretroviral therapy (ART) in health post; ART_{PC}= ART in private clinic; CAGs= community ART groups; law= filling gaps in law

"……. the same is true with HIV disclosure. There must be a legal framework that obligate partners to disclose their status. Otherwise, the harm will be beyond the individual partners. For example, it is a risk to the coming baby. There should be a law……" (Assistant Professor, Psychiatry Department, University).

Other members, however, suggested having counselling and voluntary notification rather than prosecution. Mandatory notification may inhibit people from being tested if the law obligates them to tell their status to their partner. For example, one expert said,

"It is good idea in terms of protecting the partner (or preventing HIV transmission). However, it has its own downsides. If the notification is solely mandatory, people may not get tested– they have a fear that the law obligates them to tell their status to their partner. We better do a sort of promotion on voluntarily notification and legal framework as a final option." (Associate Professor, Health Service Management, University).

Another gap in existing legislation is the absence of a legal framework for when traditional healers or religious ministers declare HIV cured, and/or order patients with HIV to discard ART pills. Participants recognised this as a problem and against the current HIV science. Patients may be deceived into thinking that they were free of the virus and may have unsafe sex leading to increased HIV transmission. The religious ministers' advice may also mislead patients to discard their ART pills, leading to poor progress and decline in patients' survival. Furthermore, such non-compliance with ART drugs may lead to drug resistance. To limit these problems, the expert panel pointed out that there should be a law that makes traditional healers and/or religious ministers responsible for their acts. The panel members suggested that the inclusion of legal provision for such scenarios will improve HCT programs. For example, an expert from Psychiatry Department stated that

"Collaboration with religious leaders? It is good and bad. It is good because patients can get psycho-social and spiritual supports. But if we can come to treatment and cure, the religious fathers are not good. They shouldn't declare that somebody is cure from HIV, and the government should develop a rule to sue them. "(Assistant Professor, Psychiatry Department, University)

Other participants were reluctant to suggest imposing a law on religious or traditional healers. They stated that it may result in a reverse effect on the HCC, because religious leaders may bless their whole congregation but it is up to the interest of the individual patients to accept the decision. Instead, participants proposed raising awareness of patients with HIV, religious leaders and traditional healers and the community at large. Alternatively, they suggested

designing a positive reinforcement strategy rather than legal actions or putting rules and regulations in place. For example, a certificate could be awarded to partners who notify their HIV status voluntarily.

7.3.2 Self-HIV testing (SHT)

SHT is a process whereby a person who wants to know his/her HIV status collects a specimen, performs a test and interprets the result privately. This is a screening test and any positive result will be confirmed by a health worker. The panel members discussed that SHT was a novel program and could reduce HIV related stigma. Panel members suggested a combination of SHT and facility-based HIV counselling for more effective outcomes. The SHT program will provide the opportunity for people to receive adequate counselling in health facilities while self-testing at their convenience. By providing such an opportunity, the program will focus on higher risk groups who do not engage with HIV care services, assuming that those who willingly visit a health facility are being tested. In addition, it was also recognized that the SHT program would be instrumental in limiting HIV transmission and promoting early presentation for HIV care. A panellist stated,

> *"With the issue of self-HIV testing, why don't do the combination? For example, a patient can get counselling service in a clinic but could do HIV testing by him- or herself where ever he wants. One way, the program is focusing in higher risk groups and, the other way, it avoids the minuses of self-HIV testing you have mentioned like suicidal attempt, stigma, etc." (Assistant Professor, Epidemiology, University)*

Furthermore, the expert panel revealed that an appropriate algorithm, special population, age, level of education, could be developed to map out the populations that this program could attract. The most at risk populations (MARPs) such as sex workers, long-distance truck drivers, factory workers and mobile merchants would be the appropriate population for SHT. Apart from combining with facility-based counselling, experts argued that SHT could also be a very effective program if combined with new programs such as H2H or the TTLT model. They also suggested that peer educators or other HIV care providers could provide home-based counselling where all potential household members can test themselves as needed. A reproductive health specialist, for example, quoted the following:

> *"Home-based HIV testing? If we are going to use HEWs, there will be a problem. However, if partners need to be tested in their home by peer educators or health workers or we integrate with the self-HIV testing, it can work." (Associate Professor, Reproductive Health, University).*

However, implementing this program has some limitations, including fears about how patients would cope with getting a positive result, attempting suicide, taking revenge on others or not linking to care after testing positive. The participants stated that the use of SHT and facility-based HIV counselling could reduce these challenges.

7.3.3 Teach, Test, Link and Trace model (TTLT)

Peer educators are volunteers who are HIV positive and who have disclosed their status and work in health facilities to counsel, test and trace patients with HIV who have been LTFU. Assigning peer educators with HEWs involves formally employing and assigning them to educate the community about HIV, conduct HIV testing, engage in ART care and trace the patients LTFU, called the TTLT model. In the past, HIV was considered a death sentence. However, because patients who are HIV positive themselves are being involved in HIV care activity, the fear of HIV is reducing. As the participants noted, in hospitals and health centres it is becoming customary to send newly diagnosed patients with HIV to peer educators for counselling before putting them on treatment. As a result, the experts stated that peer educators have had a positive effect on reducing HIV related stigma and LTFU. In addition, peer educators significantly improve ART adherence and retention in care. A reproductive health professor said,

> *"I like HIV patients to be involved into the care… a lot of volunteers, and this is great. However, because of the issue of resources, they may stop. We see this problem in XXX health center. So, get ready for the resources and involve those patients at large. We are seeing the benefit live." (Professor, Reproductive Health, University)*

Peer educators also conduct home-based HIV testing for families or persons who have had contact with known patients with HIV, a program called Index Family Testing. It was suggested that this program could be upgraded into routine home-based HIV testing, regardless of whether or not families have contact with people who are HIV positive. Participants suggested that the use of peer educators in HIV care is important for the following reasons: 1) Peer educators are people living with HIV and by sharing their experiences, they can convince other people easily to be tested for HIV; 2) they maintain high levels of confidentiality and people will trust them compared with HEWs; and 3) because of their status, they can also secure employment from the program. Nevertheless, participants suggested that the issue of logistics may limit the implementation of such a program. Considerable resources would be required to employ peer educators nationally and it may also be challenging to get enough patients with HIV who disclose their status publicly and are willing to enrol in the program.

7.3.4 House-to-House HIV testing (H2H)

H2H refers to conducting HIV testing in every house by peer educators, HEWs or trained lay counsellors. This process includes collecting a specimen, performing a test, interpreting the result and referral for further follow-up testing or linkage. However, most panel members agreed that this is not easily feasible or acceptable. For example, if home-based HIV testing were carried out using HEWs, it would be less acceptable for the following reasons: i) HEWs might break confidentiality because most of them, especially in rural areas, are recruited from the community members they are serving; ii) HEWs are already overburdened and complain of job dissatisfaction; and iii) they have low capacity to monitor the clinical characteristics of patients with HIV. If the H2H program is to be implemented nationally, it will also require large resources, raising questions about its feasibility. The expert panel also suggested a possible fear of stigma from the family, and the fear may discourage HIV testing in homes. Experts said that because of the fear of stigma, family members may not disclose their status, and be linked late in to HIV care. A reproductive health specialist said,

> *"I don't think HEWs are capable at all. It will be a novel complication to the HIV care continuum if we involve them in the HIV testing program—the confidentiality, our society's reservation, etc. That's why people fear to share their HIV status to HEWs. Is there any known HIV patients freely declare him or herself out there in the city? Never. By the way the house to house HIV testing is logistically impossible." (Associate Professor, Reproductive Health, University).*

Despite the above pitfalls, the program was rated relevant; experts acknowledged the benefit to communities of increasing access to testing near to people's homes, and in some ways, it might reduce HIV related stigma. It was also suggested that this program could be integrated with the SHT. Overall, participants suggested that this program could be acceptable and efficient if peer educators carried out the HIV testing activities instead of HEWs.

7.3.5 Community ART Groups (CAGs)

Community ART groups (CAGs) involve groups of people obtaining their pills from a representative, who collects them from the clinic. Members of the group are patients who are stable and have disclosed their HIV status to each other or publicly, and live close to each another. They choose a leader (representative) who arranges monthly meetings to count pills and check overall ART adherence. The people on ART are encouraged to come to the clinic whenever they feel unwell. This was one suggested solution for ART retention. Although this program was rated relevant, it was less acceptable and feasible than some others. The experts

mentioned the following limitations of this program: 1) the biggest barrier for HIV care services is HIV related stigma and people may not disclose their status, therefore, it is better to design a strategy to fight stigma before implementing this program; 2) ART may be misused by the group leaders, for example, they may sell the drugs or drugs may be exchanged; 3) non-adherence and drug resistance may be too high; and 4) patients are now able to get a six-month prescription through the Appointment Spacing Model, and CAGs may not be necessary. One expert said,

> *"Community ART groups? I have heard that some patients are selling ART drugs for different reasons. So, I have a fear that they may misuse it. In addition, how can we see with the initiation of appointment spacing model? It seems a kind of duplication for me." (Public Health Specialist, HIV Program Expert, Zonal Health Department)*

However, some participants noted that the program is novel and suggested that it may be implemented in rural areas, because people in rural areas may need to travel hundreds of kilometres to receive ART services. Furthermore, the program may help group members to establish their own social networks. For example,

> *"The last intervention called community ART groups is so novel, especially to our society—our people travel hundreds of kms to get ART services. If we have one person who discloses his HIV status and doesn't fear to come to clinic, then this guy can take the pills for the other members, and this is fantastic." (Associate Professor, Reproductive Health, University)*

7.3.6 ART in private clinics (ART_{PC})

ART in private clinics refers to ART care delivered in private health clinics by the health workers employed in the clinic, with drugs provided free of charge by the government. Ethiopia started providing ART services in private hospitals in 2005, although only selected private hospitals located in Addis Ababa are delivering the service. Since many patients with HIV who do not receive ART are outside Addis Ababa, experts suggested that selected private hospitals in regional states and zones should commence ART services. Although ART in private clinics in provinces and districts is an alternative solution, the panel members had large reservations about suggesting its implementation. One important identified challenge was the potential misuse of ART drugs, and in particular a fear that selling ART drugs could lead to non-adherence and drug resistance. In addition, the associated costs for HIV care may also be very expensive compared with public health institutions, and private clinic owners may not allot

time to trace lost patients. In general, the quality of HIV care services may be poor. An expert from Zonal Health Department said,

> *"Private clinics run their money, and ART adherence may be poor. I don't think they will allow enough time for the patients to monitor their adherence. Plus, do you think they will allocate enough time to trace lost patients?" (Public Health Specialist, HIV Program Expert, Zonal Health Department)*

However, some experts supported decentralization of ART into private clinics. These experts revealed that some patients with HIV who can afford the associated costs might prefer to go to private clinics rather than public health facilities for fear of being seen by others. Based on this argument, some experts supported the plan to commence ART services in one private clinic in Jimma Town Health Office in collaboration with Regional Health Bureau. A zonal expert mentioned,

> *"We have heard that the district health office will start ART in a recognized private clinic… this is good, and become as an alternative option. I know there are rich people who prefer to go to private clinics for collecting drugs." (General Public Health Specialist, HIV Program Expert, Zonal Health Department)*

7.3.7 ART in health post (ART_{HP})

ART_{HP} is ART care delivery in health posts by HEWs. As described in Chapter one, a health post is the lowest level of primary health care unit that provides basic health promotion and prevention services. HEWs have direct contact with the residents in their catchment area. However, panel members suggested that they are not suitable for providing ART. Their level of training or competency, professionalism, ethics, overload, job satisfaction, motivation and turnover are challenges to optimal ART provision in health posts by HEWs. In addition, there is a question about managing the clinical and immunologic characteristics of patients. Most rural HEWs are recruited from their own catchment areas and participants raised concerns about a fear of breaking confidentiality, suggesting that the majority HEWs are not trusted by community members. This could result in failure of other HIV care interventions in the community. The panel members said that HEWs may also misuse drugs, and noted that the storage space available was not suitable for ART. The commencement of Appointment Spacing Model provided an alternative option to reduce the frequency of appointments. Thus, from the patients' perspective and surrounding environment, ART_{HP} may not work or be necessary at this time. For example, one researcher stated,

"ART in health posts is good as we bring the service to the community. However, there are drawbacks. HEWs are overburdened since everybody puts everything into them (hot potato syndrome …. laughing). There are different issues of retention, motivation and turnover with those HEWs. Your qualitative finding suggested that even the HEWs themselves do not want to start the (ART) services. So, we are only thinking what we want to be done by them not what they want and how they can efficiently work. In addition, will they be able to manage the adverse effect of ART? What if the patients develop co-morbidities?" (Associate Professor, Health Service Management, University).

However, HIV program managers in the Zonal and Woreda levels did not agree with the argument that ART_{HP} is a complicated issue. Observing the success of community tuberculosis management programs and maternal and child health services, they argued that ART provision in health posts could be successful. However, the experts pinpointed the need for capacity building and strict supervision as preconditions to rolling the program out. This was supported by a quote from a general public health specialist, who said,

"Decentralization of ART service into health posts? I don't think this is a difficult issue. We have seen this practically in community Tb program. So why not for HIV? My fear is, they may not have a capability to monitor the clinical and immunologic managements." (General Public Health Specialist, HIV Program Expert, Zonal Health Department)

7.4 Discussion

This study is the first of its kind in Ethiopia where multidiscipline expert panellists evaluate solutions for each stage of the continuum of HIV care. The participants in this NGT study represented a wide range of experts from various organizations, which helped to obtain multidimensional perspectives on the suggested solutions. The outcomes from this NGT are expected to be used to improve practices, guide future HIV policy development and generate new research ideas for further studies to improve responses to the 90-90-90 targets. Although the study has direct relevance to Ethiopia, it is hoped that the suggested policy and practice solutions also have relevance for other low- and middle-income countries. The panellists evaluated seven suggested solutions to determine how they can improve the policy and practice. They provided a wide range of opinions from diverse disciplines, expertise and professional roles. They also advised combinations of the suggested programs. The participants found that the NGT process was very easy and participatory. Moreover, the selection of NGT

(i.e. involvement of face-to-face discussion) made it easier to discuss and subsequently reach consensus. The panellists discussed the merits and demerits of each suggested solution in relation to their ranking of them.

The provision of a legal framework for mandatory notification of HIV status to partners was supported by many of the experts. The inclusion of mandatory notification in the country's legislation seems plausible and logical from the provided scenario and the existing problem on the ground. If, for example, a woman does not notify her HIV status to her partner and he becomes infected with the virus, he will be exposed to delayed HIV care and its complications. Similarly, if a man does not disclose his HIV status to his wife she will not receive timely HIV care services and be exposed to different HIV related complications. Furthermore, if the HIV positive wife becomes pregnant and does not get prophylaxis or treatment, her baby is less likely to be free from the virus. Studies reported that effective and timely ART prophylaxis during pregnancy reduces transmission of HIV from mother to child [579 580]. Thus, to prevent the adult and child health complications following delayed notification of HIV status, it is beneficial to enact legislation requiring disclosure of HIV status to partners. The positive reinforcement strategy suggested by the experts is also important to improve HIV status disclosure. However, it will be very difficult to enact legislation against traditional healers or religious ministers who forbid bringing pills into holy places or who order people there to discard pills. It was suggested that it would be better to raise the awareness of traditional and religious healers so that they teach patients to take their pills simultaneously. Furthermore, patients who are declared cured should be encouraged to confirm their status in health facilities.

SHT was also highly rated by the expert panel, and this program can be very effective either alone (to specific groups in the population) or in combination with other programs. The program may be more acceptable when the test kits are oral[205]. Previous studies reported that SHT is a key to achieve the first 90 of the UNAIDS target[581]. Kenya[204] has designed a national policy that encompasses self-HIV testing, and southern African countries such as Malawi[205] and Zimbabwe[206]are on target to introduce it. Since mid-July 2016, the world market has developed four rapid HIV tests (have high diagnostic accuracy) for SHT[582]. Of these, three tests use whole blood collected by fingerpick and one test uses oral fluid.

The use of peer educators in HIV counselling and testing, ART linkage and ART retention was ranked in the top three of the seven suggested solutions. Involvement of patients with HIV in HIV care is becoming an effective intervention to enhance testing coverage, ART linkage, ART retention, and subsequently virological suppression. Different countries found this program very effective [57 190 471]. In Ethiopia, peer educators work with HEWs to perform

their own packages, with counselling, testing, linking and tracing. ART provision in selected private clinics was not supported by most of the expert panellists. Nevertheless, in the qualitative findings of this project, district health officials mentioned that they were ready to commence ART services in one private clinic and HIV testing services in three selected private clinics. There are a number of people who are HIV positive who want to take ART in private clinics. In addition, people want to take ART after working hours and patients can access private clinics that are open all hours. However, there should be strict support and supervision from district health offices and zonal health departments, and referral linkage with public hospitals. Private clinics should be fully aware of and ready to address problems in ART care, particularly ART discontinuation, non-adherence, resistance, misuse and tracing lost patients. Because suitably equipped private clinics are mostly based at zonal levels, the government could start ART in private clinics located at Zonal levels, not at district levels. The government could also keep decentralizing services to public health facilities at district levels to increase ART coverage. For instance, only 20% of health facilities in Oromia region have started ART care services[542].

The expert panellists were reluctant to suggest decentralization of ART care services to the level of health posts in the current situation. Most patients with HIV, service providers and all community members (including HEWs themselves) who were involved in our qualitative inquiry did not recommend starting ART services in health posts. The current level of knowledge and competency of HEWs does not enable them to manage even minor complications following ART initiation. There are also frustrations with HEWs about their confidentiality, commitment and job satisfaction.

Regarding H2H, even though the expert panellists supported the peer educators running it, they did not want HEWs to conduct home based HIV testing. Other studies noted that H2H is essential for identifying persons who are HIV positive and further reducing HIV transmission[190 583]. Home-based HIV testing through community health workers or lay counsellors was found very effective in southern Africa[190 583]. CAGs could be another important program to improve ART services particularly in reducing frequency of appointments, discontinuation of ART because of distance, burden on health facilities, and creating HIV community. The use of peer educators in the ART program may reduce limitations of this program, especially HIV related stigma and ART misuse. Previous studies in Africa suggest that CAGs are user friendly, cost effective and successful[190].

The NGT used in the present study has some limitations. Firstly, experts may suggest recommendations that they know in theory but which have very limited applicability in

practice, the so called 'self-fulfilment prophecy'[584]. For example, experts recommended use of biological ID to solve the problem of patients registering for ART at more than one site. This suggestion is too 'ideal' for Ethiopia in its current status. Secondly, reaching consensus was a challenge in the NGT, a common limitation of all consensus methods[396]. For example, the use of HEWs in ART care and initiation of ART in private ART clinics led to discussion and ended up without consensus. Nevertheless, ultimate consensus was not the aim and minority suggestions were also considered. Furthermore, the experts provided insights into explanations for the differences in agreement. Thirdly, although the expert panellists were identified carefully, some disciplines, geographic areas and professions were possibly not as well represented as others. Hence, results may have limited application to other regions. However, the main interest of this study was to obtain a wide range of opinions and feedback about the possible implementation of ways to improve HCT, not to achieve generalizability. Fourthly, although the intention of the discussion was to polarise opinions more, there were no statistical differences for the suggested solutions between the two rounds. This may be due to having compressed values on the Likert scale instrument (1-3). Additionally, the panel of experts were also heterogeneous having a wide level of background knowledge (the professional mix of the experts was from BSc to Professorship level), and this may have contributed to the difference.

Despite the above limitations, the involvement of a variety of experts gave the potential for multiple positive outcomes, including to ensure the interests of a variety of beneficiaries, enhance the ownership of the coming research (as researchers were also among the participants), and influence clinical practice in particular and policy in general.

7.5 Conclusions and Recommendations

Considering the criterion of importance, filling gaps in legislation, SHT and TTLT models were the top three recommended solutions from our NGT. Raising awareness and applying positive reinforcement to enhance disclosure could be better than legislation for partner notification. To address the gaps in the law related to traditional healing and HIV care, improving service integration and collaboration with religious leaders is needed. Further, the government could establish a local association of ministers to discuss among themselves and advise (or impose religious punishment) on those who transgress. Patients should be involved in the HCT, and the application of the TTLT model will improve the whole HCC.

Decentralization of ART services to private clinics could be a promising program provided there is strong supervision, strict monitoring and evaluation. However, it is too early to recommend decentralization of ART services down to health posts by HEWs. Home-based

HIV testing could also be a successful program if peer educators assigned to the program and HEWs received further capacity building. Finally, CAGs could also be another important program to improve ART care services in rural settings. The suggested solutions evaluated by the panel of experts are currently implemented in other African countries, and the current study gave a glimpse of how these programs could be rolled out in Ethiopia. However, before considering implementing these interventions, a nationwide based study should be carried out using multiple methods approach to assess the feasibility and acceptability of suggested solutions.

Chapter 8

General Discussion

CHAPTER 8 - GENERAL DISCUSSION

8.1 Introduction

Since the emergence of HIV more than 30 years ago, there have been extraordinary global responses in inventing drugs to treat this scourge and establishing national programs including the $44.3 billion budget (2004-2012) by PEPFAR to prevent the disease[585 586]. Despite the efforts to date, HIV and AIDS remain global public health problems. Literature confirmed that efforts to halt the global HIV epidemic go well beyond distribution of condoms or ART adherence. Rather, HCT comprises complex behaviours that are affected by multiple ecologic levels[351]. Little was known about the entities of the whole HCC burden, facilitators, barriers and solutions, from multiple perspectives. Using a case study of Southwest Ethiopia, this thesis has addressed these gaps through a four-phase sequential mixed methods approach.

Detailed discussions of each study have been presented in Chapters four to seven, and the current Chapter presents the overall discussion of the thesis. The findings of all chapters on the continuum of HIV care, where necessary, have been discussed in combination, and each series in the continuum has been described in relation to the UNAIDS 90-90-90 targets. The chapter is presented in four sections. Section one discusses the burdens, factors and solutions of LP. Section two discusses ART attrition and addresses the burdens, predictors or barriers and intervention approaches of ART discontinuation and mortality. Section three deals with magnitude, trend, predictors and ways forward to improve immunologic failure. The final section of the chapter discusses the methodological reflections from the thesis.

8.2 Late presentation for HIV care: implication for UNAIDS target 1

The HCC begins with HIV diagnosis and linkage to care[33]. Evidence has shown that early HIV diagnosis and timely engagement with ART has substantial benefits, including enhancing the efficacy of ART, improving the quality of life and increasing survival[587 588]. Nevertheless, like in other parts of the world[38 61-64 144], a significant proportion of patients with HIV (65%) presented late in the current study. This could reflect that only a small proportion of patients (35%) knew their HIV status early, an achievement far below the 90% UNAIDS target for HIV diagnosis[32]. The cohort study revealed that most patients with HIV who presented late had poor outcomes, and this has been confirmed by the work of others[150-152 162].

The qualitative component of this thesis revealed several reasons why patients delayed knowing their status or linking to care after diagnosis with HIV. Stigma related to HIV, using traditional healing as an alternative option, and lack of awareness of and access to HIV

counselling and testing services challenged early HIV diagnosis and ART care linkage. These barriers were also found in other studies[120-122 124-126].

The cohort study revealed that patients who were female younger age, co-infected with Tb/HIV and not previously tested before HIV diagnosis were the patients with HIV who were at higher risk of LP. In particular, the finding about the association of being female and LP was different to findings in previous studies[162 455]. The present study found that females were at 20% more risk (AOR=1.2, 95% CI: 1.03-1.5) of delaying HIV care. The findings of the qualitative and retrospective cohort studies complemented each other with both finding that being female was a risk factor for LP. Additionally, the current study also found that about two-thirds of women in the cohort had never been tested for HIV before diagnosis. The qualitative component revealed that women were at higher risk of LP because the majority of them considered traditional healing as a substitute treatment. This may be associated with lower knowledge of modern treatments[123]. In addition, they had less access to HIV care services, and participants in the qualitative study identified that living in a patriarchal society affected them. The qualitative study also found that women perceived stigma more than men. This was supported by other studies that reported the presence of higher use of traditional healing[53 54] and perceptions of stigma among women[175 448].

In addition to the facilitator 'Index Family Testing', the qualitative study identified solutions that could reduce possible barriers and enhance timely testing and linkage coverage. SHT, H2H and the TTLT model were suggested for improving HIV diagnosis and ART linkage. SHT was supported by more than half the participants in the qualitative study. However, these and other participants who opposed the program mentioned pitfalls that could hamper implementation of the program. For example, participants said that some people may not cope when faced with positive results and some may attempt or commit suicide. The possibility of some individuals willingly transmitting the virus to others once they knew their status was also mentioned. Furthermore, it was mentioned that some people could disengage from care after HIV diagnosis because of many factors including the fear of being known by others. These factors were also echoed by the experts consulted in the NGT study. Because these drawbacks could result from the lack of counselling or understanding, the expert panellists advised that the SHT program could be combined with the existing facility-based HIV counselling and testing program. Such combination would enable people to receive counselling at the health facility but test their HIV status themselves in a private setting. The expert panel added that if people did not want or were unable to go to a health facility, the SHT program could be combined with home-based HIV testing programs, where trained peer

educators would provide the counselling to people who wanted self-testing while at home. WHO suggests that to keep people calm and improve their coping skills HIV testing could be undertaken by someone who is trusted by the individuals concerned [589].

The other big challenge of SHT that the qualitative study participants raised was that the program could be inconvenient for some groups of the population, particularly younger people and those with low literacy status. This was also a concern of the expert panel, although they suggested the development of a special algorithm to identify specific at-risk groups. For example, SHT could be suitable for commercial sex workers, village merchants, and long-distance truck drivers who are potentially underserved or hard to reach populations. The expert suggestions about suitability of SHT for some groups is in conformity with the WHO protocol on SHT[589]. The protocol indicates that SHT enhances uptake of HIV testing, particularly in high-risk population groups who may have less access to services. Testing oral fluid rather than fingerpick blood would make sample collection easier and does not need high literacy status[205]. Oral fluid testing offers additional advantages over blood-based testing[590], including convenience, easiness (could be done outside clinics) and user-friendliness[591 592]. OraQuick® Rapid HIV-1 antibody test (OraQuick®) is the only available oral swab test and was approved by Food and Drug Administration (FDA) of the United States in 2004[593]. Studies found that OraQuick® has 99% sensitivity and specificity respectively[594 595], and is acceptable to people of different classes, disciplines, income and settings[590 596]. SHT can reduce stigma, address potentially underserved and high-risk populations, and increase testing uptake and linkage rates, and also improves the first 90 of the UNAIDS targets as described elsewhere[581]. Based on the recommendation from WHO[589], other African countries have implemented the program and found results promising[204-206].

The implementation of TTLT and H2H programs were also recommended by the qualitative study participants to reduce delays in HIV care presentation. According to participants, H2H enhances testing rates and addresses some of the challenges faced by people who are unable to access testing in a health facility. For example, the existing 'Index Family Testing' program is tailored to cater for known families or persons living with HIV. This may expose them to stigma because it is well known that health workers only visit those particular homes. However, if the testing program was carried out in homes, the chance of being suspected of having HIV which could lead to stigma would be lower, or none at all. There was, however, a big unanswered question raised by the qualitative study participants, "*Who will do the H2H testing*?" They believed that the use of health workers to visit every home would not be feasible because there was a shortage of health workers and it would be expensive. The use

of HEWs was not considered safe because of concerns over confidentiality, and use of peer educators might not be successful because patients with HIV may struggle to disclose their status in public.

The expert panel made suggestions about who should perform testing during H2H. Acknowledging potential patients' lack of trust in the HEWs and the severe shortage of human resources in the country, the panellists recommended use of peer educators in the TTLT model. Through sharing their own experiences, peer educators could convince other patients with HIV and would be trustworthy and more committed compared with other people because they knew what HIV and its impact meant. The number of peer educators in each facility could be increased by offering a constant salary and some incentives so that they would feel valued and employed. Therefore, involving peer educators to conduct H2H would improve the testing coverage and early HIV diagnosis. Home-based HIV testing[190 515], and use of community workers and lay counsellors[57 190 471] have also been used in other African countries.

The suggested solutions from the NGT including SHT, H2H and TTLT all lend themselves to *repeated HIV testing*, meaning people could be tested frequently. These testing programs also seem to have the ability to close the gender gap in LP. While there was debate about mandatory notification between partners in the qualitative study, the NGT suggested to make partner notification of HIV status mandatory after further counselling and other positive reinforcement strategies.

In summary, the cohort study reported the presence of significant LP and identified population groups at higher risk. The qualitative study explored why LP was a significant problem and why the identified groups were at higher risk. The NGT study provided optional solutions by discussing the merits and disadvantages of the suggested solutions from the qualitative study. As noted from the implications of the systematic review and observed in the findings of cohort study of the thesis, the consequences of LP reach beyond the diagnostic and testing series of the HCC. LP affects the retention in care and virological suppression. The magnitude, predictors and solutions of ART attrition are discussed in the next section.

8.3 Attrition from ART care: implication for UNAIDS target 2

The next step in the continuum after HIV diagnosis and linkage is lifelong treatment with ART[33]. In the era of free and universal ART, uninterrupted ART retention has paramount benefits to patients with HIV, including improved life expectancy. Evidence from countries where the test and treat strategy was launched early demonstrates that patients with HIV have a similar life expectancy to the general population[597 598]. Similar achievements have also been reported in some parts of Africa including Ethiopia, even though the gain is different[19 598-600].

For example, in Uganda, it was estimated that patients with HIV who start ART at ages 20, 35 or 50 are likely to live for additional 27, 28 or 24 years respectively [601]. Nevertheless, ART attrition is an important impediment to improvements in quality of life and life expectancy which could potentially be accrued from ART[4 80 81 241 463 464]. In the current study, out of the 8172 patients with HIV in 2003–2015, only 65% (5299) patients received ART, showing that the region was 25% short of the second 90 goal of the UNAIDS 90-90-90 treatment targets[32]. Moreover, even after initiation of treatment (5299 on ART), the magnitude of ART attrition was high, recorded in about one-third of patients (1154 discontinuations and 326 deaths).

The qualitative study explored reasons for the ART attrition and found stigma to be one of the most common reasons for patients to discontinue treatment. Participants revealed that patients with HIV fear being seen by others while routinely visiting ART clinics for pill collection or other HIV care services. Additionally, study participants stated that when patients found ART to be non-curable and a lifelong treatment they worried about developing ART treatment fatigue. Thus, they could consider discontinuing treatment to search for alternative options, such as treatment by traditional healers. Regular unavailability of ART services in the local health centres and misconceptions about ART were additional reasons for ART attrition. In addition to current strategies such as 'Appointment Spacing Model' and 'test and treat strategy', the qualitative study participants suggested decentralizing ART to health posts and private clinics, CAGs, integrating NCD services to ART care and collaborating with traditional healers as solutions to enhance ART retention. Participants in the NGT gave further critiques of these proposed solutions.

ART in health posts and the provision of ART services by HEWs in health posts were further solutions suggested by HIV care program managers and some of the health workers in the qualitative study. Neither the interviewed patients, community advocates, most health workers nor the HEWs themselves agreed with the implementation of these programs. After discussing the advantages and disadvantages of the program, the experts in the NGT study also ranked ART in health posts lowest. Instead of providing ART services in health posts, the experts suggested equipping available health facilities and decentralizing the services to health centres where ART has not been initiated. Similarly, as discussed in chapter seven, the participants identified that there were several problems associated with HEWs including staff incompetence, poor levels of confidentiality and high staff workload. Based on these concerns, the majority of study participants suggested HEWs not to be involved in HIV care services provision in the health post. Instead, some participants suggested that HEWs could be involved in HIV testing and counselling services or tracing discontinued patients with HIV, and several

techniques were presented in chapter six to address limitations of ART in health post. HEWs routinely move door-to-door to implement their packages and the HIV counselling, testing and tracing could part of the package. They could also help in improving overall awareness of HIV, early diagnosis and linkage. In this way, HEWs could be a local solution to a global problem. Community health workers in other African countries[602] such as in Uganda[603] and Zimbabwe[264] have been involved in HIV testing and linkage to ART care since 2003.

Outside of Addis Ababa (the capital city), ART is provided solely by public health centres and hospitals. The provision of free ART in privately owned hospitals or clinics, was another solution suggested by patients in the qualitative study to curb poor attrition rates. These participants believed that receiving ART from private clinics would reduce their exposure of being seen by many people, hence reducing the possibility of stigma and waiting times. Private clinics are also open after hours which would make ART available at extended times. Evidence from the systematic review in this thesis and other studies demonstrate that patients who are from rural settings are at a higher risk of ART attrition[33 130]. Based on this evidence, the Jimma district health office has decided to provide a licence for one private hospital in Jimma town to deliver ART care services (sub-section 6.5.3). However there has been strong resistance by some participants to ART provided by private clinics because of fear of ART misuse, drug resistance, poor tracing when patients discontinue treatment, and poor monitoring by facilities of the clinical and immunologic problems of patients with HIV. The majority of experts in the NGT study did not support programs where ART would be delivered by private clinics, despite the benefits identified by others.

Traditional healing has been mentioned as a cross-cutting facilitator to ART attrition. The retrospective cohort study reported that females were at higher risk of discontinuation, and in the qualitative study, it emerged that this could be because of higher use of traditional healing by women. In addition, the systematic review and meta-analysis also revealed that the rate of discontinuation was high in people with low literacy status. The qualitative study showed that people with low literacy status visited traditional healing more than those with higher literacy status. The systematic review also showed that people from rural settings were more likely to discontinue treatment than their urban comparators. Similarly, people from rural settings visited traditional healing more than people from urban areas. Therefore, to address these challenges comprehensively, the qualitative and NGT study participants recommended the need for strong collaboration between the modern and traditional health care institutions to address and close the inequity in ART services. The NGT experts also suggested that there should be a strong effort to convince (through collaboration) traditional healers to preach to

their congregations to continue taking ART even while visiting traditional healing places. Additionally, although with great caution, the NGT experts proposed the need for a legal framework that stipulates strategies to address the issue of traditional healers declaring patients with HIV to be cured and telling them to discard their medicines.

As reported in previous studies[431 568], the systematic review and meta-analysis found that people with mental illness were at higher risk of discontinuation of ART. The qualitative finding also showed that people with chronic illnesses had to co-ordinate multiple appointments and this interrupted their regular ART intake. Furthermore, as found elsewhere[433 604 605], the systematic review and meta-analysis also showed that chronic alcohol drinking (Pooled OR: 2.9, 95% CI: 1.9-4.4) and cigarette smoking (Pooled OR=2.6, 95% CI: 1.6-4.3) were associated with ART discontinuation. The qualitative study and NGT suggested integrating chronic diseases management with ART care services, which has been found very effective in different African countries[235 569-573]. In the systematic review study patients with HIV and Tb were found to be less likely to discontinue treatment than their comparator but findings from the retrospective cohort revealed the opposite, with Tb/HIV co-infection identified as a risk factor for discontinuation. Patients co-infected with Tb/HIV could be at higher risk of ART discontinuation because Tb facilitates deterioration to AIDS, which could further reduce patients' ability to take ART consistently[261]. Conversely, the systematic review reported Tb/HIV co-infection as a protecting factor. Patients with HIV diagnosed with tuberculosis may be less likely to discontinue than those without Tb because the fear of complications of both diseases might encourage them to regularly take their medicine. Therefore, this needs further research because there might be several reasons why Tb/HIV co-infection is a protective or a risk factor.

The systematic review and meta-analysis and the retrospective cohort found that patients with HIV who were bedridden at the start of ART, presented late for HIV care, developed immunologic failure and were at a higher risk of ART attrition than their comparator. The qualitative study also supported the finding that several people delayed their presentation to HIV clinics until they developed serious illnesses. These findings confirm other studies[248 538 539] elsewhere. These findings show that there seemed to be a vicious circle which led to disadvantages at each stage of treatment, and improvement in ART attrition rates could be achieved by improving LP and immunologic failure. The qualitative and NGT studies both identified ways to improve LP and attrition as described in Chapters six and seven.

Finally, ART attrition was also found to be a problem in children. There are a number of reasons why children should be given special attention. First, children have widely disparate

physiological parameters[606]. Access to treatment is unacceptably low among children, with three out of four (76%) eligible children not receiving ART[4]. If ART is not taken consistently children are more vulnerable than adults to OIs and other illnesses[607]. Compared with adults, more children who discontinue fail to re-engage with care. For example, in a tracing study conducted in Uganda among people infected with HIV who discontinued ART, [239] 60% of adults returned to care but over 50% of children did not do so. While the side effects of drugs are more severe among children than adults[608]there is a dearth of information on pharmacokinetics, pharmacodynamics, efficacy and safety of ART drugs in children [606].

In summary, the systematic review and meta-analysis and the cohort study reported that ART attrition had occurred in a considerable number of people over the last 12 years and these studies informed the predictors of ART attrition. The qualitative study explored why the magnitude ART discontinuation and mortality is still a challenge and why certain groups of patients with HIV interrupted their treatment. Finally, the qualitative study and NGT recommended intervention approaches to improve ART retention, and as such, to achieve the second 90 of the UNAIDS goal and beyond. Tackling ART attrition is not limited to achieving the second target of the UNAIDS 90-90-90 goals but will also foster improvements in virological suppression, the third 90 target. The surrogate marker of virological suppression, immunologic failure, is discussed in the next section.

8.4 Immunologic failure: implication for UNAIDS target 3

The final stage of HCC and the ultimate goal of ART is virological suppression[33]. Achieving virological suppression does not mean being cured of the virus, but living with good quality health for a longer period and reducing the chance of HIV transmission to others[57 108]. Even though significant improvement has gradually been recorded since the introduction of ART[522], several countries have not achieved the ambitious goal proposed by UNAIDS[107 108]. In the present study, approximately two-thirds of patients with HIV on ART achieved immunologic and clinical successes. Considering immunologic and clinical successes as surrogate markers for virological suppression with undetectable viral load, only 66% of the UNAIDS target has been achieved.

The retrospective cohort study found that LP and ART attrition associated with discontinuation made a significant contribution to immunologic failure. Furthermore, women (AOR=4.8, 95% CI: 1.7-–13.2) and patients with HIV who had lower baseline CD4 count (AOR=5.5, 95% CI: 4.1-–7.4) were at higher risk of immunologic failure. The qualitative study did specifically not explore why immunologic failure was paramount and why these patients

with HIV were at an elevated risk of immunologic failure. Nonetheless, the study explored why patients presented late for HIV care and discontinued from ART, the triggers of immunologic failure. Thus, if patients presented early and followed their ART regularly as a result of the interventions for LP (section 8.2) and ART attrition (section 8.3), their clinical and immunologic outcomes would be improved, as would their virological suppression.

Interventions for LP and ART attrition to improve immunologic failure recommended by the qualitative and NGT studies were also found to be effective elsewhere. For example, a recent study reported that SHT is one strategy that uses POC tests to help achieve the three 90s of the UNAIDS goals[609]. The qualitative and NGT studies recommended CAGs to enhance ART retention to gain immunologic and clinical successes. Consistent with this, other studies also found community-based ART interventions to be effective in improving engagement[610], increasing CD4 counts[611] and achieving virological suppression[612]. Similarly, the involvement of peer educators has been found to be effective[57 190 471]. The experts in the NGT also identified the important role of peer educators in the TTLT model.

In summary, immunologic failure rate was higher among older adults, women and those with LP, indicating that interventions for immunologic failure should target these groups of patients with HIV.

8.5 Methodological reflections: strengths and limitations of the thesis

The strengths and limitations of each study in the thesis are presented in Chapters four to seven. This section presents the overall strengths and limitations of the thesis, and practical, pragmatic and political reflections on the methodology. The findings of the thesis add to the global literature on HCT, and Ethiopia's progress to achieving the UNAIDS 90-90-90 treatment targets. In particular, this thesis contributes to the limited information on the application of the SEM to the HCC framework. This is the most comprehensive research in Ethiopia so far that explores the facilitators, barriers and interventions for all stages of HCC at multiple ecological levels.

The thesis confirms that the HIV care outcomes that were mentioned at the epicentre of the model were influenced by factors at the four levels of the SEM, individual, microsystem, mesosystem and macrosystem. This study found that using the SEM contextualizes individual behaviour using different intrapersonal dimensions such as knowledge, attitude or behaviour. For example, selling ART in illicit markets could be associated with the individual's level of knowledge of ART use. This practice will subsequently influence the community and the policy level program practices. The micro- and mesosystems, being closest to the intrapersonal or individual characteristics, influenced HIV care outcomes significantly.

The general discussion on HCC in this thesis demonstrated the interrelated effect of multiple ecologic levels on intrapersonal HIV care practices but in doing so, it underplayed the effects of the other levels of the SEM. To show the influence of these more clearly, the relationship of gender and mental health with negative HIV care outcomes will be used as examples. At the individual level, the retrospective cohort found that women had higher risk of negative HCT outcomes than men. This was because they made fewer visits to ART clinics and did not access care, a concept that demonstrates the effect of the microsystem level. Furthermore, the study found that stigma, visiting traditional healing and living in a patriarchal society contributed to women's poor access to ART, a concept that demonstrates factors operating at the mesosystem level. The lack of policies to empower women, address stigma at different ecologic levels and close the gaps in legislation about partner HIV status disclosure and malpractices by traditional healers about ART demonstrate the operation of factors at the macrosystem level. Similarly, patients with HIV diagnosed with mental health disorders were more likely than others to discontinue ART, and one reason was that patients could not get access to mental health services, a concept that demonstrates factors at the microsystem level. The double stigma from both diseases held by the community challenged patients to take their treatment regularly, a concept that demonstrates effects of the mesosystem level. Finally, the absence of policies that organize integrated HIV and mental health services contributed much to ART discontinuation, a concept that demonstrates the operation of factors at the macrosystem level. Similar interpretations can be applied to the other characteristics of patients with HIV in the current studies.

Findings from the multiphase mixed methods study suggest contextual modification for the application of SEM on HCC. A new model (figure 8.1) is presented based on the deductive analysis derived from the model presented in figure 1.6 and inductive analysis from current studies included in this thesis. These were mainly at the individual and policy levels and are presented in red in figure 8.1. At individual level, ART in *black markets* was the new challenge explored through the qualitative study. At policy level, the newly emerged entities included strategies related to HIV testing and ART linkage such as SHT, H2H, TTLT model; ART distribution system programs such as CAGs, ART_{HP}, ART_{PC}; and gaps in legislation about HIV status disclosure between partners and interference of traditional healers in the HCC system. The implementation of these strategies and programs either promote or reduce the success of ART program.

The thesis has several strengths that include the methodological approaches and researcher strengths. The thesis addressed the whole HCC: HIV diagnosis, ART linkage, ART

retention and virological suppression. This was assessed using a multiphase mixed methods approach including four study designs: systematic review and meta-analyses, retrospective cohort study, qualitative inquiry and NGT. Such an approach enabled the assessment of multiple entities of a complete package i.e. reviewed the existing evidence, quantified the problems, explored the reasons further, suggested solutions, and prioritized the suggested solutions sequentially. As far as is known, this is the first time such a comprehensive project has been conducted in Ethiopia on HCC. Data for the project were collected from multiple groups involving patients, health workers, community members, program managers and experts.

The intertwined findings of the thesis have also been presented in a workshop[613] that involved experts from a variety of organisations and disciplines including HIV industry, health system, government and non-government organizations and academia who provided a broad range of views. Program managers who participated in the workshop showed a positive response and took a note to implement on some of the findings. The workshop outcomes showed a positive result to translate the output into policy and practice to improve HIV care, and some of the stakeholders participated in the workshop started to immediately work further on the outcomes. Furthermore, the findings from all studies have been disseminated widely to the HIV community and the scientific community. From the thesis outputs, six papers have been published[130-134 372] and twelve abstracts[407-418] have been presented at a range of international conferences[41]. Additionally, a media release was prepared and broadcast widely, enabling the findings of the thesis to enhance public health knowledge[419].

This PhD student has had access to data from the retrospective cohort from Ethiopia while in Australia and this opportunity had numerous advantages. It helped the PhD student to analyse early and write the results, and subsequently publish papers. The additional feedback from the reviewers of reputable journals enriched the subsequent chapters and the thesis as a whole.

