# Children diagnosed with HIV on antiretroviral therapy in Ethiopia:The family caregivers' lived experience and treatment outcome

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# Children diagnosis with HIV on antiretroviral therapy in Ethiopia

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# Children diagnosed with HIV on antiretroviral therapy in Ethiopia

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Abstract

While the introduction of antiretroviral therapy has led to significant improvements in the survival of children living with HIV, several factors hamper its ultimate success in resource-limited settings. These factors include lack of proper management of the child's treatment and follow-ups due to the existing fragile health and social systems and psychosocial and economic strains of family caregivers. The overall aim of this thesis was to contribute to the improvement of care for children living with HIV on antiretroviral therapy in Ethiopia through enhanced knowledge and understanding of the family caregivers' experience and factors of importance for the children's outcomes. The knowledge will serve as a basis for further planning of care and informed decision making in the area. A mixed method design study including both qualitative and quantitative methods was carried out. Two studies described in four interrelated papers were derived from a cohort of children less than 14 years of age prospectively enrolled to ART and their respective family caregivers. Qualitative interviews using a hermeneutic phenomenology approach illuminated the caregivers' lived experiences from the child's diagnoses and over two years. Quantitative methods were used to describe caregiver-reported ART non-adherence and its predictors among children in the early stages of treatment and to determine rates and predictors of mortality and lost to follow-up among children on ART.

In the qualitative study, in-depth interviews were conducted among family caregivers at two different time points, when the child was enrolled in ART, Paper I (n=21) and two years after, Paper III (n=18). A prospective cohort study was conducted to evaluate ART non-adherence and its predictors in the early stages of treatment, Paper II (n=306)) and to examine the association between predictors and times to attrition among children, Paper IV (n=304).

The result showed that at the beginning of the child's enrollment in ART the caregivers' lived experience was described as surviving overwhelming challenges. They felt overwhelmed due to the caring burdens and felt uncomfortable about their child's HIV and treatment status. However, their commitment to caring for their child, their belief in God and treatment and the support from health workers empowered and helped them to survive their challenges. As the years went on, caregivers felt relieved from their burden of caring after their child's health restored due to the treatment and support given by the health facilities. The caregivers experienced regained normality in their life and they felt hope even if they faced challenges in terms of stigma in the community and dealing with conflicts especially when they had not revealed the diagnosis to their child.

Children whose caregivers were not undergoing HIV treatment and care themselves were less likely to be non-adherent during the first week of treatment and the children whose caregivers did not use a medication reminder after one month of treatment initiation were more likely to miss the prescribed dose. One month after the treatment initiation, those receiving protease inhibitor (LPV/r) or ABC-based treatment regimens were more likely to be non-adherent. At 12 months of follow-up, 24 attritions were recorded, yielding an attrition rate of 8.3 per 100 PYO. Six children were reported to be dead, leading to a mortality rate of 2.1 per 100 PYO, and five were transferred to another facility. Child age below three years and baseline Hgb in g/dl <10 g/dl had the higher risk of attrition. Baseline Hgb in g/d <10 g/dl and WHO stage III or IV were found to predict the death of the child (Paper IV).

The findings from this thesis revealed that the need of support for family caregivers during their child's HIV diagnosis and treatment initiation is part of a continuum of care. It also suggests a context-based guiding procedure and psychosocial support to ease children's HIV disclosure and minimize the risk of fear of HIV stigma, providing medication reminders, careful selection of ART regimens and improving child–caregiver communication. In addition, there is a need to pay greater attention to younger children as they are at greater risk of death due to lower blood hemoglobin and as they have developed advanced disease at treatment initiation.



Key words. Family caregivers, experience, Antiretroviral therapy, non-adherence, predictors, stigma, attrition, children, HIV, Ethiopia.

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*This thesis is for my wife, Addisalem,*
*and our children, Mastewal and Halleluya*

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# Abstract

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# Original papers

This thesis is based on the following papers referred to in the text by their Roman numerals:

I Biru M, Lundqvist P, Molla M, Jerene D, Hallstrom I. Surviving Overwhelming Challenges: Family Caregivers' Lived Experience of Caring for a Child Diagnosed with HIV and Enrolled in Antiretroviral Treatment in Ethiopia. Issues in Comprehensive Pediatric Nursing. 2015;38(4):282-99.

II Biru M, Jerene D, Lundqvist P, Molla M, Abebe W, Hallstrom I. Caregiver-reported antiretroviral therapy non-adherence during the first week and after a month of treatment initiation among children diagnosed with HIV in Ethiopia. AIDS CARE. 2016.1257098

III Biru M, Lundqvist P, Molla M, Jerene D, Hallstrom I. Hope for the future but fear the risk of stigma: Ethiopian family caregivers' lived experience of caring for their HIV positive child two years after starting antiretroviral treatment. (Accepted in Comprehensive Child and Adolescent Nursing).