The strengths of the thesis have resulted from the cumulative experiences and research training of the current PhD student. His experiences working in a HIV clinic for a year before starting the PhD helped him to conduct successful interviews with patients with HIV and obtain adequate data. While working as a clinician, the PhD student worked as a coordinator of HEP located in the catchment area of the health centre. This experience helped him to approach and obtain in-depth information from community advocates. In addition, having had two years'

[41] An abstract was presented more than once (in different conferences).

working experience as the head of a health centre and vice head of district health office in the Ethiopian health care system helped him to communicate effectively with government, and local and global non-government officials and program managers. In the Ethiopian health system, local or global NGOs working in a health centre implement their actions through or in collaboration with the district health office. Based on the above cumulative experiences, the communication with the invited experts for the NGT study was smooth and participatory, and supported the thesis findings to produce important steps forward.

However, to make the above experiences viable, the PhD student's academic experiences and PhD research training were irreplaceable. The PhD student's academic experiences in Ethiopia enhanced his quantitative research methods and methodology. The PhD research training provided further opportunity for him to improve his capacity for both quantitative and qualitative study methodologies. For example, multiple imputation and meta-analyses were some of the new skills he learned. The communications skills including from several oral presentations in local and international conferences, and experiences of manuscript paper writing gained from the PhD research training process helped the thesis substantially and improved his personal development significantly. Furthermore, the student's qualitative methodology experiences such as designing, analyses and software, quality assurance and write up techniques were learnt from the PhD research training. This enabled the student to explore a complex research problem. The PhD student did not previously know about the NGT method and the *Wilcoxon Signed rank test* and *content analyses* used in the fourth study. This study further introduced the student to the variety of techniques for consensus methods study designs. Above all, all these experiences in combination upgraded his knowledge of HCT, and his personal development in the mixed methods world.

Despite the above strengths, the study has some limitations. First, the study was conducted using the pragmatic mixed methods approach. In this approach, positivist and interpretivist epistemologies, and quantitative and qualitative methodologies were mixed. Such mixing of approaches may be against the principles held by purists that argue the incompatibility of mixing of approaches with different paradigms or philosophical assumptions[370]. Second, except for the retrospective cohort, the target population for the other three studies were adults living with HIV, and issues surrounding children were not fully addressed in the assessment of the entire HCC. Third, it was planned to collect data from a health centre and a hospital. The rationale for this was that the types of patients being treated in a health centre and hospital are different, in that most patients coming to hospital are seriously ill. Thus, the number of patients who present with advanced HIV treatment outcomes in the hospital could be different from

those in the health centre, and this would have implications for factors affecting negative HIV treatment outcomes. Additionally, the NGOs supporting the HIV care services in the health centre and hospital were different, and this would have implications for resources allocation, health professional capacity building, and data management system. The facilities, staffing, services range and patient flow also vary between the health centre and hospital. These factors affect the whole HCC and would provide a comprehensive insight on the factors and possible interventions. However, it was not possible to obtain data from JHC because of the significant incompleteness of independent and dependent variables in the study. Data were only gathered from JUTH. To address this, the researcher made an effort to include participants from the health centre in the qualitative and NGT studies.

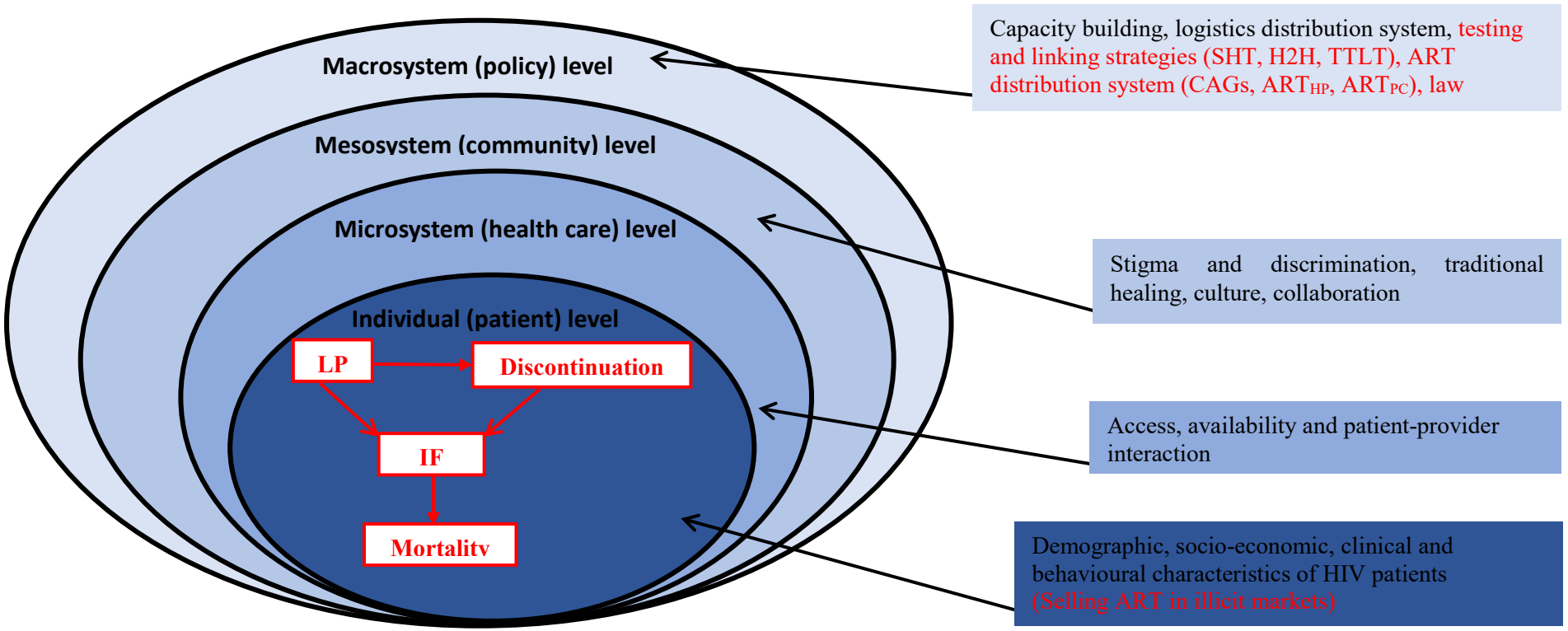

Figure 8-1 The application of socio-ecological model to HIV care continuum outcomes, adapted from the social-ecological systems theory (Bronfenbrenner, 1989)

This figure shows the application of SEM in the HCC framework. The rectangular box and straight lines in red in the centre of the circles show the negative clinical outcome of each series of HIV care continuum and the statistical relationship between each other. The arrows in red show the statistical significance that was found from the analysis of cohort study described in Tables 5.3, 5.6, 5.7 and 5.8. LP (late presentation for HIV care) was statistically associated with ART discontinuation (discontinuation) and IF (immunological failure); discontinuation was statistically associated with IF; and IF was statistically associated with mortality. The statistical pathway relationship and list of variables highlighted in red are new findings that were found in the current study using the potential model presented in figure 2.1. The overlapping circles in the model shows how factors at one level affect factors at another level[42]. SHT (self-HIV testing), H2H (house-to-house HIV testing), TTLT (*teach-test-link-treat* strategy), CAGs (community ART groups), ART_{HP} (antiretroviral therapy in health post, ART_{PC} (antiretroviral therapy in private clinic).

[42] This figure needs to be viewed in colour but the colour intensity is only used to separate one level from the other not to demonstrate the rank of importance of the levels.

There were also other challenges in the field. Political instability in the study setting during the data collection period limited interviews with potential traditional healers, and visits and observations in traditional healing places. These traditional healing places and the traditional healers are located in villages and travel was not possible during the civil unrest. This slightly affected the desired depth of the qualitative findings and the subsequent NGT study because of the lack of voice of traditional healers who seemed to play an important role in the HCC in the study setting. Nevertheless, because the study participants involved in both primary studies of the project were familiar with the context, this limitation might not be significant. It was also very difficult to meet the appointed participants from community advocates and program managers due to other engagements. This was solved by repeatedly changing the appointment dates for the participants.

If the researcher had a chance to conduct this study again, at least: (i) '*lost'* patients could be traced and their outcome status assessed, (ii) the traditional healing sites could be observed and traditional healers could be interviewed on the barriers and possible solutions for HCT, and (iii) possible solutions for HIV related stigma at all socio-ecological levels could be explored. Despite the above limitations and weaknesses, the project was completed successfully and leaves the door open for further studies.

Chapter 9

Conclusions, recommendations and implications

CHAPTER 9 - CONCLUSIONS, RECOMMENDATIONS AND IMPLICATIONS

9.1 Introduction

The conclusions, recommendations and implications for policy, research and program of the project have been presented for findings in the respective chapters. This final chapter briefly synthesises and summarises the conclusions, recommendations and implications of the thesis as a whole.

9.2 Concluding comments

With several countries, including Ethiopia, instituting a *"treat all"* policy, more people who are HIV positive but who feel healthy will demand and become eligible for ART. This implies the need for more evidence to understand and address LP and ART attrition. Understanding why patients with HIV do or do not screen for HIV, initiate ART, and take ART without interruption entails explicating the complex risks of HIV and treatment seeking behaviours that are predisposed by predictors at multiple levels. In this thesis, four interrelated and sequential studies were employed to assess the continuum of HCT using primary and secondary data from Southwest Ethiopia. The thesis was initiated by reviewing the existing information about the problem (study one, chapter four) followed by study two (chapter five) that quantified each outcome of the continuum of HIV care. Using study two as a base, study three (chapter six) further explored what were the emerging facilitators, barriers, and solutions from a variety of groups using a qualitative inquiry. The fourth study (chapter seven) was employed to seek further advice on how to implement and prioritize these recommended solutions.

Chapter four of the thesis revealed that patients with HIV who had poor access to (rural dwellers) and lacked awareness of (less educated) HIV care, and those who had chronic behavioural (cigarette smoking and alcohol drinking) and clinical (mental illness) problems had higher risk of discontinuation from ART. Discussion of the chapter reflected that the burden of discontinuation from ART was substantial but limited evidence was established. In Chapter five, LP, ART attrition and immunologic failure were assessed and these negative outcomes were found to be significant. Additionally, women, patients with no previous history of HIV testing before diagnosis, and with poor baseline clinical and immunologic symptoms were at higher risk of these poor outcomes.

Chapter six found that HIV treatment outcomes improved through time because of the introduction of new programs, improving knowledge and trust in ART and support from multiple groups. However, these improvements in the outcomes of HIV treatment were not as expected because of several barriers such as stigma, misconceptions, misuse of ART, traditional healing practices and access. Therefore, improving early diagnosis through self-and home-based HIV

testing, and ART linkage and retention through TTLT model, CAGs, integration and collaboration were recommended. Furthermore, one of the keys for getting HIV care support is disclosing one's HIV status, and the need for promotion of disclosure including mandatory notification to a partner was suggested. Chapter seven prioritized solutions that emerged in chapter six and finally found that addressing the legal issue of mandatory HIV status notification and traditional healing, SHT and TTLT model were the top three relevant, feasible and acceptable solutions.

9.3 Recommendations and implications for program, policy and research

There are numerous key results from this thesis with potential implications for clinical outcomes and public health practice, strategic development for future policy and further research into HCC in Ethiopia and beyond. Although this research has the potential for new policy and program development, the inferences of findings of this thesis are a contemplation of how existing national policies can be changed into practice contextually, as detailed in the discussion section of each chapter.

SHT and H2H programs could make the ambitious 'HIV diagnosis' UNAIDS goal achievable while also addressing stigma. This could be complemented by peer educators bringing doorstep counselling, testing, linking and tracing activities to community members in their homes. Such early diagnosis will help patients clinically to limit OIs, enhance the benefit of ART, and increase their survival. However, it seems that SHT may be better for implementation among high-risk groups in its earlier phase and in the general population at the next phase. Furthermore, if the testing and detection coverage increase through the existing and new testing strategies recommended in this thesis, the number of patients on ART should increase. Thus, in addition to the established test and treat strategy, access to ART at all existing health facilities should be increased. Additionally, private clinics should be considered as another component of ART retention as discussed earlier, provided that monitoring and evaluation is strong. The authorities, however, need to address shortages of HIV testing logistics and ART drugs because there will be more people in need when the SHT and H2H are implemented and ART is started in private clinics.

ART attrition may still remain a major challenge when the number of diagnosed patients increase substantially. Therefore, ART retention strategies must be demedicalized and the community should take part in the HIV care system. The presence of peer educators in most HIV clinics is a good asset and a program should be built on it to improve the HCC. The TTLT model should be considered for action because it addresses every stage of the HCT continuum and has been found to be very effective in other studies, as discussed earlier. The integrated management of other chronic illnesses with HIV care will improve the quality of life of patients with HIV. There has to be a new and innovative strategy to monitor the selling of free ART in illicit markets because

this has several clinical practice and public health implications. In general, the high level of LP, ART discontinuation and immunologic failure are concerns. In view of the serious implications of the negative outcomes of HIV infection for public health, there is a necessity for targeted interventions to enhance favourable outcomes.

Fear of HIV status disclosure in relation to the still-rampant HIV related stigma discourages many patients with HIV from commencing and continuing ART. It is therefore important to counsel patients with HIV to lessen internalized stigma, and also to implement community-based interventions to decrease externalized stigma and discrimination. In general, innovative strategies should be designed to confront different domains of stigma, perceived, internalized, and enacted, at different socio-ecological levels i.e. individual, group, community and policy. Involving HIV positive people and great opinion leaders to deliver information sessions consistently and contextually on disclosure, social support and coping with stigma in health facilities, churches and other community meetings could improve HIV care clinical practice. The HIV testing and diagnosis programs should also be used to address stigma. The new HIV testing programs mentioned above are designed to reduce HIV related stigma.

Traditional healing was also found to be a cross-cutting barrier to HIV diagnosis, linkage and retention in care. Although amending legislation was the suggested solution, in a very religious society it may not be wise to suggest providing a legal framework on the issue. Instead, the government should consider undertaking efforts that will improve religious leaders' and traditional health practitioners' understanding of epidemiology of the disease and how it is transmitted and strengthen collaboration with them. Furthermore, recommendations are needed for traditional health practitioners to inform, educate and advise their communities in general and their patients in particular, to use modern HIV medicine simultaneously if traditional medicine is also used in HIV management in the study setting.

The findings from this thesis will serve as a springboard for further studies in Ethiopia and similar settings. Of particular importance, a nationwide study based on primary data is required to assess performance on the UNAIDS targets in Ethiopia to determine how well the nation is achieving the desired goals. Additionally, the association of social determinants of health and HIV care services should be assessed contextually because there is limited evidence on these. Moreover, it would be informative to explore and develop indictors to monitor inequity and assess progress towards equity in these groups. Further advanced research (e.g. experimental studies) to assess the acceptability rate and effectiveness of the suggested new programs in a wider context would also shed light on further strategies needed to combat HIV and AIDS. The assessment and exploration of different domains of stigma and respective interventions would also require additional research.

Further research is also needed to address the complex nature of the continuum of HIV care and treatment. Research is needed to assess HIV care among women to prioritize which groups of women are most at risk of negative outcomes. Given that women are vulnerable to negative HIV outcomes, benchmarking interventions targeted at women should be explored and developed. Rural dwellers and those with low literacy status were also found to be at higher risk of poor HIV outcomes. This calls for action to address the role of social determinants in women, rural dwellers and people with low literacy who have HIV. It is also interesting to study the exploration, assessment and interventions of the '*ART for sale*' issues in illicit drugs because it could also be a problem in other regions. The qualitative study revealed that trust in the ART care system had improved gradually. However, other study participants believed this was still a challenge. Therefore, institutional and interpersonal trust in ART care systems must be studied in depth. Overall, it will be essential to shift the research interest from assessing and exploring barriers to interventions in conditions where several barriers are assessed in similar contexts.

Finally, the literature review and complex findings of the project provide a glimpse of the modification of the HIV care framework and SEM. The available HIV care framework shows a linear relationship, but the cross-level analyses that assessed the barriers to and among HIV diagnosis, ART linkage and retention in care, and the networking and mechanisms that lead to poor HIV outcomes inform the need to review the existing framework. Additionally, although an attempt has been made to use the existing SEM to guide assessment from the individual, social and structural perspectives, the model has several limitations as discussed in detail in chapter eight. For example, the model did not test the association between the list of variables and did not endeavour to identify mechanisms of relationships. Additionally, there is no model that is specifically designed to assess the whole HCC contextually. For this reason, further research is needed to re-assess the model to answer complex questions about the HCC.

To conclude, this innovative project produced important findings which have informed policy to improve the survival and quality of life for patients with HIV and generally frame the HCC. The thesis also identified the most important ways forward for forthcoming research. In concrete, the recommendations of this thesis could help Ethiopia and similar countries achieve greater testing coverage, ART uptake, and virological suppression, and allow the full population to benefit from the health advantage of the *"treat all"* strategy.

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ANNEXES

Annex 1.1. Health Extension Program Packages

Hygiene and environmental sanitation:

(1) Proper and safe excreta disposal system,

(2) Proper and safe solid and liquid waste management,

(3) Water supply safety measures,

(4) Food hygiene and safety measures,

(5) Healthy home environment,

(6) Arthropods and rodent control,

(7) Personal hygiene,

Disease prevention and control

(8) HIV/AIDS prevention and control,

(9) TB prevention and control,

(10) Malaria prevention and control,

(11) First aid,

Family health services

(12) Maternal and child health,

(13) Family planning,

(14) Immunization,

(15) Adolescent reproductive health, and

(16) Nutrition.

Health education and communication: Cross cutting.

Annex 3.1. Publication 1- Systematic review and meta-analysis on ART discontinuation

PLOS ONE

RESEARCH ARTICLE

Discontinuation from Antiretroviral Therapy: A Continuing Challenge among Adults in HIV Care in Ethiopia: A Systematic Review and Meta-Analysis

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OPEN ACCESS

Citation: Gesesew HA, Ward P, Hajito KW, Feyissa GT, Mohammadi L, Mwanri L (2017) Discontinuation from Antiretroviral Therapy: A Continuing Challenge among Adults in HIV Care in Ethiopia: A Systematic Review and Meta-Analysis. PLoS ONE 12(1): e0169651. doi:10.1371/journal.pone.0169651

Editor: Matt A Price, International AIDS Vaccine Initiative, UNITED STATES

Received: June 28, 2016

Accepted: December 20, 2016

Published: January 20, 2017

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: The authors received no specific funding for this work.

Competing Interests: The authors have declared that no competing interests exist.

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; HIV, human immunodeficiency

Abstract

Background

Discontinuation of antiretroviral therapy (ART) reduces the immunological benefit of treatment and increases complications related to human immune-deficiency virus (HIV). However, the risk factors for ART discontinuation are poorly understood in developing countries particularly in Ethiopia. This review aimed to assess the best available evidence regarding risk factors for ART discontinuation in Ethiopia.

Methods

Quantitative studies conducted in Ethiopia between 2002 and 2015 that evaluated factors associated with ART discontinuation were sought across six major databases. Only English language articles were included. This review considered studies that included the following outcome: ART treatment discontinuation, i.e. 'lost to follow up', 'defaulting' and 'stopping medication'. Meta- analysis was performed with Mantel Haenszel method using Revman-5 software. Summary statistics were expressed as pooled odds ratio with 95% confidence intervals at a p-value of <0.05.

Results

Nine (9) studies met the criteria of the search. Five (5) were retrospective studies, 3 were case control studies, and 1 was a prospective cohort study. The total sample size in the included studies was 62,156. Being rural dweller (OR = 2.1, 95%CI: 1.5–2.7, I^2 = 60%), being illiterate (OR = 1.5, 95%CI: 1.1–2.1), being not married (OR = 1.4, 95%CI: 1.1–1.8), being alcohol drinker (OR = 2.9, 95%CI: 1.9–4.4, I^2 = 39%), being tobacco smoker (OR = 2.6, 95%CI: 1.6–4.3, I^2 = 74%), having mental illness (OR = 2.7, 95%CI: 1.6–4.6, I^2 = 0%) and being bed ridden functional status (OR = 2.3, 95%CI: 1.5–3.4, I^2 = 37%) were risk

virus; JBI-MAStARI, Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument; LTFU, lost to follow up; MAT, Medication-Assisted Therapies; PLHIV, people living with HIV; Tb, tuberculosis.

factors for ART discontinuation. Whereas, having HIV positive partner (OR = 0.4, 95%CI: 0.3–0.6, I^2 = 69%) and being co-infected with Tb/HIV (OR = 0.6, 95%CI: 0.4–0.9, I^2 = 0%) were protective factors.

Conclusion

Demographic, behavioral and clinical factors influenced ART treatment discontinuation. Hence, we recommend strengthening decentralization of HIV care services in remote areas, strengthening of ART task shifting, application of seek-test-treat-succeed model, and integration of smoking cession strategies and mental health care into the routine HIV care program.

Background

Since its emergence in the 1980s, the human immunodeficiency virus (HIV) has infected people of all ages, sexes, races and income status, leading to poor health and socio-economic outcomes across the world[1]. Since recognition of the acquired immune deficiency syndrome (AIDS) epidemic, almost 78 million people have been infected and about half of these people have died[2]. By the end of 2015, globally, 38.8 million (37.6–40.4 million) people were living with HIV[3].

Africa, Asia and Latin America were the major continents affected by the disease[4]. Sub-Saharan Africa (SSA) is the home for 76% of the global morbidity and 75% of the global mortality[3]. In 2015, Ethiopia had 39, 140 new HIV infections, 768, 040 people living with HIV, and 28, 650 HIV/AIDS deaths [3].

The advent of anti-retroviral therapy (ART), known to prolong the life of HIV patients, was a significant achievement[5]. If the quality of life and survival of people living with HIV (PLHIV) are to be improved, further effort needs to be made to ensure ART retention and its positive outcomes[6]. Discontinuation from ART (hereon in referred to as discontinuation) is the major contributor to attrition, and further to poor quality of life and death [7–13]. Discontinuation is defined as interruptions to ART due to LTFU, defaulting, transferring out and stopping medication while remaining in care[14]. Discontinuation reduces the immunological benefit of treatment and increases HIV-related complications, including AIDS-related re-admission, morbidity, mortality and drug resistance [14–19].

Discontinuation is known to be a significant problem across the globe[20–22], and Ethiopia is no exception. Studies conducted in Aksum St Marry Hospital[8], Mizan Aman General Hospital[10], Jimma University Specialized Hospital[23] and University of Gondar[24] reported that the proportion of LTFU was 9.8%, 26.7%, 28% and 31.4%, respectively. Additionally, a retrospective study from Ethiopia reported that retention of patients in care was a major challenge and varied across health facilities[25].

Primary studies conducted in Ethiopia reported socio-demographic, behavioral, clinical and institutional factors as contributors to discontinuation[7–10]. However, different studies showed conflicting association, and the existence of additional factors challenging interventions. Furthermore, the risk factors for discontinuation are still poorly understood in many developing countries including Ethiopia.

The absence of a clear and uniform definition of discontinuation is also another challenge. A study from five East African countries revealed the existence of 14 different definitions of ART defaulting were in use[26]. Currently, the definition of LTFU in Ethiopia is also not

uniform, and has included a patient discontinuing from ART for more than one[8], two[9], three[10,27–29] or twelve[30] months. Additional studies have considered a 'defaulter' when a patient discontinues from ART for more than two months [7,23].

Until a better understanding of these risk factors is gained, attempts to increase retention rates will be ad hoc and likely to be cost ineffective. As far as is known, there is no published systematic review and meta-analysis on this topic. Additionally, the lack of high quality data on the association between discontinuation and its risk factors is a challenge preventing national HIV/AIDS control programs from providing accurate data to inform tailored intervention strategies. This study examined risk factors for discontinuation from ART among PLHIV adults in Ethiopia.

Methods and Participants

This review has been reported using PRISMA reporting guidelines for systematic review[31] (S1 Table).

Study protocol

A protocol for this study has been published elsewhere[32].

Study design

A systematic review and meta-analysis was performed on studies conducted in English language in Ethiopia between 2002 and 2015. We selected 2002 as a start date for the search because this was when ART has been introduced in Ethiopia.

Types of participants

The detail of the study participants has been described in the published protocol[32].

Types of exposures

The review considered studies that examined risk factors for discontinuation including: age, sex, educational status, place of residence and matrimonial status, disclosure, partner's HIV status, mental status, smoking tobacco and drinking alcohol, tuberculosis HIV (Tb/HIV) co-infection, isoniazid (INH) prophylaxis provision, cotrimoxazole or opportunist infection (OI) prophylaxis provision, presence of side effects, baseline CD4 counts, baseline WHO clinical stage, baseline functional status, baseline body mass index (BMI) level, baseline hemoglobin level and regimen substitution, distance from the facility and facility type.

Types of outcome measures

The review considered studies that included discontinuation. Patients were considered 'discontinued' when they had been on ART and had missed at least one clinical appointment (one month) but had not yet been classified as "dead" or "transferred out", or when they had stopped treatment due to any reason while they have remained in care.

Search methods for identification of studies

An initial limited search of Google Scholar, MEDLINE, CINAHL and SCOPUS was undertaken followed by an analysis of the text words contained in the title and abstract, and of the index terms used to describe the article. A second search using all identified keywords and index terms was undertaken across the following databases: MEDLINE, PubMed, CINAHL,

SCOPUS, ProQuest and Web of Science. Finally, bibliographies of all articles were reviewed to identify for additional relevant studies. Studies published in English between 2002 and 30 December 2015 were considered for inclusion in this review. The key words for this review included discontinuation, LTFU, defaulting, retention, attrition, stopping medication, interruption and Ethiopia. Full search strategy can be found in S1 Table.

Selection of studies and quality appraisal

The types of studies to be included in the review has been described in the published protocol [32]. The selected papers were assessed by two independent reviewers, HAG and GTF, for methodological validity prior to inclusion in the review using standardized critical appraisal instruments from the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI) (S1 doc, S2 Table). Any disagreements between the reviewers were resolved through discussion. The appraisal form comprises 9 questions about the quality of the study for which articles receive values representing the extent to which they met the following criteria: Yes, No, Unclear and Not applicable. For cohort studies, appraisal based on "has bias been minimized in relation to selection of cases and of controls" was interpreted as "has bias been minimized in relation to selection of exposed and of unexposed adults living with HIV/AIDS". Risk of bias was also assessed based on Agency for Healthcare Research and Quality (AHRQ) criteria[33]. Authors of primary studies were contacted to clarify missing or unclear data. Articles were retained if at least one search term for the outcome concept was found. Articles that did not meet all eligibility criteria were excluded and reasons were noted (Fig 1).

Data extraction

The data extraction procedure has been described in the published protocol[32]. Authors of five studies were contacted via e-mail and requested to extract row by column tables: number of patients being reported discontinuation from ART treatment vs. not, and exposures of interest.

Data syntheses

The quantitative data were abstracted into an Excel 2007 spreadsheet and included details of study design, outcome and its measurement, sample size, number of participants with and without the event by the exposures of interest and summary of the study. Clinical heterogeneity was assessed by the authorship team and was acceptable to add each outcome to meta-analysis. Statistical heterogeneity was assessed statistically using the standard Chi-square and I^2 tests, with significant heterogeneity detected at the P value < 0.05. Meta-analyses were conducted separately for discontinuation and each exposure of interest using RevMan-5 Software [34]. Meta-analysis was considered if I^2 was below 85%[35]. Mantel Haenszel statistical method was used to calculate effect sizes, and forest plots to describe for the meta-analyses of exposures of interest with the event.

Pooled odds ratio (OR)[36] estimates and their 95% confidence intervals (CI) were calculated using random or fixed effect meta-analysis based on the degree of heterogeneity[35]. However, when the number of studies that reported the exposure of interest was small ($n<5$), only fixed effect model was considered irrespective of the level of heterogeneity[37,38]. Pooling was considered when at least two studies assessed the outcome and the exposure of interest. Publication bias was assessed using funnel plot.

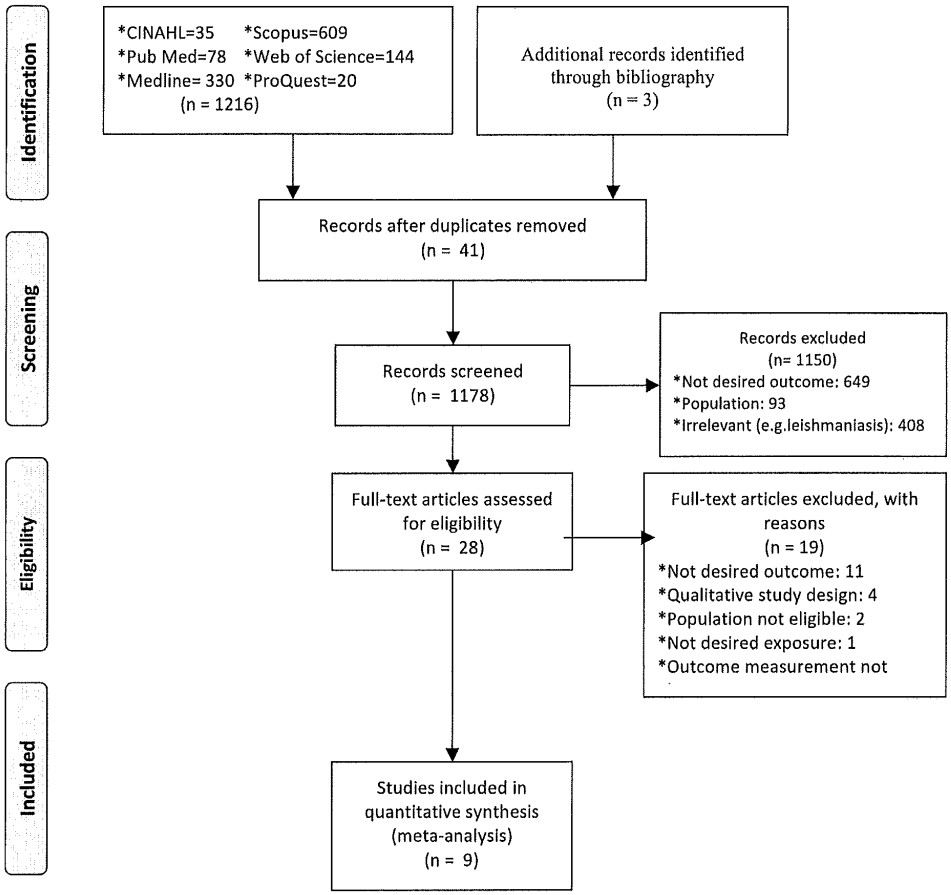

Fig 1. PRISMA 2009 flow diagram. This figure presents the results of the systematic search and reasons of exclusion.

doi:10.1371/journal.pone.0169651.g001

Results

Description of articles

One thousand two hundred and nineteen (1219) potential studies including from literature search (1216) and bibliographic review (3) were identified. Fig 1 reports the results of the search and reasons of exclusion. A total of nine studies were included to assess the association between discontinuation and at least one of the aforementioned exposures of interest.

Table 1 presents the main characteristics and outcomes of reviewed studies[7–10,23,28–30,39]. Studies were conducted from across Ethiopia and the majority of them were from the northern (4) and southern (3) part of the nation. All studies had relatively high sample size

Table 1. Characteristics of included articles (n = 9).

Author	Year	Sample size (n)	Study design	Outcome of interest	Measurement	Setting	Summary
Deribe et al. [23]	2008	1094	Case control	Defaulting	Individuals who had missed two or more clinical appointments (i.e. had not been seen for the last two months)	Jimma, South west Ethiopia	Not taking hard drugs (cocaine, cannabis and IV drugs) (AOR = 0.02, 95%CI: 0.003–0.17), excessive alcohol consumption (AOR = 6, 95%CI: 3.3–11.1), being bedridden (AOR = 5.7, 95% CI: 1.6–20.2), living outside Jimma town (AOR = 2.2, 95%CI: 1.4–3.5) and having an HIV negative (AOR = 3.5, 95%CI: 1.1–11.1) or unknown (AOR = 1.7, 95% CI: 1.02 = 2.9) HIV status partner were associated with defaulting ART.
Asefa et al. [7]	2013	236	Case control	Defaulting	Cases were individuals who had missed two or more clinical appointments (i.e. had not been seen for the last two months)	Nekemtie, South west Ethiopia	Living far from the facility (AOR = 4.1, 95%CI: 1.86–9.42), being dependent for source of food (AOR = 13.9, 95%CI: 4.23–45.99], not being mentally at ease (AOR = 4.7, 95%CI: 1.65–13.35], having HIV negative partner (AOR = 5.1, 95%CI: 1.59–16.63), having a partner who hadn't been tested for HIV or unknown (AOR = 2.8, 95%CI: 1.23–6.50] and fear of stigma (AOR = 8.3, 95%CI: 2.88–23.83) had statistically significant association with LTFU compared to their counterparts.
Wubshet et al.[39]	2013	2461	Retrospective cohort	LTFU	Adult patients who were three months late for their appointment to pick-up their antiretroviral drugs	Gondar, Northwest Ethiopia	Reasons for non-deaths losses include: stopping antiretroviral treatment due to different reasons, 135(53.36%), and relocation to another antiretroviral treatment program by self- transfer, 118 (46.64%).
Berheto et al.[10]	2014	2133	Retrospective cohort	LTFU	Not taking ART refill for a period of three months or longer from the last attendance and not yet classified as 'dead' or 'transferred-out'	Mizan, Southwest Ethiopia	Patients with regimen substitution (HR = 5.2, 95% CI: 3.6–7.3), non-isoniazid (INH) prophylaxis (HR = 3.7, 95% CI: 2.3–6.2), adolescent (HR = 2.1, 95% CI: 1.3–3.4), and had a baseline CD4 count < 200 cells/mm3 (HR = 1.7, 95% CIs: 1.3–2.2) were at higher risk of LTFU. WHO clinical stage 3 (HR = 0.6, 95% CIs: 0.4–0.9) and 4 (HR = 0.8, 95% CI: 0.6–1.0) patients at entry were less likely to be LTFU than clinical stage 1 patients
Tadesse et al.[8]	2014	520	Retrospective cohort	LTFU	Patients who had missed one or more clinical appointments	Axum, Northern Ethiopia	The independent predictors of LTFU of patient were being smear positive pulmonary Tb (AHR = 2.05, 95% CI: 1.02, 4.12), male gender (AHR = 2.73, 95%CI: 1.31, 5.66), regiment AZT-3TC-NVP (AHR = 3.47, 95%CI: 1.02,11.83) and weight ≥60kg (AHR = 0.24, 95% CI: 0.06,0.96).
Bucciardini et al.[28]	2015	512	Prospective cohort	LTFU[1], Stopped treatmen[2]	[1]patients who missed scheduled visit to the same health facility more than three months after the last visit; [2]patients known to have discontinued ART for any reasons	South Tigray, North Ethiopia	Active Tb (HR = 1.72, 95% CI: 1.23–2.41) and gender (HR = 1.64, 95% CI: 1.10–2.56) were also significantly associated with attrition.
Dessalegn et al.[9]	2015	727	Case control	LTFU	Patients who had missed two or more clinical appointments	Wukro, Northern Ethiopia	Presence of bereavement concern (AOR = 0.1, 95%CI: 0.01–0.3), not being provided with isoniazide prophylaxis (AOR = 3.04, 95%CI: 1.3–7.3), and presence of side effects (AOR = 12.3, 95%CI: 4.9–31.4) were found to be associated with increased odds for being LTFU
Melaku et al. [30]	2015	53,300[a]	Retrospective longitudinal	LTFU	If patients were not recorded as dead, transferred, or initiating ART, and if they did not have a recorded visit for 12 months or more with no subsequent visit	Ethiopia	Younger age, female gender, never being married, no formal education, low CD4+ cell count, and advanced WHO clinical stage were associated with increased LTFU

(*Continued*)

Table 1. (*Continued*)

Author	Year	Sample size (n)	Study design	Outcome of interest	Measurement	Setting	Summary
Teshome et al.[29]	2015	1173	Retrospective cohort	LTFU	If he or she failed to visit the health facility for more than 3 months after the last appointment date.	Southern, Nations, Nationalities and Peoples Region, South Ethiopia	The competing-risk regression model showed that body mass index > = 18.5 vs <18.5(AHR = 0.6, 95%CI: 0.4–0.9), WHO clinical stage late vs early (AHR = 1.4, 95%CI: 1.02–1.9), isoniazid prophylaxis no vs yes (AHR = 1.9, 95%CI = 1.1–3.2), age 26–39 vs 15–25 years (AHR = 0.6, 95%CI: 0.4–0.8), facility type health center vs hospital (AHR = 0.7, 95%CI: 0.5–0.9), and educational status 2^{0+} vs no (AHR = 0.6, 95%CI: 0.4–0.7) were independently associated with LTFU.

doi:10.1371/journal.pone.0169651.t001

and the total sample size was 62,156. The studies were analytical in type including: three case control studies[7,9,23], five retrospective cohort studies[8,10,29,30,39] and one prospective cohort study[28]. The majority of the studies (n = 7)[8–10,28–30,39] assessed factors associated with LTFU and the remaining two studies[7,23] assessed defaulting. One study that assessed LTFU[28] also assessed 'stopped treatment'.

Methodological quality

Three case-control studies[7,9,23] met seven out of nine JBI critical appraisal criteria, and six cohort studies[8,10,28–30,39] met eight out of nine JBI critical appraisal criteria. S2 Table presents outcome of the quality appraisal of each studies.

In addition, summary of risk of bias of the included studies was assessed based on Agency for Healthcare Research and Quality (AHRQ) criteria (S3 Table). The extent of risk bias was almost similar, and the studies had 'low risk' bias in the majority of areas. Due to inapplicability of design nature of the studies, they had 'unclear risk' judgment in a few criteria assessing the bias.

Measurement of discontinuation from ART

Measures of discontinuation were based on LTFU, defaulting or stopping medication. Four studies[10,28,29,39] considered LTFU when HIV positive patients on ART treatment had missed three or more monthly clinical appointments and not yet been classified as "dead" or "transferring out". One study[8] measured LTFU when adult patients were one month late for their appointment to pick-up their antiretroviral drugs whereas one other study[9] defined LTFU when patients had missed two or more clinical appointments. Another study[30] defined LTFU if they did not have a records of patients' visit for 12 months or if there were no more subsequent visit.

The remaining two studies[7,23] measured defaulting, and both considered 'defaulter' for individuals who had missed two or more clinical appointments. One study[28] assessed 'stopped treatment' and defined 'stopped treatment' when HIV positive patients who have been on ART treatment but have stopped treatment due to any reason while they remained in care.

Factors associated with discontinuation from ART among adults living HIV/AIDS

Socio-demographic determinants. The following socio-demographic factors were analyzed to assess their relationship with discontinuation: age, sex, place of residence, marital

status and educational status. All studies assessed the relationship of age with discontinuation. All studies have measured the association of age and discontinuation, and 3 studies[10,30,39] found that patient's age had significant association with discontinuation. Similarly, all studies have assessed the relationship between sex and discontinuation, and four studies[8,28,30,39] found a significant association. Two[23,39] of the four studies[7,9,23,39] that assessed the association between place of residence and discontinuation reported a significant association. Out of the six studies[7–9,23,29,30] that assessed correlation between marital status and discontinuation, only Melaku and colleagues [30] reported significant association. Seven studies[7–9,23,28–30] assessed the association between educational status and discontinuation, and only Melaku and colleagues [30] found statistical association.

Behavioral determinants. The following behavioral factors were the reported to be influential to discontinuation: disclosure, partner's HIV status, mental status, smoking tobacco and drinking alcohol. Asefa and colleagues [7] and Deribe and colleagues [23] discussed the association of tobacco use with discontinuation, however their odds were non-significant. Both studies also assessed the correlation of alcohol with discontinuation, of which Deribe and colleagues found a statistical difference. Two [7,23] of the three studies [7,9,23] that assessed association of partner's HIV status and discontinuation observed significant association. Dessalegn and colleagues [9] and Teshome and colleagues [29] studied the association of HIV disclosure status with discontinuation, however both found non-statistical association.

Clinical determinants. The following clinical factors were reported about their association with discontinuation: mental status, Tb/HIV co-infection, INH prophylaxis provision, cotrimoxazole or OI prophylaxis provision, presence of side effects, baseline CD4 counts, baseline WHO clinical stage, baseline functional status, baseline BMI level, baseline hemoglobin level and regimen substitution. Asefa and colleagues [7] and Deribe and colleagues [23] reported that having mental health problem was a risk factor for defaulting, and both reported statistically significant association. Among the three studies[7,9,29] that assessed the association between ART side effects and discontinuation, Dessalegn and colleagues[9] informed statistical significance. Seven studies[7–10,23,29,39] measured the correlation between baseline functional status and discontinuation, and only Berheto and colleagues [10] and Deribe and colleagues [23] reported the statistical significance.

Of the seven studies[7,8,10,23,28,29,39] that assessed the association between Tb status or being on Tb treatment and discontinuation, three[8,28,39] studies reported statistical difference. None of the four studies[7,8,10,23] that assessed the relationship between OI treatment or cotrimoxazole prophylaxis and discontinuation reported statistical significance. All studies assessed the correlation between baseline CD4 counts and discontinuation, and two studies [10,30] found statistical significance. WHO clinical stage as a factor for discontinuation was also assessed by six studies[9,10,28–30,39], and three of them[10,29,40] reported a statistical significance. All three studies[9,10,40] that assessed the relationship between INH prophylaxis and discontinuation reported statistical significance. Berheto and colleagues [10] and Dessalegn and colleagues [9] assessed the association between ART regimen substitution and discontinuation, but only Berheto and colleagues[10] reported significant association between these variables.

Institutional determinants. Distance to the health care facility[7,9] and the facility type [28,29] were the reported institutional factors influencing discontinuation. Asefa and colleagues[7] reported the presence of significant association between distance and discontinuation, and Bucciardini and colleagues [28] and Teshome and colleagues [29] reported the presence of significant association between the facility type and discontinuation.

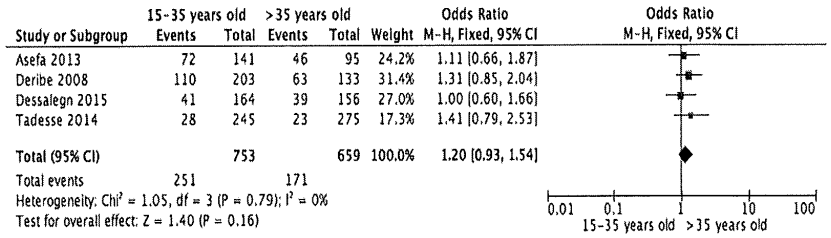

Fig 2. Forest plot of meta-analytic association between age and discontinuation from ART. It shows that the risk of ART discontinuation is not different by age.

doi:10.1371/journal.pone.0169651.g002

Meta analysis of factors affecting ART discontinuation

This meta-analysis identified determinants of discontinuation among adults living with HIV using proportions of the factors for the response variable assessed in primary studies[7–10,23,28–30,39]. Random effects meta-analysis model was considered for studies having moderate heterogeneity level when combined, whereas, fixed effect model was used for studies having low or no heterogeneity level[35]. However, when the number of studies reporting the exposure of interest was small (n<5), only fixed effect model was considered irrespective of the level of heterogeneity[37,38]. ART side effect was excluded from the meta-analysis because studies[7,23] reporting this variable showed severe heterogeneity (I2 = 90%). The Mantel Haenszel statistical method was used to calculate effect sizes and forest plots for the meta-analyses of socio-demographic, behavioral, clinical and institutional factors are shown in Figs 2–13.

Of the socio-demographic variables, rural dwellings (Fig 4; OR = 2.1, 95%CI: 1.5–2.7, I^2 = 60%), no literacy status (Fig 5; OR = 1.5, 95%CI: 1.1–2.1) and being not married (Fig 6; OR = 1.4, 95%CI: 1.1–1.8) had higher odds of discontinuation than their comparator. Among the behavioral factors influencing for discontinuation, partners' HIV positive status was found a protective factor (Fig 7; OR = 0.4, 95%CI: 0.3–0.6, I^2 = 69%) where as alcohol drinking (Fig 8; OR = 2.9, 95%CI: 1.9–4.4, I^2 = 39%) and tobacco smoking (Fig 9; OR = 2.6, 95%CI: 1.6–4.3, I^2 = 74%) were found risk factors. Of the clinical factors, Tb/HIV co-infection was associated with lower odds of discontinuation (Fig 10; OR = 0.6, 95%CI: 0.4–0.9, I^2 = 0%). Where as,

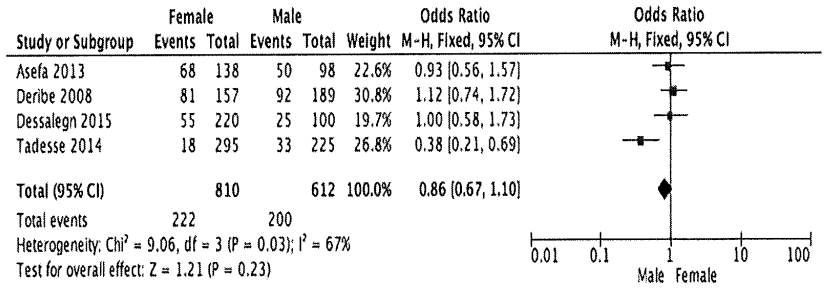

Fig 3. Forest plot of meta-analytic association between sex and discontinuation from ART. It shows that the risk of ART discontinuation is not different by sex.

doi:10.1371/journal.pone.0169651.g003

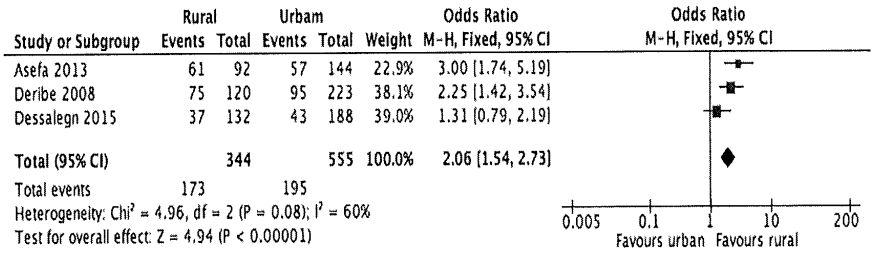

Fig 4. Forest plot of meta-analytic association between residence and discontinuation from ART. It shows that the risk of ART discontinuation is higher for rural than urban.

doi:10.1371/journal.pone.0169651.g004

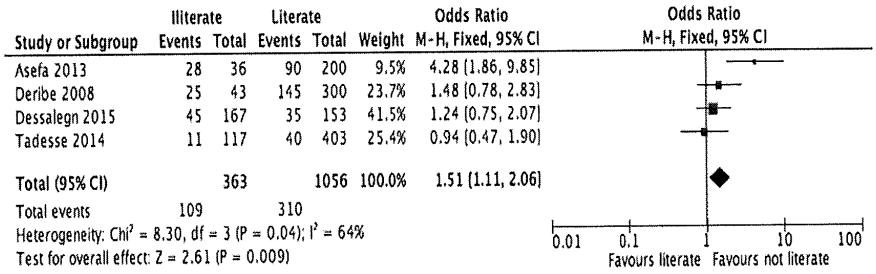

Fig 5. Forest plot of meta-analytic association between level of education and discontinuation from ART. It shows that the risk of ART discontinuation is higher for patients with no literacy status than literates.

doi:10.1371/journal.pone.0169651.g005

having bedridden functional status (Fig 11; OR = 2.3, 95%CI: 1.5–3.4, I^2 = 37%) and having mental illness (Fig 12; OR = 2.7, 95%CI: 1.6–4.6, I^2 = 0%) were another risk factors. As shown in Fig 10, the article by Tadesse and colleagues [8] was removed from the meta-analysis calculation to prevent the introduction of significant heterogeneity.

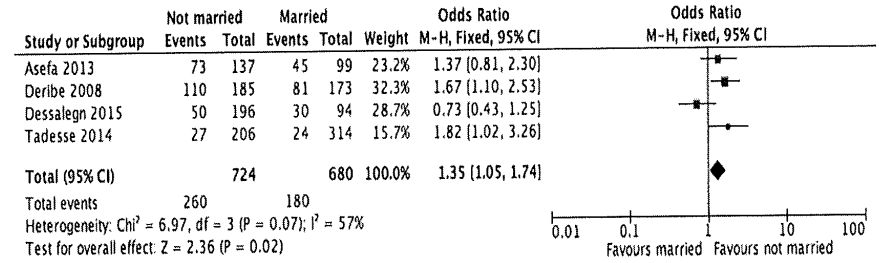

Fig 6. Forest plot of meta-analytic association between marital status and discontinuation from ART. It shows that the risk of ART discontinuation is higher for not-married than married.

doi:10.1371/journal.pone.0169651.g006

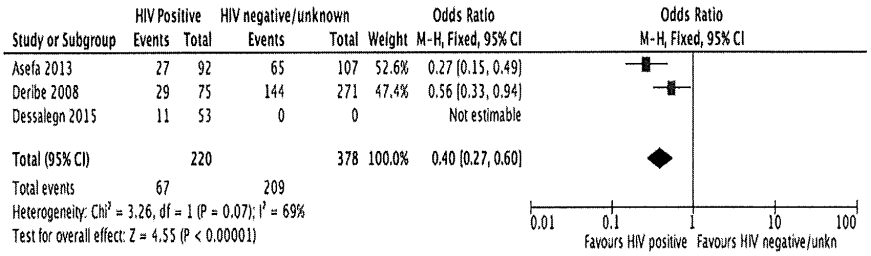

Fig 7. Forest plot of meta-analytic association between partners' HIV status and discontinuation from ART. It shows that the risk of ART discontinuation is lower for patients with HIV positive partner than HIV negative/unknown partner.

doi:10.1371/journal.pone.0169651.g007

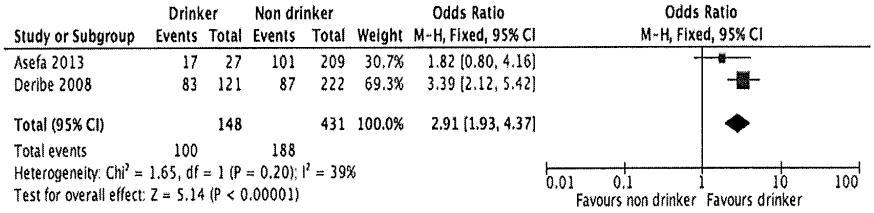

Fig 8. Forest plot of meta-analytic association between alcohol drinking and discontinuation from ART. It shows that the risk of ART discontinuation is higher for alcohol drinkers than non-drinkers.

doi:10.1371/journal.pone.0169651.g008

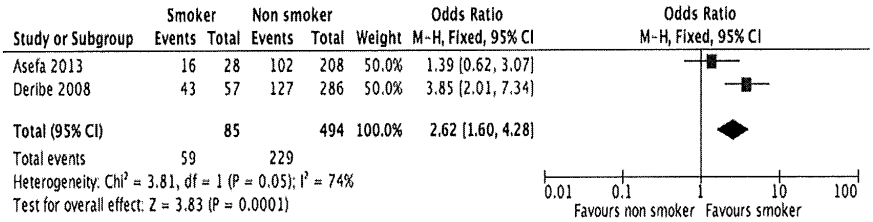

Fig 9. Forest plot of meta-analytic association between tobacco smoking and discontinuation from ART. It shows that the risk of ART discontinuation is higher for cigarette smokers than non-smokers.

doi:10.1371/journal.pone.0169651.g009

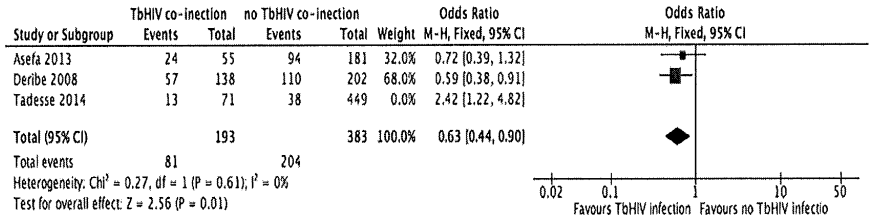

Fig 10. Forest plot of meta-analytic association between Tb/HIV co-infection and discontinuation from ART. It shows that the risk of ART discontinuation is lower for Tb/HIV co-infected patients than HIV alone.

doi:10.1371/journal.pone.0169651.g010

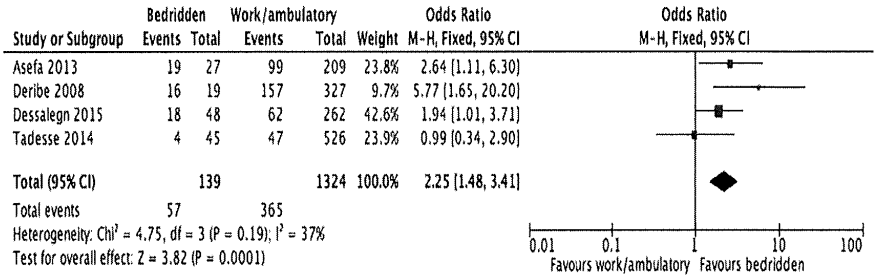

Fig 11. Forest plot of meta-analytic association between baseline functional status and discontinuation from ART. It shows that the risk of ART discontinuation is higher for patients with bedridden than working functional status.

doi:10.1371/journal.pone.0169651.g011

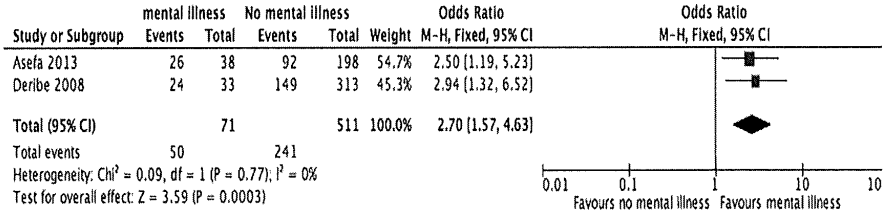

Fig 12. Forest plot of meta-analytic association between mental status and discontinuation from ART. It shows that the risk of ART discontinuation is higher for patients with mental status than their comparator.

doi:10.1371/journal.pone.0169651.g012

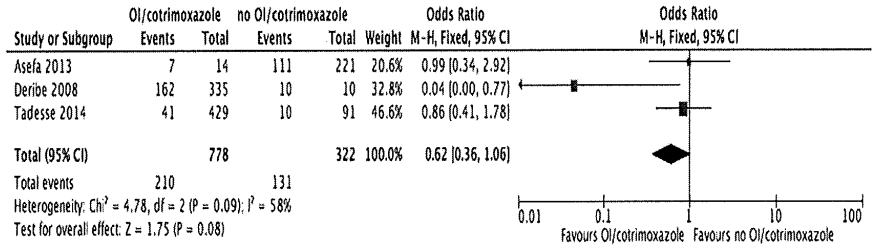

Fig 13. Forest plot of meta-analytic association between cotrimoxazole or opportunistic infections prophylaxis and discontinuation from ART. It shows that the risk of ART discontinuation is not different by the status of cotrimoxazole or opportunistic infections prophylaxis.

doi:10.1371/journal.pone.0169651.g013

Discussion

Studies examining retention in HIV care in Ethiopia have identified discontinuation as a key challenge for patient retention[11–13]. Studies in the current systematic review and meta-analysis[7–10,23,28–30,39] have identified a number of determinants. In Ethiopia, even though a large number of HIV-infected patients discontinue after engagement with ART treatment,

little research has been published as demonstrated by the low number of articles (nine studies) over a 13-year period included in this meta-analysis. This systematic review and meta-analysis identified studies conducted in three regional states of Ethiopia. The current study identified that being a rural dweller, being illiterate, being not married, being alcohol drinker, being tobacco smoker, having mental illness and being bed ridden functional status were risk factors for ART discontinuation, whereas, having HIV positive partner and being co-infected with Tb/HIV were protective factors for ART discontinuation.

The setting where the participant lived had significant influence to discontinuation with rural dwellers being more likely to discontinue compared to their urban counter parts. This finding was not a surprise as could be attributed to factors such as accessibility of the health care and availability of the transportation services[41,42]. It is therefore, plausible to hypothesise that strengthening decentralization and service integration of HIV care in remote areas would be a key for patient retention[43]. This hypothesis is also currently supported by WHO recommendations[44] of task shifting. The ART task shifting has commonly been practiced with tasks being shifted from doctors to health officers or nurses. This act has been observed to reduce patient attrition and also stated to be viable approach in rural areas. In additional to WHO recommendation, the task shifting was corroborated by a nationwide study in Ethiopia confirming that ART provision in health centers, based on health officers and nurses, is feasible, effective and acceptable[45]. Community engagement in HIV care continuum can also address the gap in inequity, particularly in rural-urban arena[46]. It is for this reason that a new model called seek-test-treat-succeed model—a model that aims at seeking out of HIV-infected individuals, offering them HIV testing and treatment, and providing support to retain—for HIV care has been promoted[47]. In addition, addressing long-term physical barriers such as roads and transportation facilities could also improve ART treatment retention [48–50].

The risk of discontinuation among patients with low literacy status was about two times higher when compared to the risk among literates. Several studies have suggested that improving knowledge of HIV care as an intervention could influence the retention of HIV positive people[51,52]. Furthermore, according to the seek-test-treat-succeed model, literate HIV infected people[53] have the capacity to provide almost 40% of HIV service-related tasks[54] and could lead to retention and re-engagement into care[47].

The risk of discontinuation among bedridden patients was two times higher when compared to the risk among working or ambulatory status. This poor baseline functional status might be due to late presentation for HIV care, a big challenge in the HIV care continuum [55]. Tobacco smokers also had high risk of discontinuation. Smoking has been noted to have a number of toxic effects that induce inflammation and weakening of the immunity, leading to failure to thrive and hindering patients from taking HIV care services continuously[56]. In addition, smokers are more likely to expose to risky sexual behaviors and this might facilitate to poor HIV/AIDS prognosis and subsequently deter from seeking HIV care services[57]. Thus, interventions for smoking cession such as Medication-Assisted Therapies (MAT) with behavioral counseling[58] and group behavior therapy programs[59] among HIV infected population should be instituted and be integrated with comprehensive HIV care.

Patients with mental illness had high probability of discontinuation than their comparator. It is well recognised that HIV and mental illness cause a serious bidirectional and synergistic combination of illness in which HIV escalates lifetime prevalence of mental illness, and mental illness increases the risk of HIV infection [60]. In addition, stigma and discriminating among HIV positive people with mental health issues can deter them from HIV care seeking[60]. This indicates the need for the inclusion of mental health into routine HIV care program.

The meta-analysis association suggests that having unknown or negative HIV partner was associated with higher odds of discontinuation than having HIV positive partner. The plausible justification might be due to negligence of counseling related to partner by health professionals[61]. It is therefore necessary to trace LTFU patients and design strict counseling for them and their partners. Additionally, it is necessary to invite patients with their partners because partners play key role in supporting patients in their HIV care continuum. Tb/HIV co-infection was associated with lower odds of discontinuation, a finding supported by a previous systematic review from sub-Saharan Africa[61]. It is plausible to hypothesize that if patients have Tb/HIV co-infection, they may attend and continue the care due to the fear of sequel of both diseases and this might have influence in retaining HIV patients in HIV care. However, further exploration is needed to examine the role of Tb/HIV co-infection in HIV care retention when compared to patients with HIV alone.

The current evidence on determinants of discontinuation has several important gaps. Measures for LTFU and defaulting were disparate to be analyzed systematically. This limitation is suggestive of weaknesses in definition of discontinuation which continues to lack a 'gold standard' measurement method[62]. All the studies were conducted in the three major regional states of Ethiopia named Tigray, Amhara and Oromiya in which HIV prevalence was below 2% compared to other regions such as Gambella with higher prevalence of 6.5%[63]. It is possible that regions with higher prevalence could have dissimilar risk factors for discontinuation and as such urgent attention would be warranted to establish these.

Another gap relates to the outcome status of discontinuation. Only Wubshet and colleague [39] reported the number of patients who died, survived and returned to HIV care after LTFU. Previous research reported that only 14% and 60% of LTFU patients re-engaged to HIV care at three and six months respectively[64], and those patients who re-engaged accessed the care after their health had deteriorated[65]. This shows a significant oversight for the need of future research involving the role and benefits of establishing the community-tracking system[66]. Finally, the majority of articles were retrospective cohort studies. For this reason, potential risk factors of discontinuation such as HIV related stigma were not assessed. Thus, primary studies, which may include qualitative study designs, are encouraged to explore the factors of discontinuation.

Findings of the current systematic review and meta-analysis highlight an imperative need to continue planning, implementing and evaluating intervention modalities aimed at improving retention in HIV care. To date, interventions such as reminding patients with mobile phones, text messaging and diary cards, and arranging treatment supporters have targeted the improvement of ART adherence[67,68]. Strengthening and adapting these interventions for improving patient retention could also be very effective.

Interpretations of the current study findings should consider the following important limitations. As stated, only one of the included studies in this review was prospective. This implies that meta-analytic findings can be viewed as an association and may not be causally related. The search strategy was limited to English language- a common example of reporting bias[69]. A funnel plot to detect publication bias in studies included in the meta-analysis was not reported due to the limited number of studies per each exposure ($n<10$)[69]. Geographic skewness and inclusion of few studies could influence the generalizability of the findings. Transferred out cases were excluded. However, we acknowledged that patients who were transferred out could continue the care in another institution resulting in overestimate of the proportion of discontinuation.

Some of the studies did not explicitly report absolute numbers of patients who discontinued by exposures of interest. Efforts to contact authors of the corresponding studies were fruitless and hence, we have been unable to report findings of meta-analytic association of the following

variables: WHO clinical stage of HIV, CD4 level, regimen substitution, hemoglobin level, INH prophylaxis and facility type. We focused the systematic review on HIV positive adults, but such analysis should be followed by another work to assess risk factors for discontinuation among children. Regimen wise, studies included in the current meta-analysis were about discontinuation from first line ART treatments and this may limit the transferability of the findings to second line ART drugs.

Conclusion

Our review identified several risk factors for ART discontinuation. Therefore, addressing the above determinants using multiple retention strategies is crucial to reduce attrition rate due to discontinuation. In addition, the retention strategies should involve multi-levels i.e. at individual-, system- and structural-level barriers.

Supporting Information

S1 doc. JBI Critical Appraisal instruments. It shows the critical appraisal checklist for each study designs.
(DOCX)

S2 doc. JBI Data extraction instruments. It shows the data extraction checklist for each study designs.
(DOCX)

S1 Table. Full searching strategy by databases. It shows the detailed searching strategy across data bases.
(DOCX)

S2 Table. Assessment of methodological quality (n = 9). It shows the result of the methodological quality assessment.
(DOCX)

S3 Table. Risk of Bias Assessment within the studies (n = 9). It shows the result of the risk bias assessment.
(DOCX)

Acknowledgments

We acknowledge the authors of included studies for partaking their data for the meta-analysis. We are grateful to Dr. Pamela Lyon, Visiting Research Fellow in Southgate Institute for Health, Society and Equity at Flinders University for editing draft of the manuscript. This systematic review was conducted for the partial fulfillment of a PhD in Public Health at Faculty of Medicine, Nursing and Health Sciences, Flinders University. The authors did not receive any specific grant for this research.

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Annex 3.2. Publication 2- Systematic review protocol on ART discontinuation

JBI Database of Systematic Reviews & Implementation Reports 2016;14(2):26-37

Factors associated with discontinuation of anti-retroviral therapy among adults living with HIV/AIDS in Ethiopia: a systematic review protocol

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Review question/objective

The aim of this review is to assess the best available evidence regarding risk factors for discontinuation from anti-retroviral therapy (ART) in Ethiopia.

Specifically, the review will be assessing the association between discontinuation from ART and the following:

- Socio-demographic and economic factors
- Behavioral factors
- Clinical factors
- Institutional factors.

Background

Since its emergency in the 1980s, the human immunodeficiency virus (HIV) has been infected people of all ages, sexes, races and income status, leading to poor health and socio-economic outcomes across the world.[1] Since its epidemic recognition, almost 78 million people have been infected and about half of these people have died of its sequel, AIDS.[2] By the end of 2013, globally, 35 million (33.2–37.2 million) people were living with HIV, of whom nearly 0.8% were adults aged 15-49 years.[2]

doi: 10.11124/jbisrir-2016-2451

Africa, Asia and Latin America were the major continents affected by the disease.[3] A total of 24.7 million people were infected with HIV whereby Sub-Saharan Africa was the hardest hit subcontinent.[2] The subcontinent was home for nearly 71% of people infected with HIV, and one in every 20 adults was living with the virus.[2] At the end of 2013, in Ethiopia, the prevalence of HIV was 1.2% with approximately 0.8 million people living with the virus.[4] Given that there is currently no cure and any human being is susceptible to this scourge, the advent of its treatment, anti-retroviral therapy, known to prolong the life of HIV patients, was a significant achievement.[5]

Over time since its recognition, the uptake and scaling up of ART treatment has been increasing. For example, in 2013, a total of 12.9 million patients were receiving ART, of which 11.7 million were from low- and middle-income countries.[6] There was a 5.6 million increase in the number of people receiving ART from 2010 to the end of 2013.[6] In Ethiopia alone, the number of people enrolled in ART rose from 900 in 2005 to 300,000 in 2010, and the number of facilities providing the same increased from four in 2003 to 481 in 2009.[5,7] If the quality of life and survival of people living with HIV PLWHIV are to be improved, further effort needs to be made to ensure that once started the treatment is continued effectively to the desirable level.[8] Discontinuation from ART treatment (hereon in referred to as discontinuation), is the major contributor, among many others, to poor quality of life and death of patients.[9-12] Discontinuation is defined as interruptions to ART therapy due to lost to follow-up, drop out or defaulting, transferring out and stopping medication while remaining in care.[13] Treatment discontinuation reduces the immunological benefit of ART and increases HIV-related complications, including AIDS-related morbidity, mortality, admission and drug resistance.[13-18]

Discontinuation is becoming a significant problem across the globe. For example, a study conducted in India showed that the overall dropout rate was 38.1 per 100 person-years.[19] In Malawi, the attrition rate was 33 and 36 person-years for hospitals and health centers, respectively.[20] Additionally, a retrospective analysis conducted in three sub-Saharan African countries indicated that the dropout rate was 2.1 per 100 person-years.[21] In Ethiopia, lost to follow-up was as prevalent as in other countries. Studies conducted in Aksum St Marry Hospital[10], Mizan Aman General Hospital[12], Jimma University Specialized Hospital[22] and University of Gondar[23] reported that the proportion of lost to follow-up was 9.8%, 26.7%, 28% and 31.4%, respectively. Another retrospective longitudinal study from Ethiopia reported that retention of patients in care was a major challenge and varied across health facilities.[24]

Primary studies conducted in Ethiopia reported that socio-demographic and -economic, behavioral, clinical and institutional factors contributed to discontinuation.[9-12] For example, males were reported to be most affected by discontinuation from being away from home, resulting in discontinuation of medication.[10] Similarly, drug addicted people may be faced with drug-drug toxicity and might discontinue from treatment.[12] The fear of HIV-related stigma has also been reported to keep patients away from treatment.[10] Patients with advanced clinical stage (WHO stage 3 or 4) at entry have been recognized to have a better chance of adhering to treatment as treatment leads to improvement.[2] Lastly, distance from ART clinics has also been noted to discourage patients from returning for treatment due to long travel and waiting times.[9] Patients dependent on food supplies, patients with mental problems, patients whose partners were HIV negative, patients not being provided with isoniazid prophylaxis, and patients with baseline CD4 <200 cells/mm^3 were at risk of discontinuation.[9-

[12] However, these factors were not uncovered based on systematic reviews, and the studies did not offer recommendations on priority interventions.

There have been very few systematic reviews on patient retention rates conducted in Sub-Saharan Africa. A systematic review conducted in 2007 indicated that there was monthly weighted mean attrition rates of 3.3%/month, 1.9%/month, and 1.6%/month for studies reporting at six, 12 and 24 months, respectively.[13] This systematic review assessed retention rates rather than risk factors. In Ethiopia, the issue has been given less attention. One systematic review[25] on ART non-adherence or non-compliance was conducted but it did not specifically identify the predictors of loss to follow-up, defaulting and total stoppage from treatment. As far as the authors know, there is no published systematic review and meta-analysis so far on his topic. Furthermore, the lack of high quality data on the association between the treatment discontinuation and its risk factors is an issue, preventing national HIV/AIDS control programs from providing accurate data to inform tailored intervention strategies. Additionally, the absence of a clear and uniform definition of discontinuation is also another challenge. Further evidence is needed to develop a consistent definition. A study from five East African countries revealed the existence of 14 different definitions of ART treatment defaulting were in use.[26] Currently, in Ethiopia, lost to follow-up refers to a patient discontinuing for less than three months, and dropping/defaulting if discontinued for more than three months.[27]

This systematic review will assess the association between known factors and discontinuation of HIV treatment. The review will use studies conducted in Ethiopia since the start of ART in 2002 using the pooled proportion of discontinuation from ART treatment variables and its factors. The authors conducted a preliminary search of databases (Medline [PubMed interface], EMBASE, CINHAL and SCOPUS), and found no current or underway systematic reviews on this or a similar topic in Ethiopia.

Keywords

Discontinuation; defaulting; lost to follow-up; ART; Ethiopia

Inclusion criteria

Types of participants

This review will consider studies reporting on HIV-positive participants aged 15 years and older who have commenced ART. Patients who have been transferred out will be excluded. Patients should have at least one follow-up time. If studies include both adult and pediatrics, and are not stratified by age (pediatrics and adults) during analysis, they will be excluded. Besides, if the studies focus on attrition (mortality or discontinuation) and are not stratified by mortality and discontinuation during analysis, the study will also be excluded.

Types of exposure

This review will consider studies that have examined risk factors for ART treatment discontinuation. These include socio-demographic and economic risk factors such as age, sex, income and being dependent on food supplies; behavioral risk factors such as mental status, presence of bereavement, the partner's HIV status and fear stigma; clinical factors such as isoniazid prophylaxis provision, presence of side effects, baseline CD4 counts and regimen substitution; and institutional risk factors such as distance from the facility and waiting times.

Types of outcomes

This review will consider studies that include the following outcomes: ART treatment discontinuation, i.e. lost to follow up, drop out or defaulting and stopping medication while remaining in care.

- *Lost to follow-up*: HIV positive patient who have been on ART treatment and have missed one to three months of clinical appointments but have not yet been classified as "dead" or "transferring out"
- *Drop out or defaulting:* HIV positive patient who have been on ART treatment and have missed three or more monthly clinical appointments and have not yet been classified as "*dead*" or "*transferring out*"
- *Stopping medication*: HIV positive patient who have been on ART treatment but have stopped treatment due to any reason while they have remained in care.

Types of studies

This review will consider for inclusion both experimental and epidemiological study designs including randomized controlled trials, non-randomized controlled trials, quasi-experimental studies, before and after studies, prospective and retrospective cohort studies, case control studies and analytical cross sectional studies conducted in Ethiopia. The review will also consider for inclusion descriptive epidemiological study designs including case series, individual case reports and descriptive cross sectional studies for inclusion.

Context

The review will consider studies conducted in Ethiopia between 2002 and 2015.

Search strategy

The search strategy aims to find both published and unpublished studies. A three-step search strategy will be utilized in this review. An initial limited search of Google Scholar, MEDLINE (Pub med platform), CINAHL and SCOPUS will be undertaken followed by an analysis of the text words contained in the title and abstract, and of the index terms used to describe the article. A second search using all identified keywords and index terms will then be undertaken across all included databases. Thirdly, the reference list of all identified reports and articles will be searched for additional studies. Studies published English between 2002 and 2015 will be considered for inclusion in this review.

The databases to be searched include:

Medline [PubMed interface], EMBASE, CINHAL, SCOPUS

The search for unpublished studies will include:

Hand searches of studies and different sources of grey literatures from ProQuest Dissertations and Theses [PQDT], Google Scholar, Med Nar, World Bank, WHO and Ministry of Health Data

Initial keywords to be used will be:

ART, antiretroviral, HAART defaulting, dropout, attrition, lost to follow up, retention, linkage, engagement, transfer out, stoppage, interruption, Ethiopia

Assessment of methodological quality

Papers selected for retrieval will be assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardized critical appraisal instruments from the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI) (Appendix I). Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer. Authors of primary studies will be contacted to clarify missing or unclear data.

Data extraction

Data will be extracted from papers included in the review using the standardized data extraction tool from JBI-MAStARI (Appendix II). The data extracted will include specific details about the exposures, populations, study methods and outcomes of significance to the review question and specific objectives.

Data synthesis

Quantitative data will, where possible be pooled in statistical meta-analysis using RevMan Software.[28] All results will be subject to double data entry. Some variables might need to be measured by more than one item, and might vary among studies. For example, HIV related stigma might be measured using Berger HIV stigma[29] or The People Living with HIV Stigma Index[30] scales. In this case, the acceptable range of validity and reliability will be considered. Effect sizes expressed as relative risk for cohort studies and odds ratio for case control studies (for categorical data) and mean difference (for continuous data), and their 95% confidence intervals will be calculated for analysis. Heterogeneity will be assessed statistically using the standard Chi-square and I^2 tests, and explored using subgroup analysis. Where statistical pooling is not possible the findings will be presented in narrative form including tables and figures to aid in data presentation where appropriate.

Conflicts of interest

The authors declare no competing interests.

Acknowledgements

Our gratitude goes to Flinders University for covering the cost of articles with fees. Thank you to Mr Andrew Craig, Topic Coordinator, Office of Graduate Research, Flinders University, for editing this protocol.

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Appendix I: Appraisal instruments

MAStARI appraisal instrument

JBI Critical Appraisal Checklist for Randomised Control / Pseudo-randomised Trial

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Was the assignment to treatment groups truly random?	☐	☐	☐	☐
2. Were participants blinded to treatment allocation?	☐	☐	☐	☐
3. Was allocation to treatment groups concealed from the allocator?	☐	☐	☐	☐
4. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
5. Were those assessing outcomes blind to the treatment allocation?	☐	☐	☐	☐
6. Were the control and treatment groups comparable at entry?	☐	☐	☐	☐
7. Were groups treated identically other than for the named interventions	☐	☐	☐	☐
8. Were outcomes measured in the same way for all groups?	☐	☐	☐	☐
9. Were outcomes measured in a reliable way?	☐	☐	☐	☐
10. Was appropriate statistical analysis used?	☐	☐	☐	☐
	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

JBI Critical Appraisal Checklist for Descriptive / Case Series

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Was study based on a random or pseudo-random sample?	☐	☐	☐	☐
2. Were the criteria for inclusion in the sample clearly defined?	☐	☐	☐	☐
3. Were confounding factors identified and strategies to deal with them stated?	☐	☐	☐	☐
4. Were outcomes assessed using objective criteria?	☐	☐	☐	☐
5. If comparisons are being made, was there sufficient descriptions of the groups?	☐	☐	☐	☐
6. Was follow up carried out over a sufficient time period?	☐	☐	☐	☐
7. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	☐	☐
9. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (including reason for exclusion)

JBI Critical Appraisal Checklist for Comparable Cohort/ Case Control

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Is sample representative of patients in the population as a whole?	☐	☐	☐	☐
2. Are the patients at a similar point in the course of their condition/illness?	☐	☐	☐	☐
3. Has bias been minimised in relation to selection of cases and of controls?	☐	☐	☐	☐
4. Are confounding factors identified and strategies to deal with them stated?	☐	☐	☐	☐
5. Are outcomes assessed using objective criteria?	☐	☐	☐	☐
6. Was follow up carried out over a sufficient time period?	☐	☐	☐	☐
7. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	☐	☐
9. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

Appendix II: Data extraction instruments

MAStARI data extraction instrument

JBI Data Extraction Form for Experimental / Observational Studies

Reviewer _____ Date _____

Author _____ Year _____

Journal _____ Record Number _____

Study Method

RCT	☐	Quasi-RCT	☐	Longitudinal	☐
Retrospective	☐	Observational	☐	Other	☐

Participants

Setting

Population

Sample size

Group A _____ Group B _____

Interventions

Intervention A

Intervention B

Authors Conclusions:

Reviewers Conclusions:

Study results

Dichotomous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number

Continuous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number

Annex 3.3. Full searching strategy of the systematic review on ART discontinuation

Medline searching strategy

1	exp HIV Infections
2	Antiretroviral Therapy, Highly Active
3	(HIV or AIDS or HIV-AIDS or Acquired Immunodeficiency Syndrome or Human immunodeficiency virus).tw.
4	(HIV adj1 (treat* or therap* or care or medication*)).tw.
5	(antiretroviral* or anti-retroviral* or HAART or ART or anti-hiv).tw.
6	Or/1-5
7	lost to follow up
8	(discontinu* or stop* medication* or "drop out" or default* or "los* to follow up" or LTFU or interrupt* or attrition or retention or link* or persist*).tw.
9	Or/7-8
10	africa, eastern/ or ethiopia
11	(east* Africa* or "Horn of Africa*" or ethiopia* or Addis Ababa* or Afar* or Semera* or Amhara* or Bahir Dar* or Benishangul-Gumuz* or Asosa* or Dire Dawa* or Gambela* or Harar* or Oromia* or Somali* or Jijiga* or Hawassa* or Tigray* or Meke'ele* or "Southern Nations Nationalities and peoples region" or SNNPR).tw.
12	Or/10-11
13	6 and 9 and 12

Pub med searching strategy

1	((((HIV OR aids OR hiv-aids OR acquired immunodeficiency syndrome OR human immunodeficiency virus OR antiretroviral OR anti-retroviral OR haart ART OR anti-hiv OR (HIV AND(treatment OR therapy OR care OR medication))))
2	(discontinue* OR stop* medication OR "drop out" OR default* OR "lost to follow up" OR ltfu OR interruption OR attrition OR retention OR link* OR persist)
3	((east africa OR "Horn of Africa" OR ethiopia OR addis ababa OR afar OR semera OR amhara OR bahir dar OR benshangul gumz OR asosa OR dire dawa OR Gambela OR harar OR oromiya OR Somali OR jijiga OR hawassa OR tigray OR meke'le OR "southern nations nationalities and peoples region) NOT Medline[sb])" LIMITED to English
4	1 AND 2 AND 3

Web of Science searching strategy

1	((HIV or AIDS or HIV-AIDS or Acquired Immunodeficiency Syndrome or Human immunodeficiency virus) AND ((antiretroviral* or anti-retroviral* or HAART or ART or anti-hiv) OR (HIV NEAR/1 (treat* or therap* or care or medication*)))
2	(discontinu* or stop* medication* or "drop out" or default* or "los* to follow up" or LTFU or interrupt* or attrition or retention or link* or persist*)
3	(east* Africa* or "Horn of Africa*" or ethiopia* or Addis Ababa* or Afar* or Semera* or Amhara* or Bahir Dar* or Benishangul-Gumuz* or Asosa* or Dire Dawa* or Gambela* or Harar* or Oromia* or Somali* or Jijiga* or Hawassa* or Tigray* or Meke'ele* or "Southern Nations Nationalities and peoples region" or snnpr))
4	1 AND 2 AND 3; Limited by language (English) and countries/territories (to Ethiopia)

Proquest searching strategy

1	((HIV OR AIDS OR HIV-AIDS OR Acquired Immunodeficiency Syndrome OR Human immunodeficiency virus)
2	((antiretroviral OR anti-retroviral OR heart OR ART OR anti-hiv) OR (HIV NEAR/1 (treat OR therapy OR care OR medication))) AND (discontinue OR stop medication OR "drop out" OR default OR "los to follow up" OR LTFU OR interrupt OR attrition OR retention OR persist)
3	(east Africa OR "Horn of Africa" OR ethiopia OR Addis Ababa OR Afar OR Semera OR Amhara OR bahr Dar OR Benishangul-Gumuz OR sosa OR Dire daiwa OR Gambela OR harare OR Oromia OR Somali OR Jijiga OR Hawassa OR Tigray OR Meke'ele OR "Southern Nations Nationalities and peoples region" OR SNNPR))
4	1 AND 2 AND 3; *Limited to full text, English language, b/n 2002 and 2015, location=Ethiopia, scholarly articles and conference proceedings*

Scopus searching strategy

1	ALL ((antiretroviral* OR anti-retroviral* OR haart OR art OR anti-hiv) OR (hiv W/1 (treat* OR therap* OR care OR medication*)) OR hiv OR aids OR “acquired immunodeficiency syndrome” OR “human immunodeficiency virus”)
2	ALL (discontinue* OR “stop* medication” OR “drop out” OR default* OR “lost* to follow up” OR ltfu OR interrupt* OR attrition OR retention OR link* OR persist*)
3	ALL (ethiopia OR addis ababa OR oromiya OR afar OR tigray OR amhara OR afar OR harar OR benshangul gumz OR Somali OR OR Gambela OR dire dawa OR “southern nations nationalities and peoples region OR snnpr)
4	1 AND 2 AND 3; Limited to country, Ethiopia AND Subject area medicine/sociology/psychology AND English

CINAHL Searching strategy

S13	S10 AND S11 AND S12
S12	S1 OR S2 OR S3 OR S7
S11	S6 OR S9
S10	S4 OR S5 OR S8
S9	Tx discontinu* or stop* medication* or "drop out" or default* or "los* to follow up" or LTFU or interrupt* or attrition or retention or link* or persist*
S8	east* Africa* or "Horn of Africa*" or ethiopia* or Addis Ababa* or Afar* or Semera* or Amhara* or Bahir Dar* or Benishangul-Gumuz* or Asosa* or Dire Dawa* or Gambela* or Harar* or Oromia* or Somali* or Jijiga* or Hawassa* or Tigray* or Meke'ele* or "Southern Nations Nationalities and peoples region" or SNNPR
S7	hiv or "acquired immunodeficiency syndrome" or "HIV infections" or AIDS or "Human Immunodeficiency virus" or "antiretroviral treat*" or "highly active antiretroviral therapy or HAART or ART or HIV treat* or "anti-retroviral agent"
S6	(MH "After Care")
S5	(MH "Africa, Eastern")
S4	(MH "Ethiopia")
S3	(MH "Antiretroviral Therapy, Highly Active")
S2	(MH "Acquired Immunodeficiency Syndrome")
S1	(MH "HIV Infections")

Annex 3.4: JBI Critical Appraisal instruments

JBI Critical Appraisal Checklist for Descriptive / Case Series

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Was study based on a random or pseudo-random sample?	☐	☐	☐	☐
2. Were the criteria for inclusion in the sample clearly defined?	☐	☐	☐	☐
3. Were confounding factors identified and strategies to deal with them stated?	☐	☐	☐	☐
4. Were outcomes assessed using objective criteria?	☐	☐	☐	☐
5. If comparisons are being made, was there sufficient descriptions of the groups?	☐	☐	☐	☐
6. Was follow up carried out over a sufficient time period?	☐	☐	☐	☐
7. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	☐	☐
9. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

JBI Critical Appraisal Checklist for Comparable Cohort/ Case Control

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Is sample representative of patients in the population as a whole?	☐	☐	☐	☐
2. Are the patients at a similar point in the course of their condition/illness?	☐	☐	☐	☐
3. Has bias been minimised in relation to selection of cases and of controls?	☐	☐	☐	☐
4. Are confounding factors identified and strategies to deal with them stated?	☐	☐	☐	☐
5. Are outcomes assessed using objective criteria?	☐	☐	☐	☐
6. Was follow up carried out over a sufficient time period?	☐	☐	☐	☐
7. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	☐	☐
9. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

Annex 3.5. Risk of Bias Assessment within the studies (n=9)

Study	Random Sequence Generation (Selection bias)	Allocation Concealment (Selection bias)	Blinding of Participants and personnel (Performance bias)	Blinding of outcome Assessment (Detection bias)	Incomplete Outcome Data (attrition bias)	Selective reporting (Reporting bias)	Other

[a] = Not applicable due to type of study design

Annex 3.6 JBI Data extraction instruments

JBI Data Extraction Form for Experimental / Observational Studies

Reviewer _____ Date _____

Author _____ Year _____

Journal _____ Record Number _____

Study Method

RCT	☐	Quasi-RCT	☐	Longitudinal	☐
Retrospective	☐	Observational	☐	Other	☐

Participants

Setting

Population

Sample size

Group A _____ Group B _____

Interventions

Intervention A

Intervention B

Authors Conclusions:

Reviewers Conclusions:

Study results

Dichotomous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number

Continuous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number

Annex 3.7. Publication 3- Retrospective cohort study of late presentation for HIV care

Gesesew et al. BMC Infectious Diseases (2018) 18:59
DOI 10.1186/s12879-018-2971-6

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Late presentation for HIV care in Southwest Ethiopia in 2003–2015: prevalence, trend, outcomes and risk factors

Hailay Abrha Gesesew[1,2*], Paul Ward[1], Kifle Woldemichael[2] and Lillian Mwanri[1]

Abstract

Background: Early presentation for HIV care is vital as an initial tread in the UNAIDS 90–90–90 targets. However, late presentation for HIV care (LP) challenges achieving the targets. This study assessed the prevalence, trends, outcomes and risk factorsfor LP.

Methods: A 12 year retrospective cohort study was conducted using electronic medical records extracted from an antiretroviral therapy (ART) clinic at Jimma University Teaching Hospital. LP for children refers to moderate or severe immune-suppression, or WHO clinical stage 3 or 4 at the time of first presentation to the ART clinics. LP for adults refers to CD4 lymphocyte count of < 200 cells/ μl and < 350 cells/μl irrespective of clinical staging, or WHO clinical stage 3 or 4 irrespective of CD4 count at the time of first presentation to the ART clinics. Binary logistic regression was used to identify factors that were associated with LP, and missing data were handled using multiple imputations.

Results: Three hundred ninety-nine children and 4900 adults were enrolled in ART care between 2003 and 15. The prevalence of LP was 57% in children and 66.7% in adults with an overall prevalence of 65.5%, and the 10-year analysis of LP showed upward trends. 57% of dead children, 32% of discontinued children, and 97% of children with immunological failure were late presenters for HIV care. Similarly, 65% of dead adults, 65% of discontinued adults, and 79% of adults with immunological failure presented late for the care. Age between 25-< 50 years (AOR = 0.4,95% CI:0.3–0.6) and 50+ years (AOR = 0.4,95% CI:0.2–0.6), being female (AOR = 1.2, 95% CI: 1.03–1.5), having Tb/HIV co-infection (AOR = 1.6, 95% CI: 1.09–2.1), having no previous history of HIV testing (AOR = 1.2, 95% CI: 1.1–1.4), and HIV care enrollment period in 2012 and after (AOR = 0.8, 95% CI: 0.7–0.9) were the factors associated with LP for Adults. For children, none of the factors were associated with LP.

Conclusions: The prevalence of LP was high in both adults and children. The majority of both children and adults who presented late for HIV care had died and developed immunological failure. Effective programs should be designed and implemented to tackle the gap in timely HIV care engagement.

Keywords: Trend, Outcomes, Late presentation, Retrospective cohort, Ethiopia

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[2]Epidemiology, Jimma University, Jimma, Ethiopia

Background

The Joint United Nations Program on HIV and AIDS (UNAIDS) has developed a 90–90–90 treatment target framework in order to end AIDS globally which aims at 90% of people living with HIV knowing their HIV status, 90% of HIV diagnosed patients receiving sustained treatment, and 90% of those on HIV treatment achieving viral suppression [1]. While diagnosing HIV infection is vital as the initial tread in the 90–9090 targets, diagnosis per se is no longer sufficient [2]. Early diagnosis and access to treatment helps people with HIV to timely get and appropriately use HIV treatment [3] that further reduces the virus load and risk of morbidity and mortality. Nevertheless, late presentation for HIV care (LP) has been recognized as an impediment to meet the above mentioned UNAIDS targets.

LP is the result of being late in HIV diagnosis and/or late in linking with or in accessing HIV care [4]. The definition of LP is disparate and is contextualized using the threshold for ART eligibility [5]. To date, numerous definitions have been used including: i) when the baseline CD4 count is < 200 or < 350 cells/μl and/or with an AIDS defining disease [3, 6, 7], ii) when AIDS defining conditions are diagnosed either before or during the period to an HIV diagnosis [8], iii) when AIDS defining conditions are diagnosed in the subsequent 6 months period to an HIV diagnosis [9], or iv) when AIDS defining conditions are diagnosed 12 months period to an HIV diagnosis [10].