IV Biru M, Hallstrom I, Lundqvist P, Jerene D. Rates and predictors of attrition in the first year of follow-up among children on antiretroviral therapy in Ethiopia: a prospective cohort study. In manuscript

# Abbreviations

| | |
|---|---|
| 3TC | Lamivudine |
| ABC | Abacavir |
| AIDS | Acquired Immunodeficiency Syndrome |
| ART | Antiretroviral therapy |
| ARV | Antiretroviral (drug) |
| AZT | Zidovudine (also known as ZDV) |
| BMI | Body mass index |
| CD4 | T-lymphocyte cell bearing CD4 receptor |
| CDC | Center for Disease Control |
| CI | Confidence interval |
| CNS | Central nervous system |
| CTX | Cotrimoxazole |
| D4T | Stavudine |
| DNA | Deoxyribonucleic acid |
| EFV | Efavirenz |
| ELISA | Enzyme-linked immunosorbent assay |
| FCC | Family-centered care |
| FDRE | Federal Democratic Republic of Ethiopia |
| FHAPCO | Federal HIV/AIDS Prevention and Control Office |
| FMOH | Ethiopian Federal Ministry of Health |
| FTC | Emtricitabine |
| HAART | Highly active antiretroviral therapy |
| HIV | Human immunodeficiency virus |
| HICs | High-income countries |

| | |
|---|---|
| IMCI | Integrated management of childhood illness |
| IRIS | Immune reconstitution inflammatory syndrome |
| IPT | Isoniazid preventive therapy |
| LPV | Lopinavir |
| LPV/r | Lopinavir/ritonavir |
| LTFU | Loss to follow-up |
| LTRs | Long terminal repeats |
| MSM | Men who had sex with men |
| MTCT | Mother-to-child transmission (of HIV) |
| NAT | Nucleic acid test |
| NNRTI | Non-nucleoside reverse-transcriptase inhibitor |
| NRTI | Nucleoside reverse-transcriptase inhibitor |
| NVP | Nevirapine |
| OI | Opportunistic infection |
| PCP/PJP | Pneumocystis (jirovecii) pneumonia |
| PCR | Polymerase chain reaction |
| PI | Protease inhibitor |
| PLHIV | People living with HIV |
| PMTCT | Prevention of mother-to-child transmission (of HIV) |
| RNA | Ribo Nucleic Acid |
| TB | Tuberculosis |
| UNAIDS | Joint United Nations Programme on HIV/AIDS |
| UNCRC | UN Convention on the Rights of the Child |
| UNICEF | United Nations Children's Fund |
| WHO | World Health Organization |

# Introduction

Over the last three decades, human immunodeficiency virus (HIV) has become a major developmental challenge worldwide, particularly in low-income countries. Globally, the number of children younger than 15 years receiving antiretroviral therapy (ART) is increasing and has reached 870,000, which is almost a doubling during a five year period between 2010 and 2015 (WHO, 2016b, 2016c). However, half of the 1.8 million children living with HIV remain without ART (UNICEF, 2016), and thus the global fast-track approach of zero infection among children might not be achieved without intensified HIV prevention, treatment and care strategies (WHO, 2016b).

Ethiopia is one of the 35 countries that need intensified action of HIV prevention, treatment and care as these countries are found to account for more than 90% of people newly infected with HIV from the global totals (WHO, 2016b). Ethiopia has expended an enormous effort to combat the HIV epidemic since it became one of the leading causes of developmental challenges in the country (FHAPCO, 2012, 2014). The country has developed policies and phased strategic roadmaps intended to halt the rapid spread of HIV and its effects through accelerating and universal access to care and treatment. Moreover, in response to the devastating impacts of HIV epidemics, Ethiopia established national HIV/AIDS control program in 1987 and developed the first policy on HIV/AIDS in 1998 (FMOH, 1998). The first road map developed for the period 2004–2006 focused on free antiretroviral therapy (ART) in a rollout program with accelerating access to HIV treatment in Ethiopia. The second road map 2007–2008 was developed with more emphasis on providing comprehensive and quality service with access to treatment, care and support services for everyone (MOH, 2007). The development of pediatric HIV care and treatment guidelines was part of the second road map (MOH, 2007; F. MOH, 2007), which was delayed almost four years after the development of adult HIV treatment guidelines in Ethiopia (DACA, 2003). However, the country has committed with accelerated action plans to improve pediatric HIV treatment, care and support (MOH, 2013) in line with the global commitment to reach the ambitious goals and end the HIV epidemic by 2030 (UNAIDS, 2016c; UNICEF, 2016).

Several factors are found to influence adherence to ART and treatment success among children living with HIV, including characteristics of the caregiver, the child and family function, drug regimen and society and cultural characteristics (Haberer & Mellins, 2009). Of these factors, the role of the caregivers is found to be the pillar for the child's

ART success since a child is partially or in some cases totally dependent on the caregiver for his/her treatment to be taken properly (Haberer & Mellins, 2009).

However, the role of caregivers' effectiveness in terms of caring also depends on the characteristics of the caregiver including the caregiver-child relationship, the extent of caregiver permanence as caregivers may have died, may be too ill to provide care, or the caregiver may have changed due to other commitments (Kajubi, Whyte, Kyaddondo, & Katahoire, 2016). Other characteristics such as the caregiver perception and commitment towards child care, comprehension and the level of knowledge of ART administration, psychosocial function and disclosure status of caregivers may further affect the treatment outcome (Haberer & Mellins, 2009).

There are several directive documents on how to treat and take care of children living with HIV on ART (UNICEF, 2016; WHO, 2010a, 2013). However, in resource-limited settings including Ethiopia there is a lack of contextualized, culturally accepted guiding documents based on the evidence of caregivers' experiences and children's needs. Moreover, resource-limited settings lack resources to facilitate the availability of these documents and follow their practice (Kidman & Heymann, 2016; UNICEF, 2016). Evidence about the experiences of caregivers caring for their child diagnosed with HIV and enrolled in ART including the various and emerging needs of the child in the course of treatment, caregivers' reactions and communication with their child in a comprehensive fashion is lacking or limited (Bejane, 2013; Kidman & Heymann, 2016; Potterton, Stewart, & Cooper, 2007).