LP is associated with increased risk of HIV transmission [11], ART drug resistance [11], and health care expenses [12]. Additionally, LP has been acknowledged as a challenge for the achievement of the ambitious UNAIDS 90–90-90 targets [13, 14]. For the first 90, high magnitude of late HIV diagnosis reflects that there are a number of people who did not know their HIV status. For the second 90, LP results in poor health outcomes and this interrupts the sustainable uptake of the treatment [13]. Furthermore, LP significantly contributes for pre-ART deaths and, this in turn, reduces the number of HIV diagnosed patients on ART [15]. For example, a study from South Africa reported that ART initiation at the time of first presentation to ART clinic boosted treatment uptake by 36% [16]. For the third 90, LP lowers the number of CD4 cells and increases the number of viral counts, and this causes clinical, immunological or virological failure [14, 17]. Previous studies have shown that late diagnosis appeared to be the main reason for virological failure, and ART initiation at first visit increased viral suppression by 26% [16].

LP has been reported to be a significant problem across the globe. In Europe, overall prevalence of 15–66% has been reported [18, 19]. The magnitude of LP in Asia was very significant (72–83.3%) [20], and in Africa, the overall prevalence has been reported to be between 35 and 65% [21, 22]. Nonetheless, heterogeneity in its measurement limited direct comparisons [23]. In Ethiopia in 2015, there were 39,140 new infections, 768, 040 people living with HIV and 28, 650 HIV/ADS deaths [24]. Universal access to ART in the country was launched in 2005 [25], and to date, the coverage of ART—the percentage of people on ART among those in need of treatment [26]— is 52% [24]. However, the status of timely presentation for HIV care is yet to be assessed. One cross-sectional study from northern part of the country has reported a LP prevalence of 68.8% [27].

Demographic, behavioural and clinical factors contributed for LP [6, 20, 28, 29]. For instance, being female, older age, rural dwellers, alcohol users, '*Khat*' chewers, cigarette smokers, being diagnosed with sever co-morbidities, perceiving HIV related stigma, having contact with commercial sex workers and being exposed to risky sexual behavior were the factors associated with LP [6, 20, 28, 29]. In Ethiopia, other studies have assessed factors affecting LP [6, 27, 29], and all except one were from the northern part of the country.

However, it is well known that the southwestern part of the nation has different cultural and socioeconomic characteristics. It also has the highest HIV prevalence (6.5%) in the country [30] and may have different LP factors which need to be understood to address HIV in these settings. In addition, for patients who started ART, no study has been conducted to assess the outcome and trends of LP. The prevalence of LP among children has also not been determined. Given the above gaps, and the clinical and public health importance of early HIV diagnosis on timely ART commencement, it is imperative to comprehend the LP situation and recommend effective programs that facilitate early presentation for HIV care in Ethiopia. Furthermore, addressing LP may have a substantial contribution for SDG-3 to have good health and wellbeing, and particularly for SDG-3.3 to end HIV epidemics by 2030. This paper examines the prevalence, trend, outcomes and risk factors of LP among children and adults enrolled for ART in Jimma University Teaching Hospital (JUTH), Southwest Ethiopia.

Methods

Study design, setting and participants

A retrospective cohort study was undertaken using data extracted from the ART clinic at JUTH using patient records from June 2003 to March 2015. Details of the study setting has been described elsewhere [31]. The study population was all HIV patients enrolled for ART care in JUTH.

Data source and procedures

The data were extracted from JUTH electronic medical records (EMR) system called comprehensive care center patient application database (C-PAD) that was in place since 2007. HIV care providers record patient clinical and non-clinical information on paper form, which is then entered into the EMR by data clerks. Two data clerks perform the data entry process to ensure completeness. The International Center for AIDS Care and Support (ICAP) at Colombia University was also delivering technical assistance on the electronic patient level data management, and has been conducting random check up of data completeness. This ensures the accuracy and reliability of the EMR data. Weekly patient summary generated from the EMR system helps to flag patients with conditions that seek follow-up. If baseline CD4 and WHO clinical staging were not recorded, records would be excluded.

Study variables and definitions

The dependent variable was the time when a patient presented for HIV care and was dichotomized as late or early. We defined LP for adults when the baseline CD4 cells count is < 200 cells/μl or < 350 cells/μl (pre-and post-revision of national ART guideline) irrespective of WHO clinical staging, or WHO clinical stage 3 or 4 irrespective of CD4 count at the time of first presentation to an ART clinic [3, 6]. Early presentation for HIV care (EP) is the opposite of LP. LP and EP for children are defined in Table 1. The independent variables included age, sex, marital status, educational status, religion, Tb/HIV co-infection, baseline functional status, history of HIV testing, and HIV care enrollment period. History of previous HIV testing refers to testing (one or more times) for HIV before diagnosis. HIV care enrollment period was dichotomized as enrolled for HIV care in 2003–11, and 2012 and after.

Possible outcomes of LP were ART discontinuation, immunological failure and mortality. ART discontinuation is attributed to lost to follow up (LTFU), defaulting and stopping medication while remaining in care. LTFU was if patients had been on ART treatment and had missed at least three clinical appointments but had not yet been classified as "dead" or "transferred out" (TO). Defaulting was if patients had been on ART treatment and had missed less than three clinical appointments but had not yet been classified as "dead" or "TO". Stopping medication was definedwhen patients had stopped treatment due to any reason while they have remained in care. TO is the official transferring of the patient to another ART clinic within or outside a catchment area. Immunological failure was defined based on the definitions provided by WHO [32]. Mortality (all cause mortality) is the death of people on ART in the reporting period. Table 1 reports the measurements of LP.

Statistical analyses

Ten year trends (data for years 2003 and 2015 were excluded since their number of months were incomplete) for LP was described by line graphs, and best-fit equation for the trend line was developed. We described the percentage of LP by ART discontinuation, immunological

Table 1 Measurements for late presentation for HIV care (LP)

Adults		Late presentation for HIV care [6, 35][a]	
	Enrolled in 2003–11	Enrolled in 2012–15	
	CD4 lymphocyte count of < 200 cells/ μl irrespective of WHO clinical stage at the time of first presentation to the HIV care	CD4 lymphocyte count of < 350 cells/ μl irrespective of WHO clinical stage at the time of first presentation to the HIV care	
	WHO clinical stage 3 or 4 irrespective of CD4 count at the time of first presentation to the HIV care [b]	WHO clinical stage 3 or 4 irrespective of CD4 count at the time of first presentation to the HIV care	
Children[c]		Late presentation for HIV care [70]	
		Moderate immune-suppression (damage) if CD4 count between	Severe immune-suppression (damage) if CD4 count between
	0–12 months	750–1500 cells/ μl	< 750 cells/ μl
	1–5 years	500–1000 cells/ μl	< 500 cells/ μl
	≥ 6 years	200–500 cells/ μl (enrolled in 2003–2011)	< 200 cells/ μl (enrolled in 2003–11)
	≥ 6 years	350–500 cells/ μl (enrolled in 2012–2015)	< 350 cells/ μl (enrolled in 2012–2015)

ART: antiretroviral therapy; CD4: cluster for differentiation 4; WHO: World Health Organization; Tb: Tuberculosis; PCP: pneumocystis carinii (juvenii) pneumonia
[a]The definition for LP among Tb/HIV co-infected population was only based on the CD4 criteria [4]
[b]WHO clinical Stage 3was defined if one of the following is present in an HIV diagnosed patient: weight loss of > 10% body weight, chronic diarrhea for > 1 month, fever for > 1 month, oral candidiasis, oral hairy leukoplakia, or pulmonary Tb within the previous year, or severe bacterial infections; WHO clinical Stage 4 was defined if one of the following is present in an HIV diagnosed patient: HIV wasting syndrome, PCP, toxoplasmosis of the brain, cryptosporidiosis or isosporiasis with diarrhea for > 1 month, cytomegalovirus disease of an organ other than liver, spleen or lymph node, herpes simplex virus infection, progressive multifocal leukoencephalopathy, candidiasis, extra-pulmonary Tb, lymphoma, kaposi's sarcoma, HIV encephalopathy
[c]LP is also defined if WHO clinical stage 3 or 4 at first visit to the ART clinics

failure and mortality to show the outcomes of LP. The differences between LP and its outcomes were checked using Chi square tests. We used binary logistic regression to identify factors that were associated with LP. Multicollinearity was checked using variance inflation factor and none was found. In addition, we checked for potential two-way interactions and none was found.

Missing data was treated using multiple imputations ($n = 5$) assuming missing at random (MAR) pattern [33] and the model was reported with pooled imputed values [34]. We developed an imputation model for adults, however; for children, we did not decide to do the multiple imputations analysis since the missing values for the great majority of the variables were not significant (below 5%). Bivariate logistic regression analysis was conducted to determine the presence of crude association and nominate the candidate variables ($P < 0.25$ was considered) to multiple logistic regression. P-value ≤ 0.05 was considered as a cutoff value for statistical significance in the final multiple logistic regression model. We applied Hosmer and Lemeshow test to check goodness of fit of the final model and was found fit (P−value = 0.17). We reported odds ratio and 95% confidence interval to summarize the data. We used Statistical Package for the Social Sciences (SPSS) version 22.0 for all data analyses.

Results

Of the 8172 patients enrolled for HIV care between 21 June 2003 and 15 March 2015, 5299 (64.8%) patients on ART, the study population for the study, were included. Of the total patients enrolled for ART, 4900 (92.5%) were adults and 399 (7.5%) were children.

Table 2 demonstrates the characteristics of HIV patients on ART. Among the children, 58.1% were aged 5–15 years, 52.4% were males, and 73.9% were Christians. The majority of the children (79.4%) had moderate or severe immune-suppression, and half of the children had baseline WHO clinical stage 3 or 4. A total of 114 (28.6%) children had Tb/HIV co-infection. The median time on ART and estimated survival time, respectively, was 40 and 104.2 (99.8–108.5) months. Among adults, three fifth (59.8%) were females, about half (48.7%) were married and 39% had primary school education. Two fifth (41.6%) of adults had no history of HIV testing. A significant number of adults (73.6%) had baseline CD4 count below 200 cells/mm^3, and 54.3% had WHO clinical stage 3 or 4. Over a quarter of adults (27.9%) had Tb/HIV co-infection. Twenty nine (0.9%) adults changed ART regimen during the course of the period. The median time on ART was 49 months, and the median estimated survival time was 121.9 (95%CI: 120.3–123.5) months.

Prevalence, trend and outcomes of LP

The overall prevalence of LP was 65.5%, and females accounted for the majority (64.3%).In total, 215 children (57%) and 1788 adults (66.7%) were late presenters. In the period between 2004 and 2014 the percentage of LP decreased from 83% to 62%. Fig. 1 shows the trend in LP among HIV infected people on ART.

Table 3 reports the outcomes of LP among HIV infected children and adults enrolled in HIV care. Of the children, 57.1% of those who died, 32.3% of those who discontinued care, and 96.9% of those who had immunologic failure were late presenters for HIV care. Of adults, 64.7% of those who died, 65.3% of those who discontinued care, and 78.7% of those who had immunologic failure presented late for the HIV care. The chi-square analysis showed that the difference between LP and, immunologic failure and discontinuation for children was statistically significant. For adults, LP was not statistically different with mortality and ART discontinuation.

Risk factors for LP

Table 4 presents the multiple logistic regression analysis of factors for LP obtained from the complete case analyses. Predictors of LP among adults included being older adult, female, having Tb/HIV co-infection, having no previous history of HIV testing and HIV care enrollment period in 2012 and after. Older adults aged between 25- < 50 years (AOR = 0.4, 95% CI: 0.3–0.6) and 50+ years (AOR = 0.4, 95% CI: 0.2–0.6) were 60% each less likely to present late for HIV care compared to those aged between 15 and 25 years. Females were 20% high likely (AOR = 1.2, 95% CI: 1.03–1.5) to present late for HIV care than their comparator. HIV patients with Tb/HIV co-infection were about 2 times at risk of LP (AOR = 1.6, 95% CI: 1.09–2.1) than HIV patients alone. In addition, while having no previous history of HIV testing (AOR = 1.2, 95%CI: 1.1–1.4) was a risk factor for LP, HIV care enrollment period in 2012 and after (AOR = 0.8, 95% CI: 0.7–0.9) was a protective factor for LP. No statistically significant predictor was found for LP among children.

Multiple imputations (MI)

To handle the missing data, we applied MI using five imputed data sets. We have presented the results from MI and complete case analyses in Table 4. In estimating factors associated with LP among adults, results were similar in both MI and complete case analyses except for variables Tb/HIV co-infection and previous history of HIV testing were marginally statistically significant in the MI analysis.

Discussion

LP has been described as a sizable obstacle to attaining the UNAIDS 90–90-90 and 95–95-95 targets [7, 14].

Table 2 Clinical & non-clinical characteristics of HIV infected people enrolled in ART care in Southwest Ethiopia from 2003 to 2015

Variable		Children (*N* = 399) *N* (%)	Adult (*N* = 4900) *N* (%)
Age in years	< 1	21 (5.3)	–
	1- < 5	146 (36.6)	–
	5- < 15	232 (58.1)	–
	15- < 25	–	711 (14.5)
	25- < 50	–	3937 (80.3)
	50+	–	252 (5.2)
	Median (range) age in years	6 (< 1–14)	30 (15–81)
ART follow up time in months, median (range)		40 (0–116)	49 (0–137)
Estimated survival time in months, median (95%CI)		104.2 (99.8–108.5)	121.9 (120.3–123.5)
Sex	Male	209 (52.4)	1971 (40.2)
	Female	190 (47.6)	2929 (59.8)
Marital status	Never married	–	897 (18.3)
	Married	–	2094 (42.7)
	Separated/divorced/widowed	–	1311 (26.8)
	Missing	–	598 (12.2)
Education	No education	–	945 (19.3)
	Primary	–	1687 (34.4)
	Secondary and above	–	1685 (34.4)
	Missing	–	583 (11.9)
Religion	Muslim	47 (11.8)	1402 (28.6)
	Christian[b]	133 (33.3)	2893 (59)
	Missing	219 (54.9)	605 (12.3)
Baseline WHO classification	1 or 2	108 (27.1)	1355 (27.7)
	3 or 4	110 (27.6)	1608 (32.8)
	Missing	181 (45.3)	1937 (39.5)
Baseline CD4 count category	No damage	72 (20.6)	–
	Moderate or severe damage	277 (79.4)	–
	Median (range) CD4 count	282 (0–2250)	–
Baseline CD4 count (cells/mm3)	< 200	156 (39.1)	3275 (66.8)
	≥ 200	193 (48.4)	1174 (24)
	Missing	50 (12.5)	451 (9.2)
	Median (range)	282 (0–2250)	156 (0–1313)
History of Tb/HIV co-infection	No	285 (71.4)	3533 (72.1)
	Yes	114 (28.6)	1367 (27.9)
ARV adherence	Good	319 (79.9)	4064 (82.9)
	Fair or poor	80 (20.1)	836 (17.1)
Cotrimoxazole adherence	Good	315 (78.9)	4119 (84)
	Fair or poor	84 (21.1)	762 (15.6)
	Missing	–	19 (0.4)
History of HIV testing	Yes	399 (100)	2860 (58.4)
	No	0 (0)	2040 (41.6)
ART shift	No	214 (97.7)	3190 (65.1)

Table 2 Clinical & non-clinical characteristics of HIV infected people enrolled in ART care in Southwest Ethiopia from 2003 to 2015 *(Continued)*

Variable		Children (*N* = 399)	Adult (*N* = 4900)
		N (%)	*N* (%)
	Yes	5 (2.3)	29 (0.6)
	Missing	180 (45.1)	1681 (34.3)
Baseline functional status	Appropriate	170 (42.6)	–
	Delay or regression	229 (57.4)	–
Baseline functional status	Work or Ambulatory	–	3064 (62.5)
	Bedridden	–	1437 (29.3)
	Missing	–	399 (8.1)
Timing to HIV care presentation	Early	162 (40.6)	894 (18.2)
	Late	215 (53.9)	1788 (36.5)
	Missing	22 (5.5)	2218 (45.3)
Baseline CD4 count in cells/mm3 by HIV care enrollment period (median (range))	enrolled in 2003–11	273 (0–2000)	119 (0–1641)
	enrolled in 2012 and after	368 (3–2247)	178 (0–1638)

[a]Orthodox, Catholic, Protestant

This study has shed light on the general problems of late HIV care—magnitude, trend, outcomes and its risk factors. In the current study, the overall prevalence of LP was considerably high (65.5%). Furthermore, the trends of LP had shown persistently elevated prevalence (between 54% and 83%) although a lessening pattern was observed. This finding is consistent with another finding conducted in the country [27]. The prevalence of LP in the current study (65.5%) was lower (72–83.3%) than the prevalence from studies conducted in Asia [20], but higher than the findings from other studies in Africa that reported between 35 and 65% [21, 22]. This implies that LP in Ethiopia is still highly prevalent even after the introduction of universal ART.

The high and persistent LP prevalence may be due to: i) lack of information [35], ii) persistently high level of HIV related stigma [3, 27], iii) low HIV risk perception [27, 35] especially among high risk groups [36], iv) use of traditional treatment [27], v) poor integration between modern medicine and traditional healers, and vi) phasing out of international funding agencies [37].

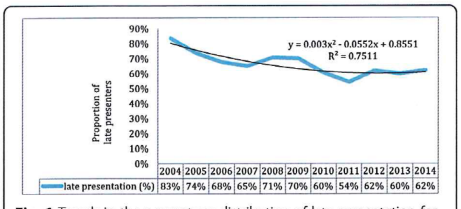

Fig. 1 Trends in the percentage distribution of late presentation for HIV care among HIV infected people on ART, Southwest Ethiopia, 2004-2014

Additionally, it could also be attributed to poor access to HIV services [37, 38]. For example, only 79% of the total health facilities in Ethiopia deliver HIV counseling and testing services [39]. Primary Health Care principles and scholars describe characteristics of accessible health systems to be approachable, acceptable, available, affordable and appropriate for the target population [40, 41], and thus raising a question whether HIV services are accessible to all HIV patients in Ethiopia. As such, LP issues should be given top priority if Ethiopia is to meet the UNAIDS targets.

Several strategies including the use of technology have been recommended to reduce LP prevalence in developing countries. For example, in collaboration with UNICEF, Amukele and colleagues successfully piloted unmanned aerial systems (drones) for transporting laboratory specimens to reduce late infant diagnosis in Malawi [42]. Other programs such as using mobile text messages [14], home [43] and community-based HIV testing [44, 45] have also been recommended to meet the HIV diagnosis target. Furthermore, encouraging repeat HIV testing [46, 47], HIV testing services delivery by lay workers [48], and self-testing [49] can tackle the substantial gap in HIV diagnosis in low-income countries like Ethiopia. The mandatory HIV testing strategy that has been implemented in China since 2005 for testing at-risk groups such as drug users, inmates, and commercial sex workers along with their clients was found to be an effective strategy to heighten early HIV diagnosis [7] that Ethiopia could consider. Interventions such as lay counselor home visits [50], home visits by peer supporters [51] and informational brochure provision [52] were also important programs in linking patients to ART clinics timely after HIV testing. In

Table 3 Outcomes of late presentation for HIV care among HIV infected children and adults enrolled in HIV care in southwest Ethiopia, 2016

Age	Variable	Mortality		Discontinuation		Immunological status	
		Alive, n(%)	Death, n(%)	Retained, n(%)	Discontinued, n(%)	IS, n(%)	IF, n(%)
Children	EP	64 (44.8)	3 (42.9)	64 (44.8%)	21 (67.7)	40 (25.3)	1 (3.1)
	LP	79 (55.2)	4 (57.1)	79 (55.2%)	10 (32.3)	118 (74.7)	31 (96.9)
	Total	143 (100)	7 (100)	143 (100)	31 (100)	158 (100)	32 (100)
	P-value (of X^2)	0.921		0.020		0.005	
Adults	EP	459 (33.1)	65 (35.3)	459 (33.1)	184 (34.7)	682 (36.5)	99 (21.3)
	LP	927 (66.9)	119 (64.7)	927 (66.9)	347 (65.3)	1187 (63.5)	365 (78.7)
	Total	1386 (100)	184 (100)	1386 (100)	531 (100)	1869 (100)	464 (100)
	P-value (of X^2)	0.550		0.524		< 0.001	

EP early presentation for HIV care, *LP* late presentation for HIV care presentation, *IF* immunologic failure, *IS* Immunologic success, X^2 Chi-square

addition, the application of rapid or point of care CD4 count technology has shown to enhance the number of eligible patients for ART whereby the frequency of appointments is reduced, and early ART initiation is increased [53].

Compared to the early presenters, great majority of late presenters had died in the current study, and this is similar with findings from other studies conducted elsewhere [54, 55]. It is plausible therefore to argue that late presentation leads to a greater risk of: rapid progression to advanced AIDS stage, compromised immune response, poor treatment response, and finally death [3]. Similarly, consistent with findings of other studies [56, 57], the majority of adults who presented late for care had discontinued and developed immunologic failure. This could be highly possible since late presenters progress easily to advanced AIDS stage, a stage characterized by marked CD4 reduction, multiple comorbidities and poor overall functional status [58, 59]. Subsequently, this leads to poor immune recovery even after treatment initiation, and increases the likelihood of ART toxicity that deters patients to take the treatment regularly [60]. The prevalence of LP among adults was higher than children. This might largely be due to the 'opt out' screening programs for pregnant women and delivery of HIV care (testing and treatment) to children born to affected mothers timely [61].

Adult late presenters were more likely to be younger, females, Tb/HIV co-infected, with no history of HIV testing and enrolled to HIV care in 2011 and before. Unlike other studies in Africa [62, 63], older adults were less likely to delay for HIV care than their younger counterparts. We found the finding surprising. HIV disease progresses with time, and it would be expected, that individuals diagnosed with HIV at a higher age would also have advanced disease progression (lower CD4 cell count) because they, on average, had a longer time span between time of infection and time of diagnosis. However, the presence of high HIV related stigma among young adults [64] hampers HIV testing and may be linked to delays in seeking HIV care. In addition, it is also possible that older adults assume a caring responsibility for their family and might realise the need to access HIV care service consistently increase their longevity and to achieve the self-imposed caring responsibility. Unlike in some others [56, 63], females were more likely than males to delay for HIV care. This might be because females have low understanding and comprehensive HIV care knowledge [3]. The high probability of females for LP might also be explained by the fact that 62% of females in care did not have a previous history of HIV testing. Females are also known to use traditional healers more than males, which may lead to commencing the HIV care late [3, 35].HIV related stigma is higher among females than males [65]. It is also known that the health seeking behaviours of females in urban and rural southwest Ethiopia are lower compared to males [66].

The association between Tb/HIV co-infection with increased LP replicate findings from other studies [4]. It has been stated that Tb is inextricably linked with HIV, causes a synergistic combination of illness with HIV, facilitates the progression of HIV disease to advanced stage, and thereby deters patients from linking to care timely [31]. Furthermore, focus has to be given for Tb/HIV co-infection, as Tb remains the highest mortality risk among HIV infected patients [13]. The absence of previous history of HIV testing in association with LP could be linked with poor awareness of the care [3], less access to HIV testing and/or ART clinic [39], high HIV related stigma [67], fear of diagnosis [68] and feeling of wellbeing [69].HIV patients who were enrolled for HIV care in 2012 and after were less likely to present late for HIV care as compared to those enrolled in 2011 and before. This may be attributed to: i) improving

Table 4 Logistic regression findings of factors linked with late presentation for HIV care in HIV infected people, JUTH, Southwest Ethiopia, 2016

Variable		Children		Adults		Children		Adults		
		Time at presentation for HIV care		Time at presentation for HIV care						
		Early, n (%)	Late, n (%)	Early, n (%)	Late, n (%)	COR (95%CI)	AOR (95%CI)	COR (95%CI)	AOR (95%CI): Complete cases	AOR (95%CI): Multiple imputations
Age	< 1	7 (36.8)	12 (63.2)	–	–	1	1	–	–	–
	1- < 5	56 (42.1)	77 (57.9)	–	–	0.8 (0.3–2.2)	0.5 (0.1–2.6)	–	–	–
	5- < 15	99 (44)	126 (56)	–	–	0.7 (0.3–1.9)	0.4 (0.1–2.2)	–	–	–
	15- < 25	–	–	96 (73.8)	340 (26.2)	–	–	1	1	1
	25- < 50	–	–	739 (35.2)	1362 (64.8)	–	–	0.5 (0.4–0.7)[a]	0.4 (0.3–0.6)[a]	0.5 (0.4–0.7)[a]
	50+	–	–	59 (40.7)	86 (59.3)	–		0.4 (0.3–0.7)[a]	0.4 (0.2–0.6)[a]	0.4 (0.3–0.6)[a]
Sex	Male	91 (46.2)	106 (53.8)	359 (37.1)	609 (62.9)	1		1	1	1
	Female	71 (39.4)	109 (60.4)	535 (31.2)	1179 (68.8)	1.4 (0.9–1.9)		1.3 (1.1–1.5)[a]	1.2 (1.03–1.5)[a]	1.2 (1.003–1.4)[a]
Marital status	Never married	–	–	151 (30.2)	349 (69.8)	–	–	1	1	1
	Married	–	–	391 (33.6)	772 (66.4)	–	–	0.9 (0.7–1.1)	0.8 (0.7–1.07)	0.8 (0.7–1.05)
	Separated or divorced or widowed	–	–	238 (31.9)	509 (68.1)	–	–	0.9 (0.7–1.2)	0.9 (0.6–1.1)	0.9 (0.7–1.2)
Educational status	No education	–	–	149 (32.5)	309 (67.5)	–	–	1		
	Primary	–	–	320 (34.8)	599 (65.2)	–	–	0.9 (0.7–1.2)		
	Secondary and above	–	–	313 (30.2)	722 (69.8)	–	–	1.1 (0.9–1.4)		
Religion	Muslim	16 (37.2)	27 (62.8)	245 (33.1)	496 (66.9)	1		1		1
	Christian [b]	52 (40.9)	75 (59.1)	535 (32.3)	1123 (67.7)	0.9 (0.4–1.7)	0.9 (0.4–1.9)	1.1 (0.9–1.3)		1.02 (0.9–1.2)
Tb/HIV co-infection	No	120 (45.5)	144 (54.5)	656 (34.5)	1244 (65.5)	1	1	1	1	1
	Yes	42 (37.2)	71 (62.8)	238 (30.4)	544 (69.6)	1.4 (0.9–2.2)	1.3 (0.7–2.7)	1.2 (1.01–1.4)[a]	1.6 (1.09–2.1)[a]	1.2 (1.00–1.4)[a]
Baseline functional status	Appropriate	66 (42.6)	89 (57.4)	–	–	1	1	–	–	–
	Delay or regression	96 (43.2)	126 (56.8)	–	–	1.03 (0.7–1.6)	1.1 (0.5–1.9)	–	–	–
Baseline functional status	Working or ambulatory	–	–	542 (32)	1150 (68)	–	–	1	1	1
	Bedridden	–	–	293 (36.9)	500 (63.1)	–	–	0.8 (0.7–1.1)	0.8 (0.6–1.002)	0.8 (0.7–1.001)
History of previous HIV testing	Yes	162 (43)	215 (57)	529 (34.4)	1008 65.6)	–	–	1	1	1
	No	0	0	365 (31.9)	780 (68.1)	–	–	1.1 (0.9–1.3)	1.2 (1.1–1.4)[a]	1.1 (1.00–1.3)[a]
HIV care enrollment period	enrolled in 2003–11	128 (42.2)	175 (57.8)	698 (32.1)	1478 (67.9)	1		1	1	1
	enrolled in 2012 and after	34 (45.9)	40 (54.1)	196 (38.7)	310 (61.3)	0.9 (0.5–1.4)		0.7 (0.6–0.9)[a]	0.8 (0.7–0.9)[a]	0.7 (0.5–0.9)[a]

COR crude odds ratio, *AOR* adjusted odds ratio, *CI* confidence interval, *Tb/HIV* tuberculosis/HIV, *ART* antiretroviral therapy, [a]statistically significant at *P*-value = 0.05; [b]orthodox, protestant, catholic

awareness to HIV care; ii) improving access and availability to HIV care; and iii) reducing perceived HIV related stigma.

The study has the following limitations. Firstly, data were collected from JUTH, a referral hospital that also receives referrals of patients with advanced stage. Hence, these study participants are not necessarily representative of HIV patients who attend their follow up in health centers or lower health care setups. Secondly, we did not assess the annual proportions of LP across HIV testing strategies (voluntarily counseling and testing, provider initiated HIV testing and counseling (PITC), Outreach or 'opt out). Previous studies have shown that PITC was not found more effective program for early HIV diagnosis than targeted HIV counseling [7]. Thirdly, the use of conservative definitions for LP is not able to differentiate whether the late presentation is before diagnosis, between diagnosis and first entry to care, and between first entry to care and ART initiation. A gold standard definition for LP among general HIV positive population and special groups such as HIV positive mothers and Tb/HIV co-infected patients for low-income countries is yet to be established. Fourthly, we found no statistically significant predictor for LP among children, and this could be due to small sample size. Finally, the presence of incomplete data may bias the precision of estimates.

However, even with the aforementioned limitations, the study sheds light and underpins the high prevalence of LP. Furthermore, the research assessed outcomes and risk factors for LP across ages, recommended effective programs and benchmarking strategies to tackle LP, and further achieve the ambitious UNAIDS targets.

Conclusions

In summary, three of five HIV infected people presented late for HIV care, and the annual proportions of LP persistently remained high across the 10 year period. The majority of HIV infected children and adults who presented late for care had discontinued, transferred out and developed immunologic failure. Late presenters (adults) were more likely to be younger, females, Tb/HIV co-infected, no history of HIV testing before diagnosis, and enrolled to HIV care before 2012. A large sample size should be considered to assess factors influencing for LP among children. Prioritizing the aforementioned risk factors, tremendous efforts are necessary to curb LP and further achieve the UNAIDS goal. Some of the strategies and programs that help to decline LP are use of innovative technologies, home and community based HIV testing, encouraging repeat and self-HIV testing, mandatory HIV testing and effective linking strategies to care after HIV diagnosis. HIV related stigma should also contextually be tackled since it continues to be a lingering issue among HIV infected people.

Abbreviations

AOR: Adjusted odds ratio; ART: Antiretroviral therapy; CD4: Cluster of differentiation 4; CI: Confidence interval; COR: Crude odds ratio; HIV: Human immunodeficiency virus; JUTH: Jimma University Teaching Hospital; LP: Late presentation for HIV care; PITC: Provider initiated HIV testing and counseling; Tb: Tuberculosis; UNAIDS: The Joint United Nations Program on HIV and AIDS; WHO: World Health Organization

Acknowledgements

The authors acknowledge Jimma University Teaching Hospital for providing access to the data.

Funding

None

Availability of data and materials

The dataset supporting the conclusions of this article is included within the article.

Authors' contributions

HAG, PW, KW and LM conceived of and designing the study. HAG performed the data collection, data analysis and initial draft manuscript. HAG, PW, KW and LM reviewed the manuscript critically. All authors read and approved the final manuscript.

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Ethics approval and consent to participate

Ethical clearance was obtained from Social and Behavioral Research Ethics Committee (SBREC) at Flinders University (Project number: 7086) and Institutional Review Board (IRB) of College of Health Sciences at Jimma University (Ref No: RPGC/386/2016). De-identified data were extracted from the database, and its access permission was obtained from JUTH board.

Consent for publication

Not Applicable

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

Received: 22 February 2017 Accepted: 19 January 2018
Published online: 30 January 2018

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Annex 3.8. Publication 4- Retrospective cohort study of ART discontinuation

PLOS ONE

RESEARCH ARTICLE

Prevalence, trend and risk factors for antiretroviral therapy discontinuation among HIV-infected adults in Ethiopia in 2003-2015

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OPEN ACCESS

Citation: Gesesew HA, Ward P, Woldemichael K, Mwanri L (2017) Prevalence, trend and risk factors for antiretroviral therapy discontinuation among HIV-infected adults in Ethiopia in 2003-2015. PLoS ONE 12(6): e0179533. https://doi.org/10.1371/journal.pone.0179533

Editor: Giovanni Maga, Istituto di Genetica Molecolare, ITALY

Received: March 4, 2017

Accepted: May 31, 2017

Published: June 16, 2017

Data Availability Statement: All relevant data are within the paper. The SPSS data of individual patients is not permitted to be provided to other bodies, as outlined by the Ethics Committee who approved the study. However, Hailay (hailushepl@grnail.com) can provide an anonymized data set for researchers who need further clarification.

Funding: This study was conducted for the partial fulfillment of a PhD in Public Health at Faculty of Medicine, Nursing and Health Sciences, Flinders

Abstract

Background

It is well acknowledged that antiretroviral therapy (ART) discontinuation hampers the progress towards achieving the UNAIDS treatment targets that aim to treat 90% of HIV diagnosed patients and achieve viral suppression for 90% of those on treatment. Nevertheless, the magnitude, trend and risk factors for ART discontinuation have not been explored extensively. We carried out a retrospective data analysis to assess prevalence, trend and risk factors for ART discontinuation among adults in Southwest Ethiopia.

Methods

12 years retrospective cohort analysis was performed with 4900 HIV-infected adult patients between 21 June 2003 and 15 March 2015 registered at the ART clinic at Jimma University Teaching Hospital. ART discontinuation could be loss to follow-up, defaulting and/or stopping medication while remaining in care. Because data for 2003 and 2015 were incomplete, the 10 years data were used to describe trends for ART discontinuation using a line graph. We used binary logistic regression to identify factors that were correlated with ART discontinuation. To handle missing data, we applied multiple imputations assuming missing at random pattern.

Results

In total, 4900 adult patients enrolled on ART, of whom 1090 (22.3%) had discontinued, 954 (19.5%) had transferred out, 300 (6.1%) had died, 2517 (51.4%) were alive and on ART, and the remaining 39 (0.8%) had unknown outcome status. The trend of ART discontinuation showed an upward direction in the recent times and reached a peak, accounting for a magnitude of 10%, in 2004 and 2005. Being a female (AOR = 2.1, 95%CI: 1.7–2.8), having an immunological failure (AOR = 2.3, 1.9–8.2), having tuberculosis/HIV co-infection (AOR = 1.5, 1.1–2.1) and no previous history of HIV testing (AOR = 1.8, 1.4–2.9) were the risk factors for ART discontinuation.

University. We acknowledge Australian Government Research Training Program Scholarship for supporting the PhD program. The scholarship provider had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors did not receive any specific grant for this research.

Competing interests: The authors have declared that no competing interests exist.

Abbreviations: AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; CD4, cluster of differentiation 4; MIs, multiple imputations; JUTH, Jimma University Teaching Hospital; HIV, Human Immunodeficiency virus; SSA, Sub-Saharan Africa; Tb, tuberculosis; UNAIDS, The Joint United Nations Program on HIV and AIDS; WHO, World Health Organization.

Conclusions

One out of five adults had discontinued from ART, and the trend of ART discontinuation increased recently. Discontinued adults were more likely to be females, tuberculosis/HIV co-infected, with immunological failure and no history of HIV testing. Therefore, it is vital to implement effective programs such as community ART distribution and linkage-case-management to enhance ART linkage and retention.

Introduction

Globally, 38.8 million people were living with human immunodeficiency virus (HIV), 2.5 million new HIV infections, and 1.2 million HIV/AIDS (acquired immunodeficiency syndrome) deaths in 2015[1]. Sub-Saharan Africa (SSA) contributed 76% (29 million) of the total HIV-infected people, 76% (1.9 million) of the total new HIV infections, and 75% (0.9 million) of the total HIV/AIDS deaths[1]. The advent of antiretroviral therapy (ART) in 1996 significantly reduced HIV-related deaths[2]. The global ART coverage in 2015 was low[3] (40.6%), with North Africa and Middle East having the lowest coverage (19%). High-income countries had the highest coverage (67%), and SSA had coverage of about 42%[1]. In Ethiopia, there were 768,040 HIV-infected people, 39,140 new HIV infections, and 28,650 HIV/AIDS deaths in 2015[1]. The ART coverage in Ethiopia in 2015 was moderate[3] (52%)[1].

Optimum clinical and public health achievements of ART requires consistent long-term adherence[4]. Nevertheless, ART discontinuation—interruptions to ART due to loss to follow-up (LTFU), defaulting or total stoppage of the treatment—is a big challenge. Additionally, ART discontinuation (discontinuation) causes drug resistance[5], diminishes the immunological benefit of treatment [6, 7], and increases AIDS-related morbidity and mortality [5, 8]. Discontinuation has been recognized as an impediment for attainment of the second 90 of the Joint United Nations Program on HIV and AIDS (UNAIDS) 90-90-90 treatment targets (sustainable provision of treatment for 90% of patients diagnosed with HIV) as it affects the sustainable intake of the treatment. Furthermore, discontinuation affects the performance of the third 90 of the UNAIDS 90-90-90 that aimed at achieving 90% of the virological success of patients on ART. This is because ART interruption lowers the efficacy of the treatment and subsequently leads to diminishing the number of CD4 cells, increases the number of viral counts[5], and then to failing immunological or virological success. Uganda reported 84% of virological suppression due to strong retention[9].

The magnitude of discontinuation in 2009 and 2012 was between 9–34% in Asia[10, 11] and 13.7–57.4% in Africa[12, 13]. In Ethiopia, the prevalence of discontinuation in 2012 and 2014 was between 9.8–31.4%[14, 15]. Previous studies in Ethiopia reported that demographic, behavioral, clinical and institutional factors were reported to contribute for discontinuation [14–18]. For example, smearing positive pulmonary tuberculosis, male gender, CD4 count <200 cells/μL, ambulatory functional status, having a mental illness, having HIV-negative partner, fear of stigma and side effects were the risk factors associated with discontnuation [14–18]. However, the previous studies that assessed either the prevalence[14, 18] or factors [14, 16–23] for discontinuation were all from the northern part of the country except two[16, 19]. This was also confirmed by our meta-analysis that reported that there were inadequate researches about ART discontinuation despite the large number of discontinued patients, and all the previous studies were concentrated on the northern and western part of Ethiopia[24].

The two studies[16, 19] that were conducted in the west part of the nation were case control studies and assessed only factors contributing for defaulting, reflecting that the magnitude of the problem was not explored. LTFU, another major contributor for discontinuation was not assessed. Unlike the rest of Ethiopia, the Southwest region is composed of different population groups. A refugee camp located near Jimma city, which takes refugees from different east African countries, contributes a number of HIV-infected patients enrolled in the ART clinic in Jimma University Teaching Hospital (JUTH). Furthermore, Jimma is also near Gambella region (Southwest Ethiopia), a region known to have the highest prevalence rate (6.5%) of HIV in Ethiopia[25], and the JUTH caters for both Jimma and Gambella zones. Since the prevalence of HIV in Southwestern region is higher (6.5%) than in other parts of the nation (<2%), it is necessary to understand whether the high prevalence is associated with other than factors for discontinuation identified in similar studies in Ethiopia.

Given the above gaps, and the clinical and public health significance of discontinuation, we have assessed the prevalence, trend and risk factors for ART discontinuation among adults by using 12 years (2003–2015) ART clinic data from JUTH in southwest Ethiopia. It is imperative to comprehensively understand the magnitude of the discontinuation problem and its influential factors in order to contextualise interventions to retain HIV patients in in care and to contribute to the Nation's second and third UNAIDS treatment targets.

Methods

Study design, setting and participants

A retrospective cohort study was performed using data from 21 June 2003 to 15 March 2015 from the ART clinic at JUTH, Jimma, Southwest Ethiopia. The details of the study setting have been described in elsewhere [26]. The treatment protocol for Ethiopia is implemented using World Health Organization (WHO) ART treatment guideline [27] and National Guidelines for Comprehensive HIV Prevention, Care and Treatment: Federal Democratic Republic of Ethiopia, MoH [28]. According to the current treatment guidelines, HIV infected adults are eligible to start ART if their CD4 cell count is $\leq$ 500 cells/mm3 irrespective of WHO clinical stage, their WHO clinical stage is 3 or 4 irrespective CD4 cell count, and they are pregnant, breast feeding women, sero-discordant couples or diagnosed with active tuberculosis irrespective CD4 cell count. For all HIV-infected children below 15 years of age, ART is recommended irrespective of WHO clinical stage and CD4 cell count. All HIV-infected adults aged $\geq$15 years enrolled in ART care in JUTH were the target population. If the recorded outcome were death, transferred out or unknown, participants would be excluded from this study.

Data source and procedures

The data were extracted from JUTH electronic medical records (EMR) system called comprehensive care center patient application database (C-PAD). This system was designed since 2007, and data registered before 2007 were copied retrospectively to the electronic record. Fig 1 presents the schematic presentation of data extraction of discontinuation among HIV-infected adults in JUTH. In total, 4900 HIV-infected adults on ART were eligible or the study in the period between 2003 and 2015, and 3607 of them were included in the analysis. Clinicians record the clinical and non-clinical characteristics of the patients on paper, and afterward, data clerks entered the data into the EMR.

Two data clerks perform the data entry process, and this ensures the accuracy and reliability of the data. The International Center for AIDS Care and Support (ICAP) at Colombia University has been providing expertise assistance on the data management process and has also been providing checkups on completeness of the data. Weekly patient summary generated from the

EMR system helps to flag patients with conditions that seek follow-up. Records would be excluded from a complete case analysis if outcome status of the person was death, transferred out or not recorded.

Study variables and measurements

The dependent variable was discontinuation and was dichotomized as 1) alive and on ART, and 2) discontinued. Discontinuation refers to LTFU, defaulting and/or stopping medication while remaining in care. LTFU refers to patients who had been on ART treatment and had missed at least three clinical appointments but had not yet been classified as "dead" or "transferred out" (transferred). Defaulting refers to patients who had been on ART treatment and had missed less than three clinical appointments but had not yet been classified as "dead" or "transferred". Stopping medication refers to patients who had stopped treatment due to any reason while they have remained in care. Transferred is an official transferring of patient to another ART clinic within or outside a catchment area.

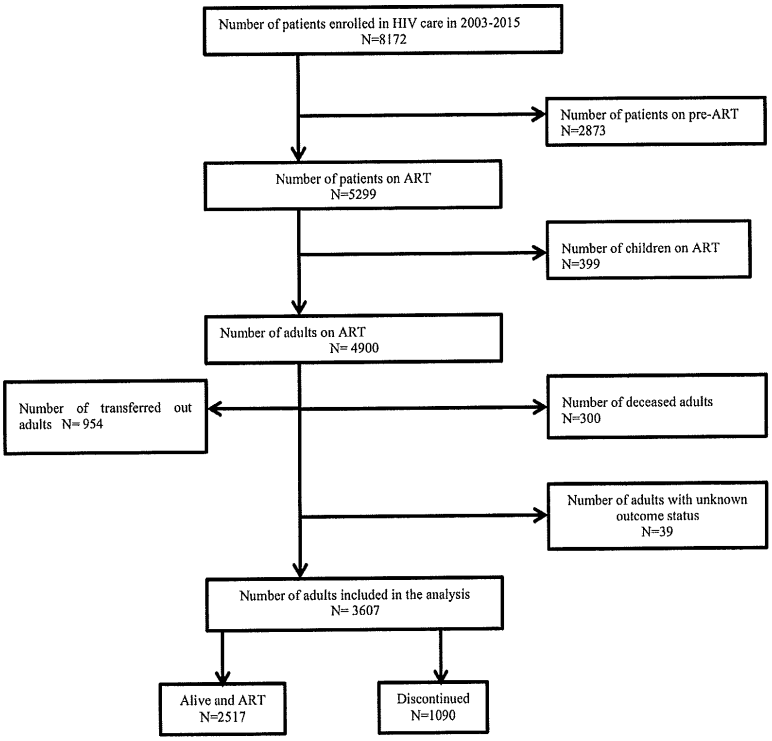

Fig 1. Schematic presentation of data extraction of ART discontinuation among HIV-infected adults in Jimma University Teaching Hospital, Southwest Ethiopia, 2003–2015. This figure presents the graphical demonstration of the data extraction process.

https://doi.org/10.1371/journal.pone.0179533.g001

Table 1. Measurements for late presentation for HIV care, adherence, and immunological, clinical & treatment failures.

Late presentation for HIV care [a] [31–34]	
Enrolled in 2003–11	**Enrolled in 2012–15**
CD4 lymphocyte count of <200 cells/ μl irrespective of WHO clinical stage at the time of first presentation to the HIV care	CD4 lymphocyte count of <350 cells/ μl irrespective of WHO clinical stage at the time of first presentation to the HIV care
WHO clinical stage 3 or 4 irrespective of CD4 count at the time of first presentation to the HIV care [b]	WHO clinical stage 3 or 4 irrespective of CD4 count at the time of first presentation to the HIV care

Adherence status [c] [35]			
Status	**Percentage of prescribed ART intake**	**Number of missing doses out of 30**	**Number of missing doses out of 60**
Good	≥ 95%	<3	<4
Fair	85–95%	3–5	4–9
Poor	< 85	≥6	≥9

Immunological and clinical failure [36]		
Clinical failure	**Immunological failure**	**Treatment failure**
New clinical condition indicating severe immunodeficiency (with the exception of Tb, WHO clinical stage 4) after 6 months on ART	CD4 count falling to the baseline (or below) persistent CD4 levels below 100 cells/mm3 after or after 6 months	Having either clinical or immunological failures

ART: antiretroviral therapy; CD4: cluster for differentiation 4; HIV: human immunodeficiency virus; WHO: World Health Organization; Tb: Tuberculosis

[a] The definition for late presentation for HIV care among Tb/HIV co-infected population was only based on the CD4 criteria.

[b] **WHO clinical Stage 3** was defined if one of the following is present in an HIV diagnosed patient: weight loss of >10% body weight, chronic diarrhea for >1 month, fever for >1 month, oral candidiasis, oral hairy leukoplakia, or pulmonary Tb within the previous year, or severe bacterial infections; **WHO clinical Stage 4** was defined if one of the following is present in an HIV diagnosed patient: HIV wasting syndrome, PCP, toxoplasmosis of the brain, cryptosporidiosis or isosporiasis with diarrhea for >1 month, cytomegalovirus disease of an organ other than liver, spleen or lymph node, herpes simplex virus infection, progressive multifocal leukoencephalopathy, candidiasis, extra-pulmonary Tb, lymphoma, kaposi's sarcoma, HIV encephalopathy

[c] Clinicians and pharmacists ask patients and check the pill container to collect the number of missing doses or days

https://doi.org/10.1371/journal.pone.0179533.t001

The independent variables included age, sex, marital status, educational status, religion, ART adherence, cotrimoxazole adherence, clinical failure, immunological failure, treatment failure, late presentation for HIV care (LP), tuberculosis (Tb)/HIV co-infection, baseline functional status, history of HIV testing and ART shift. Educational status was categorized in to no education (could not read and write), primary (grade 1–8), and secondary and above (grades ≥9). Functional status was classified in to the following categories: i) work—able to perform usual work, ii) ambulatory—able to perform activity of daily living, and iii) bedridden—not able to perform activity of daily living. Table 1 reports the operational definitions of LP, adherence, clinical, immunological and treatment failures.

Statistical analyses

Data cleaning and exploration were performed prior to analysis. Descriptive analysis was undertaken to explore the frequency tables and proportions for categorical data; and mean, median, range and line graph for continuous data. We described ten years trends for discontinuation (data for years 2003 and 2015 were excluded since the number of months was incomplete) using a line graph. The number of alive and on ART patients was calculated by subtracting the number of patients who dead, discontinued and Transferred from the total number of patients on the cohort. We checked for multicollinearity and potential interactions, and none was found.

We used binary logistic regression to identify factors that were correlated with discontinuation. To choose the candidate variables (P<0.25 was considered) to multiple logistic regression, we applied bivariate logistic regression analysis. P-value $\leq$ 0.05 was considered as a cutoff value for statistical significance in the final model. To handle missing data, we performed multiple imputations (n = 5) assuming missing at random (MAR) pattern[29], and we reported a model with pooled imputed values[30]. To check goodness of fit of the final model, we applied Hosmer and Lemeshow test and was found fit. To summarize the data, we reported odds ratio and 95% confidence interval. For all data analyses, we used Statistical Package for the Social Sciences (SPSS) version 22.0.

Ethical statement

Ethical clearance was sought from Social and Behavioral Research Ethics Committee (SBREC) at Flinders University (Project number: 7086) and Institutional Review Board (IRB) of College of Health Sciences at Jimma University (Ref No: RPGC/386/2016). The data access permission was obtained from JUTH board, and the IRB waived the need for consent. No participant was involved in the study—we did simply extract anonymised data from the record.

Results

Characteristics of study participants

Of 8172 patients enrolled in HIV care program from 21 June 2003 to 15 March 2015, 4900 HIV-infected adults had documented commencement of ART (Fig 1). Table 2 demonstrates the characteristics of HIV patients on ART. Of the total, 80.3% were aged 25–50 years, 59.8% were females, 48.7% were married, 67.4% were Christians, and 39.1% completed primary education. The median CD4 count was 156 (0–1313) cells/mm3, and 54.3% of the participants had baseline WHO clinical stage 3 or 4. A total of 1367 (27.9%) patients were deemed Tb/HIV co-infection over the whole study period. The median time on ART was 49 months, and the estimated survival time was 121.9 (120.3–123.5) months.

Prevalence and trend of ART discontinuation

In total, 1090 (22.3%) had discontinued, 954 (19.6%) had transferred out, 300 (6.2%) had died, 2517 (51.4%) were alive and on ART, and the remaining 39 (0.8%) had unknown outcome status in the period between 2003 and 2015 (Table 3). Of the 1090 adults who had discontinued from ART, 906(83.1%) adults had defaulted, 145(13.3%) adults had LTFU and 39(3.6%) adults had stopped during the 12 years study. The prevalence of discontinuation was consistently high between 2004 and 2007. In the period between 2008 and 2011, the proportion of discontinuation showed a different trend with a sharp decline from 6% in 2008 to 2% in 2009, a sharp rise from 2% in 2009 to 6% in 2010, and then falling in 2011 to 3%. In the recent times, the proportion of discontinuation is increasing. Table 3 shows the trend in discontinuation among HIV-infected adults on ART.

Risk factors for ART discontinuation

The results from the multiple logistic regression analysis found from the analysis of a complete case and multiple imputations (MIs) are reported in Table 4. Being female (AOR = 2.1, 95%CI: 1.7–2.8), having immunological failure (AOR = 2.3, 1.9–8.2), having Tb/HIV co-infection (AOR = 1.5, 1.1–2.1) and no previous history of HIV testing (AOR = 1.8, 1.4–2.9) were the risk factors for discontinuation.

Table 2. Clinical & non-clinical characteristics of HIV infected people enrolled on ART care in South-west Ethiopia from 2003 to 2015.

Variable		N (%), N = 4900
Age in years	15-<25	711 (14.5)
	25-<50	3937 (80.3)
	50+	252 (5.2)
	Median (range) age in years	30 (15–81)
ART follow up time in months, median (range)		49 (0–137)
Estimated survival time in months, median (95%CI)		121.9 (120.3–123.5)
Sex	Male	1971 (40.2)
	Female	2929 (59.8)
Marital status [b]	Never married	897 (20.9)
	Married	2094 (48.7)
	Separated or divorced	837 (19.4)
	Widowed	474 (11.0)
Education [b]	No education	945 (21.9)
	Primary	1687 (39.1)
	Secondary and above	1685 (39)
Religion [b]	Muslim	1402 (32.6)
	Christian [a]	2893 (67.4)
Baseline WHO classification [b]	1 or 2	1355 (45.7)
	3 or 4	1608 (54.3)
Baseline CD4 count (cells/mm3) [b]	<200	3275 (73.6)
	≥ 200	1174 (26.4)
	Median (range)	156 (0–1313)
History of Tb/HIV co-infection [b]	No	3533 (72.1)
	Yes	1367 (27.9)
ARV adherence [b]	Good	4064 (82.9)
	Fair or poor	836 (17.1)
Cotrimoxazole adherence [b]	Good	4119 (94.4)
	Fair or poor	762 (15.6)
History of HIV testing [b]	Yes	2860 (58.4)
	No	2040 (41.6)
ART shift [b]	No	3190 (99.1)
	Yes	29 (0.9)
Baseline functional status [b]	Work or Ambulatory	3064 (68.1)
	Bedridden	1437 (31.9)
Timing to HIV diagnosis	Early	894 (33.3)
	Late	1788 (66.7)
Clinical failure [b]	No	2261 (80.5)
	Yes	546 (19.5)
Immunologic failure [b]	No	3164 (80.3)
	Yes	775 (19.7)
Treatment failure [b]	No	1493 (65.7)
	Yes	780 (34.3)

[a] Orthodox, Catholic, Protestant

[b] only valid percentage is calculated

https://doi.org/10.1371/journal.pone.0179533.t002

Table 3. Annual number of HIV infected adults on ART care and their outcomes, Southwest Ethiopia, 2003–15.

Year	New enrollment a	Death b, n(%)	Discontinuation c, n(%)	Transferred out d, n(%)	Alive & on ART e, n(%)	Total in Cohort f
2003[a]	8	0 (0)	1 (13)	0 (0)	7 (88)	8
2004	62	1 (1)	7 (10)	1 (1)	60 (87)	69
2005	468	27 (5)	51 (10)	8 (2)	442 (84)	528
2006	905	63 (5)	88 (7)	71 (5)	1125 (84)	1347
2007	574	50 (3)	148 (9)	132 (8)	1369 (81)	1699
2008	496	41 (2)	105 (6)	93 (5)	1626 (87)	1865
2009	508	39 (2)	50 (2)	103 (5)	1942 (91)	2134
2010	452	20 (1)	139 (6)	74 (3)	2161(90)	2394
2011	420	26 (1)	88 (3)	100 (4)	2367 (92)	2581
2012	352	10 (0)	96 (4)	96 (4)	2517 (93)	2719
2013	300	14 (0)	112 (4)	102 (4)	2589 (92)	2817
2014	296	7 (0)	166 (6)	147 (5)	2565 (89)	2885
2015[a]	59	2 (0)	39 (1)	27 (1)	2556 (97) [b]	2624 [b]
Overall		300 (6.1%)	1090 (22.3%)	954 (19.5%)	2517 (51.4%)	4900 [b]

[a] data from years 2003 and 2015 were not from complete number of months and were excluded from describing outcomes by a trend graph

[b] included 39 (0.8%) patients with unknown outcome status; e = f-b-c-d; where f = e (previous year) + a (current year); b, n(%) = (b/f)*100%; c, n(%) = (c/f) *100%; d, n(%) = (d/f)*100%; e, n(%) = (e/f)*100%

https://doi.org/10.1371/journal.pone.0179533.t003

Multiple imputations (MI)

We have undertaken MI to address the missing data using five imputed data sets, and we reported a model with pooled imputed values (Table 4). In estimating factors associated with discontinuation among adults, results were similar in both MI and complete case analyses except for ART adherence and history of HIV testing. ART adherence was found to be statistically significant in the MI analysis but not in the complete case analyses, and to the contrary, history of HIV testing was not found to be statistically significant in the MI analysis unlike in the complete case analyses.

Discussion

The UNAIDS target has declared three new and ambitious goals by 2020 to end AIDS epidemic by 2030: diagnosing 90% of people living with HIV, providing ART for 90% of those diagnosed with HIV, and achieving viral suppression for 90% of patients receiving treatment [37]. Nevertheless, discontinuation from treatment challenges the success of the last two goals [38]. One in five people on ART (22.3%) had discontinued from the treatment in the current study. When compared to findings elsewhere in Ethiopia, discontinuation rate in the current study was higher than findings from the Tigray's study [14] and lower than findings from the Amhara's study [15]. In addition, this rate was lower than findings from studies conducted in Guinea-Bissau (51.1%)[39], Nigeria (28%)[40], and a multi-clinic study from Republic of Congo, Cameron and Burundi (83%)[41]. The dissimilarity in measurement[42], access to HIV care services[43], and innovation, adoption and implementation of cost-effective retention strategies could be the possible reasons of differences[44, 45].

For example, HIV care services such as ART accessibility affects the discontinuation rate. The estimated ART coverage[1] in Ethiopia (52%) is higher than from Guinea-Bissau (25%), Nigeria (29%), Republic of Congo (25%), Cameron (22%) and Burundi (38%). This could be one of the reasons why discontinuation rate in our finding is lower than those countries. Furthermore, the introduction of innovative programs such as Health Extension Workers

Table 4. Logistic regression findings of factors affecting for discontinuation in HIV infected adults, JUTH, 2003–15.

Variable		Discontinuation status (n, %)		COR (95%CI)	AOR (95%CI): Complete cases	AOR (95%CI): Multiple imputations
		Retained	Discontinued			
Age (years)	15-<25	380 (15.1)	174 (16)	1	1	
	25-<50	2004 (79.6)	855 (78.4)	0.9 (0.8–1.1)	0.8 (0.6–1.3)	0.9 (0.7–1.1)
	50+	133 (5.3)	61 (5.6)	0.9 (0.7–1.4)	0.9 (0.5–1.1.4)	0.8 (0.5–1.2)
	Median	30	30			
Sex	Male	482 (44.2)	903 (35.9)	1	1	1
	Female	608 (55.8)	1614 (64.1)	1.4 (1.2–1.6) [a]	2.1 (1.7–2.8) [a]	1.7 (1.4–2.0) [a]
Marital status	Never married	188 (25.5)	397 (25.1)	1	1	1
	Married	356 (48.2)	731 (46.2)	0.9 (0.8–1.2)		0.8 (0.4–1.6)
	Other [a]	194 (26.3)	453 (28.7)	1.1 (0.9–1.4)		1.1 (0.9–1.3)
Educational status	No education	169 (23)	315 (19.6)	1		
	Primary	301 (40.9)	656 (40.8)	1.2 (0.9–1.4)	1.1 (0.6–8.3)	1.9 (0.5–5.4)
	Secondary & above	266 (36.1)	635 (39.5)	1.3(1.0–1.6)	1.8 (0.7–11.2)	1.7 (0.6–9.9)
Religion	Muslim	251 (34.2)	506 (31.7)	1		
	Christian [b]	482 (65.8)	1091 (68.3)	1.1 (0.9–1.4)		
Baseline WHO status	Stage 1 or 2	276 (43.5)	706 (48)	1	1	1
	Stage 3 or 4	359 (56.5)	764 (52)	0.8 (0.7–1.0)	0.5 (0.2–1.8)	0.8 (0.3–2.1)
Baseline CD4 (cells/ul)	<200	731 (78.9)	1657 (69.9)	1	1	
	> = 200	195 (21.1)	712 (30.1)	1.6 (1.3–1.9) [a]	1.8 (0.9–2.1)	
	Median	177	129			
Clinical failure	No	495 (80.1)	1157 (81.4)	1		1
	Yes	123 (19.9)	265 (18.6)	0.9 (0.7–1.2)		0.8 (0.6–1.8)
Immunologic failure	No	726 (87.8)	1808 (77.8)	1		
	Yes	101 (12.2)	516 (22.2)	2.05 (1.6–2.6)	2.3 (1.9–8.2) [a]	1.5 (1.3–1.9) [a]
HIV diagnosis	Early	459 (33.1)	184 (34.7)	1		
	Late	927 (66.9)	347 (65.3)	0.9 (0.7–1.3)	0.8 (0.6–1.8)	
History of Tb/HIV co-infection	No	636 (71.7)	1305 (69)	1	1	
	Yes	251 (28.3)	587 (31)	1.1 (0.9–1.4)	1.5 (1.1–2.1) [a]	1.4 (1.2–1.8) [a]
ART adherence	Good	727 (82)	1520 (80.3)	1	1	1
	Fair or poor	160 (18)	372 (19.7)	1.1 (0.9–1.4)	1.3 (0.8–1.7)	1.6 (1.2–2.3) [a]
Cotrimoxazole adherence	Good	737 (83.1)	1541 (81.8)	1		
	Fair or poor	148 (16.7)	342 (18.2)	1.1 (0.9–1.4)		
Baseline functional status	Working	32 (3.8)	82 (4.7)	1	1	
	Ambulatory /bedridden	801 (96.2)	1664 (95.3)	0.8 (0.5–1.2)	0.9 (0.7–2.8)	
History of HIV testing	Yes	643 (59)	1436 (57.1)	1		
	No	447 (41)	1081 (42.9)	1.1 (0.9–1.2)	1.8 (1.4–2.9) [a]	1.1 (0.9–1.3)
ART shift	No	703 (100)	1599 (98.2)			
	Yes	0	29 (1.8)			

[a] statistically significant at p-value ≤0.05

[b] Orthodox, Protestant or Catholic

https://doi.org/10.1371/journal.pone.0179533.t004

(HEWs) and Health Development Army (HDA) to HIV care services[9]—programs that are not implemented in Guinea-Bissau, Nigeria, Republic of Congo, Cameron and Burundi—could affect the discontinuation rates.

The trend for discontinuation was different across years. The proportion of discontinuation in the beginning year (2004) was very high (10%) because ART was not freely available. Discontinuation had also increased from 6% in 2006 to 9% in 2007. This could be because: i) ART

was universally scaled up without preparations [7]; and ii) there was inequity and limitations in access to HIV care services, a justification corroborated by 24% of the health facilities in Ethiopia provide ART care and 59% of the health facilities in the country provide prevention of mother to child transmission services[46].

The trend of discontinuation had dramatically decreased from 9% in 2007 to 2% in 2009. The overall HIV care services have been improved[6] and had a profound contribution to the reduction of discontinuation. Also, HIV was included as one of the 16 packages in a new program called health extension program (HEP)—an innovative community based health service delivery system aiming at provision of essential primary health care services—, and this program could reduce the proportion of discontinuation[47]. Nevertheless, as of 2011, the discontinuation has been growing, because non-governmental organizations has been phasing out. To the contrary, local governments have been allocating little budget for health developments, particularly for HIV/AIDS[48]. We should seriously heed the issue since the developmental assistance for health budgeted by local governments is expected to grow only slightly[49].

Hence, the magnitude of discontinuation in the current study reflects that it is a considerable number and its trend is increasing in the recent times. Programs such as community based ART distribution[9, 50], improving adherence via medication diary for care givers[51], home based nursing interventions[52] and adherence clubs[53] could increase linkage to and retention in care and further reduce discontinuation. People living with HIV should also meaningfully be involved in the continuum of care to improve retention programs[54]. The universal test, treat and keep strategy would dramatically improve ART retention and is fundamental in cost-effective HIV care[55].

Compared to males, females were more likely to discontinue from ART, a similar finding to previous studies [56, 57]. Part of the reasons for this could be due to: (i) HIV related stigma which is known to be higher in females than in males, and prohibits them out from HIV care seeking [58, 59]; (ii) Lower literacy status in females than males, which is a big challenge that prevent women from optimising the benefit of HIV care [60], (iii) higher usage in females than males of traditional healers which hinders females from taking ART consistently [61], and (v) lack integration between modern and traditional medicines which has been identified as one of the key factors in for a consistent uptake of ART programs in Ethiopia [62]. Similar to findings by Meloni and colleagues[63], discontinuation was higher among patients with immunological failure than their comparator. HIV-infected patients with immunological failure are susceptible to multiple opportunistic infections and do progress to the advanced stage of HIV/AIDS rapidly leading to quick deterioration of their health status[64, 65]. Poor health status can also be among significant factors that deter them from uptaking HIV care services consistently [66]. To address ART discontinuation problem, Programs such as linkage-case-management (LCM)[67] that focus on multiple points of HIV care to enhance retention have been suggested as a good practice.

Although it has been stated that Tb/HIV co-infection mortality and morbidity was reduced dramatically in the era of ART [68, 69], in the current study, the odds of discontinuation was higher in Tb/HIV con-infected patients than in patients with HIV infections alone. These results are consistent with findings from earlier studies [70–72]. The intimate linkage between HIV and Tb enables the progression of HIV disease to advanced stage rapidly and thereby disallowing patients from regular treatment intake [26, 73]. In addition, the double stigma related to Tb/HIV coinfection as well as the double burden of having to take multiple pills for both conditions (pill effect) could be a compounding factor for discontinuation within this cohort. Because the burden of Tb/HIV confection is a serious problem in Ethiopia and in similar settings, it is vital to implement intervention strategies that strengthen access to universal Tb/HIV co-infection care throughout the country. It is necessary for the special attention to be

given to Tb/HIV co-infection because it is well known that Tb causes the highest mortality among HIV-infected patients[38]. The lack of history of HIV testing in association with discontinuation could be linked with poor awareness of the care[7, 74], high HIV-related stigma [59], and feeling of wellbeing[75]. Although the outcomes status of current study was not known, previous studies in Ethiopia and elsewhere have shown that 9% of transferred out and 40–86% of LTFU cases failed to re-engage to the care[76], and half of LTFU patients after tracing were found deceased [7, 23].

It is necessary to acknowledge limitations of the current study including: i) some variables such as stigma and mental illness were not assessed due to the nature of the study design—previous studies reported that stigma[77] and mental illness[24] affect ART discontinuation; ii) the outcome status of discontinued patients was not known, iii) findings of this study might not infer the other level of health facilities such as health centers or private hospitals; and iv) the comparison for discontinuation may not be appropriate due the dissimilarity in definition between studies.

Conclusions

The magnitude of discontinuation was recorded among one in five patients, and the trend has increased recently. Discontinued patients were more likely to be females, Tb/HIV co-infected, with immunological failure and no history of HIV testing. Additionally, in order to ensure the best outcomes and enhance the course of HIV care it is necessary that patients should be tracked to establish whether they have defaulted, transferred out, or died. We recommended implementing community ART distributions, strengthening adherence clubs, and adopting benchmarking programs such as linkage-case-management to enhance ART linkage and retention which have demonstrated to be effective in similar settings. Ethiopia has to subscribe into the East African International epidemiologic Databases to Evaluate AIDS (EA-IeDEA) Consortium[78], not only to share uniform measurements and gain research networks, but learn good practices in implementing HIV/AIDS treatment and overall care and management.

Acknowledgments

The authors acknowledge to Jimma University Teaching Hospital for providing access to the data. This study was conducted for the partial fulfillment of a PhD in Public Health at Faculty of Medicine, Nursing and Health Sciences, Flinders University. We acknowledge Australian Government Research Training Program (RTP) Scholarship for supporting the PhD program. The scholarship provider had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors did not receive any specific grant for this research.

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Conceptualization: HAG PW KW LM.

Formal analysis: HAG.

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Annex 3.9. Publication 5- Retrospective cohort study of immunologic failure

Open access Research

BMJ Open

Immunological failure in HIV-infected adults from 2003 to 2015 in Southwest Ethiopia: a retrospective cohort study

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To cite: Gesesew HA, Ward P, Woldemichael K, *et al*. Immunological failure in HIV-infected adults from 2003 to 2015 in Southwest Ethiopia: a retrospective cohort study. *BMJ Open* 2018;**8**:e017413. doi:10.1136/bmjopen-2017-017413

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2017-017413).

Received 30 April 2017
Revised 13 June 2018
Accepted 10 July 2018

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ABSTRACT

Objective To assess the prevalence, trend and associated factors for immunological failure (IF), and the magnitude of antiretroviral therapy (ART) shift among adults infected with HIV in Southwest Ethiopia.

Setting A retrospective cohort study was undertaken using the data from ART clinic at Jimma University Teaching Hospital from 21 June 2003 to 15 March 2015.

Participants Retrospective analysis of 4900 HIV-infected adult patient records dating from June 2003 to March 2015 was conducted.

Primary outcome measure The primary outcome was IF defined when cluster for differentiation 4 (CD4) count falls to the baseline (or below) or persistent CD4 levels below 100 cells/mm^3 after 6 months of ART treatment. The analyses included descriptive and inferential statistics.

Results 546 (19.5%) adults had developed clinical failure (CF), 775 (19.7%) adults had developed IF and 1231 (25.1%) had developed either CF or IF or both. The prevalence of IF was consistently high throughout the decade. Age 25 to ≤50 years adjusted OR (AOR 1.5, 9% CI 1.2 to 2.4), being female (AOR 1.8, 95% CI 1.3 to 1.9), late presenter for HIV care (AOR 2.2, 95% CI 1.6 to 2.7) and having baseline CD4 count below 200 cells/mm^3 (AOR 5.5, 95% CI 4.1 to 7.4), and having no history of HIV testing before diagnosis (AOR 0.7, 95% CI 0.5 to 0.9) were the predictors for IF. Only 29 (0.9%) adults infected with HIV were shifted to second-line ART regimen.

Conclusions The magnitude of CF or IF or both was found significant and consistently high throughout the calendar year although ART shift was found minimal. HIV-infected adult patients with IF were early age adults, females, late presenters for HIV care, and those who had low baseline CD4 counts and history of HIV testing before diagnosis.

Strengths and limitations of this study

- The study included 12-year retrospective follow-up, and had involved large sample size bigger than several other similar studies.
- The study assessed the outcomes of immunological failure, and this was not studied so far.
- The source of the data was a record based and could have incompleteness.
- The context of treatment failure attributed to immunological and/or clinical failure could be a spuriously biased estimate.
- The findings may not infer to another level of health institutions such as health centres or private hospitals.

INTRODUCTION

The advent of highly active antiretroviral therapy (ART) since 1996 has significantly reduced HIV-related diseases, improved quality of life of patients with HIV and decreased deaths associated with HIV.[1 2] Even though the ART is scaled up worldwide, the coverage is still low. As of 2015, the majority of countries had low (<50%) ART coverage, few countries had moderate (50%–80%) and none had high (>80%) coverage.[2 3] The estimated global ART coverage in 2015 was low (40.6%), of which North Africa and Middle East had the lowest coverage (19%) and high-income countries had the highest (67%).[2] Sub-Saharan Africa (SSA) had also low ART coverage (42.35%) in 2015 and Ethiopia, one of the countries in SSA, had 51.9% coverage.[2] The impediments in the ART programmes are not limited to the issue of coverage. A substantial number of patients had developed immunological,[4–7] clinical failure (CF)[5 8 9] and/or treatment failure (TF).

Immunological failure (IF) was considered as a surrogate marker for virological failure.[10 11] Thus, IF vividly influences the performance of a virological suppression goal of the UNAIDS (Joint United Nations Programme on HIV and AIDS) 90-90-90 targets[12] that aimed at achieving 90% of the virological success of patients on ART. Research has reported an IF magnitude of 23%–33.1% in Europe,[13] 9%–18% in Asia[14 15] and 11%–39% in Africa.[16] In Ethiopia, few studies have assessed IF[4 6 7 17] and reported a prevalence of 6.8%–21%. The above studies presented the following risk factors, but not limited to: unemployment, low baseline cluster for differentiation 4 (CD4) cell, baseline WHO clinical stage 4, poor adherence to treatment, not disclosing HIV status and

development of new opportunistic infection (OI) after starting treatment.

However, all the studies that assessed the prevalence and risk factors of IF[4 6 7 17 18] were conducted in the settings where the prevalence of HIV was below 2%. Jimma—the current study setting—is near Gambella region (Southwest Ethiopia), a region known to have the maximum prevalence rate (6.5%) of HIV in Ethiopia.[19] The hospital serves both Jimma and Gambella zones. Since the prevalence of HIV in Southwestern region is higher (6.5%) than other parts of the nation (<2%), it is essential to comprehend whether the high prevalence is linked with other factors than the ones reported in similar studies in Ethiopia. In addition, unlike the rest of Ethiopia, the Southwest region is composed of diverse population groups. A substantial number of HIV-infected patients enrolled in the ART clinic in Jimma University Teaching Hospital (JUTH) come from a refugee camp situated near Jimma, which hosts refugees from different East African countries.

The exposure of ART—if not taken according to the recommendations—leads to drug resistance and subsequent clinical and/or IF. Therefore, timely switching to alternatives (second-line or third-line drugs) is immensely needed.[20] Late shifting of regimens further increases the risk of viral resistance and endangers the long-term prognosis.[20] ART switch is less common in under-resourced settings than in resourced countries.[21] In Ethiopia, the magnitude of shifting to second-line ART drugs due to TF attributed to IF and/or CF has not been assessed. Furthermore, the trend and outcomes across the immunological status of HIV-infected adults in Ethiopia is yet to be addressed. Hence, it is crucial to explore IF contextually. The performance assessment of virological suppression of the UNAIDS 90-90-90 treatment targets was also never assessed in the nation. We performed a historical data analysis to assess the prevalence, trend, outcomes and associated factors of IF, and the magnitude of shifting to second-line ART drugs among adults in Southwest Ethiopia.

METHODS

Study design, setting and participants

A retrospective cohort study was carried out using data from 21 June 2003 to 15 March 2015 from the ART clinic at JUTH. We have described the study setting elsewhere.[22 23] The target population included all HIV-infected adult patients age ≥15 years enrolled in ART care at JUTH in Southwest Ethiopia. Patients should be followed for at least 6 months after ART initiation. If the CD4 level or WHO clinical stage of the patients was not recorded, at least, at two points—beginning and after 6 months of ART initiation—records would be excluded from the analysis. Baseline refers the time when ART was started for the first time.

Data source and procedures

Data were extracted from JUTH electronic medical records (EMRs) system called comprehensive care centre patient application database (C-PAD). This system was designed in 2007, and data recorded before 2007 were retrospectively copied from the paper in to the EMR system. In 2003–2015, 4900 adults were on ART out of 8172 HIV-infected patients in the care, and 3939 (81%) of them were included in the analysis for IF (figure 1). Health workers record the clinical and non-clinical characteristics of the patients on a paper followed by entering into the EMR by data clerks. To ensure completeness, reliability and validity of the information, two data clerks enter the data. In addition, International Center for AIDS Care and Support at Colombia University assists the patient-level data management system.

Study variables and measurements

WHO[24] has set definitions for IF, CF and TF. The response variable was IF and dichotomised as yes and no. IF (yes) was defined if CD4 count of the HIV-infected adults falls to the baseline (or below) or persistent CD4 levels below 100 cells/mm^3 after 6 months of ART treatment.[24] The independent variables included age, sex, marital status, educational status, religion, ART adherence, cotrimoxazole adherence, baseline WHO clinical staging, baseline CD4 count, late presentation for HIV care, tuberculosis (TB)/HIV coinfection, baseline functional status, history of HIV testing before diagnosis and ART shift. CF was defined when new or recurrent clinical conditions denoting WHO clinical stage 4 6 months after an effective treatment.[24] TF refers to a combination of CF and IF. ART discontinuation was either loss to follow-up (LTFU), defaulting and/or stopping medication while remaining in care. LTFU was defined when patients had been on ART treatment and missed at least three clinical appointments but not yet been classified as 'dead' or 'transferred out' (TO). Defaulting was defined when patients had been on ART treatment and missed less than three clinical appointments but not yet been classified as 'dead' or 'TO'. In addition, stopping medication was defined when patients had stopped treatment due to any reason while they have remained in care. TO is the official transferring of the patient to another ART clinic. Functional status was categorised in to work (able to perform usual work), ambulatory (able to perform activity of daily living) and bedridden (not able to perform activity of daily living). ART switching is a change from first-line to second-line ART drugs. History of HIV testing refers to testing (one or more times) for HIV before diagnosis. Table 1 demonstrates the measurements of late presentation for HIV care and level of adherence. If poor HIV outcomes such as IF, CF and TF were occurred more than once, the latest outcome was considered for analysis. The assessment for other outcomes such as discontinuation, adherence and ART shift was conducted at the end of follow-up time.

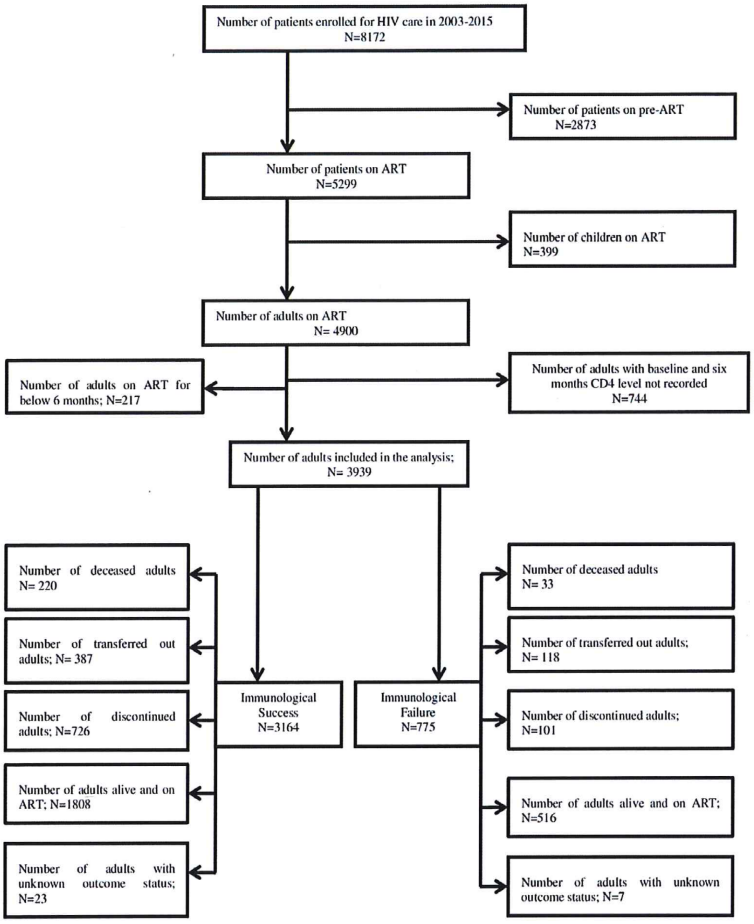

Figure 1 Immunological status and their outcomes of HIV-infected adults in Jimma University Teaching Hospital in Southwest Ethiopia, 2003–2015. This figure presents the flow chart of immunological status and their outcomes of HIV-infected adults. ART, antiretroviral therapy; CD4, cluster for differentiation 4.

Statistical analyses

We undertook the analysis of descriptive and inferential statistics. Descriptive statistics included frequency tables and proportions for categorical data, and median, range and line graph for continuous data. The 10-year trends for IF (data for years 2003 and 2015 were excluded since the number of months was incomplete) was described by line graph using a cumulative frequency percentage. The cumulative frequency percentage or proportion of patients with IF, denoted in Y-axis in figure 2, is calculated using the cumulative number of patients with IF (cumulative frequency for numerator) and eligible cumulative number of patients for IF (cumulative frequency for denominator) for each calendar year. Binary logistic regression was applied to assess factors associated with IF. Bivariate logistic regression analysis was performed to select the candidate variables to multiple logistic regression, and variables with $p<0.25$ were included as candidate variables to multivariable logistic regression. $P\leq0.05$ was considered a criterion for statistical significance in the final model. We performed multiple imputations (MIs) (n=5) assuming missing at random (MAR) pattern[25] to treat missing data, and we reported a model with pooled imputed values.[26] We used Hosmer and Lemeshow test to check goodness of fit of the final model. We summarised the data using OR and 95% CI. We used SPSS V.22.0 for all data analyses.

Patient and public involvement

We did not involve patients and public in the study—we simply extracted data from records.

Table 1 Measurements for late presentation for HIV care and ART adherence, 2016

Late presentation for HIV care*[53]			
Enrolled in 2003–2011		**Enrolled in 2012–2015**	
CD4 lymphocyte count of <200 cells/μL irrespective of WHO clinical stage at the time of first presentation to the HIV care.		CD4 lymphocyte count of <350 cells/μL irrespective of WHO clinical stage at the time of first presentation to the HIV care.	
WHO clinical stage 3 or 4 irrespective of CD4 count at the time of first presentation to the HIV care.†		WHO clinical stage 3 or 4 irrespective of CD4 count at the time of first presentation to the HIV care.†	
Level of adherence‡[54]			
Status	**Percentage of prescribed ART intake**	**No of missing doses out of 30**	**No of missing doses out of 60**
Good	≥95%	<3	<4
Fair	85%–95%	3–5	4–9
Poor	<85	≥6	≥9

*The definition for late presentation for HIV care among TB/HIV-coinfected population was only based on the CD4 criteria.[22]
†WHO clinical stage 3 was defined if one of the following is present in an HIV-diagnosed patient: weight loss of >10% body weight, chronic diarrhoea for >1 month, fever for >1 month, oral candidiasis, oral hairy leukoplakia or pulmonary TB within the previous year or severe bacterial infections; WHO clinical stage 4 was defined if one of the following is present in an HIV-diagnosed patient: HIV wasting syndrome, PCP (Pneumocystis carinii pneumonia), toxoplasmosis of the brain, cryptosporidiosis or isosporiasis with diarrhoea for >1 month, cytomegalovirus disease of an organ other than liver, spleen or lymph node, herpes simplex virus infection, progressive multifocal leucoencephalopathy, candidiasis, extrapulmonary TB, lymphoma, Kaposi's sarcoma, HIV encephalopathy.
‡Clinicians and pharmacists ask patients and check the pill container to collect the number of missing doses or day.
ART/ARV, antiretroviral therapy; CD4, cluster for differentiation 4; TB, tuberculosis.

RESULTS

Description of study participants

In total, 8172 patients were enrolled in HIV care programme from 21 June 2003 to 15 March 2015 of whom 4900 adult patients had been documented commencement of ART (figure 1). demonstrates the characteristics of adult patients with HIV on ART. Of 4900 HIV-infected patients on ART, four out of five were aged 25–50 years, three out of five were females, one out of two were married, two out of three were Christians and two out of five completed primary education. The median CD4 count was 156 (0–1313) cells/mm3, and more than half (54.3%) of the participants had baseline WHO clinical stage 3 or 4. The magnitude of TB/HIV coinfection over the study period was 27.9%. The median time on ART was 49 months, and the estimated survival time was 121.9 (120.3–123.5) months.

IF, CF and ART regimen switching

Of the 4900 patients enrolled on ART in 2003–2015, 217 patients were on ART for below 6 months, and baseline and 6 months CD4 level of 744 patients was not recorded. In total, 775 out of the 3939 patients (19.7%) had developed IF. Out of the patients with IF, 83 (10.7%), 88 (11.3%) and 604 (77.9%) patients, respectively, were followed for 6 to ≤12, 12 to ≤24 and ≥24 months. Among the patients who developed IF, 33 (4.3%) patients had died, 101 (13%) patients had discontinued, 118 (15.2%) patients had TO and 516 (66.6%) were alive and on ART (figure 1). The magnitude of IF was steadily high since 2008 and reached a peak in 2009 accounting for 24% followed by 21% in 2014. Figure 2 shows the trend in IF in HIV-infected patients on ART. In addition, 2807 patients were eligible for CF of whom 546 (19.5%) had developed the CF. A total of 1231 out of 4470 had developed either CF or IF or both—82 patients had both CF and TF. Twenty-nine (0.9%) patients were shifted to second-line ART drugs.

Factors associated with IF among adult patients with HIV

Table 3 demonstrates the outputs from the multivariable logistic regression analysis of factors for IF obtained from the analysis of a complete case and MIs. Age between 25 and ≤50 years, being female, late presenter for HIV care and having a baseline CD4 count below 200 cells/mm^3 were factors for IF, and having no history of HIV testing before diagnosis was a protective factor against IF. HIV-infected adults age 25 to ≤50 years were 50% adjusted OR (AOR 1.5, 9% CI 1.2 to 2.4) more likely to develop IF than those aged 15 to ≤25 years. Females were 80% more likely than males (AOR 1.8, 95% CI 1.3 to 1.9) to develop IF. Patients who presented late for HIV care had double the risk of IF than early presenters (AOR 2.2, 95% CI 1.6 to 2.7). In addition, patients with baseline CD4 count below 200 cells/mm^3 had nearly six times higher risk for IF than those with ≥200 cells/mm^3 (AOR 5.5, 95% CI 4.1 to 7.4). Patients who had no history of HIV testing before diagnosis were 30% less likely (AOR 0.7, 95% CI 0.5 to 0.9) to develop IF as compared with those who had previous record of HIV testing.

Multiple imputations

The MIs analysis result (table 3) revealed that except for baseline CD4 count, all statistically significant variables in the complete case analysis were also reported to have a statically significant difference in the MIs analysis. TB/HIV coinfection, a variable that was not statistically significant in the complete case analysis, was found to be a

Table 2 Characteristics of adult HIV-infected patients enrolled on ART care in Southwest Ethiopia from 2003 to 2015, Jimma, Ethiopia

Variable	n=4900, n (%)
Age in years	
15 to ≤25	711 (14.5)
25 to ≤50	3937 (80.3)
50+	252 (5.2)
Median (range) age in years	30 (15–81)
ART follow-up time in months, median (range)	49 (0–137)
Estimated survival time in months, median (95% CI)	121.9 (120.3 to 123.5)
Sex	
Male	1971 (40.2)
Female	2929 (59.8)
Marital status*	
Never married	897 (20.9)
Married	2094 (48.7)
Separated/divorced/widowed	1311 (30.5)
Education*	
No education	945 (21.9)
Primary	1687 (39.1)
Secondary and above	1685 (39)
Religion*	
Muslim	1402 (32.6)
Christian†	2893 (67.4)
Baseline WHO classification*	
1 or 2	1355 (45.7)
3 or 4	1608 (54.3)
Baseline CD4 count (cells/mm^3)*	
<200	3275 (73.6)
≥200	1174 (26.4)
Median (range)	156 (0–1313)
Hx of TB/HIV coinfection*	
No	3533 (72.1)
Yes	1367 (27.9)
ARV adherence*	
Good	4064 (82.9)
Fair or poor	836 (17.1)
Cotrimoxazole adherence*	
Good	4119 (94.4)
Fair or poor	762 (15.6)
Hx of HIV testing*	
Yes	2860 (58.4)
No	2040 (41.6)
ART shift*	
No	3190 (99.1)
Yes	29 (0.9)
Baseline functional status*	
Work or ambulatory	3064 (68.1)
Bedridden	1437 (31.9)
Timing to HIV diagnosis	
Early	894 (33.3)
Late	1788 (66.7)
Clinical failure*	
No	2261 (80.5)
Yes	546 (19.5)
Immunological failure*	
No	3164 (80.3)
Yes	775 (19.7)
Treatment failure*	
No	3239 (72.5)
Yes	1231 (27.5)

*Only valid percentage is calculated.
†Orthodox, catholic, protestant.
ART/ARV, antiretroviral therapy; CD4, cluster for differentiation 4; TB, tuberculosis.

statistically significant in MIs analysis in which patients with TB/HIV-coinfection had a greater risk of developing IF than patients with HIV alone.

DISCUSSION

The current study was undertaken to assess IF in (and near) high HIV epidemic area and revealed a prevalence rate of 19.7% with a sharp trend increase in the recent times. This prevalence is similar to a finding from a study conducted by Melsew Yayehird *et al*[4] but is higher than the findings of studies conducted in the other part of the nation that was reported to be between 6.7% and 17.6%.[6 7 17]

The result shows that the prevalence rate of IF is significant particularly when compared with the other part of the nation. Thus, we can hypothesise that patients who come from high HIV-prevalence areas or attending their HIV care services near to high HIV-endemic settings has higher IF than patients who are attending their care in or near to low HIV-prevalence settings. The following explanations could partly justify the difference: (1) the presence of variety HIV-1 strains among people living with HIV in HIV prevalent areas is very high and this could challenge the immunological response benefited from the treatment[27 28]; (2) ART drug resistance is higher in high than low HIV-prevalence settings, and the drug resistance diminishes the immunological benefit of the treatment[29] and (3) HIV-infected people who come from high HIV-prevalence settings have less access to health services, lower economic status and lower HIV care-related knowledge[30] and this could negatively influence the immunological benefit of ART. For instance,

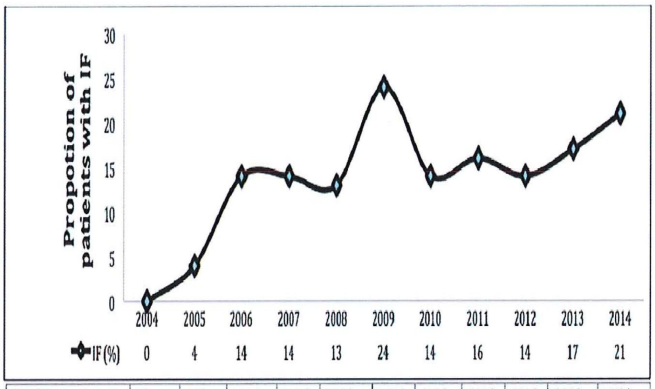

Figure 2 Trends in the percentage distribution of IF in HIV-infected adults on ART, Southwest Ethiopia, 2004–2014. This figure presents the trend of IF. Y-axis shows the cumulative frequency percentage of patients with IF for each calendar year. ART, antiretroviral therapy; IF, immunological failure.

the 2016 Ethiopian Demographic Health Survey ([31] stated that two-thirds (66%) of Tigray (a regional state located in Northern Ethiopia) women versus less than half (43.9%) of Gambella (a regional state located in Southwest Ethiopia) women stated that HIV can be prevented by using condoms and limiting sexual intercourse to one uninfected partner. Similarly, this survey described that more than three-fourths (84.2%) of Tigray men versus two-thirds (69.2%) of Gambella men stated that HIV can be prevented by using condoms and limiting sexual intercourse to one uninfected partner. Therefore, intensive effort has to be done to reduce the IF and subsequently a virological failure.