It is crucial to have a favorable and supporting system to practice and thus to improve the quality of care provision for the family caregivers to achieve ultimate treatment success among children enrolled in ART.

Therefore, this thesis aimed to contribute to the improvement of care for children living with HIV on antiretroviral therapy in Ethiopia through enhanced knowledge and understanding of the family caregivers' experience and factors of importance for the children's outcomes. The knowledge will serve as a basis for further planning of care and informed decision making in the area.

# Background

## Historical aspects of HIV

In 1981, the first five patients, previously healthy men who had sex with men (MSM), were treated for pneumocystis carinii (now pneumocystis jiroveci) pneumonia (PCP) in three Los Angeles hospitals in the United States (US). (CDC, 1981; De Cock, Jaffe, & Curran, 2012; Luce, 2013). This condition was named Acquired Immunodeficiency Syndrome (AIDS) in 1982 (Luce, 2013). AIDS was first described among children 18 months later (CDC, 1982), and its sexual route of transmission, including heterosexual, was confirmed in subsequent studies (CDC, 1983; Jaffe et al., 1983). Further studies showed additional routes of infection including mother-to-child transmission (CDC, 1982; Thomas et al., 1984), injection drug use (Ammann et al., 1982; De Cock et al., 2012; Desposito, McSherry, & Oleske, 1988; Ehrenkranz et al., 1982), blood transfusion and occupational risk (Marcus, Kay, & Mann, 1989). (Garsia et al., 1987; Lowe, 1987). Later on the etiologic agent causing AIDS was identified (Gallo & Montagnier, 2003) and was given the name HIV in 1986.

The first study conducted in Zaire, Africa, identified a large number of AIDS cases among heterosexual patients, thus the finding suggested that central Africa is one of the emerging settings for the world AIDS pandemic (Piot et al., 1984). In addition, AIDS was identified among African children and was a cause of death at early age, before the child's second birthday (Ninane et al., 1985). In Ethiopia there was no evidence of HIV until it was detected in 1984 from the serological survey conducted in various parts of Ethiopia between 1982 and 1987.

## Epidemiology

### Global

As of 2016, HIV has infected around 78 million people and around 35 million people have already died due to AIDS-related disease (UNAIDS, 2016b). In 2015 there were about 36.7 million people living with HIV (PLHIV), of whom about 17.1 million were unaware of their HIV status (UNAIDS, 2016a). Of the global totals 1.8 million were

children below 15 years (UNAIDS, 2016a). New cases of HIV infection among children aged 0–14 numbered 150,000 in 2015 and nearly 85% of them are from Sub-Saharan Africa (UNICEF, 2016). Even though there was a decline in new HIV cases by 38% among adults between 2001 and 2013 (UNAIDS, 2014), no further reduction in new HIV infections has taken place since 2010. However, a dramatic decline by 50% has been recorded among children during the same period due to the implementation of accelerated prevention of mother-to-child HIV transmission (PMTCT) program for pregnant women living with HIV (UNAIDS, 2014). In addition, in countries where an option B+ (all pregnant women living with HIV are offered life-long triple ARVs as soon as diagnosed, regardless of their CD4 count) (WHO, 2012) was practiced using an integrated service delivery model, with the result that retention in care on ART increased (van Lettow et al., 2014) and MTCT fell below the elimination threshold (Gamell et al., 2017).

With the aim of reversing the existing challenge caused by HIV, the Joint United Nations Programme on HIV/AIDS (UNAIDS) set an ambitious target with the priority focus of intensifying particular locations and populations to achieve the goal of ending the HIV epidemic by 2030. This is planned to be achieved to 90% of each target: enabling of people to know their HIV status; ensuring access to treatment for PLHIV; and reaching suppressed viral loads for people on treatment (UNAIDS, 2016c). Regardless of this, globally less than half, 46%, of PLHIV had access to ART (UNAIDS, 2016a; WHO, 2016b).

In eastern and southern Africa, the progress in terms of HIV treatment coverage reached 54%, which is higher than the global average of 46% (WHO, 2016b). However, in resource-constrained settings including Sub-Saharan Africa, progressing towards these targets might be affected by several impeding factors including the existing fragile health and social systems in these settings (UNAIDS, 2016c).

## Ethiopia

In Ethiopia, there were approximately 800,000 PLHIV at the end of 2013, of which approximately 200,000 were children, accounting for 25% of the total. Children aged 5–14 account for more than 80% of all HIV-infected people in the pediatric population, who acquired HIV in earlier years when the practice of PMTCT was low in the country (FDRE, 2014). In the same year, about 45,000 AIDS-related deaths and 850,000 AIDS orphans were reported in Ethiopia.

Since the occurrence of HIV epidemics, Ethiopia has used various strategies to combat HIV-related crises. These successful national responses include calls for HIV mainstreaming, multisector collaboration to achieve the reduction of HIV vulnerability through effective behavioral change interventions (FDRE, 2014) and scale-up of treatment and care for both the adult and pediatric population (MOH, 2007; F. MOH, 2007). Behavioral change activities, such as community conversation (CC) led by the

government, were widely implemented on a regular basis and resulted in a visible change in creating public awareness and behavioral change. Additionally, the interventions have focused on the most at-risk populations such as: female sex workers, mobile workers, police and armed forces, prisoners, long distance truck drivers and couples who have HIV-discordant results (FDRE, 2014).