In the current study, most patients (78%) with IF were followed in ART care for ≥2 years. This shows that the prevalence of IF grows when the follow-up time increases, and this was similar to the previous studies conducted elsewhere.[4 8] The relationship between longer duration of treatment and IF could be justified by multiple explanations, and needs further study. But it may be partly justified by the frequent (and inappropriate) change in dose or types of ART, non-adherence when patients are on ART for long periods and ART resistance.[8 9] Thus, long-term retention requires serious attention. Plasma HIV-1 RNA is not available for routine viral load monitoring in resource-limited countries such as Ethiopia.[18] Hence, WHO[32] and several other studies[10 11 33] recommended immunological success as a surrogate marker for the virological suppression. In the current study, 19.7% of patients had IF; said in another way, 80.3% of patients had immunological success. This 80% (even lower) performance of virological suppression is less than the current goal of virological suppress of the UNAIDS 90-90-90 target that aimed 90% viral suppression for those on treatment.[12] Nevertheless, as the predictive accuracy is low, immunological success overestimates virological suppression.[34 35] Therefore, plasma HIV viral load testing should be accessible to regularly monitor the patients. The use of GenXpert for HIV viral load testing[36] is also another option for resource-limited countries.

HIV-infected patients with IF were more likely to be between 25 and ≤50 years of age, females, late presenters for HIV care, and those who had low baseline CD4 counts and history of HIV testing before diagnosis. Age was reported to have a significant influence on probability of IF. In fact, other literatures[37 38] reported that older adults are more likely to develop IF than younger group. The impairment in immune recovery due to age-related reduction in thymic function and other regenerative mechanisms could justify the link between older adults and IF.[38] Older adults are also highly likely to be diagnosed late with HIV than the younger ones,[39] a phenomenon that prevents an immunological benefit from ART.[40] Even though, majority of the literatures[41–43] reported no statistical difference between sex and IF, the proportion in the current study and one other study[16] revealed that females were more likely to develop IF than males. In the present study, females were the majority of the study participants. This shows that females are still the vulnerable groups, and are at a greater risk of negative HIV care outcomes. This could be attributed to high levels of stigma,[44 45] low literacy status[46] and use of traditional medicine.[47] Thus, attention has to be given for females in each series of the cascade of care.

Similar to findings from other studies,[16 48] low baseline CD4 counts were linked with IF. Furthermore, late presenters for HIV care had a greater risk of IF than early presenters, and this finding was supported by findings from studies conducted in SSA.[49 50] Research has shown that delayed presenter and patients with low baseline

Table 3 Logistic regression findings of factors affecting IF in patients with HIV infection, 2003–2015, Jimma, Ethiopia

Variable	IF (n, %†) No	IF (n, %†) Yes	COR (95% CI)	AOR (95% CI): complete cases	AOR (95% CI): multiple imputations
Age (years)					
15 to ≤25	488 (15.4)	74 (9.5)	1	1	1
25 to ≤50	2560 (80.9)	674 (87)	1.7 (1.3 to 2.3)*	1.5 (1.2 to 2.4)*	1.8 (1.7 to 2.1)*
50+	116 (3.7)	27 (3.5)	1.5 (0.9 to 2.5)	1.3 (0.7 to 2.9)	2.3 (1.9 to 2.7)*
Sex					
Male	1488 (47)	274 (35.4)	1	1	1
Female	1676 (53)	501 (64.6)	1.6 (1.4 to 1.9)*	1.8 (1.3 to 1.9)*	1.7 (1.6 to 1.8)*
Marital status					
Never married	632 (23.3)	152 (21.7)	1		1
Married	1316 (48.5)	357 (51.1)	1.1 (0.9 to 1.4)		1.04 (0.0 to 1.1)
Separated/divorced/ widowed	766 (28.2)	190 (27.2)	1.03 (0.8 to 1.3)		1.9 (0.7 to 2.1)
Educational status					
No education	559 (20.5)	145 (20.8)	1	1	1
Primary	1089 (39.9)	287 (41.1)	1.01 (0.8 to 1.3)	1.3 (0.7 to 2.9)	1.03 (0.9 to 1.1)
Secondary and above	1084 (39.7)	266 (38.1)	0.9 (0.8 to 1.2)	0.7 (0.4 to 3.7)	0.9 (0.8 to 1.1)
Religion					
Muslim	871 (32)	239 (34.5)	1		1
Christian‡	1849 (68)	453 (65.5)	0.9 (0.8 to 1.06)		0.8 (0.7 to 1.9)
Baseline WHO status					
Stage 1 or 2	842 (45.1)	216 (46.6)	1	1	
Stage 3 or 4	1027 (54.9)	248 (53.4)	0.9 (0.8 to 1.2)	1.7 (0.8 to 3.9)	
Baseline CD4					
≥200 cells/μL	2558 (80.8)	350 (45.2)	1	1	1
<200 cells/μL	606 (19.2)	425 (54.8)	5.1 (4.3 to 6.06)*	5.5 (4.1 to 7.4)*	1.8 (0.9 to 3.01)
Clinical failure					
No	1493 (81.3)	352 (80.5)	1	1	1
Yes	343 (18.7)	85 (19.5)	1.1 (0.8 to 1.4)	1.3 (0.9 to 1.8)	2.8 (0.7 to 4.9)
HIV care presentation					
Early	682 (36.5)	99 (21.3)	1	1	1
Late	1187 (63.5)	365 (78.7)	2.1 (1.7 to 2.7)*	2.2 (1.6 to 2.7)*	1.1 (1.01 to 1.2)*
Hx of TB/HIV coinfection					
No	2229 (70.4)	536 (69.2)	1	1	1
Yes	935 (29.6)	239 (30.8)	1.06 (0.9 to 1.3)	1.8 (0.7 to 4.9)	1.08 (1.01 to 1.2)*
ART adherence					
Good	2595 (82)	648 (83.6)	1		1
Fair or poor	569 (18)	127 (16.4)	0.9 (0.7 to 1.1)		0.9 (0.8 to 1.9)
Cotrimoxazole adherence					
Good	2632 (83.5)	639 (82.5)	1		
Fair or poor	521 (16.5)	136 (17.5)	0.9 (0.8 to 1.2)		
Baseline functional status					
Working or ambulatory	1992 (68.1)	549 (74.7)	1	1	
Bedridden	933 (31.9)	186 (25.3)	0.7 (0.6 to 0.9)*	0.8 (0.6 to 1.02)	
Hx of HIV testing					
Yes	1793 (56.7)	468 (60.4)	1	1	1
No	1371 (43.3)	307 (39.6)	0.9 (0.7 to 1.0)	0.7 (0.5 to 0.9)*	0.8 (0.7 to 0.9)*

Continued

Table 3 Continued

Variable	IF (n, %†) No	IF (n, %†) Yes	COR (95% CI)	AOR (95% CI): complete cases	AOR (95% CI): multiple imputations
ART shift					
No	2086 (98.9)	500 (99.2)	1		1
Yes	24 (1.1)	4 (0.8)	0.7 (0.2 to 2.01)		0.8 (0.6 to 1.03)

*Statistically significant at p≤0.05.
†Only valid percentage is considered.
‡Orthodox, protestant or catholic.
AOR, adjusted OR; ART, antiretroviral therapy; CD4, cluster for differentiation 4; COR, crude OR; IF, immunological failure; TB, tuberculosis.

CD4 counts are at an elevated risk for OIs and multiple comorbidities.[51] This prevents patients from taking the treatment consistently and gaining the immunological benefit.[40] Frequent screening and opt-out testing would normalise HIV testing, reduce stigma associated with HIV care and help those infected with HIV find out earlier.[52]

Finally, people who had history of HIV testing before diagnosis were less likely to gain an immunological response compared with those who had not. This might be justified by the fact that those who had history of HIV testing before diagnosis and once got HIV-negative result might feel sense of well-being and get tested late. Thus, the delayed HIV diagnosis and then delayed presentation to ART care could challenge the immunological gain from ART.[40] However, it is interesting that ART adherence was not statistically associated with IF, and this needs further research. Out of the 775 patients who developed IF or 546 patients who developed CF, only 29 adults switched to second-line ART drugs. This shows that the great majority of patients diagnosed with TF attributing to IF and/or CF were not moved onto second-line therapy.

The study has some limitations: (1) the retrospective nature of the study does not assure the cause–effect relationship as some of the variables could be measured after the occurrence of the outcome; (2) the possibility of having incomplete information could reduce the precision of estimates for the included variables; nonetheless, we have addressed this using MIs; (3) the source of information—being from public referral hospital—may not infer to another level of health institutions such as health centres or private hospitals; (4) the lack of viral load to detect TF is another limitation and (5) while including the latest episode of a poor outcome in an analysis of predictors, factors associated with first poor outcome may be different from factors associated to a poor outcome in a person who has already been on ART for several years and experienced multiple previous poor outcomes. Furthermore, we are unable to extract some data prior to each episode of IF to conduct further analyses, and explicitly identify associated factors for each episode.

CONCLUSIONS

In conclusion, the 19.7% prevalence of IF is higher in or near high HIV-prevalence settings—the current study setting—than low HIV-prevalence settings in Ethiopia that reported an IF prevalence of 6.7%–17.6%. However, great majority of the associated factors from the current study are incongruent to the findings of previous studies conducted in the country and elsewhere. Patients with IF were more likely to be early age adults, females, late presenters for HIV care, and have a low (<200 cells/mm^3) baseline CD4 count and history of HIV testing before diagnosis. Very few patients were shifted to second-line ART drugs despite the high prevalence of CF and/or IF. Research has shown that delayed ART regimen switching increases the risk of viral resistance and endangers the long-term prognosis of HIV-infected patients on ART. Hence, to further improve immunological response of the patients, benchmarking practices and effective programmes should be developed to diagnose and link HIV-infected patients timely, improve retention care and increase the regular immunological and virological monitoring of the patients.

Acknowledgements We acknowledge Jimma University Teaching Hospital for providing access to the data.

Contributors HAG, PW, KW and LM conceived and designed the study. HAG performed the data collection, data analysis and initial draft manuscript. HAG, PW, KW and LM reviewed the manuscript critically. All authors read and approved the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Not required.

Ethics approval Ethical clearance was obtained from Social and Behavioural Research Ethics Committee (SBREC) at Flinders University (Project number: 7086) and Institutional Review Board (IRB) of College of Health Sciences at Jimma University (Ref No: RPGC/386/2016). JUTH board has provided the data access permission.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement All data supporting our findings will be shared on request. Contact Hailay via hailushepi@gmail.com.

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Annex 3.10. Publication 6- Retrospective cohort study of HIV related mortality

PLOS ONE

RESEARCH ARTICLE

Early mortality among children and adults in antiretroviral therapy programs in Southwest Ethiopia, 2003–15

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OPEN ACCESS

Citation: Gesesew HA, Ward P, Woldemichael K, Mwanri L (2018) Early mortality among children and adults in antiretroviral therapy programs in Southwest Ethiopia, 2003–15. PLoS ONE 13(6): e0198815. https://doi.org/10.1371/journal.pone.0198815

Editor: Giuseppe Vittorio De Socio, Azienda Ospedaliera Universitaria di Perugia, ITALY

Received: January 15, 2018

Accepted: May 27, 2018

Published: June 18, 2018

Data Availability Statement: All relevant data are within the paper. The SPSS data of individual patients is not permitted to be provided to other bodies, as outlined by the Ethics Committee who approved the study. Anonymized data sets may be provided to researchers by contacting the following addresses: (gese0002@flinders.edu.au) (hailushepi@gmail.com).

Funding: The authors received no specific funding for this work.

Abstract

Background

Several studies reported that the majority of deaths in HIV-infected people are documented in their early antiretroviral therapy (ART) follow-ups. Early mortality refers to death of people on ART for follow up period of below 24 months due to any cause. The current study assessed predictors of early HIV mortality in Southwest Ethiopia.

Methods

We have conducted a retrospective analysis of 5299 patient records dating from June 2003-March 2015. To estimate survival time and compare the time to event among the different groups of patients, we used a Kaplan Meir curve and log-rank test. To identify mortality predictors, we used a cox regression analysis. We used SPSS-20 for all analyses.

Results

A total of 326 patients died in the 12 years follow-up period contributing to 6.2% cumulative incidence and 21.7 deaths per 1000 person-year observations incidence rate. Eighty-nine percent of the total deaths were documented in the first two years follow up—an early-term ART follow up. Early HIV mortality rates among adults were 50% less in separated, divorced or widowed patients compared with never married patients, 1.6 times higher in patients with baseline CD4 count <200 cells/μL compared to baseline CD4 count ≥200 cells/μL, 1.5 times higher in patients with baseline WHO clinical stage 3 or 4 compared to baseline WHO clinical stage 1 or 2, 2.1 times higher in patients with immunologic failure compared with no immunologic failure, 60% less in patients with fair or poor compared with good adherence, 2.9 times higher in patients with bedridden functional status compared to working functional status, and 2.7 times higher with patients who had no history of HIV testing before diagnosis compared to those who had history of HIV testing. Most predictors of early mortality remained the same to the predictors of an overall HIV mortality. When discontinuation was assumed as an event, the predictors of an overall HIV mortality included age between 25–50 years, base line CD4 count, developing immunologic failure, bedridden functional status, and no history of HIV testing before diagnosis.

Competing interests: The authors have declared that no competing interests exist.

Abbreviations: AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; HIV, human immunodeficiency virus; HCC, HIV care continuum; JUTH, Jimma University Teaching Hospital; LTFU, loss to follow up; MIs, multiple imputations; SSA, Sub-Saharan Africa; Tb, tuberculosis; UNAIDS, The Joint United Nations Program on HIV and AIDS; WHO, World Health Organization.

Conclusions

The great majority of deaths were documented in the first two years of ART, and several predictors of early HIV mortality were also for the overall mortality when discontinuation was assumed as event or censored. Considering the above population, interventions to improve HIV program in the first two years of ART follow up should be improved.

Introduction

Worldwide in 2015, 38.8 million people were living with human immunodeficiency virus (HIV), 2.5 million new HIV infections, and 1.2 million HIV/AIDS (acquired immunodeficiency syndrome) deaths were estimated, and sub-Saharan Africa (SSA) accounted for 76% of the global morbidity and 75% of the global mortality [1]. Ethiopia, one of the countries in SSA, had an estimate of 39,140 newly HIV-infected people, 768,040 people living with HIV, and 28,650 HIV/AIDS deaths in 2015 [1]. Ethiopia contributed 3% each to the global death and number of HIV-infected people in SSA respectively [2]. Antiretroviral therapy (ART) program in Ethiopia was commenced in 2003 in 12 hospitals at cost to the patients [3], and then since 2005, it was provided free of charge in 22 hospitals with the help of the international donors such as Global Fund, World Bank, and President's Emergency Plan for AIDS Relief (PEPFAR) [3, 4]. A total of 270,460 people were on ART in 913 health facilities in 2012–13 [3, 5] and the coverage rose to 339,043 adults and 22,955 children in 2014 [6].

The effectiveness of a country's ART program depends on the HIV treatment cascade or HIV care continuum. HIV care continuum is a series of steps in which a person with HIV takes from initial diagnosis through their successful treatment with HIV medication [7, 8] that includes HIV diagnosis, assessment for ART eligibility, retention, and virological suppression. The success of The Joint United Nations Program on HIV and AIDS (UNAIDS) treatment targets—diagnosing 90% of people living with HIV, providing 90% of those diagnosed antiretroviral therapy (ART), and achieving viral suppression for 90% of patients receiving treatment—is affected by several factors [8–11]. Particularly, in order to meet the second and third 90s of the UNAIDS treatment targets, patient retention is a key program. However, attrition has been a routine impediment and remains monotonous in the thirty years of targeted HIV diagnosis and 20 years since ART rollout. Mortality from HIV, death of HIV-infected patients in the period of ART due to any cause, is one of the major contributors to attrition.

Recent global, regional and national estimates for mortality reported that 0.03 million deaths in high-income countries, 0.1 million deaths in middle-income countries, and 0.4 million deaths in low-income countries were recorded [1]. Similarly, several studies [12–19] that assessed the magnitude and predictors of mortality in Ethiopia are growing. Accordingly, the incidence of mortality has been reported between 2 and 25.9%, and the factors affecting for mortality of Ethiopian patients included but are not limited to male, primary level of education, single marital status, weight loss, bed-ridden functional status, low baseline cluster of differentiation 4 (CD4) count, advanced World Health Organization (WHO) clinical staging, tuberculosis (Tb)/HIV co-infection, severe anemia and substance abuse. In addition, the majority of the previous studies from Ethiopia reported high mortality is recorded in < 24 months since ART starting [13–15, 17, 20].

However, firstly, none of these studies assessed what predictors determined for the mortality in the early follow up periods. Secondly, none of the studies were also carried out in the southwestern part of the nation. Southwest Ethiopia has different cultural and socioeconomic

characteristics, and according to the 2011 Ethiopian census, the regional state has the highest HIV prevalence (6.5%) in the nation than the other parts of the country (<2%) where the previous studies have been carried out. Therefore, the predictors that determine mortality may be different and need to be understood contextually to design interventions tailored to the individual regional states. Thirdly, all studies that assessed the predictors of mortality considered LTFU as censored, and none of them assumed the outcome of discontinued patients could be a death. Previous tracing studies from Ethiopia and Kenya reported that 40–86% of LTFU cases failed to re-engage to the care [21], and 50% of LTFU patients were found dead [22, 23]. Such failing to assume LTFU patients as deceased would lead to a biased estimate and spuriously low risk or odds ratio calculation. Fourthly, the great majority of the retrospective cohort studies from Ethiopia reported from a short-term durability of ART follow up periods or relatively low sample size.

The current study assessed the incidence and predictors of mortality in the early follow up periods using a 12-years data from the ART clinic at Jimma University Teaching Hospital (JUTH) in Southwest Ethiopia. The study also compared the predictors of early mortality with the cumulative mortality, and added another model assuming a worst-case scenario whereby all discontinued patients were assumed dead.

Methods

Study design, setting and participants

We used retrospective cohort study in ART clinic at JUTH in Southwest Ethiopia using patient records from June 2003 to March 2015. Details of the study setting has been described elsewhere [24–26]. All HIV-infected children and adults enrolled for ART care in JUTH were the target population. The details of the treatment protocol for Ethiopia is described elsewhere [27].

Data source and procedures

We extracted the data from JUTH electronic medical records (EMR) system designed since 2007. Clinicians record clinical and non-clinical information of patients on paper form, and then data clerks entered into the EMR system. Two data clerks undertake the data entry process to warrant completeness. The International Center for AIDS Care and Support (ICAP) at Colombia University has been delivering technical assistance on the electronic patient level data management, and carrying out check up of data completeness. This ensures the accuracy and reliability of the EMR data. If outcome status of a patient were not recorded or transferred out, records would be excluded from the analysis. Fig 1 demonstrates the schematic presentation of data extraction HIV infected children and adult enrolled in the period 2003–2015 in Jimma University Teaching Hospital, Southwest Ethiopia.

Study variables and measurements

The response variables were the survival time in months and events related to HIV. ART patients were followed until the date of the event, discontinuation or the end of the study. We defined mortality as the death of people on ART in the reporting period due to any cause [22]. Patients who are alive and on ART until March 2015, and discontinued from ART—LTFU, defaulting and stopping medication—were considered as a censored i.e. they were assumed to be alive for the time period they had been under follow up. ART outcomes—mortality, discontinuation or alive and on ART—were the outcomes that were recorded in the final date of the data collection. ART duration was dichotomized as early and short. Short-term follow up

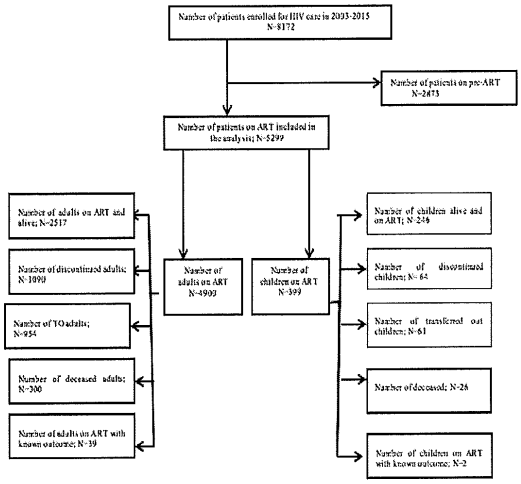

Fig 1. Schematic presentation of data extraction of HIV infected patients on ART in 2003–15 in Jimma University Teaching Hospital, Southwest Ethiopia—This figure shows the data extraction flowchart.

https://doi.org/10.1371/journal.pone.0198815.g001

period was defined if the ART follow-up period was below 24 months [22]. The independent variables included age, sex, marital status, educational status, religion, ART adherence, Cotrimoxazole adherence, late presentation for HIV care (LP), clinical failure, immunological failure, treatment failure, Tb/HIV co-infection, baseline functional status, history of HIV testing and ART shift. History of HIV testing refers to testing (one or more times) for HIV before HIV diagnosis. ART shift is switching of first line to second line ART regimen. Attrition refers to a condition where HIV-infected patients fail to retain in care i.e. mortality, lost to follow up from ART, defaulting from ART or stopping ART. Table 1 reports the operational definitions for variables related to attrition (mortality and discontinuation). Table 2 reports the measurements of LP, adherence, clinical, immunological and treatment failures.

Statistical analyses

We edited and cleaned up the data, to summarize the characteristics of cohort, we used descriptive statistics that included median and range values for continuous data; percentage, frequency tables, and graphs for categorical data. The calculation for cumulative incidence (CI) and incidence rate (IR) of mortality is presented in Table 1. For children, the event (death) was occurred only in 26 participants, and this small event occurrence does not allow us to conduct further inferential statistics—the cox regression analysis. For adults, we used Kaplan Meir curve to estimate survival time and compare the time to event among the different groups of patients. The log-rank test was used to check any significant differences in survival among different levels of the categorical variables measured in the study. We calculated the estimated survival time in months using the time between date of treatment initiation and date of death or censoring.

Table 1. Measurements for variable related to death and ART attrition (mortality and discontinuation).

Variable	Definition	Numerator	Denominator
Cumulative incidence	The number of deaths among patients enrolled on ART during the follow-up	Number of deaths during the entire ART follow-up period (2003–15)	Number of patients during the entire follow up period (2003–15)
Incidence rate	Number of deaths among patients enrolled on ART in a person-time observations	Number of deaths during the entire follow up period	Time each person was observed, totaled for all persons (total person-years observations)
Annual death rate	The death rate in a specific calendar year among patients enrolled on ART during that calendar year	Number of deaths in a specific calendar year	Number of patients died plus alive and on ART plus discontinued plus transferred out during the specific calendar year
Calendar year	The year which the death rate is calculated	Not applicable (NA)	NA
LTFU	If patients had been on ART treatment and had missed at least three clinical appointments but had not yet been classified as "dead" or "transferred out (transferred)".	NA	NA
Defaulting	If patients had been on ART treatment and had missed less than three clinical appointments but had not yet been classified as "dead" or "TO".	NA	NA
Stopping medication	If patients had stopped treatment due to any reason while they have remained in care.	NA	NA
Transfer out	Transferred is the official transferring of the patient to another ART clinic within or outside a catchment area.	NA	NA

ART: antiretroviral therapy; LTFU; lost to follow up; NA: not applicable

https://doi.org/10.1371/journal.pone.0198815.t001

We applied bivariate cox regression analysis to see the existence of crude association and select candidate variables (with *P* value below 0.25) to multiple cox regression. We carried out a multiple cox regression analysis to identify independent predictors of mortality using a step-wise variable selection. We assessed the assumption for proportional hazard graphically. We checked the goodness of fit of the final model using Hosmer and Lemeshow test and was found fit. We also checked the collinearity diagnosis between selected independent variables. *P*-value of <5% was considered significant in the final model. Three models were constructed. Model I shows the predictors of early mortality among HIV-infected patients attending short-term (<24 months) ART follow-ups. Model II—real case assumption—shows the predictors of an overall mortality (cumulative) among HIV-infected patients attending ART assuming discontinuation as censored. Model III—worst case assumption or intention-to-treat analysis —shows the predictors of an overall mortality (cumulative) among HIV-infected patients attending ART assuming discontinuation as event(death) in addition to the real event. We used Statistical Package for the Social Sciences (SPSS) version 22.0 for all data analyses.

Ethical approval

The ethical clearance was obtained from the Social and Behavioral Research Ethics Committee (SBREC) at Flinders University (Project number: 7086) and Institutional Review Board (IRB) of College of Health Sciences at Jimma University (Ref No: RPGC/386/2016). A de-identified data was extracted from the database, and its access permission was obtained from JUTH board.

Results

The study included 8,172 ART patients enrolled from 21 June 2003 to 15 March 2015, with a median follow up times of 49 months. Of total, 5,299 (64.8%) patients were on ART of whom 4,900 (92.5%) were adults and 399 (7.5%) were children. Table 3 presents the clinical and non-

Table 2. Measurements for late presentation for HIV care, ART or cotrimoxazole adherence, and immunological, clinical & treatment failures.

Adults	Late presentation for HIV care[28–30] [a]			
	Enrolled in 2003–11		Enrolled in 2012–15	
	CD4 lymphocyte count of <200 cells/μL irrespective of WHO clinical stage at the time of first presentation to the HIV care		CD4 lymphocyte count of <350 cells/μL irrespective of WHO clinical stage at the time of first presentation to the HIV care	
	WHO clinical stage 3 or 4 irrespective of CD4 count at the time of first presentation to the HIV care [b]		WHO clinical stage 3 or 4 irrespective of CD4 count at the time of first presentation to the HIV care [b]	
Children [c]	Late presentation for HIV care[31]			
		Moderate immuno-suppression if CD4 count between	Severe immunosuppression if CD4 count between	
	0–12 months	750–1500 cells/μL	<750 cells/μL	
	1–5 years	500–1000 cells/μL	<500 cells/μL	
	≥ 6 years	200–500 cells/μL (enrolled in 2003–2011)	<200 cells/μL (enrolled in 2003–11)	
	≥ 6 years	350–500 cells/μL (enrolled in 2012–2015)	<350 cells/μL (enrolled in 2012–2015)	
Children and adults	Adherence status to ART or cotrimoxazole[32][d]			
	Status	Percentage of prescribed ART intake	Number of missing doses out of 30	Number of missing doses out of 60
	Good	≥ 95%	<3	<4
	Pair	85–95%	3–5	4–9
	Poor	< 85	≥6	≥9
	Clinical, immunological and treatment failures for children and adults [33]			
	Clinical failure		Immunological failure	Treatment failure
Children	New clinical condition indicating severe immunodeficiency (WHO clinical stage 3 and 4 with the exception of Tb) after 6 months on ART		Persistent CD4 counts <200 cells/mm^3 for children age<5 years, or <100 cells/mm^3 for children age≥ 5 years	Having both clinical and immunological failures
Adults	New clinical condition indicating severe immunodeficiency (WHO clinical stage 4) after 6 months on ART		If CD4 count of the HIV-infected adults falls to the baseline (or below) or persistent CD4 levels below 100 cells/mm3 after six months of ART treatment	

ART: antiretroviral therapy; CD4: cluster for differentiation 4; WHO: World Health Organization; Tb: Tuberculosis; PCP: pneumocystis carinii (juvenii) pneumonia

[a]The definition for LP among Tb/HIV co-infected population was only based on the CD4 criteria[25].

[b] **WHO clinical Stage 3** was defined if one of the following is present in an HIV diagnosed patient: weight loss of >10% body weight, chronic diarrhoea for >1 month, fever for >1 month, oral candidiasis, oral hairy leukoplakia, or pulmonary Tb within the previous year, or severe bacterial infections; **WHO clinical Stage 4** was defined if one of the following is present in an HIV diagnosed patient:HIV wasting syndrome, PCP, toxoplasmosis of the brain, cryptosporidiosis or isosporiasis with diarrhea for >1 month, cytomegalovirus disease of an organ other than liver, spleen or lymph node, herpes simplex virus infection, progressive multifocal leukoencephalopathy, candidiasis, extra-pulmonary Tb, lymphoma, kaposi's sarcoma, HIV encephalopathy

[c]LP is also defined if WHO clinical stage 3 or 4 at first visit to the ART clinics

[d] Clinicians/pharmacists ask patients and check the pill container to collect the number of missing doses or days.

https://doi.org/10.1371/journal.pone.0198815.t002

clinical characteristics of HIV-infected adults and children on ART. Of the children, the majority (58.1%) were age 5-<15 years, half (52.4%) were males, and three-quarter (73.9%) were Christians. Four out of five children (79.4%) had moderate or severe immunosuppression, and half (50.5%) of the children had baseline WHO clinical stage 3 or 4. The prevalence of Tb/HIV co-infection among children was 28.6%.

The median time on ART was 40 months where as the estimated survival time was 104.2 (99.8–108.5) months. Of the adults, 59.8% were females, 48.7% were married and 39% had

Table 3. Clinical & non-clinical characteristics of HIV infected people enrolled in ART care in Southwest Ethiopia from 2003–15.

Variable		Children (N = 399)	Adult (N = 4900)
		N (%)	N (%)
Age in years	<1	21 (5.3)	
	1-<5	146 (36.6)	
	5-<15	232 (58.1)	
	15-<25		711 (14.5)
	25-<50		3937 (80.3)
	50+		252 (5.2)
	Median (range) age in years	6 (<1–14)	30 (15–81)
Sex	Male	209 (52.4)	1971 (40.2)
	Female	190 (47.6)	2929 (59.8)
Marital status[b]	Never married		897 (20.9)
	Married		2094 (48.7)
	Separated/divorced/widowed		1311 (30.5)
Education[b]	No education		945 (21.9)
	Primary		1687 (39.1)
	Secondary and above		1685 (39)
Religion[b]	Muslim	47 (26.1)	1402 (32.6)
	Christian[a]	133 (73.9)	2893 (67.4)
Baseline WHO classification [b]	1 or 2	108 (49.5)	1355 (45.7)
	3 or 4	110 (50.5)	1608 (54.3)
Baseline CD4 count category [b]	No damage	72 (20.6)	
	Moderate or severe damage	277 (79.4)	
	Median (range) CD4 count	282 (0–2250)	
Baseline CD4 count (cells/mm3) [b]	<200		3275 (73.6)
	≥ 200		1174 (26.4)
	Median (range)		156 (0–1313)
History of Tb/HIV co-infection [b]	No	285 (71.4)	3533 (72.1)
	Yes	114 (28.6)	1367 (27.9)
ART adherence [b]	Good	319 (79.9)	4064 (82.9)
	Fair or poor	80 (20.1)	836 (17.1)
Cotrimoxazole adherence [b]	Good	315 (78.9)	4119 (94.4)
	Fair or poor	84 (21.1)	762 (15.6)
History of HIV testing [b]	Yes	399 (100)	2860 (58.4)
	No	0 (0)	2040 (41.6)
ART shift [b]	No	214 (97.7)	3190 (99.1)
	Yes	5 (2.3)	29 (0.9)
Baseline functional status [b]	Appropriate	170 (42.6)	
	Delay or regression	229 (57.4)	
Baseline functional status [b]	Work or Ambulatory		3064 (68.1)
	Bedridden		1437 (31.9)
HIV care presentation	Early	162 (43)	894 (33.3)
	Late	215 (57)	1788 (66.7)
Clinical failure [b]	No	165 (77.1)	2261 (80.5)
	Yes	49 (22.9)	546 (19.5)
Immunologic failure [b]	No	295 (84.8)	3164 (80.3)
	Yes	53 (15.2)	775 (19.7)

(*Continued*)

Table 3. (Continued)

Variable		Children (N = 399)	Adult (N = 4900)
		N (%)	N (%)
Treatment failure [b]	No	126 (31.6)	1493 (65.7)
	Yes	61 (15.3)	780 (34.3)
Duration of ART	Short (<24 months)	143 (7.8)	1697 (92.2)
	Long (> = 24 months)	193 (8)	2210 (92)

[a]Orthodox, Catholic, Protestant

[b] only valid percentage is calculated; ART: antiretroviral therapy; CD4: cluster for differentiation 4; WHO: World Health Organization; Tb: Tuberculosis

https://doi.org/10.1371/journal.pone.0198815.t003

primary school education. Three quarters (73.6%) of HIV-infected adults had baseline CD4 count below 200 cells/mm^3, and 54.3% had WHO clinical stage 3 or 4. Tb/HIV co-infection was diagnosed in about a quarter of adults (27.9%). In addition, 29(0.9%) HIV-infected adults were switched to second line ART drugs.

Cumulative incidence (CI) and incidence rate (IR) of mortality in HIV-infected patients

Of the 5299 ART patients, 2763 (52.5%) patients were alive and on ART, 1154 (21.9%) patients discontinued from the treatment, and 1015 (19.3%) patients transferred to other sites by the end of march 2015(Table 4). The remaining 326 (6.2%) patients died contributing to a CI of 6.5% (26/399) in children and 6.1% (300/4900) in adults. Of the total deaths, 220 deaths (67.5%) occurred in the first six months of ART follow up, 37 (11.3%) occurred in between 6-<12 months, 32 (9.8%) occurred in between 12-<24 months and the remaining 37 (11.3%) deaths occurred ≥24 months.

The total follow-up period encompassed 15, 051 person-years observations, and an estimated survival time of 121.9 (95%CI: 120.3–123.5) months. The overall IR was 21.7 deaths (22.2 deaths for children and 21.6 deaths for adults) per 1000 person-years observations. The magnitude of mortality had peaked in 2006 but reduced significantly and remained low in subsequent years of follow-up (Table 4). Fig 2A–2D respectively show mortality status of study participants by baseline CD4 count, immunologic failure, history of Tb/HIV co-infection and functional status using Kaplan-Meier graphs. Accordingly, the hazard distribution of ART clients for sex, baseline CD4 count and history of Tb/HIV co-infection was statistically significant.

Predictors for mortality among adult HIV patients on ART

Table 5 demonstrates the findings from three models of the cox regression analysis. Model I presents results of the bivariate and multivariable cox regression analysis of predictors for early mortality among adult HIV patients attending short-term ART follow-ups. Predictors of early mortality included being separated/divorced/ widowed, having a baseline CD4 count below 200 cells/μL, baseline WHO clinical staging, developing immunologic failure, fair or poor ART adherence, bedridden functional status and no history of HIV testing. HIV patients who were separated, divorced, or widowed were 50% less likely (AHR = 0.5, 95%CI: 0.3–0.8) to die compared to those who never married. Compared to patients with baseline CD4 count 200 cells/μL and above, the hazard of death was higher (AHR = 1.6, 95%CI: 1.05–2.5) among patients with baseline CD4 count <200 cells/μL. In addition, compared to patients with baseline WHO clinical stage 3 or 4, the hazard of death was higher (AHR = 1.5, 95%CI: 1.05–2.5)

Table 4. Annual number of patients enrolled in ART care and their outcomes.

Year	New enrolment (a)	Outcome final, n (%)				
		Death (b)	Discontinuation (c)	Transfer out (d)	Alive and on ART (e)	Total in Cohort (f)
2003	8	0 (0)	1 (12.5)	0 (0)	7 (87.5)	8
2004	62	1 (1.4)	7 (10.1)	1 (1.4)	60 (87.0)	69
2005	484	28 (5.1)	51 (9.4)	9 (1.7)	456 (83.8)	544
2006	973	66 (4.6)	90 (6.3)	71 (5.0)	1202 (84.1)	1429
2007	622	53 (2.9)	155 (8.5)	137 (7.5)	1479 (81.1)	1824
2008	555	45 (2.2)	112 (5.5)	97 (4.8)	1780 (87.5)	2034
2009	566	42 (1.8)	54 (2.3)	109 (4.6)	2141 (91.3)	2346
2010	481	23 (0.9)	152 (5.8)	81 (3.1)	2366 (90.2)	2622
2011	461	29 (1.0)	93 (3.3)	112 (4.0)	2593 (91.7)	2827
2012	383	11 (0.4)	101 (3.4)	103 (3.5)	2761 (92.8)	2976
2013	324	17 (0.6)	117 (3.8)	107 (3.5)	2844 (92.2)	3085
2014	320	9 (0.3)	179 (5.7)	158 (5.0)	2818 (89.1)	3164
2015	60	2 (0.1)	42 (1.5)	30 (1.0)	2763 (97.4)	2878
Overall		326 (6.2)	1154 (21.9)	1015 (19.3)	2763 (52.5)	5299

e = f-b-c-d; where f = e (previous year) + a (current year); The annual percentages for death, discontinuation, transfer out, and alive and on ART is calculated by dividing the number of patients on ART with respective outcomes in a calendar year to the number of patients on ART in the cohort in that calendar year.

https://doi.org/10.1371/journal.pone.0198815.t004

among patients with baseline WHO stage 1 or 2. Patients who developed immunologic failure were two times (AHR = 2.1, 95%CI: 1.4–3.01) at risk to die than those who did not develop immunologic failure. The hazard of death was 40% less among patients with poor or fair ART adherence compared to those with good adherence. Patients with bedridden functional status were more likely (AOR = 2.9, 95%CI: 2.02–4.07) to die than their comparator. Patients with no history of HIV testing before diagnosis had also a higher risk of mortality (AHR = 2.7, 95%CI: 1.9–3.8) than those who had history of HIV testing.

Model II—real case assumption—reports results of the bivariate and multiple cox regression analysis of predictors for overall mortality (cumulative) among HIV patients attending ART assuming discontinuation and alive as censored. Predictors of mortality included being separated/widowed/divorced, having baseline CD4<200cells/μL, short ART duration, bedridden functional status and no history of HIV testing. Females had 40% lesser probability (AHR = 0.5, 95%CI: 0.3–0.8) to die than males. HIV-infected patients who were separated, divorced or widowed were less likely (AHR = 0.5, 95%CI: 0.2–0.9) to die than those who never married. Patients with baseline CD4 count <200 cells/μL had an elevated risk of death (AOR = 2.01, 95%CI: 1.5–3.5) than those with baseline CD4 count 200 cells/μL and above. HIV patients with longer ART duration has less likely (AHR = 0.08, 95%CI: 0.05–0.1) to die than those who were on short ART duration. Having bedridden functional status (AHR = 2.2, 95%CI: 1.4–3.9) and no history of HIV testing (AHR = 2.7, 95%CI: 1.9–3.8) were also another risk factors for the overall mortality.

Model III—worst case assumption or intention-to-treat approach—presents results of the bivariate and multiple cox regression analysis of predictors for overall mortality among HIV-infected patients attending ART assuming discontinuation as event. In addition to baseline CD4 count, functional status and history of HIV testing—predictors of mortality in the real case assumption—, age and immunological failure had statistically significant association when discontinuation is assumed as an event.

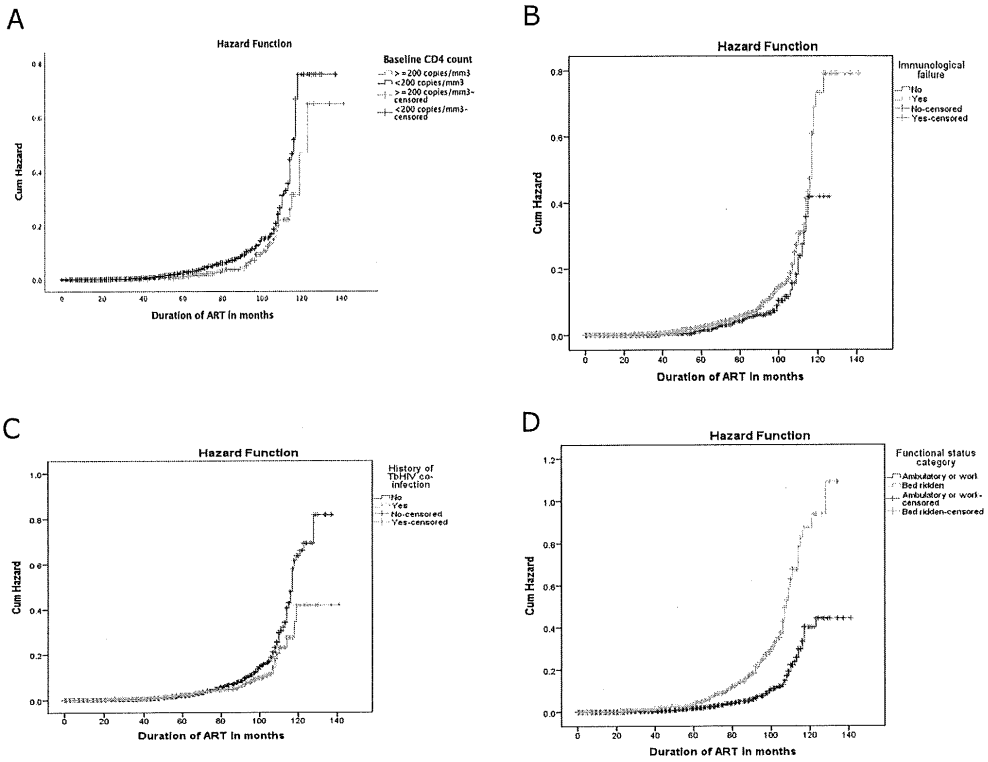

Fig 2. (a-d) Kaplan-Meier plot of hazard function stratified according to baseline CD4 count, immunologic failure, Tb/HIV co-infection and functional status among a cohort of ART clients respectively; JUTH hospital, Southwest Ethiopia; 2016—This figure presents the association between baseline CD4 count immunologic failure, Tb/HIV co-infection and functional status, and HIV mortality.

https://doi.org/10.1371/journal.pone.0198815.g002

Discussion

In this study, the cumulative incidence mortality for HIV-infected patients on ART was found to be 6%, which is lower than was reported in studies carried out in another parts of Ethiopia such as Tigray [15], Southern Nations, Nationalities and Peoples Region (SNNPR)[19] and Amhara [34], where the CI were 9%, 10% and 41% respectively. Despite that, participants of the current study setting are diversified (i.e. from high HIV prevalence rate settings, low HIV prevalence rate settings, and refugee camps), the magnitude of death was not higher than from the other settings. This may be attributed to several reasons. First, the magnitude of death may be attributed to the level of late HIV care presentation. For example, 65% of the participants in the present study were late presenters as compared to 69% in Tigray [35]. Second, the magnitude of death may be attributed to the level of adherence to ART. For example, 20% of the participants in the present study were non-adherent as compared to 26% in the SNNPR [36].

Table 5. Factors related to HIV-associated mortality among HIV-infected adults in 2003–2015, JUTH, Southwest Ethiopia.