In Ethiopia, pediatric HIV care and treatment guidelines were launched in 2007, aimed to provide comprehensive services for both HIV-exposed and HIV-infected children (FMOH, 2007). Various intervention strategies including provision of family-centered care, prevention of pediatric infection through PMTCT, care of HIV-exposed infants and care and treatment of HIV infected children (FMOH, 2007). These strategies have been practiced with substantial attention, and with a decentralized policy to cover the needs of all children diagnosed with HIV in all segments of the country (FDRE, 2014). This action placed the country among the few countries that decreased AIDS-related death significantly by 37% between 2009 and 2013 (UNAIDS, 2014). However, Ethiopia is still categorized as one of the 21 global priority countries to eliminate new pediatric infections (UNAIDS, 2014).

## Transmission

The most common route for HIV-1 transmission is heterosexual contacts, having contacts with HIV-infected blood and blood products and mother-to-child (vertical) transmission (Hansasuta & Rowland-Jones, 2001). However, more than 90% of infections in children are acquired through mother-to-child transmission (MTCT) of HIV-1 during pregnancy, delivery or breastfeeding (Cruz, 1988; Luzuriaga & Mofenson, 2016). Nevertheless, the relative contribution of these transmissions routes is not well- documented (Cruz, 1988; Newell, 1998). The risk of HIV-1 transmission in children significantly relies on the maternal viral load, which means that MTCT rates are very high with the replication of HIV-1 and vice versa (Cooper et al., 2002; Luzuriaga & Mofenson, 2016). In addition, about 10% of HIV transmission in children is likely due to exposure to contaminated blood and blood products, affecting recipients of blood transfusions, hemophiliacs, sexually abused children and infants of intravenous drug abusers. However, the development of screening and testing procedures has virtually averted the risk of transmission via blood and blood products along with successful ART since 1985 (Cruz, 1988; WHO, 2013; Violari et al., 2008).

The evidence in Africa indicates that the risk of perinatal HIV transmission was estimated to be 21%. However, the risk of MTCT was found to be 30–45% in Sub-Saharan Africa due to an additional 14% risk of transmission related to prolonged breastfeeding (De Cock et al., 2012; Dunn, Newell, Ades, & Peckham, 1992). In high-income countries, breastfeeding does not make any significant contribution to HIV transmission unless a child has already been infected in utero. However, it is difficult

to substitute breast¬feeding practice in resource-limited setting because it is the only secure source of total nutrition for the child (Ramachandran, 1988). Though there has been a substantial decrease in MTCT due to the availability of ARV drug options, breastfeeding is found to be the remaining challenge as it is the major route of HIV transmission in children. Therefore, with the shift of timing in MTCT there is an urgent need to combat it (UNICEF, 2016).

# The natural course of HIV

## Pathogenesis

HIV contains single-stranded ribonucleic acid (RNAs) and the three important viral proteins include: a reverse transcriptase, an integrase and protease (Fanales-Belasio, Raimondo, Suligoi, & Butto, 2010). HIV is categorized as a retrovirus because it cannot replicate itself unless transcribed into double-stranded ribonucleic acid (DNA). Figure 1 shows the lifecycle of HIV.

The continuous cycle of HIV replication in the host cell results in increasing reduction of CD4+ cells. This eventually leads the host to be susceptible to developing opportunistic infections due to progressive depletion of immune system of the host (Cruz, 1988). Evidence indicates that there is no difference between Africans and others in the natural course of the disease due to inherent differences or viral sub-types. However, regardless of higher CD4 cell counts, shorter survival with AIDS in African patients is related to exposure to easily treatable acute infections, tuberculosis and wasting syndrome and lack of access to manage these complications (Williams & De Cock, 1996). Unless an appropriate treatment intervention is carried out, HIV infection in infants and children progresses very fast and results in death in about

50–52% of children below the age of two years in resource-limited settings (F. MOH, 2007; UNICEF, 2016; WHO, 2013).

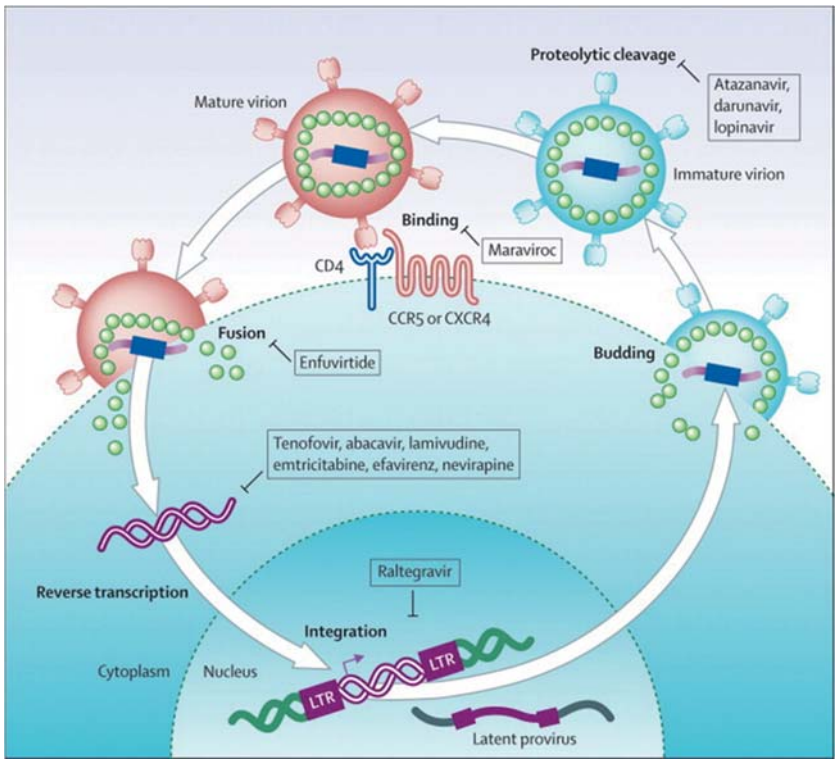


**Figure 1.** HIV life cycle and antiretroviral drug targets. Reprinted from (Volberding & Deeks, 2010 p. 50) by permission of Elsevier.

## Clinical Manifestation

Unlike several other infectious diseases, in HIV there are conditions to determine the occurrence of clinical presentation including: the susceptibility of the host to various opportunistic infections and the presence of malignancies over the years (Morgan & Whitworth, 2001). However, the duration and frequency of clinical presentation vary among individuals. Infants and children infected with HIV are in general asymptomatic or do not as frequently develop opportunistic infections (OIs) as adults (Cruz, 1988; Oleske, Connor, Grebenau, & Minnefor, 1988). In children, the symptom usually takes six months to two years to appear. However, children are unlikely survive beyond two years of age after they are diagnosed with HIV and go without ART (Cruz, 1988; WHO, 2013; Vreeman, Scanlon, McHenry, & Nyandiko, 2015).

Children with HIV infection often present with symptoms such as failure to thrive and unusually severe and recurrent bacterial infections. However, they do not often develop

various OIs as adults but they usually die due to PCP within the first year or they may survive until three years and then die due to other OIs (Cruz, 1988; Ramachandran, 1988; WHO, 2010a, 2013). These OIs appear at different clinical stages in the body due to the continuous viral replication, and related depletion of the immune system makes the host susceptible to acquiring opportunistic infections (Figure 2).

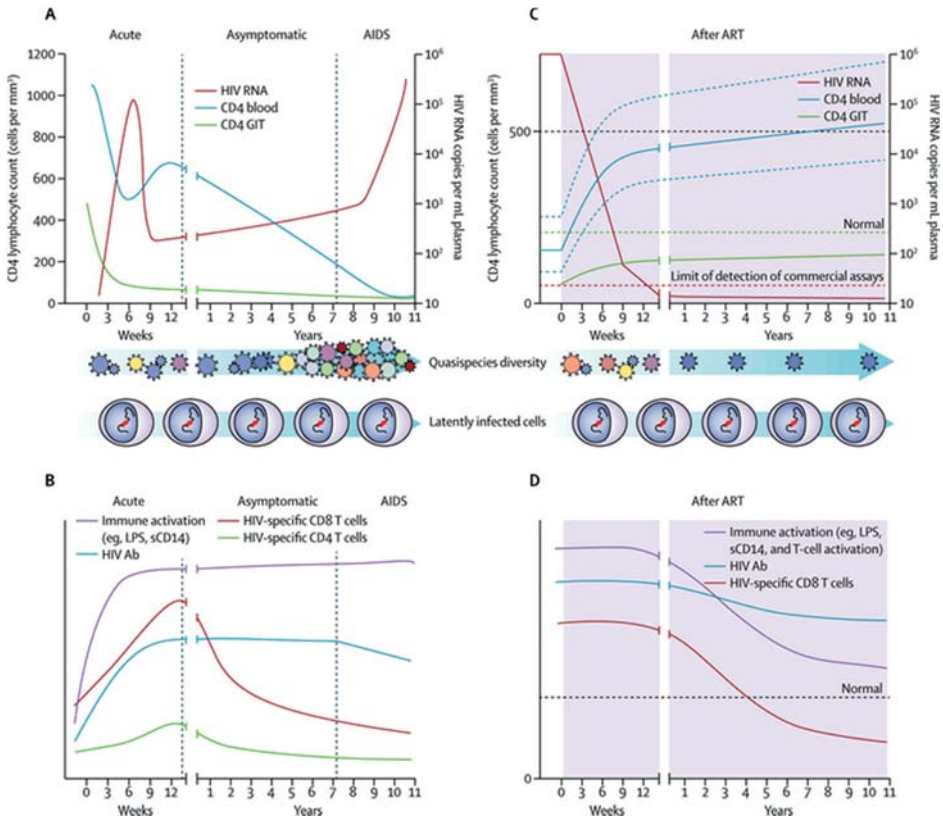


**Figure 2.** Natural history of untreated HIV infection and changes after antiretroviral therapy. Reprinted from Maartens, Celum, & Lewin, 2014, p. 261, with permission. Copyright Elsevier

The spectrum of the impaired immune system of an individual living with HIV is clinically categorized in four stages for adults and children (Table 1):

- Clinical stage 1: HIV infection in children is asymptomatic or present with persistent generalized lymphadenopathy.
- Clinical stage 2: Children can develop unexplained persistent hepatosplenomegaly, recurrent or chronic upper respiratory tract infections and/or various types of skin lesions.
- Clinical stage 3: Characterized by unexplained moderate malnutrition not adequately responding to standard therapy and unexplained persistent diarrhea lasting >14 days and unexplained persistent fever lasting >1 month and others (WHO, 2013).
- Clinical stage 4: Children is characterized by severe immunodeficiency or advanced AIDS syndrome (WHO, 2013).