Variable		Status (Short-term follow up)		Model I: <24 months of follow-up (Short-term follow up)		Model II: Cumulative (0–140 months of follow-up) (Real case assumption)		Model III: Cumulative (0–140 months of follow-up) (Worst case assumption)	
		Censored, n (%)	Event, n (%)	CHR (95%CI)	AHR (95% CI)	CHR (95%CI)	AHR (95% CI)	CHR (95%CI)	AHR (95% CI)
Age	15–25 years)	554 (95.2)	28 (4.8)	Reference	Reference	Reference	Reference	Reference	Reference
	25–50 years	2859 (92)	249 (8)	0.9 (0.7–1.00)	0.8 (0.6–1.2)	1.3 (0.9–1.9)	1.3 (0.9–1.9)	0.8 (0.7–0.98) [a]	0.8 (0.6–0.9) [a]
	50+ years	194 (89.4)	23 (10.6)	1.2 (0.9–1.6)	1.1 (0.7–1.8)	2.5 (1.4–4.3) [a]	1.9 (0.4–3.3)	1.2 (0.9–1.6)	0.8 (0.4–1.5)
Sex	Male	1385 (91.2)	134 (8.8)	Reference	-------	Reference	-------	Reference	-------
	Female	2222 (93)	166 (7)	1.02 (0.9–1.1)	-------	1.06 (0.84–1.3)	-------	1.02 (0.9–1.1)	-------
Marital status	Never married	686 (90.7)	70 (9.3)	Reference	Reference	Reference	Reference	Reference	Reference
	Married	1503 (91)	149 (9)	1.4 (1.2–1.6) [a]	0.8 (0.5–1.1)	0.99 (0.7–1.3)	0.7 (0.5–1.05)	1.4 (1.2–1.6) [a]	1.3 (0.9–1.7)
	Other [b]	896 (93.6)	6.4	1.2 (1.06–1.5) [a]	0.5 (0.3–0.8) [a]	0.7 (0.5–1.02)	0.5 (0.2–0.9) [a]	1.2 (1.06–1.5) [a]	1.09 (0.9–1.5)
Educational status	No education	679 (94.4)	40 (5.6)	Reference	-------	Reference	-------	Reference	Reference
	Primary	1227 (91.8)	109 (8.2)	1.00 (0.8–1.1)	-------	1.6 (0.97–2.2)	-------	0.9(0.8–1.2)	1.00 (0.7–1.4)
	Secondary & above	1197 (89.9)	135 (10.1)	1.2 (1.01–1.4) [a]	-------	1.9 (0.8–2.7)	-------	1.2 (1.01–1.4) [a]	1.3 (0.9–1.8)
Religion	Muslim	1026 (92.3)	85 (7.7)	Reference	-------	Reference	-------	Reference	-------
	Christian [c]	2060 (91.3)	197 (8.7)	1.01 (0.9–1.1)	-------	1.2 (0.9–1.5)	-------	1.009 (0.9–1.1)	-------
Baseline WHO status	1 or 2	982 (91.5)	91 (8.5)	Reference	Reference	Reference	Reference	Reference	Reference
	3 or 4	1123 (90.6)	116 (9.4)	1.07 (0.9–1.2)	1.5 (1.05–2.01) [a]	1.0 (-1.4)	1.1 (0.6–1.5)	1.07 (0.9–1.2)	1.1 (0.9–1.2)
Baseline CD4 count	> = 200 cells/μL	907 (95.3)	45 (4.7)	Reference	Reference	Reference	Reference	Reference	Reference
	<200 cells/μL	2388 (91.6)	218 (8.4)	1.3 (1.1–1.5) [a]	1.6 (1.05–2.5) [a]	1.6 (1.1–2.1) [a]	2.01 (1.5–3.5) [a]	1.3 (1.1–1.5) [a]	1.1 (1.07–1.3)
Clinical failure	No	1652 (91.6)	151 (8.4)	Reference	-------	Reference	-------	-------	-------
	Yes	388 (88.6)	50 (11.4)	0.8 (0.7–1.0)	-------	1.03 (0.7–1.4)	-------	-------	-------
Immunologic failure	No	617 (94.9)	33 (5.1)	Reference	Reference	Reference	Reference	Reference	Reference
	Yes	2534 (92)	220 (8)	1.5 (1.3–1.8) [a]	2.1 (1.4–3.01) [a]	1.4 (0.9–2.02)	1.2 (0.5–2.4)	1.5 (1.3–1.8) [a]	1.4 (1.09–1.8) [a]
HIV care presentation	Early	643 (90.8)	65 (9.2)	Reference	-------	Reference	-------	Reference	
	Late	1274 (91.2)	119 (8.5)	1.00 (0.8–1.1)	-------	1.01 (0.7–1.2)	-------	1.00 (0.8–1.1)	
ART duration	Short	-------	-------	-------	-------	Reference	Reference	-------	-------
	Long	-------	-------	-------	-------	0.07 (0.05–0.11) [a]	0.08 (0.05–0.1) [a]	-------	-------
Tb/HIV co-infection	No	2546 (91.5)	238 (8.5)	Reference	Reference	Reference	Reference	Reference	Reference
	Yes	1061 (94.5)	62 (5.5)	0.85 (0.75–0.97) [a]	0.7 (0.6–0.9)	0.7 (0.5–0.9) [a]	0.9 (0.6–1.3)	0.85 (0.76–0.97) [a]	1.1 (0.9–1.4)
ART adherence	Good	2938 (91.8)	264 (8.2)	Reference	Reference	Reference	-------	Reference	Reference
	Fair or poor	667 (94.9)	36 (5.1)	0.7 (0.6–0.8) [a]	0.4 (0.2–0.7) [a]	0.6 (0.5–0.8) [a]	-------	0.7 (0.6–0.8) [a]	0.9 (0.7–1.1.3)
Cotrimoxazole adherence	Good	2983 (91.7)	269 (8.3)	Reference	Reference	Reference	-------	Reference	Reference
	Fair or poor	609 (95.3)	30 (4.7)	0.8 (0.7–0.9) [a]	0.7 (0.4–1.09)	0.6 (0.4–0.9) [a]	-------	0.8 (0.7–0.9) [a]	0.8 (0.6–1.3)
Functional status	Working/ Ambulatory	3103 (94.8)	171 (5.2)	Reference	Reference	Reference	Reference	Reference	Reference
	Bedridden	442 (81.1)	103 (18.9)	2.5 (2.3–2.8) [a]	2.9 (2.02–4.07) [a]	2.8 (2.1–3.6) [a]	2.2 (1.4–3.9) [a]	2.5 (2.3–2.9) [a]	3.00 (2.3–4.0) [a]

(*Continued*)

Table 5. (Continued)

Variable		Status (Short-term follow up)		Model I: <24 months of follow-up (Short-term follow up)		Model II: Cumulative (0–140 months of follow-up) (Real case assumption)		Model III: Cumulative (0–140 months of follow-up) (Worst case assumption)	
		Censored, n (%)	Event, n (%)	CHR (95%CI)	AHR (95% CI)	CHR (95%CI)	AHR (95% CI)	CHR (95%CI)	AHR (95% CI)
History of HIV testing	Yes	2079 (93.2)	152 (6.8)	Reference	Reference	Reference	Reference	Reference	Reference
	No	1528 (91.2)	148 (8.8)	1.9 (1.7–2.1) [a]	2.7 (1.9–3.7) [a]	2.9 (2.3–3.6) [a]	2.7 (1.9–3.8) [a]	1.9 (1.7–2.1) [a]	1.9 (1.6–2.4) [a]
ART shift	Yes	2302 (91)	228 (9)	-------	-------	-------	-------	-------	-------
	No	29 (100)	0 (0)	-------	-------	-------	-------	-------	-------

[a] statistically significant at p-value ≤0.05

[b] Separated/divorced/widowed

[c] Orthodox, Protestant or Catholic

https://doi.org/10.1371/journal.pone.0198815.t005

Third, the magnitude of death may be attributed to the magnitude of Tb/HIV co-infection. For example, 28% of the participants in the present study had Tb/HIV co-infection as compared to 44% in Amhara [37].

The majority of deaths happened during the first 6 months after treatment initiation, but reduced substantially in the first year of treatment, and remained low in subsequent years of follow-up as reported elsewhere [19, 22, 38–40]. This has an implication with the criteria for ART initiation. The treatment protocol for Ethiopia is implemented using WHO ART treatment guideline [41] and National Guidelines for Comprehensive HIV Prevention, Care and Treatment: Federal Democratic Republic of Ethiopia, Ministry of Health [42]. These protocols consider baseline CD4 count and/or WHO clinical staging. According to these protocols, patients were used to wait until their CD4 count and/or WHO clinical staging dropped down to the criteria. Recently, since the end of 2016, the initiation of test and treat strategy in the country will have an impact on reducing early HIV mortality. This program should be strengthened throughout the nation. The HIV mortality had peaked in 2005–07, and this could possibly be: i) the free introduction of ART in 2005–6 in Ethiopia was without intensive preparation [22]; ii) high rate of late HIV diagnosis (70–74%) was recorded in the period in the current study; iii) there was poor awareness about the modern medicine, and to the contrary, traditional medicine was more well-known and accessible in Ethiopia[43]; iv) negative belief about ART treatment could be another reason [44]; and v) there was a scarcity of ART supply and the referral linkage was very poor since the system was at an early stage. Since 2008, the HIV mortality has markedly declined as reported by the previous studies [45–47]. Since the scale up of ART in 2005, the overall mortality rate decreased by 40%, 85% and 100%, respectively, in 2007, 2011 and 2014. The Government of Ethiopia that has made a significant improvement in health infrastructure—health-care institutions, laboratories, and capacity building of health professionals—has contributed to the significant reduction of HIV mortality [3, 5]. The remarkable reduction of death could also be attributed to the introduction of effective combination of ART [48–50],early initiation of ART due to lowering the CD4 based ART initiation criteria [51], and the expansion of ART programs to primary health care facilities [52].

Findings of the current study, as consistent as other findings, revealed that predictors of early mortality included no history of HIV testing [53], low baseline CD4 count[19, 54, 55], advanced WHO clinical stage [22, 55], immunologic failure[56] and bedridden functional status [14, 19, 22]. Such patients with low CD4 count, advanced WHO clinical stage,

immunologic failure and bedridden functional status are vulnerable to advanced stage of disease and subsequently death [22]. Additionally, patients who had no history of HIV testing could be diagnosed late, and rapidly progress to advanced stage of the HIV/AIDS[53]. This particularly calls for earlier HIV diagnosis and timely initiation of ART, and generally cues consolidation of the HIV care continuum to diminish early HIV-related mortality[19]. In the present study, it is very surprising that patients with fair or good adherence has less probability of dying than those HIV patients with good adherence, and this needs further study. Despite the development of significant immunological or clinical failure, only 29 (0.9%) patients were switched to second line ART drugs, as explained in a previous study[54] that reported 6 (0.2%) patients were switched to second line ART drugs.

The study should be interpreted in light of the following strengths and limitations. The study included all age groups, very large sample and long follow up times (since the commencement of ART history), and these increase the power to detect differences in mortality by the study variables. In addition, the study participants involved in the current study area were from different socio-demographic characteristics. There are a number of HIV-infected people from Gambella, a regional state where the highest prevalence of HIV (6.5%) was recorded. On the other hand, majority of people were from Oromiya regional state, where the prevalence of HIV is similar (1.2–2%) to the other regional states of the nation. A considerable number of people were also attending the HIV clinic from a refugee camp located near Jimma.

However, the following limitations should be taken in to consideration: (1) being a single reference center may not reflect the situation of a whole country; (2) the CI of mortality might slightly be affected, as outcome status of 32 patients (2 children and 30 adults) was not recorded; (3) there might be a misclassification bias of deaths among discontinued patients; (4) the intention-to-treat analysis may underestimate survival functions since all discontinued patients were assumed dead; (5) The data for analysis used date back to 2015, and this did not include data after the *'test and treat'* strategy has been initiated; and (6) the association of some important variables such HIV-related stigma that has significant impact in the cascade of HIV care [57] was not assessed due to retrospective nature of the study design.

Conclusions

The magnitude of mortality was considerable (21.7 deaths per 1000 person-years), and majority of deaths (89%) occurred within 24 months of ART follow-up; however, the annual rate of mortality has been decreasing significantly. Thus, to retain patients long with a favourable quality of life, a thoughtful consideration should be given to the early HIV care services targeting to the above-mentioned predictors. Predictors of early mortality were also predictors of the overall mortality even in the intention-to-treat analysis. This suggests that applying interventions focusing on these predictors will reduce not only the death of patients attending ART care but also those who had discontinued.

Acknowledgments

We acknowledge Jimma University Teaching Hospital for providing access to the data. This study was conducted for the partial fulfilment of a PhD in Public Health at Faculty of Medicine, Nursing and Health Sciences, Flinders University. We acknowledge Australian Government Research Training Program Scholarship for supporting the PhD program. The scholarship provider had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors did not receive any specific grant for this research.

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Annex 3.11: Letter of introduction to HIV patients, HIV care providers, community advocates and program managers

Re: Mr Hailay Abrha Gesesew's Research

Letter of introduction to HIV patient participants

This letter is to introduce Hailay Abrha Gesesew who is a research higher degree (PhD) student at Flinders University, Australia. He is undertaking a research that aimed to explore the barriers, facilitators and ways to improve HIV care in Ethiopia. He will be most grateful if you would volunteer to assist in this project, by granting an interview that covers certain aspects of this topic. A maximum of 60 minutes on one occasion would be required.

Any information provided will strictly be kept confidential and none of the participants will be individually identifiable in the resulting output— thesis, report or other publications. You are, of course, entirely free to stop your participation at any time or to decline to answer particular questions.

Once you provide your consent, Hailay will record the interview. Your name or identity is not revealed, and the recording will not be made available to any other person. As an acknowledgement for your time he is offering participants a $35 cash. If you are willing to participate, Hailay is waiting you in room number _____ (to be filled after arranging on the site).

Should you have any enquiries concerning this project, please do not hesitate to contact me on +61(08) 7221 8417, or e-mail lillian.mwanri@flinders.edu.au

Thank you for your attention and assistance.

Yours sincerely

Dr Lillian Mwanri (MD, FAFPHM, PhD), Principal Supervisor

Re: Mr Hailay Abrha Gesesew's Research

Letter of introduction to HIV care provider participants

This letter is to introduce Hailay Abrha Gesesew who is a research higher degree (PhD) student at Flinders University, Australia. He will produce his student card, which carries a photograph, as proof of identity. He is conducting a research that aimed to explore the barriers, facilitators and ways to improve HIV care in Ethiopia. He will be most grateful if you would volunteer to assist in this project, by granting an interview that covers certain aspects of this topic. About 45-60 minutes on one occasion would be required.

Any information provided will strictly be kept confidential and none of the participants will be individually identifiable in the resulting output— thesis, report or other publications. You are, of course, entirely free to stop your participation at any time or to decline to answer particular questions.

He intends to record the interview on condition that your name or identity is not revealed, and the recording will not be made available to any other person. As an acknowledgement for your time he is offering participants a $35 cash. If you are willing to participate, please contact Hailay via +251913819135, or e-mail gese0002@flinders.edu.au.

Should you have any enquiries concerning this project, please do not hesitate to contact me on +61(08) 7221 8417, or e-mail lillian.mwanri@flinders.edu.au

Thank you for your attention and assistance.

Yours sincerely

Dr. Lillian Mwanri (MD, FAFPHM, PhD), Principal Supervisor

Re: Mr Hailay Abrha Gesesew's Research

Letter of introduction to advocate/ member of community participants

This letter is to introduce Hailay Abrha Gesesew who is a research higher degree (PhD) student at Flinders University, Australia. He will produce my student card, which carries a photograph, as proof of identity. He is conducting a research that aimed to explore the barriers, facilitators and ways to improve HIV care in Ethiopia. He will be most grateful if you would volunteer to assist in this project, by granting an interview that covers certain aspects of this topic. About 45-60 minutes on one occasion would be required.

Any information provided will strictly be kept confidential and none of the participants will be individually identifiable in the resulting output— thesis, report or other publications. You are, of course, entirely free to stop your participation at any time or to decline to answer particular questions.

He intends to record the interview after seeking your consent on condition that your name or identity is not revealed. The recording will not be made available to any other person. As an acknowledgement for your time he is offering participants a $30 cash. If you are willing to participate, please contact Hailay via +251913819135, or e-mail gese0002@flinders.edu.au.

Should you have any enquiries concerning this project, please do not hesitate to contact me on +61(08) 7221 8417, or e-mail lillian.mwanri@flinders.edu.au

Thank you for your attention and assistance.

Yours sincerely

Dr. Lillian Mwanri (MD, FAFPHM, PhD), Principal Supervisor

Re: Mr Hailay Abrha Gesesew's Research

Letter of introduction to HIV care system administrator participants

This letter is to introduce Hailay Abrha Gesesew who is a research higher degree (PhD) student at Flinders University, Australia. He will produce his student card, which carries a photograph, as proof of identity. He is conducting a research that aimed to explore the barriers, facilitators and ways to improve HIV care in Ethiopia. He will be most grateful if you would volunteer to assist in this project, by granting an interview that covers certain aspects of this topic. About 45-60 minutes on one occasion would be required.

Any information provided will strictly be kept confidential and none of the participants will be individually identifiable in the resulting output— thesis, report or other publications. You are, of course, entirely free to stop your participation at any time or to decline to answer particular questions.

As he intends to record the interview, he will seek your consent, to record the interview, to use the recording on condition that your name or identity is not revealed. The recording will not be made available to any other person. As an acknowledgement for your time he is offering participants a $35 cash. If you are willing to participate, please contact Hailay via +251913819135, or e-mail gese0002@flinders.edu.au.

Should you have any enquiries concerning this project, please do not hesitate to contact me on +61(08) 7221 8417, or e-mail lillian.mwanri@flinders.edu.au

Thank you for your attention and assistance.

Yours sincerely

Dr. Lillian Mwanri (MD, FAFPHM, PhD), Principal Supervisor

Annex 3.12: Information sheet to HIV patients, HIV care providers, community advocates and program managers

Information sheet to HIV patient participants

Title: HIV PATIENTS', HIV CARE PROVIDERS', COMMUNITIES', AND HIV CARE ADMINISTRATORS' PERSPECTIVES ON HIV CARE CASCADES IN ETHIOPIA

Investigator:

Hailay Gesesew, Discipline of Public Health, Flinders University, Phone: +6147002 0884 or +251913819135

Description of the study:

This study aims to explore the perspectives and experiences of the HIV patients, HIV-care providers, advocates/ members of communities, and health care system administrators on barriers, facilitators and ways to improve the HIV care continuum. The involvement of study participants is totally voluntarily. This study will be carried out with ethical approval from Flinders Social and Behavioral Ethics Committee (Australia), and Jimma University College of Health Sciences and as well as with the permission from Jimma university Teaching Hospital and Jimma Health center.

Purpose of the study:

This study aims to explore barriers, facilitators, and ways to improve HIV care in Ethiopia using the perspective of HIV patients, HIV-care providers, advocates/ members of communities, and health care system administrators.

What will I be asked to do?

You are invited to attend a one-on-one interview with the researcher who will ask you a few questions about your views, perceptions and experiences towards the HIV care in Ethiopia. The interview will take about 45-60 minutes. The interview will be recorded using a digital voice recorder to help with looking at the results. Once recorded, the interview will be transcribed (typed-up) and stored as a computer file and then destroyed once the results have been finalised. This is voluntary.

What benefit will I gain from being involved in this study?

The sharing of your perspectives will improve the planning and implementation of future programs about the HIV care. We are very keen to deliver a service and resources which are as useful as possible to people

Will I be identifiable by being involved in this study?

Your name is not needed and you will be anonymous. The voice file will be destroyed once the interview has been transcribed and saved as a file. Any identifying information will be removed and the typed-up file stored on a password-protected computer that only the principal researcher will have access to. Your information will be treated with the strictest confidence and no identifying information will be published. In addition, it will

remain confidential and will not be shared to any party without your knowledge or consent. However, complete anonymity cannot be guaranteed given the involvement of the ART nurse / physician.

Are there any risks or discomforts if I am involved?

The investigator anticipates no risks from your involvement in this study. This study is completely separate to the service you are receiving, and thus, your participation will not affect your service. If you have any concerns regarding any risks or discomforts, please raise them with the researcher. If you need counselling, you can contact Mr/s.(TBD) or Dr (TBD) in Room No (TBD) in this building.

How do I agree to participate?

Your participation is voluntary. You could tell us your decision within 30 minutes after receiving services. If you are willing to participate, please contact the interviewer in Room No (TBD) in this building. You may answer 'no comment' or refuse to answer any questions and you are free to withdraw from the interview at any time without effect or consequences. A consent form accompanies this information sheet. If you agree to participate please read and sign the form.

How will I receive feedback?

The participants will not get direct feedback. However, the summary report of the project will be disseminated to the Jimma University Teaching Hospital and Jimma Health Center through which other facilities, institutions and interested parties can access the report too. The study will also be published in different journals or conference proceedings and presented during different annual conferences.

Many thanks for taking the time to read this information sheet and we hope that you will accept our invitation to be involved.

Thank you for taking the time to read this information sheet and we hope that you will accept our invitation to be involved.

This research project has been approved by the Flinders University Social and Behavioural Research Ethics Committee (Project number 7698 here following approval). For more information regarding ethical approval of the project the Executive Officer of the Committee can be contacted by telephone on 8201 3116, by fax on 8201 2035 or by email human.researchethics@flinders.edu.au

Information sheet to the HIV care provider participants

Title: HIV patients', HIV care providers', communities', and HIV care administrators' perspectives on HIV care and treatment in Ethiopia

Investigator:

Hailay Gesesew, Discipline of Public Health, Flinders University, Phone: +6147002 0884 or +251913819135

Description of the study:

This study aims to explore the perspectives and experiences of the HIV patients, HIV-care providers, advocates/ members of communities, and health care system administrators on barriers, facilitators and ways to improve the HIV care continuum. Participants will be involved on voluntarily basis. This study will be carried out with ethical approval from Flinders Social and Behavioral Ethics Committee (Australia), and Jimma University College of Health Sciences and as well as with the permission from Jimma university Teaching Hospital and Jimma Health center.

Purpose of the study:

This study aims to explore barriers, facilitators, and ways to improve the HIV care cascades in Ethiopia using the perspective of HIV patients, HIV-care providers, advocates/ members of communities, and health care system administrators.

What will I be asked to do?

You are invited to attend a one-on-one interview with the researcher who will ask you a few questions about your views, perceptions and experiences towards the HIV care in Ethiopia. The interview will take about 45-60 minutes The interview will be recorded using a digital voice recorder to help with looking at the results. Once recorded, the interview will be transcribed (typed-up) and stored as a computer file and then destroyed once the results have been finalised. This is voluntary.

What benefit will I gain from being involved in this study?

The sharing of your perspectives will improve the planning and implementation of future programs about the HIV care. We are very keen to deliver a service and resources which are as useful as possible to people

Will I be identifiable by being involved in this study?

Your name is not needed and you will be anonymous. The voice file will be destroyed once the interview has been transcribed and saved as a file. Any identifying information will be removed and the typed-up file stored on a password-protected computer that only the principal researcher will have access to.

Are there any risks or discomforts if I am involved?

The investigator anticipates no risks from your involvement in this study. If you have any concerns regarding any risks or discomforts, please raise them with the researcher.

How do I agree to participate?

Your participation is voluntary. You may answer 'no comment' or refuse to answer any questions and you are free to withdraw from the interview at any time without effect or consequences. A consent form accompanies this information sheet. If you agree to participate please read and sign the form.

How will I receive feedback?

The participants will not get direct feedback provided but they have a choice to receive summary reports or debriefing following the interview. The summary report of the project will be disseminated to the Jimma University Teaching Hospital and Jimma Health Center through which other facilities, institutions and interested parties can access the report too. The study will also be published in different journals or conference proceedings and presented during different annual conferences.

Thank you for taking the time to read this information sheet and we hope that you will accept our invitation to be involved.

This research project has been approved by the Flinders University Social and Behavioural Research Ethics Committee (Project number 7698 here following approval). For more information regarding ethical approval of the project the Executive Officer of the Committee can be contacted by telephone on 8201 3116, by fax on 8201 2035 or by email human.researchethics@flinders.edu.au

Information sheet to community representative participants

Title: HIV patients', HIV care providers', communities', and HIV care administrators' perspectives on HIV care and treatment in Ethiopia

Investigator:

Hailay Gesesew, Discipline of Public Health, Flinders University, Phone: +6147002 0884 or +251913819135

Description of the study:

This study aims to explore the perspectives and experiences of the HIV patients, HIV-care providers, advocates/ members of communities, and health care system administrators on barriers, facilitators and ways to improve the HIV care continuum. Participation of study participants is on voluntarily basis. This study will be carried out with ethical approval from Flinders Social and Behavioral Ethics Committee (Australia), and Jimma University College of Health Sciences and as well as with the permission from Jimma university Teaching Hospital and Jimma Health center.

Purpose of the study:

This study aims to explore barriers, facilitators, and ways to improve the HIV care cascades in Ethiopia using the perspective of HIV patients, HIV-care providers, advocates/ members of communities, and health care system administrators.

What will I be asked to do?

You are invited to attend a one-on-one interview with the researcher who will ask you a few questions about your views, perceptions and experiences towards the HIV care in Ethiopia. The interview will take about 45-60 minutes The interview will be recorded using a digital voice recorder to help with looking at the results. Once recorded, the interview will be transcribed (typed-up) and stored as a computer file and then destroyed once the results have been finalised. This is voluntary.

What benefit will I gain from being involved in this study?

The sharing of your perspectives will improve the planning and implementation of future programs about the HIV care. We are very keen to deliver a service and resources which are as useful as possible to people

Will I be identifiable by being involved in this study?

Your name is not needed and you will be anonymous. The voice file will be destroyed once the interview has been transcribed and saved as a file. Any identifying information will be removed and the typed-up file stored on a password-protected computer that only the principal researcher will have access to.

Are there any risks or discomforts if I am involved?

The investigator anticipates no risks from your involvement in this study. If you have any concerns regarding any risks or discomforts, please raise them with the researcher.

How do I agree to participate?

Your participation is voluntary. You may answer 'no comment' or refuse to answer any questions and you are free to withdraw from the interview at any time without effect or consequences. A consent form accompanies this information sheet. If you agree to participate please read and sign the form.

How will I receive feedback?

The participants will not get direct feedback provided but they have a choice to receive summary reports or debriefing following the interview. The summary report of the project will be disseminated to the Jimma University Teaching Hospital and Jimma Health Center through which other facilities, institutions and interested parties can access the report too. The study will also be published in different journals or conference proceedings and presented during different annual conferences.

Thank you for taking the time to read this information sheet and we hope that you will accept our invitation to be involved.

This research project has been approved by the Flinders University Social and Behavioural Research Ethics Committee (Project number 7698 here following approval). For more information regarding ethical approval of the project the Executive Officer of the Committee can be contacted by telephone on 8201 3116, by fax on 8201 2035 or by email human.researchethics@flinders.edu.au

Information sheet to HIV care system administrator participants

Title: HIV patients', HIV care providers', communities', and HIV care administrators' perspectives on HIV care and treatment in Ethiopia

Investigator:

Hailay Gesesew, Discipline of Public Health, Flinders University, Phone: +6147002 0884 or +251913819135

Description of the study:

This study aims to explore the perspectives and experiences of the HIV patients, HIV-care providers, advocates/ members of communities, and health care system administrators on barriers, facilitators and ways to improve the HIV care continuum. Participation of study participants is on voluntarily basis. This study will be carried out with ethical approval from Flinders Social and Behavioral Ethics Committee (Australia), and Jimma University College of Health Sciences and as well as with the permission from Jimma university Teaching Hospital and Jimma Health center.

Purpose of the study:

This study aims to explore barriers, facilitators, and ways to improve the HIV care cascades in Ethiopia using the perspective of HIV patients, HIV-care providers, advocates/ members of communities, and health care system administrators.

What will I be asked to do?

You are invited to attend a one-on-one interview with the researcher who will ask you a few questions about your views, perceptions and experiences towards the HIV care in Ethiopia. The interview will take about 45-60 minutes The interview will be recorded using a digital voice recorder to help with looking at the results. Once recorded, the interview will be transcribed (typed-up) and stored as a computer file and then destroyed once the results have been finalised. This is voluntary.

What benefit will I gain from being involved in this study?

The sharing of your perspectives will improve the planning and implementation of future programs about the HIV care. We are very keen to deliver a service and resources which are as useful as possible to people

Will I be identifiable by being involved in this study?

Your name is not needed and you will be anonymous. The voice file will be destroyed once the interview has been transcribed and saved as a file. Any identifying information will be removed and the typed-up file stored on a password-protected computer that only the principal researcher will have access to.

Are there any risks or discomforts if I am involved?

The investigator anticipates no risks from your involvement in this study. If you have any concerns regarding any risks or discomforts, please raise them with the researcher.

How do I agree to participate?

Your participation is voluntary. You may answer 'no comment' or refuse to answer any questions and you are free to withdraw from the interview at any time without effect or consequences. A consent form accompanies this information sheet. If you agree to participate please read and sign the form.

How will I receive feedback?

The participants will not get direct feedback provided but they have a choice to receive summary reports or debriefing following the interview. The summary report of the project will be disseminated to the Jimma University Teaching Hospital and Jimma Health Center through which other facilities, institutions and interested parties can access the report too. The study will also be published in different journals or conference proceedings and presented during different annual conferences.

Thank you for taking the time to read this information sheet and we hope that you will accept our invitation to be involved.

This research project has been approved by the Flinders University Social and Behavioural Research Ethics Committee (Project number 7698 here following approval). For more information regarding ethical approval of the project the Executive Officer of the Committee can be contacted by telephone on 8201 3116, by fax on 8201 2035 or by email human.researchethics@flinders.edu.au

Annex 3.13: Consent form to HIV patients, HIV care providers, community advocates and program manager

Consent Form for Observation of Professional Activity- HIV patients

HIV patients', HIV care providers', communities', and HIV care administrators' perspectives on HIV care cascades in Ethiopia

I, being 18+ years old, hereby consent to participate as requested in the letter of introduction for the research project on HIV patients', HIV care providers', communities', and HIV care administrators' perspectives on HIV care and treatment in Ethiopia.

1. I have read the information provided.
2. Details of procedures and any risks have been explained to my satisfaction.
3. I agree to audio/video recording of my information and participation.
4. I should retain a copy of the Information Sheet and Consent Form for future reference.
5. I understand that:
    1. I may not directly benefit from taking part in this research.
    2. While the information gained in this study will be published as explained, I will not be identified, and individual information will remain confidential.
    3. Whether I participate or not, or withdraw after participating, will have no effect on any treatment or service that is being provided to me.
    4. I may ask that the recording be stopped at any time, and that I may withdraw at any time from the session or the research without disadvantage.
    5. While information provided will be treated with the strictest confidence and no identifying information will be published, complete anonymity cannot be guaranteed given the involvement of the ART nurse / physician.
6. I agree/do not agree to the tape/transcript being made available to other researchers who are not members of this research team, but who are judged by the research team to be doing related research, on condition that my identity is not revealed.

Participant's Name …… Signature.....Date.....

I certify that I have explained the study to the volunteer and consider that she/he understands what is involved and freely consents to participation.

Researcher's name.....

Researcher's signature.....Date.....

Consent Form for Observation of Professional Activity- Health Workers

HIV patients', HIV care providers', communities', and HIV care administrators' perspectives on HIV care and treatment in Ethiopia

I, being 18+ years old, hereby consent to participate as requested in the letter of introduction for the research project on HIV patients', HIV care providers', communities', and HIV care administrators' perspectives on HIV care and treatment in Ethiopia

1. I have read the information provided.
2. Details of procedures and any risks have been explained to my satisfaction.
3. I agree to audio/video recording of my information and participation.
4. I should retain a copy of the Information Sheet and Consent Form for future reference.
5. I understand that:
    a. I may not directly benefit from taking part in this research.
    b. While the information gained in this study will be published as explained, I will not be identified, and individual information will remain confidential.
    c. Whether I participate or not, or withdraw after participating, will have no effect on my carrier.
    d. I may ask that the recording be stopped at any time, and that I may withdraw at any time from the session or the research without disadvantage.
6. I agree/do not agree to the tape/transcript being made available to other researchers who are not members of this research team, but who are judged by the research team to be doing related research, on condition that my identity is not revealed.

Participant's Name …… Signature.....Date.....

I certify that I have explained the study to the volunteer and consider that she/he understands what is involved and freely consents to participation.

Researcher's name.....

Researcher's signature.....Date.....

Consent Form for Observation of Professional Activity- Community Advocates

HIV patients', HIV care providers', communities', and HIV care administrators' perspectives on HIV care and treatment in Ethiopia

I, being 18+ years old, hereby consent to participate as requested in the letter of introduction for the research project on HIV patients', HIV care providers', communities', and HIV care administrators' perspectives on HIV care and treatment in Ethiopia.

I have read the information provided.

1. Details of procedures and any risks have been explained to my satisfaction.
2. I agree to audio/video recording of my information and participation.
3. I should retain a copy of the Information Sheet and Consent Form for future reference.
4. I understand that:
    a. I may not directly benefit from taking part in this research.
    b. While the information gained in this study will be published as explained, I will not be identified, and individual information will remain confidential.
    c. Whether I participate or not, or withdraw after participating, will have no effect on my carrier.
    d. I may ask that the recording be stopped at any time, and that I may withdraw at any time from the session or the research without disadvantage.
5. I agree/do not agree to the tape/transcript being made available to other researchers who are not members of this research team, but who are judged by the research team to be doing related research, on condition that my identity is not revealed.

Participant's Name …… Signature.....Date.....

I certify that I have explained the study to the volunteer and consider that she/he understands what is involved and freely consents to participation.

Researcher's name.....

Researcher's signature.....Date.....

Consent Form for Observation of Professional Activity- HIV Care Program Managers

HIV patients', HIV care providers', communities', and HIV care administrators' perspectives on HIV care and treatment in Ethiopia

I, being 18+ years old, hereby consent to participate as requested in the letter of introduction for the research project on HIV patients', HIV care providers', communities', and HIV care administrators' perspectives on HIV care and treatment in Ethiopia

1. I have read the information provided.
2. Details of procedures and any risks have been explained to my satisfaction.
3. I agree to audio/video recording of my information and participation.
4. I should retain a copy of the Information Sheet and Consent Form for future reference.
5. I understand that:
    a. I may not directly benefit from taking part in this research.
    b. While the information gained in this study will be published as explained, I will not be identified, and individual information will remain confidential.
    c. Whether I participate or not, or withdraw after participating, will have no effect on my carrier.
    d. I may ask that the recording be stopped at any time, and that I may withdraw at any time from the session or the research without disadvantage.
6. I agree/do not agree to the tape/transcript being made available to other researchers who are not members of this research team, but who are judged by the research team to be doing related research, on condition that my identity is not revealed.

Participant's Name ……. Signature.....Date.....

I certify that I have explained the study to the volunteer and consider that she/he understands what is involved and freely consents to participation.

Researcher's name .....

Researcher's signature.....Date.....

Annex 3.14: Interview guide for HIV patients, HIV care providers, community advocates and program managers

HIV patients', HIV care providers', communities', and health care system administrators' perspectives on HIV care cascades in Ethiopia

In-depth Interview Guide for

A. HIV patients

I, being 18+ years old, hereby consent to participate as requested in the letter of introduction for the research project on HIV CARE CONTINUUM

1. I have read the information provided.
2. Details of procedures and any risks have been explained to my satisfaction.
3. I agree to audio/video recording of my information and participation.
4. I should retain a copy of the *Information Sheet* and *Consent Form* for future reference.
5. I understand that:
    a. I may not directly benefit from taking part in this research.
    b. While the information gained in this study will be published as explained, I will not be identified, and individual information will remain confidential.
    c. Whether I participate or not, or withdraw after participating, will have no effect on any treatment or service that is being provided to me.
    d. I may ask that the recording be stopped at any time, and that I may withdraw at any time from the session or the research without disadvantage.
6. I agree/do not agree to the tape/transcript being made available to other researchers who are not members of this research team, but who are judged by the research team to be doing related research, on condition that my identity is not revealed.

Participant's signature.....Date.....

I certify that I have explained the study to the volunteer and consider that she/he understands what is involved and freely consents to participation.

Researcher's name .....

Researcher's signature.....Date.....

Target audience – HIV patients attending ART clinic at JUTH and JHC

QUESTIONS

1. **Demographic** information
    1.1. Institution: 1. Hospital 2. Health centre
    1.2. Sex: 1. Male 2. Female
    1.3. Age: ____ years
    1.4. Age at first HIV diagnosis: ____ years
    1.5. Religion: 1. Orthodox 2. Catholic 3. Muslim 4. Protestant 9. Other _____
    1.6. Ethnicity: 1. Oromo 2. Amhara 3. Guragie 9. Other _____
    1.7. Education: 1. Cannot read and write 2. Read and write (informal) 3. Literate (a. College certificate b. College diploma c. University degree and above)
    1.8. Occupation: 1. Farmer 2. Housewife 3. Merchant 4. 9. Other _____
    1.8 Marital status: 1. Never married 2. Married (living together) 3. Married (not living together) 4. Divorced/widowed/separated

1.9 Estimated annual house hold income: _____ ETB

1.10 Residence: 1. Rural 2. Urban 3. Semi-urban

1.11 Number of persons living with (excluding you): _____

1.12 Number of children: _____

1.13 Average time to reach HIV clinic _____ minutes or _____hours

1.14 Time since diagnosis _____years

1.15 Time since on HIV treatment (antiretroviral therapy) _____years

1.16 History of missing appointments or total stoppage 1. Yes (___ times) 2. No

2. Participants' opinion regarding **HIV and care knowledge**
   - What are the ways of HIV transmission?
   - What misconceptions about ways of HIV transmission did you have before you diagnosed (and/or got HIV counselling)?
   - What health care services are available for HIV patients?
   - Did you know these before your diagnosis?
3. Participants' perspectives concerning **facilitators** to HIV care and treatment
   - Why are people tested for HIV?
   - Why are some patients get tested and diagnosed early while others are critically ill (low CD4 and/or WHO) during diagnosis?
     - What complications do you think if HIV is not diagnosed early?
     - What benefits do you think HIV patients get if they start HIV medication?
     - What other reasons do encourage for people to be diagnosed early?
   - What do you think that a person should do once diagnosed with HIV?
     - Why are some patients immediately linked to HIV care and treatment while others are not?
     - Did you think people believe there is life after HIV? Any experience?
     - Do you think people know there is a medication (ART) for HIV? How is your experience?
     - Whom do you think are eligible for ART?
     - Do you think governmental or non-governmental organizations (or volunteer individuals) facilitate the link for HIV patients to start HIV medication?
     - Do you think the community health professionals such as health extension workers or health development armies help in linking with HIV care and treatment?
   - What motivates people to keep taking ART?
     - What benefits people gain from ART?

- How is the HIV care service encourages/discourages to stay in ART care? Health-care providers' interaction with HIV patients, frequency of appointment, and after hours service availability

4. Participants' view to **barriers** for HIV care and treatment
   - Why some HIV patients diagnosed late?
   - How does your community react to HIV patients? How are they treated in social events such as wedding, funeral, 'Idir', school, market, etc.? Do you think this affect for others not to get tested early?
   - What other barriers do you think for early HIV diagnosis or HIV testing?
     - Lack of knowledge, access, fear of diagnosis
   - Why are some patients not immediately linked to HIV care and treatment?
   - What is the belief/perception to ART in the community? (ART improves health condition, increase survival, not for free, is poison, is against religion)
   - Any other options/places for treating HIV patients in your community?
   - What other barriers do you think for timely linkage?
     - Stigma, discrimination, lack of knowledge, access, lack of support, disclosure
   - After starting ART, why are patients miss their appointment or totally stop?
     - Is there any reason related to the medication?
     - What challenges do you or others face when taking ART?
     - How is the HIV care service encourages/discourages to stay in ART care? Health-care providers' interaction with HIV patients, Frequency of appointment, After hours service availability
     - What alternative options do you think they consider?
   - What other barriers do you think for ART retention?
     - Stigma, discrimination, lack of knowledge, access, lack of support,
5. Participants' opinion regarding **ways to improve** HIV care and treatment
   - What do you think the ways to improve early HIV diagnosis?
     - What should be done at
       - Your (patients), communities or Health care providers level?
     - How do you see the relevance, acceptance and confidentiality of
       - Self-HIV test? House-to-house HIV testing? HIV testing by community health workers (HEWs and HAD)?
   - What do you think the ways to improve immediate ART care linkage?
     - What do patients, communities or Health care providers should do?

- How do you see the relevance, acceptance, and confidentiality of community health worker visit? HIV positive peer support?
- Any thing that should be done with the traditional healers?

- What should be done to improve ART retention?
  - What do patients, communities or Health care providers should do?
  - How do you see the relevance, acceptance, and confidentiality if ART is to be accessed from health post? Community ART distribution?
  - What other activities does encourage ART retention? (Social support, awareness, reminders, after hours ART clinic opening)

B. HIV-care providers

I, being 18+ years old, hereby consent to participate as requested in the letter of introduction for the research project on HIV CARE CONTINUUM

1. I have read the information provided.
2. Details of procedures and any risks have been explained to my satisfaction.
3. I agree to audio/video recording of my information and participation.
4. I am aware that I should retain a copy of the Information Sheet and Consent Form for future reference.
5. I understand that:
   a. I may not directly benefit from taking part in this research.
   b. While the information gained in this study will be published as explained, I will not be identified, and individual information will remain confidential.
   c. Whether I participate or not, or withdraw after participating, will have no effect on any treatment or service that is being provided to me.
6. I may ask that the recording be stopped at any time, and that I may withdraw at any time from the session or the research without disadvantage.
7. I agree/do not agree to the tape/transcript being made available to other researchers who are not members of this research team, but who are judged by the research team to be doing related research, on condition that my identity is not revealed.

Participant's signature.....Date.....

I certify that I have explained the study to the volunteer and consider that she/he understands what is involved and freely consents to participation.

Researcher's name .....

Researcher's signature.....Date.....

Target audience – HIV care providers working in ART clinics at JUTH and JHC

QUESTIONS

1. **Demographic** information
   1.1. Institution: 1. Hospital 2. Health centre
   1.2. Sex: 1. Male 2. Female
   1.3. Age: ____ years
   1.4. Religion: 1. Orthodox 2. Catholic 3. Muslim 4. Protestant 9. Other _____
   1.5. Education: 1. College certificate 2. College diploma 3. University degree and above
   1.6. Profession: 1. MD 2. HO 3. Nurse 4. Pharmacist 5. Counsellor 9. Other _____
   1.7. Total service year: ___ years
   1.8. Service year in HIV clinic: ___years
2. **General** information
   - What is your experience with the HIV care and treatment?
   - What is the purpose of ART program?
   - How is ART valued in improving the quality and survival of HIV patients?
3. HIV care providers' perspectives concerning **facilitators** to HIV care and treatment
   - How is the trend of HIV testing looks like?
   - What reasons do encourage for people to be diagnosed early?
   - What HIV testing services are available for the community?
   - Is there a link? Why are some patients linked to HIV care and treatment while others not?
   - What patient, community or health care system related facilitators are there for timely HIV care?
   - What other organizations/individuals will help for HIV patients to enrol in HIV care?
   - What are the roles of community health professionals (health extension workers or health development armies) to HIV testing or HIV care linkage?
   - What motivates people to keep taking ART?
   - What benefits do you observe of the ART for HIV patients?
   - How is the HIV care service encourages/discourages to stay in ART care?
   - What other patient, community or health care system related facilitators are there for ART retention?
4. HIV care providers' view to **barriers** for HIV care and treatment
   - Why are HIV patients diagnosed late?
     - Patient, community or health care system related barriers
   - How is the trend of HIV-related stigma and discrimination looks like? What negative influences in HIV testing does it have?
   - What other barriers do you think for early HIV diagnosis or HIV testing?

    - Lack of knowledge, access, fear of diagnosis
- Why are some patients not immediately linked to HIV care and treatment?
- What are the negative or positive beliefs to ART in the community? (ART improves health condition, increase survival, not for free, is poison, is against religion)
- What alternative option is considered by the patients to treat HIV?
- What other barriers do you think for timely linkage?
    - Stigma, discrimination, lack of knowledge, access, lack of support, disclosure
- After starting ART, why are patients miss their appointment or totally stop?
    - Patient, community, medication related, HIV care service related, alternative options (traditional medicine)?
- What other barriers do you think for ART retention?
    - Stigma, discrimination, lack of knowledge, access, lack of support,

5. HIV care providers' opinion regarding **ways to improve** HIV care and treatment
    - What do you think the ways to improve early HIV diagnosis?
        - What should be done at
            - Patients, communities, Health care providers, or policy level?
        - How do you see the relevance, acceptance, feasibility, and confidentiality of
            - Self-HIV test? House-to-house HIV testing? HIV testing by community health workers (HEWs and HAD)?
    - What do you think the measures/programs to improve immediate ART care linkage?
        - What do patients, communities or Health care providers should do?
        - How do you see the relevance, acceptance, feasibility, and confidentiality of community health worker visit? HIV positive peer support?
        - Any thing that should be done with the traditional healers?
    - What do you think should be done to improve ART retention?
        - What do patients, communities or health care providers should do?
        - How should LTFU patients be traced?
        - How do you see the relevance, acceptance, and confidentiality if ART is to be accessed from health post? Community ART distribution?
        - What other activities does encourage ART retention? (Social support, awareness, reminders, after hours ART clinic opening)

C. Advocates/ members of community

I, being 18+ years old, hereby consent to participate as requested in the letter of introduction for the research project on HIV CARE CONTINUUM

1. I have read the information provided.
2. Details of procedures and any risks have been explained to my satisfaction.
3. I agree to audio/video recording of my information and participation.
4. I should retain a copy of the Information Sheet and Consent Form for future reference.
5. I understand that:
    a. I may not directly benefit from taking part in this research.
    b. While the information gained in this study will be published as explained, I will not be identified, and individual information will remain confidential.
    c. Whether I participate or not, or withdraw after participating, will have no effect on any treatment or service that is being provided to me.
6. I may ask that the recording be stopped at any time, and that I may withdraw at any time from the session or the research without disadvantage.