**Table 1.** Clinical Staging of HIV for infants and children adapted from WHO 2013 (WHO, 2013)

**STAGE 1**

Asymptomatic
Persistent generalized Lymphadenopath

**STAGE 2**

Unexplained persistent hepatosplenomegaly Persistent generalized Lymphadenopath
Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis
Herpes zoster
Lineal gingival erythema
Recurrent oral ulceration
Papular pruritic eruption
Fungal nail infections
Extensive wart virus infections
Extensive molluscum contagiosum
Unexplained persistent parotid enlargement

**STAGE 3**

Unexplained moderate malnutrition not adequately responding to standard therapy
Unexplained persistent diarrhea (14 days or more)
Unexplained persistent fever (above 37.5°C, intermittent or constant, for longer than one 1 month)
Persistent oral candidiasis (after first 6 weeks of life?
Oral hairy leukoplakia
Lymph node tuberculosis
Pulmonary tuberculosis
Severe recurrent bacterial pneumonia
Acute necrotizing ulcerative gingivitis or periodontitis
Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 x 109/l) or chronic thrombocytopaenia (<50 x 109/)
Symptomatic lymphoid interstitial pneumonitis
Chronic HIV-associated lung disease, including bronchiectasis

**STAGE 4**

Unexplained severe wasting, stunting or severe malnutrition not responding standard therapy
Pneumocystis (jirovecii pneumonia
Recurrent severe bacterial infections (such as empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia
Chronic herpes simplex infection (orolabial or cutaneous of more than 1 month's duration or visceral at any site)
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Extra-pulmonary tuberculosis
Kaposi sarcoma, Cerebral or B-cell non-Hodgkin lymphoma
Cytomegalovirus infection (retinitis or infection of other organs with onset at age more than 1 month)
CNS toxoplasmosis (after the neonatal period), HIV encephalopathy, Extrapulmonary cryptococcosis, including meningitis, Progressive multifocal leukoencephalopathy
Disseminated nontuberculous mycobacterial infection
Chronic cryptosporidiosis (with diarrhea), Chronic isosporiasis
Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidioidomycosis, penicilliosis)
HIV-associated nephropathy or cardiomyopathy

# Clinical management

## Diagnosis

Rapid progression of the disease and related death among untreated HIV-infected infants and children is common in earlier age. Therefore, timely diagnosis and treatment initiation are crucial to ensure their survival (FMOH, 2007; WHO, 2016a). HIV can be diagnosed in infants and children either by using serological test to detect antibodies or by virological testing (WHO, 2010b). The most common serological or antibody detection method is enzyme-linked immunosorbent assay (ELISA) which has a high sensitivity and specificity to detect antibodies against HIV, and other serological testing approaches also include simple rapid and western blot (WB) tests in adults and children over 18 months of age (WHO, 2010b, 2016a). The virological testing is used to detect viral RNA or DNA by using the nucleic acid testing (NAT) technology analysis or viral products such as Ultrasensitive p24 antigen-based testing (Up24Ag) (Grossman, 1988; WHO, 2010b).

## Treatment

The introduction of HIV treatment has been one of the astonishing success stories during recent years. It could avert the worst situation of HIV transmission and related consequences among people with HIV all over the world (UNAIDS, 2016c). As the main transmission route, accounting for more than 90% of HIV transmission in infants, is MTCT, interventions focused on reducing MTCT are found to be the most efficient and cost-effective way to fight against pediatric HIV globally (WHO, 2010a, 2013). Without treatment, about 52% of children die before they celebrate their second birthday (WHO, 2013). This is therefore convincing evidence that priority should be given to urgent initiation of ART in infants and children (Vreeman et al., 2015). The goals of ART in children are to restore an immune function and maximum suppression of viral replication aiming to extend child survival by reducing HIV-related morbidity and mortality significantly (FMOH, 2007; UNICEF, 2016).

There are now 25 to 29 antiretroviral drugs available for adults, while the pace of establishing a similar range for children has not been remarkable (Prendergast, Essajee, & Penazzato, 2015; UNICEF, 2016). Though it is believed to be important to initiate ART in children early and immediately after HIV diagnosis, it is equally important to examine the child's health condition and discuss drug regimens, dosage, benefits, adverse reactions, adherence preparation and family readiness before the commencement of the treatment (FMOH, 2014, 2016). However, accelerated ART initiation is an emerging recognition of success of the programs found to ensure the survival of individuals who are infected with HIV, particularly infants and children

(UNICEF, 2016). Therefore, it is highly recommended to narrow the time interval between HIV diagnosis and treatment initiation (WHO, 2016a).

Highly active antiretroviral therapy (HAART) regimen in children who adhere to therapy was found to be effective in controlling the viral replication (Watson & Farley, 1999). The broad category of regimens included in HAART usually has three or more combinations of drugs from the analogues of nucleoside reverse transcriptase inhibitors (NRTI) such as AZT, lamivudine (3TC) and abacavir (ABC), non-nucleoside inhibitors (NNRTI) such as nevirapine (NVP) or efavirenz (EFV), and protease inhibitors (PI) such as lopinavi (LPV) or lopinavir/ritonavir (LPV/r) included to treat HIV-1 infected patients who had not initiated treatment before. This treatment was found to be effective in suppressing the plasma virus below the levels of detection (Shafer & Vuitton, 1999; Watson & Farley, 1999).

The consolidated ART guideline of 2013 suggested initiating ART in all children below the age of 5 years regardless of the clinical staging or CD4 counts with the priority for children aged ≤2 years or WHO stage 3 or 4 or CD4 count ≤750 cells/mm$^3$ or <25%. In children 5 years and older, CD4 ≤500 cells/mm3 or WHO stage 3 or 4 the priority in children is CD4 ≤350 cells/ mm$^3$ (WHO, 2013). Since 2014, Ethiopia has treated all children below 15 years with HIV infection regardless of CD4 count and WHO clinical stage (FMOH, 2014). The very recent and currently used recommendation by WHO is to "prevent HIV, test and treat all" regardless of clinical stage or immunological status to reach an ambitious fast-track target in 2020 (WHO, 2016b).

Based on the recent WHO consolidated guidelines, the preferred regimens of first-line ARV drugs for children under 3 are ABC or AZT + 3TC + LPV/r, for children aged from 3 to under 10 years and adolescents <35 kg, ABC + 3TC + EFV and in adolescents aged 10–19 years with >35 kg, TDF + 3TC (fixed dose combination) (FTC) + EFV. However, these regimens are likely to be changed based on the child's condition, such as a child undergoing anti-tuberculosis (TB) treatment. These first-line regimens can also be switched to second-line options when the treatment with the first line fails based on the child's age and the type of first-line regimen has been taken by the child. In children aged 10 years and above who have been taking NNRTI-containing regimen in the first line, boosted PI plus two NRTI combination is suggested. However, in children aged below 10 years who have been using a PI-based regimen for first-line ART, it is recommended to switch to two NRTI plus one NNRTI combination or maintain the PI regimen based on the child's age (WHO, 2013). Recommended first-line ART regimens is shown in Table 2.

**Table 2.** Recommended first-line ART regimens for children and adolescents, adapted from WHO 2013 (WHO, 2013)

| Regimens | Children under 3 years | Children 3 years to less than 10 years and adolescents <35 kg | Adolescents (aged 10 to 19 years) ≥35 kg |
|---|---|---|---|
| Preferred regimens | ABC or AZT + 3TC + LPV/r | ABC + 3TC + EFV | TDF + 3TC (or FTC) + EFV |
| Alternative regimens | ABC or AZT + 3TC + NVP | ABC + 3TC + NVP<br>AZT + 3TC + EFV<br>AZT + 3TC + NVP<br>TDF + 3TC (or FTC) + EFV<br>TDF + 3TC (or FTC) + NVP | AZT + 3TC + EFV<br>AZT + 3TC + NVP<br>TDF + 3TC (or FTC) + NVP |
| Special circumstances | d4T + 3TC + NVP | d4T + 3TC + EFV<br>d4T + 3TC + NVP | ABC + 3TC + EFV<br>ABC + 3TC + NVP |

The ultimate success of ART depends on several factors including treatment adherence, which should be greater than or equal to 95% of the prescribed doses during the given period. However, adherence is not limited to treatment; it also includes personal behavior, following recommended diet and lifestyle changes (WHO, 2002). ART adherence could be affected by multiple factors including individual factors such as forgetfulness, lack of interest and mental illness, medication-related factors such as adverse reactions and pill burdens, health system related factors such as traveling long distances may affect adherence to ART (FMOH, 2014). Therefore, as a part of package of adherence intervention it is suggested to provide proper counseling and education as well as use reminder and engagement tools such as mobile phone text messages, alarms, phone calls, diaries and calendars to promote ART adherence (FMOH, 2014).

Other factors affecting the treatment success include retention in care, service availability and accessibility, having adequate health manpower, laboratory and diagnostic service and uninterrupted supply chain management in place (WHO, 2013). The UNAIDS 90-90-90 target is that 90% of people living with HIV should know their HIV status, the 90% of people who know their HIV-positive status have access to treatment and that 90% of people on treatment have suppressed viral loads to end the AIDS epidemic by 2020 (UNAIDS, 2016c; UNICEF, 2016). However, beyond this ambitious target, it is highly recommended to have an adequate flow of information, innovation and intensified political and financial commitment to achieve these targets.

Innovative approaches within the health system such as EID through "point-of-care testing" (Thiha et al., 2017; UNICEF, 2016), and out-of-health-system approaches

including psychosocial support and empowerment with focused interventions such as cash transfers, parental and education support are highly recommended to be combined with biomedical interventions (Toska et al., 2016). In addition, there is a need to have an intensified political and financial commitment for the smooth progress to achieve planned targets. Integration of services is also found to improve service delivery and related health outcomes as the benefit has been demonstrated following implementation of the Integrated Management of Childhood Illness (IMCI). Intersectoral and interagency collaboration with a diversity of stakeholders who are likely to affect the pediatric treatment and care are other keys to realize the quality of care and achieve the intended outcome (Davies, Pinto, & Bras, 2015) (Figure 3).

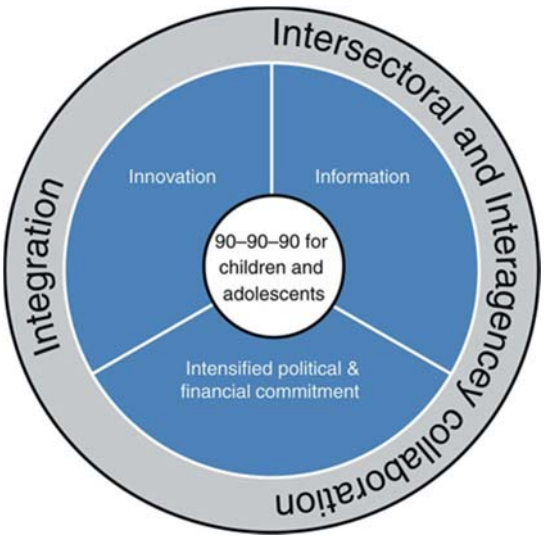


**Figure 3.** Strategies to achi eve the targets that 90% of people living with HIV should know their HIV status, that 90% of people who know their HIV-positive status have access to treatment, and that 90% of people on treatment have suppressed viral loads for children and adolescents (Davies et al., 2015) page 3.