I agree/do not agree to the tape/transcript being made available to other researchers who are not members of this research team, but who are judged by the research team to be doing related research, on condition that my identity is not revealed.

Participant's signature.....Date.....

I certify that I have explained the study to the volunteer and consider that she/he understands what is involved and freely consents to participation.

Researcher's name .....

Researcher's signature.....Date.....

Target audience - PLHIV associations, religious groups, *Idirs*, women's groups, community health extension workers (HEWs), health development army (HDA)

QUESTIONS

1. **Demographic** information
    1.1. Category: _____
    1.2. Sex: 1. Male 2. Female
    1.3. Age: ____ years
    1.4. Religion: 1. Orthodox 2. Catholic 3. Muslim 4. Protestant 9. Other _____
    1.5. Education: 1. Cannot read and write 2. Read and write (informal) 3. Literate (a. College certificate b. College diploma c. University degree and above)
    1.6. Occupation: 1. Farmer 2. Housewife 3. Community health worker 9. Other _____
    1.7. Marital status: 1. Never married 2. Married (living together) 3. Married (not living together) 4. Divorced/widowed/separated
2. **General** information
    2.1. In your view, what challenges are there when having an HIV positive partner or relative?

2.2. What misconceptions to HIV or HIV patients are there in the community?
2.3. What is your experience with supporting HIV patients?
2.4. What support is expected from advocates/ members of a community to HIV patients?
2.5. What services are available for HIV patients in the hospital or health center?

3. Advocates or community members' perspectives on **facilitators** to HIV care and treatment
   - How is the habit of knowing one's HIV status in your community?
   - Why do you think people get tested for HIV?
   - What reasons do encourage for people to be diagnosed early?
   - What HIV testing services are available for the community? Do most people aware of these services?
   - Why are some patients linked to HIV care & treatment while others not?
   - What is your role in facilitating HIV-diagnosed patients to get care & treatment timely?
   - What are the roles of community health professionals (health extension workers or health development armies) to HIV testing or HIV care linkage?
   - What other organizations/individuals will help for HIV patients to enrol in HIV care?
   - What patient/health system factors do encourage to early diagnosis & timely linkage?
   - Once started, what motivates people to keep taking ART?
   - Why are patients taking ART? Their perception? Your perception?
   - How is ART valued in the community? In Religious institutions? Or other places?
   - What benefits do you observe of the ART for HIV patients?
   - How is the HIV care service encourages/discourages to stay in ART care?
   - What other patient, community or health care system related facilitators are there for ART retention?
4. Advocates or community members' view to **barriers** for HIV care and treatment
   - How does the community treat HIV patients in social events such as wedding, funeral, 'Idir', school, market, etc.? Do you think this affect the HIV testing habit in the general community?
   - Do you think early HIV diagnosis is helpful for the patient? How?
   - Why are HIV patients diagnosed late?
     - Patient, community, health care system related barriers
   - Why are some patients not immediately linked to HIV care and treatment?
   - What are the negative or positive beliefs to ART in the community? (ART improves health condition, increase survival, not for free, is poison, is against religion)
   - What alternative option is considered by the patients to treat HIV?

- What is your view to these alternative options? Do you recommend? How?
- What other barriers do you think for timely HIV care and treatment linkage?
    - Stigma, discrimination, lack of knowledge, access, lack of support, disclosure
- How does the community see HIV patients taking ART?
- Why are patients miss their appointment or totally stop ART?
    - Patient, community, medication related, HIV care service related, alternative options (traditional medicine)?

5. Advocates or community members' opinion regarding **ways to improve** HIV care and treatment
    - What do you think the ways to improve early HIV diagnosis?
        - What should be done at
            - Patients, communities, Health care providers, or other levels?
        - How should be your contribution to early HIV diagnosis?
        - Do you think self-HIV test is relevant, acceptable, and confidential? What about house-to-house HIV testing? HIV testing by community health workers (HEWs and HAD)?
    - What do you think the measures/programs to improve immediate ART care linkage?
        - What do patients, communities or Health care providers should do?
        - What is your role in linking HIV diagnosed patients to HIV care & treatment?
        - How do you see the relevance, acceptance, feasibility, and confidentiality of community health worker visit to support and link? HIV positive peer support?
        - Any thing that should be done with the traditional healers?
    - What do you think should be done to improve ART retention?
        - How should you contribute in tracing discontinued ART patients?
        - What do patients, communities or health care providers should do?
        - Do you think is helpful if ART is to be accessed from health post? How do you see the relevance, acceptance, and confidentiality it?
        - What about if ART is distributed through community?
        - What other activities does encourage ART retention? (Social support, awareness, reminders, after hours ART clinic opening)

D. Health Care System Administrators

I, being 18+ years old, hereby consent to participate as requested in the letter of introduction for the research project on HIV CARE CONTINUUM

1. I have read the information provided.
2. Details of procedures and any risks have been explained to my satisfaction.
3. I agree to audio/video recording of my information and participation.
4. I should retain a copy of the Information Sheet and Consent Form for future reference.
5. I understand that:
    a. I may not directly benefit from taking part in this research.
    b. While the information gained in this study will be published as explained, I will not be identified, and individual information will remain confidential.
    c. Whether I participate or not, or withdraw after participating, will have no effect on any treatment or service that is being provided to me.
6. I may ask that the recording be stopped at any time, and that I may withdraw at any time from the session or the research without disadvantage.

I agree/do not agree to the tape/transcript being made available to other researchers who are not members of this research team, but who are judged by the research team to be doing related research, on condition that my identity is not revealed.

Participant's signature.....Date.....

I certify that I have explained the study to the volunteer and consider that she/he understands what is involved and freely consents to participation.

Researcher's name .....

Researcher's signature.....Date.....

Target audience - MoH HIV expert, Federal HAPCO representative, Zonal HAPCO representative, Zonal and town health office representative, local NGOs working on HIV/AIDS care and support

QUESTIONS

1. **Demographic** information
    1.1. Institution: _____
    1.2. Sex: 1. Male 2. Female
    1.3. Age: ____ years
    1.4. Education: 1. College certificate 2. College diploma 3. University degree and above
    1.5. Profession: 1. MD 2. HO 3. Nurse 4. Pharmacist 5. Counsellor 9. Other _____
    1.6. Total service year: ___ years
    1.7. Service year in HIV sector/s: ___years
2. **General** information
    - What is your experience with the HIV care and treatment?
    - What services are provided for HIV patients at community and health facility level?
    - What is the purpose of ART program?
    - How is ART valued in improving the quality and survival of HIV patients?

- How is the trend of ART use and its benefit to the patients and community?

3. HIV care system administrators' perspectives concerning **facilitators** to HIV care and treatment
    - How is the trend of HIV testing looks like?
    - What reasons do encourage for people to be diagnosed early?
    - What HIV testing services are available for the community?
    - What new or innovative programs are planned to improve early HIV diagnosis?
    - Why are some patients linked to HIV care and treatment while others not?
    - What patient, community or health care system related facilitators are there for timely HIV care?
    - What is your (organization) role in helping patients to get a timely HIV care service?
    - What other organizations/individuals will help for HIV patients to enrol in HIV care?
    - What are the roles of community health professionals (health extension workers or health development armies) to HIV testing or HIV care linkage?
    - What are the facilitators for ART retention? What patient, community or health care system related facilitators are there for ART retention?
    - What benefits do you observe of the ART for HIV patients?
    - How is the HIV care service encourages/discourages to stay in ART care?
    - Are there policies or programs that facilitate the HIV care and treatment?
4. HIV care system administrators' view to **barriers** for HIV care and treatment
    - Why are HIV patients diagnosed late?
        - Patient, community or health care system related barriers
    - How is the trend of HIV-related stigma and discrimination looks like? What negative influences in HIV testing does it have?
    - What other barriers do you think for early HIV diagnosis or HIV testing?
        - Lack of knowledge, access, fear of diagnosis
    - Why are patients not immediately linked to HIV care and treatment?
    - What are the negative or positive beliefs to ART in the community? (ART improves health condition, increase survival, not for free, is poison, is against religion)
    - What alternative option is considered by the patients to treat HIV?
    - Do any other body or your organization assessed these options?
    - What other barriers do you think for timely linkage?
        - Stigma, discrimination, lack of knowledge, access, lack of support, disclosure

- What are barriers of attrition attributed to discontinuation—missed appointment or totally stop the medication?
    - Patient, community, medication related, HIV care service related, policy or program levels
- What other barriers do you think for ART retention?
    - Stigma, discrimination, lack of knowledge, access, lack of support,

5. HIV care system administrators' opinion regarding **ways to improve** HIV care and treatment
    - What do you think the ways to improve early HIV diagnosis?
        - What should be done at
            - Patients, communities, health care providers, or policy level?
        - How do you see the relevance, acceptance, feasibility, and confidentiality of the following new programs
            - Self-HIV test? House-to-house HIV testing? HIV testing by community health workers (HEWs and HAD)?
            - Do you recommend these programs to be scaled up to Ethiopia? What challenges and opportunities are there?
    - What do you think the measures/programs to improve immediate ART care linkage?
        - What do patients, communities or health care providers should do?
        - How do you see the relevance, acceptance, feasibility, and confidentiality of community health worker visit?
        - What activities are done to decrease the stigma and discrimination?
        - Any thing that should be done with the traditional healers?
    - What do you think should be done to improve ART retention?
        - What do patients, communities or health care providers should do?
    - How do you see the relevance, acceptance, and confidentiality Community ART distribution? Do you recommend these programs to be scaled up to Ethiopia? What challenges and opportunities are there?
    - How about ART service decentralization to health post? What challenges and opportunities are there?
    - What do you do if patients are forced to move from their places to other for longer periods due to civil conflict or war or drought? How can the patient be retained in the program?

- What other activities does encourage ART retention? (Social support, awareness, reminders, after hours ART clinic opening)

Annex 3.15: Email invitation to experts and researchers

Date: December 01, 2017

Re: Cordial invitation

Hello,

I hope you find this e-mail very well.

I am planning to prepare one day workshop about ***HIV Care Continuum in Southwest Ethiopia: Barriers and Solutions*** with group of HIV experts, practitioners and researchers. As HIV expert, I cordially invite you to participate in the workshop.

Where: **Central Jimma Hotel, Jimma**

When: **21 December 2017 at 9.00 am**.

I would be very happy if you confirm me your attendance before December 14, 2017.

Kind regards,

Hailay Abrha,

Department of Epidemiology, Jimma university (P: +251 (0) 98 850 0981)

Discipline of Public Health, Flinders University, Australia

Annex 3.16: Self-administered questionnaire for HIV experts- NGT workshop

Institution/Department: _____ Position: _____ Sex: ____ Age: _____

Rate the relevance, feasibility and acceptability of the following programs for improving HIV care and treatment from 1-3, and add your own solution/s on the space provided if any.

Solutions	1=Disagree; 2=Neutral; 3=Agree			
	Relevant	**Feasible**	**Acceptable**	**Justification**
Self-HIV testing (SHT)[43]				
House-to-House HIV testing (H2H)[44]				
Assigning Peer Educators with HEWs[45]				
ART in Health Post[46]				
ART in Private Clinics[47]				
Community ART Group (CAGs)[48]				
Filling Gaps in Law[49]				

43 SHT is a process whereby a person who wants to know one's HIV status collects a specimen, perform a test and interpret the result in private—this is a screening test and any positive result will be confirmed by a health worker.

44 H2H refers to conducting HIV testing in every house by HEWs or trained lay counselors—this process includes collecting a specimen, performing a test, interpreting the result and referral for further follow up test or linkage (if the result is positive).

45 Assigning peer educators with HEWs involves formally employing and assigning of peer educators (HIV+ persons disclosed themselves publicly) with HEWs (health extension workers) to teach the community about HIV, conduct HIV testing, linking into ART care and trace lost patients—Teach–test–link–trace strategy.

46 The provision of ART in health post by HEWs.

47 The provision of ART in private health clinics by the health workers employed in the clinic—ART will be provided for free from the government.

48 CAGs is a process whereby stable HIV+ persons (who disclose publicly) living in nearby places establish a group and take their medications turn by turn or in rotation. They choose a leader who arranges monthly meeting to count pills and check the overall ART adherence. The people on ART will be told to come to the clinic whenever they feel ill.

49 The need of law to suing an HIV+ man who doesn't disclose his status to his wife after repeated counselling since this prevents from timely engagement to HIV care (and vice versa), and prevent HIV transmission to child (if pregnant). Another scenario is the need of law to suing religious leaders or witch doctors who declare HIV cure while not--as this is a false witness and against law of the nation. In addition, if the religious leaders or witch doctors tell patients to throw the pills and if patients die or sick seriously as a result of this, he/she is responsible to the death or attempt, and this is against law of the nation.

Annex 3.17: Ethical approval from the Social and Behavioural Research Ethics Committee of the Flinders University for the Retrospective cohort study

7086 Approval Notice (Negligible Risk)

Human Research Ethics <human.researchethics@flinders.edu.au>

Thu 22/10/2015 11:34 AM

Dear Hailay

Your ethics application was considered by the Executive of the Social and Behavioural Research Ethics Committee (SBREC) at Flinders University and was granted approval. Your ethics approval notice can be found below.

APPROVAL NOTICE (Negligible Risk)

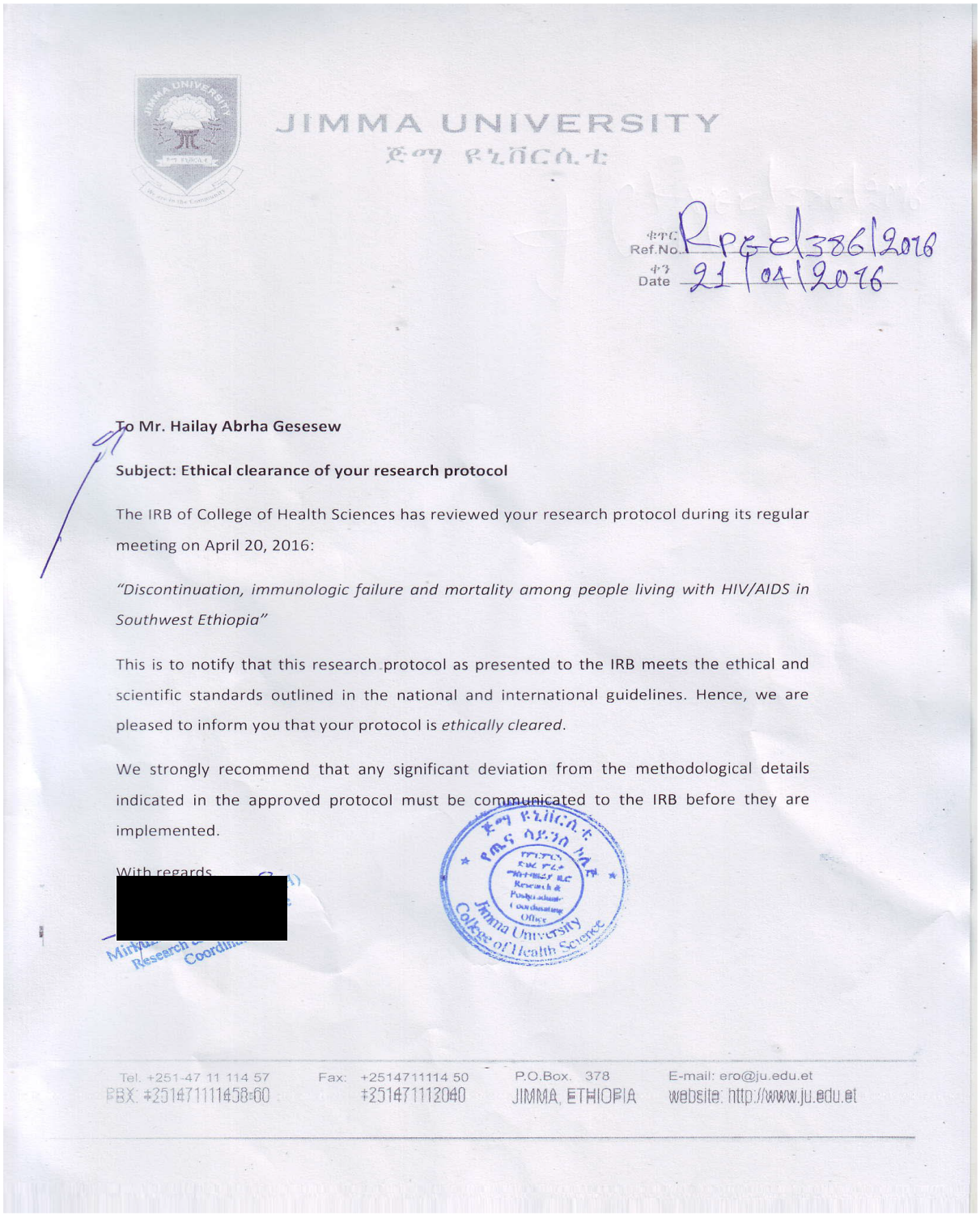
Principal Researcher:	Mr. Hailay Gesesew
Email:	gese0002@flinders.edu.au

Project Title:	Discontinuation, Immunologic Failure and Mortality among People Living with HIV/AIDS in Southwest Ethiopia

Project No.:	**7086**		Approval Date:	22 October 2015		Approval Expiry Date:	**29 September 2019**

The above proposed project fulfills the criteria for negligible risk research under chapter 2.1 (Risk and Benefit) of the *National Statement on Ethical Conduct in Human Research (March 2007)* and has been **approved** by the Executive out of session on the basis of the information contained in the application and its attachments.

Annex 3.18: Ethical approval from Institutional Review Board (IRB) of Institute of Health at Jimma University for the Retrospective cohort study



JIMMA UNIVERSITY

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ቁጥር Ref.No. Rpgcd386/2016

ቀን Date 21/04/2016

To Mr. Hailay Abrha Gesesew

Subject: Ethical clearance of your research protocol

The IRB of College of Health Sciences has reviewed your research protocol during its regular meeting on April 20, 2016:

"Discontinuation, immunologic failure and mortality among people living with HIV/AIDS in Southwest Ethiopia"

This is to notify that this research protocol as presented to the IRB meets the ethical and scientific standards outlined in the national and international guidelines. Hence, we are pleased to inform you that your protocol is *ethically cleared*.

We strongly recommend that any significant deviation from the methodological details indicated in the approved protocol must be communicated to the IRB before they are implemented.

With regards,

[redacted]

Research & Postgraduate Coordinating Office

Jimma University College of Health Science

Tel. +251-47 11 114 57 Fax: +2514711114 50 P.O.Box. 378 E-mail: ero@ju.edu.et

PBX: +251471111458-60 +251471112040 JIMMA, ETHIOPIA website: http://www.ju.edu.et

Annex 3.19. Ethical approval from the Social and Behavioural Research Ethics Committee of the Flinders University for the Qualitative study and Nominal Group Technique

Qualitative study

Dear Hailay,

The Chair of the Social and Behavioural Research Ethics Committee (SBREC) at Flinders University considered your response to conditional approval out of session and your project has now been granted final ethics approval. Your ethics final approval notice can be found below.

FINAL APPROVAL NOTICE

Project No.:	**7698**
Project Title:	HIV patients', HIV care providers', Communities', and Health Care Administrators' Perspectives on HIV Care Cascades in Ethiopia
Principal Researcher:	Mr Hailay Gesesew
Email:	gese0002@flinders.edu.au

Approval Date:	10 August 2017	Ethics Approval Expiry Date:	**30 March 2019**

The above proposed project has been **approved** on the basis of the information contained in the application, its attachments and the information subsequently provided with the addition of the following comment(s):

Additional information required following commencement of research:

1. Permissions

   Please ensure that copies of the correspondence granting permission to conduct the research from all organisations listed are submitted to the Committee *on receipt.* Please ensure that the SBREC project number is included in the subject line of any permission emails forwarded to the Committee. Please note that data collection should not commence until the researcher has received the relevant permissions (item D8 and Conditional approval response – number 12).

2. Other Ethics Committees

   Please provide a copy of the ethics approval notice from Jimma University *on receipt*. Please note that data collection should not commence until the researcher has received the relevant ethics committee approvals (item G1 and Conditional approval response – number 15).

RESPONSIBILITIES OF RESEARCHERS AND SUPERVISORS

1. Participant Documentation

Please note that it is the responsibility of researchers and supervisors, in the case of student projects, to ensure that:

- all participant documents are checked for spelling, grammatical, numbering and formatting errors. The Committee does not accept any responsibility for the above-mentioned errors.
- the Flinders University logo is included on all participant documentation (e.g., letters of Introduction, information Sheets, consent forms, debriefing information and questionnaires – with the exception of purchased research tools) and the current Flinders University letterhead is included in the header of all letters of introduction. The Flinders University international logo/letterhead should be used and documentation should contain international dialling codes for all telephone and fax numbers listed for all research to be conducted overseas.
- the SBREC contact details, listed below, are included in the footer of all letters of introduction and information sheets.

This research project has been approved by the Flinders University Social and Behavioural Research Ethics Committee (Project Number 'INSERT PROJECT No. here following approval'). For more information regarding ethical approval of the project the Executive Officer of the Committee can be contacted by telephone on 8201 3116, by fax on 8201 2035 or by email human.researchethics@flinders.edu.au.

2. Annual Progress / Final Reports

In order to comply with the monitoring requirements of the *National Statement on Ethical Conduct in Human Research (March 2007)* an annual progress report must be submitted each year on the **10 August** (approval anniversary date) for the duration of the ethics approval using the report template available from the Managing Your Ethics Approval SBREC web page. *Please retain this notice for reference when completing annual progress or final reports.*

If the project is completed *before* ethics approval has expired please ensure a final report is submitted immediately. If ethics approval for your project expires please submit either (1) a final report; or (2) an extension of time request and an annual report.

Student Projects

The SBREC recommends that current ethics approval is maintained until a student's thesis has been submitted, reviewed and approved. This is to protect the student in the event that reviewers recommend some changes that may include the collection of additional participant data.

Your first report is due on **10 August 2018** or on completion of the project, whichever is the earliest.

3. Modifications to Project

Modifications to the project must not proceed until approval has been obtained from the Ethics Committee. Such proposed changes / modifications include:

- change of project title;
- change to research team (e.g., additions, removals, principal researcher or supervisor change);
- changes to research objectives;
- changes to research protocol;
- changes to participant recruitment methods;
- changes / additions to source(s) of participants;
- changes of procedures used to seek informed consent;
- changes to reimbursements provided to participants;
- changes / additions to information and/or documentation to be provided to potential participants;
- changes to research tools (e.g., questionnaire, interview questions, focus group questions);
- extensions of time.

To notify the Committee of any proposed modifications to the project please complete and submit the *Modification Request Form* which is available from the Managing Your Ethics Approval SBREC web page. Download the form from the website every time a new modification request is submitted to ensure that the most recent form is used. Please note that extension of time requests should be submitted prior to the Ethics Approval Expiry Date listed on this notice.

Change of Contact Details

Please ensure that you notify the Committee if either your mailing or email address changes to ensure that correspondence relating to this project can be sent to you. A modification request is not required to change your contact details.

4. Adverse Events and/or Complaints

Researchers should advise the Executive Officer of the Ethics Committee on 08 8201-3116 or human.researchethics@flinders.edu.au immediately if:

- any complaints regarding the research are received;
- a serious or unexpected adverse event occurs that effects participants;
- an unforeseen event occurs that may affect the ethical acceptability of the project.

Kind regards

Rae

Nominal Group Technique

Dear Hailay,

The Chairperson of the Social and Behavioural Research Ethics Committee (SBREC) at Flinders University has reviewed and approved the modification request that was submitted for project 7698. A modification ethics approval notice can be found below.

MODIFICATION (No.1) APPROVAL NOTICE

Project No.:	**7698**
Project Title:	HIV patients', HIV care providers', Communities', and Health Care Administrators' Perspectives on HIV Care Cascades in Ethiopia
Principal Researcher:	Mr Hailay Gesesew
Email:	gese0002@flinders.edu.au

Modification Approval Date:	20 December 2017	Ethics Approval Expiry Date:	**30 March 2019**

I am pleased to inform you that the modification request submitted for project 7698 on the 7 December 2017 has been reviewed and approved by the SBREC Chairperson. Please see below for a list of the approved modifications. Any additional information that may be required from you will be listed in the second table shown below called 'Additional Information Required'.

Approved Modifications	
Extension of ethics approval expiry date	
Project title change	
Personnel change	
Research objectives change	
Research method change	x
Participants – addition +/- change	x
Consent process change	x
Recruitment process change	x
Research tools change	
Document / Information Changes	x
Other (if yes, please specify)	

Additional Information Required
Permissions Please provide copies of correspondence granting permission to conduct the research from the individuals and/or organisations outlined. Please ensure that all correspondence clearly outlines the specifics of what permission is being granted. Please note that data collection relating to the modification request should not commence until all relevant permissions have been granted.

RESPONSIBILITIES OF RESEARCHERS AND SUPERVISORS

1. Participant Documentation

Please note that it is the responsibility of researchers and supervisors, in the case of student projects, to ensure that:

- all participant documents are checked for spelling, grammatical, numbering and formatting errors. The Committee does not accept any responsibility for the above-mentioned errors.
- the Flinders University logo is included on all participant documentation (e.g., letters of Introduction, information Sheets, consent forms, debriefing information and questionnaires – with the exception of purchased research tools) and the current Flinders University letterhead

is included in the header of all letters of introduction. The Flinders University international logo/letterhead should be used and documentation should contain international dialling codes for all telephone and fax numbers listed for all research to be conducted overseas.

- the SBREC contact details, listed below, are included in the footer of all letters of introduction and information sheets.

This research project has been approved by the Flinders University Social and Behavioural Research Ethics Committee (Project Number 'INSERT PROJECT No. here following approval'). For more information regarding ethical approval of the project the Executive Officer of the Committee can be contacted by telephone on 8201 3116, by fax on 8201 2035 or by email human.researchethics@flinders.edu.au.

2. Annual Progress / Final Reports

Please be reminded that in order to comply with the monitoring requirements of the *National Statement on Ethical Conduct in Human Research (March 2007)* an annual progress report must be submitted each year on **10 August** (approval anniversary date) for the duration of the ethics approval.

If the project is completed *before* ethics approval has expired please ensure a final report is submitted immediately. If ethics approval for your project expires please submit either (1) a final report; or (2) an extension of time request and an annual report.

Student Projects

The SBREC recommends that current ethics approval is maintained until a student's thesis has been submitted, reviewed and approved. This is to protect the student in the event that reviewers recommend some changes that may include the collection of additional participant data.

Your next report is due on **10 August 2018** or on completion of the project, whichever is the earliest. The report template is available from the Managing Your Ethics Approval SBREC web page. *Please retain this notice for reference when completing annual progress or final reports.*

3. Modifications to Project

Modifications to the project must not proceed until approval has been obtained from the Ethics Committee. Such proposed changes / modifications include:

- change of project title;

- change to research team (e.g., additions, removals, principal researcher or supervisor change);
- changes to research objectives;
- changes to research protocol;
- changes to participant recruitment methods;
- changes / additions to source(s) of participants;
- changes of procedures used to seek informed consent;
- changes to reimbursements provided to participants;
- changes / additions to information and/or documentation to be provided to potential participants;
- changes to research tools (e.g., questionnaire, interview questions, focus group questions);
- extensions of time.

To notify the Committee of any proposed modifications to the project please complete and submit the *Modification Request Form* which is available from the Managing Your Ethics Approval SBREC web page. Download the form from the website every time a new modification request is submitted to ensure that the most recent form is used. Please note that extension of time requests should be submitted prior to the Ethics Approval Expiry Date listed on this notice.

Change of Contact Details

Please ensure that you notify the Executive Officer if either your mailing or email address changes to ensure that correspondence relating to this project can be sent to you. A modification request is not required to change your contact details.

4. Adverse Events and/or Complaints

Researchers should advise the Executive Officer immediately on 08 8201-3116 or human.researchethics@flinders.edu.auif:

- any complaints regarding the research are received;
- a serious or unexpected adverse event occurs that effects participants;
- an unforeseen event occurs that may affect the ethical acceptability of the project.

Kind regards

Andrea

Annex 3.20. Ethical approval from the Institutional Review Board of Jimma University for the Qualitative study and Nominal Group Technique

JIMMA UNIVERSITY
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Ref.No IHRPG/878/2017
Date 9/10/2017

Institutional Review Board (IRB)
Institute of Health
Jimma University
Tel: +251471120945
E-mail: zeleke.mekonnen@ju.edu.et

To: Mr. Hailay Abrha

Subject: Ethical approval of your research protocol

The IRB of institute of health has reviewed your research project entitled:

"HIV Patients', HIV Care Providers', Communities', and HIV Care System Administrators' Perspectives on HIV Care Continuum in Ethiopia"

This is to notify that this research protocol as presented to the IRB meets the ethical and scientific standards outlined in national and international guidelines. Hence, we are pleased to inform you that your protocol is ethically cleared.

We strongly recommended that any significant deviation from the methodological details indicated in the approved protocol must be communicated to the IRB before they are implemented.

With regards!

[redacted]

Zeleke Mekonnen (PhD)
Associate Professor, Health Research and Postgraduate Director

Institute of Health Jimma University

Annex 3.21. Permission letter to the study settings from Jimma University for the qualitative study and Nominal Group Technique

JIMMA UNIVERSITY

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We are in the Community

ቁጥር Ref.No [illegible]/893/2010

ቀን Date 1/02/2010

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"ከሠላምታ ጋር"

[redacted]

ዘለቀ መኮንን (ዶ/ር)
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Health Research and Postgraduate Director
Institute of Health Jimma University

Tel. +251-47 11 114 57
PBX: +251471111458-60
Fax: +2514711114 50
+251471112040
P.O.Box. 378
JIMMA, ETHIOPIA
e_mail: ero@ju.edu.et
website: http://www.ju.edu.et

Permission letter to the study settings from Jimma University for the Qualitative study and Nominal Group Technique (*Translated version letter annexed in 3.21)*

To

- Jimma Zone Health Department, Jimma
- Jimma District Health Office, Jimma
- Jimma Health Centre, Jimma
- Jimma Hospital, Jimma
- Family Guidance Association (FGA), Southwest region branch, Jimma
- FGA Confidential, Southwest region branch, Jimma
- FAYYA International, Southwest region branch, Jimma
- Ginjo Kebele, Jimma
- Organization Service for Social Aid (OSSA), Southwest region branch, Jimma
- HAPCO, Southwest region branch, Jimma
- ICAP, Southwest region branch, Jimma
- Marie Stops International, Southwest region branch, Jimma

Subject: requesting help

We are requesting your usual cooperation to one of our researcher Mr Hailay Abrha who is currently researching on the below title:

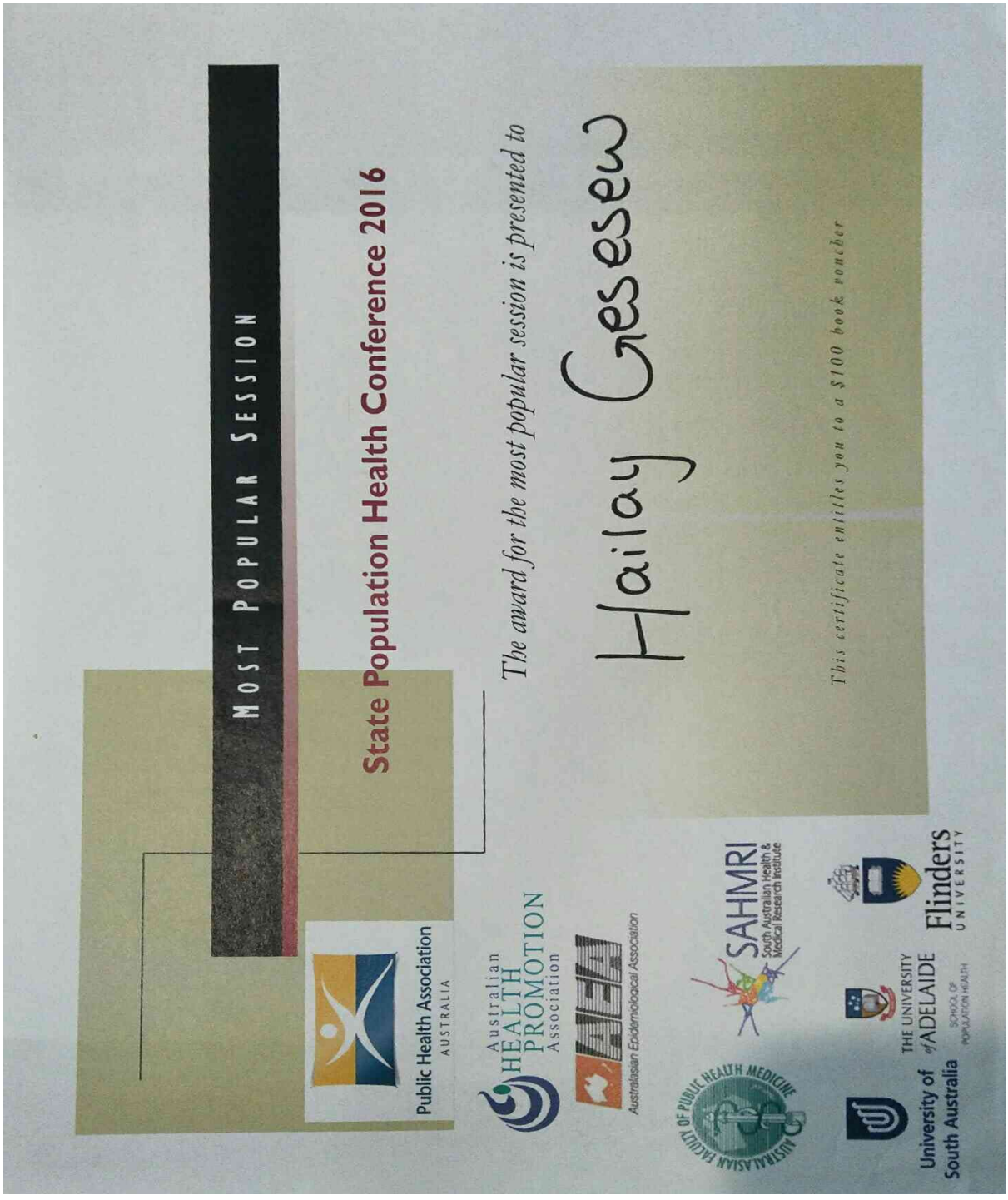
HIV Patients', HIV care providers', Communities', and HIV Care System Administrators' Perspectives on HIV care Continuum in Ethiopia

Kind regards,

Zeleke Mekonen (Dr.)

Health Research Institute and Post Graduate Office, Head

Annex 3.22 Award for being the most popular session in a Conference presentation



Annex 3.23: Media release on HIV mortality, qualitative study and Nominal Group Technique

Media release for the papers "Early mortality among children and adults in antiretroviral therapy programs in southwest Ethiopia, 2003–15"

Prepared by Flinders University communication office

Interviewed on 19 June 2018, and viwed on 20 June 2018

Posted on June 22, 2018 by newsdesk. Access link of the media release from here

Ethiopia suffers from HIV treatment fears

Village life Ethiopia - stock image.

Free public antiretroviral therapy programs have been available for more than a decade in Southwest Ethiopia to address spiralling HIV-AIDS related deaths.

However, Flinders University researchers have found that early mortality rates among those who have access to the drugs is still high.

The research paper - *Early Mortality Among Children and Adults in Antiretroviral Therapy Programs (ART) in Southwest Ethiopia, 2003-15* – assesses the impact of antiretroviral therapy (ART) medications that treat HIV. These drugs do not destroy the virus, but when taken in combination they can prevent the growth of the virus. When the virus is slowed down, so is HIV disease, but inconsistent uptake of ART medications in Southwest Ethiopia is evident through higher-than-expected mortality rates among those who started the therapy program. Flinders University Public Health PhD candidate Hailay Abrha Gesesew, who conducted the research with help from Flinders' Professor Paul Ward and Associate Professor Lillian Mwanri, and colleagues at Jimma University in Ethiopia, says it is worrying that the ART treatment program is not having the expected positive affect across the HIV-affected population.

> "Ethiopia has scaled up universal antiretroviral therapy coverage since 2005, offering the drugs for free, but powerful social stigmas attached to the disease mean that many people are reluctant to be seen in clinics," says Mr Gesesew. "This results in a patchy uptake of the necessary treatment drugs by HIV sufferers, and ultimately a high rate of death within two years of ART, despite the prevalence of medications being offered."

Retrospective analysis of 5299 patient records from June 2003 to March 2015 also found that HIV patients who were divorced or widowed were more likely to die early than people with partners or close family networks. It signals that individuals without personal support networks suffering with the virus are especially vulnerable and tend to go without vital health assistance.

> "We found that HIV patients who had low baseline CD4 count and advanced WHO clinical stage were more likely to die in their early ART follow up period," he adds.
>
> "Furthermore, patients who had no history of HIV testing before diagnosis were more likely to die than those who had history of HIV testing."

Mr Gesesew says this research shows the need for much more frequent HIV testing in Ethiopia to enable more early implementation ART medications.

Details of these findings were published in PLOS ONE.

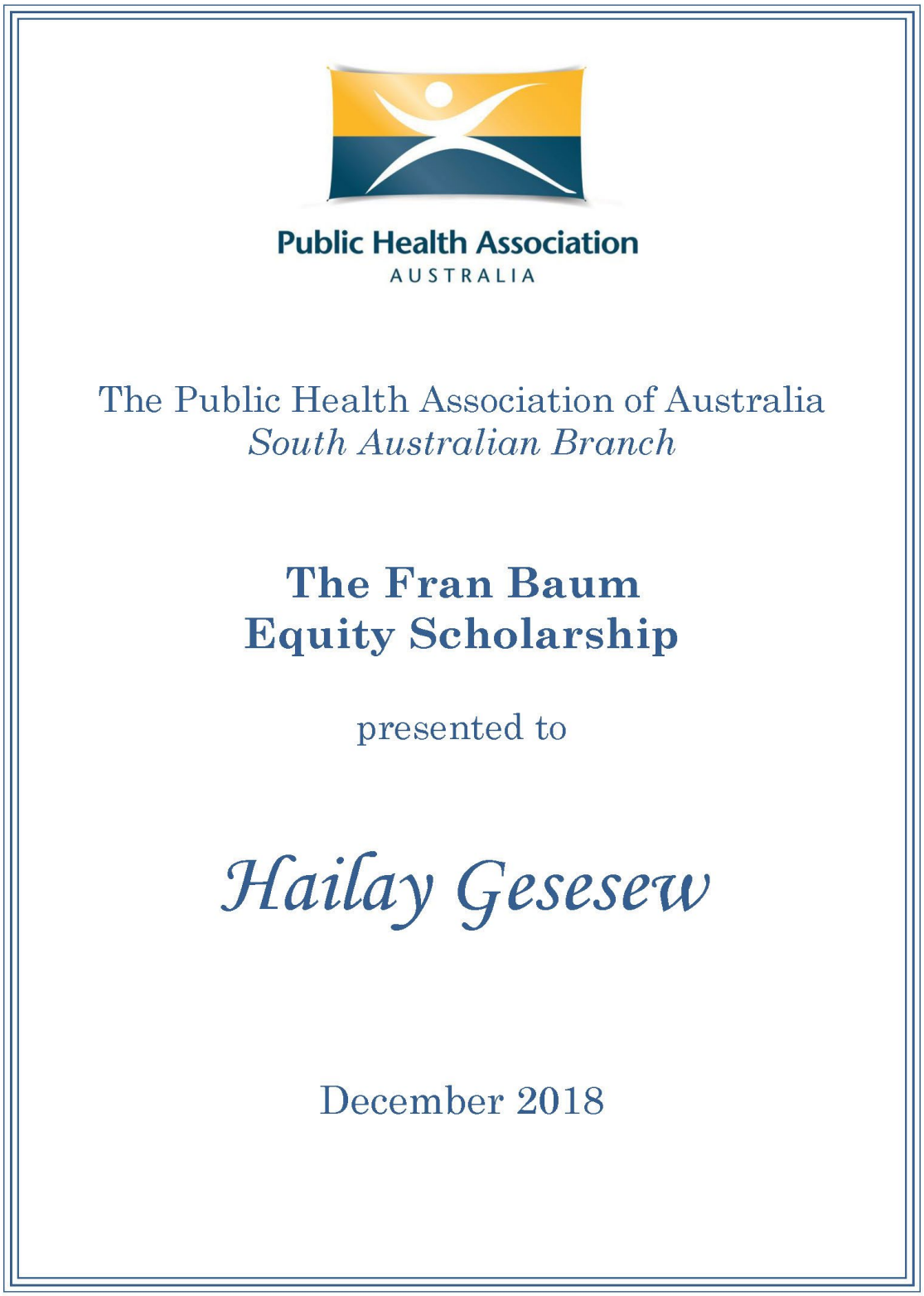
Flinders University Public Health PhD candidate Hailay Abrha Gesesew is conducting extensive research with academics in Ethiopia.

A Phase 2 study of Southwest Ethiopia's ART programs has involved in-depth interviews with HIV patients, health workers, community advocates and program managers to better understand why these groups of HIV patients are at risk of negative HIV care outcomes. These findings will be presented at the 4th International Conference on Public Health (ICOPH 2018) in Bangkok between July 19 and 21, 2018. Mr Gesesew says the research points to a need for change in the way Ethiopia promotes its methods of HIV treatments so they are better understood and accepted across the community.

> "There needs to be greater collaboration between traditional healers and modern medical carers in order to get greater acceptance of ART treatment," says Mr Gesesew. "This needs to happen to improve confidence among the broad community in Ethiopia in modern medical treatments."

'Early mortality among children and adults in antiretroviral therapy programs in Southwest Ethiopia, 2003-15, by HA Gesesew, P Ward, K Woldemichael and L Mwanri, was published on 18 June 2018 in PLOS ONE here

Annex 3.24. The 2018 Fran Baum Equity Scholarship Award



Annex 4.1. The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P)

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses,), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support; role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Annex 4.2. Assessment of methodological quality (n=9)

Asefa et al.	Y	Y	Y	Y	Y	NA	N	Y	Y	88
Berheto et al.	Y	Y	Y	Y	Y	Y	NA	Y	Y	100
Bucciardini et al.	Y	Y	Y	Y	Y	Y	N	Y	Y	89
Deribe et al.	Y	Y	Y	Y	Y	NA	N	Y	Y	88
Melaku et al.	Y	Y	Y	Y	Y	Y	NA	Y	Y	100
Dessalegn et al.	Y	Y	Y	Y	Y	NA	NA	Y	Y	100
Tadesse et al.	Y	Y	Y	Y	Y	Y	NA	Y	Y	100
Teshome et al.	Y	Y	Y	Y	Y	Y	NA	Y	Y	100
Wubshet et al	Y	Y	Y	Y	Y	Y	N	Y	Y	88

Q= Question Y=Yes; N= No; NA= Not applicable

Annex 4.3. Risk of Bias Assessment within the studies (n=9)

Study	Random Sequence Generation (Selection bias)	Allocation Concealment (Selection bias)	Blinding of Participants and personnel (Performance bias)	Blinding of outcome Assessment (Detection bias)	Incomplete Outcome Data (attrition bias)	Selective reporting (Reporting bias)	Other
Asefa et al.	Unclear risk[a]	Unclear riska	Unclear risk	Low risk	Low risk	Low risk	Low risk
Berheto et al.	Unclear risk[a]	Unclear risk[a]	Unclear risk	Low risk	Low risk	Low risk	Low risk
Bucciardini et al.	Unclear risk[a]	Unclear risk[a]	Unclear risk	Low risk	Low risk	Low risk	Low risk
Deribe et al.	Unclear risk[a]	Unclear risk[a]	Unclear risk	Low risk	Low risk	Low risk	Low risk
Melaku et al.	Unclear risk[a]	Unclear risk[a]	Unclear risk	Low risk	Low risk	Low risk	Low risk
Dessalegn et al.	Unclear risk[a]	Unclear risk[a]	Unclear risk	Low risk	Low risk	Low risk	Low risk
Tadesse et al.	Unclear risk[a]	Unclear risk[a]	Unclear risk	Low risk	Low risk	Low risk	Low risk
Teshome et al.	Unclear risk[a]	Unclear risk[a]	Unclear risk	Low risk	Low risk	Low risk	Low risk
Wubshet et al.	Unclear risk[a]	Unclear risk[a]	Unclear risk	Low risk	Low risk	Low risk	Low risk

[a] = Not applicable due to type of study design