## Management of opportunistic infections

In infants and children diagnosed with HIV, the range of treatment is not limited to provision of ART. There are OIs and comorbidities such as PCP, TB, cryptococcal infections, malaria and others that need to be prevented, assessed, and managed properly to ensure the survival of children with HIV. ART cannot cure these coinfections and comorbidities (WHO, 2013). Regardless of clinical and immunological conditions, in infants and children Co-trimoxazole (CTX) prophylaxis is recommended with priority for children below the age of 5 years and in all children

with severe immunodeficiency or CD4 count ≤350 cells/mm3. The CTX prophylaxis should be continued in infants and children until adulthood regardless of whether they are enrolled in ART if their living area is known to have a high prevalence of malaria and/or severe bacterial infections. However, the treatment could be terminated in children above the age of 5 if these circumstances are not present (WHO, 2014).

In addition, as TB is one of the top fatal diseases among patients with HIV, regular and careful TB assessment, diagnosis and proper management are crucial to combat TB-related co-morbidity and mortality (WHO, 2016a). Children should be carefully evaluated for the presence or history of TB and if they have no TB based on the evaluation, isoniazid preventive therapy (IPT) should be given regardless of their age (WHO, 2016a). There is a large amount of evidence revealing that the use of ART averts the occurrence of most OIs or calms down their appearance at low levels in high-income countries (HICs) (Buchacz et al., 2010; MR et al., 2016; Palella et al., 2006). Similarly, despite a handful of studies (Abdool Karim et al., 2010; Seddon & Bhagani, 2011; Zolopa et al., 2009), the initiation of ART is found to avert the occurrence of OIs. Without ART, large amounts of money would be spent on treating OIs, particularly in low- and middle-income countries (LMICs) (MR et al., 2016).

## Monitoring outcomes, complications and side effects of ART

In infants and children, clinical and immunological recovery is expected during the first six months after ART initiation. However, during the first few weeks' complications related to drug toxicities and/or immune reconstitution inflammatory syndrome (IRIS) are often reported in children particularly when ART is initiated with severe immunodeficiency (Smith et al., 2009). IRIS is the range of clinical signs and symptoms resulting from an inflammatory condition, also termed as a paradoxical worsening of preexisting conditions (infectious or non-infectious) after the start of ART (DeSimone, Pomerantz, & Babinchak, 2000; Hirsch, Kaufmann, Sendi, & Battegay, 2004; Shelburne, Montes, & Hamill, 2006). There is no adequate evidence about the cause of IRIS in infants and children; it occurs occasionally in children with a very low percentage of CD4+ (Kilborn & Zampoli, 2009). However, mycobacterial, including tuberculosis, atypical mycobacteria and BCG-related are the most frequently reported OIs causing IRIS in children (Boulware, Callens, & Pahwa, 2008).

For these reasons, a child may fail the initial recovery regardless of the treatment. However, this does not imply the failure to respond to the treatment as the ART needs adequate time to control the viral replication, particularly in children with severe immune deficiency. Regardless of the fact that ART decreases the rates of death in children, higher rates of children were reported to die with severe immune-deficiency, severe malnutrition or very low hemoglobin level according to the study conducted in Kenya and South Africa (Wamalwa et al., 2010; Zanoni, Phungula, Zanoni, France, & Feeney, 2011). Most of the children die due to these conditions during the first six

months after treatment initiation (WHO, 2010a). ARV side effects range from mild, usually self-limiting ones to severe forms or life-threatening. It is important to differentiate between complication of HIV disease and ART toxicity to provide appropriate management, though it is sometimes difficult to differentiate. There are only a handful of studies about the spectrum of drug toxicities in children compared to adults. However, most of the adverse reactions observed in adults similarly happened in children even though some are less common in children and vice versa. After treatment initiation, these side effects often last from days to weeks or in some conditions persist even for months (WHO, 2010a).

The most common ARV side effects in children are classified in four groups. The first one is hematological, which is characterized by drug-induced bone marrow suppression, which often happens in patients taking AZT. The second is mitochondrial dysfunction, which is commonly seen in patients under treatment with NRTI drugs (d4T and ddI are worse than others are in the same analogue) as these analogues are found to affect mitochondrial function with very common clinical presentations of hepatic toxicity, lactic acidosis, pancreatitis and peripheral neuropathy. The third is lipodystrophy and other metabolic abnormalities that are characterized by abnormal metabolic function in the body such as abnormal fat distribution and change in body habitus. The drugs under the PI analogue and d4T are primarily responsible for producing these side effects. The fourth is allergic reactions, commonly skin rashes and hypersensitivity reactions. The drugs under the NNRTI analogue are primarily reported to produce these reactions though it is also reported in patients who were taking certain NRTI analogues, such as ABC (WHO, 2010a).

Therefore, close monitoring by using clinical assessment and laboratory markers of the type of ARV regimen and availability of these laboratory test at the health facility is crucial. It is also very important to prepare the caregivers by providing appropriate information ahead about these possible drug side effects related to the specific ARV regimens. The presence of these adverse reactions was reported to affect the level of adherence regardless of their level of severity. Based on the range of adverse reaction, discontinuation or substitution of the treatment regimen is often determined by the trained clinician (WHO, 2013).

## Treatment failure

Treatment failure is defined as a persistently detectable viral load exceeding 1000 copies/ml after at least six months of using ARV drugs and it can occur with evidence of either clinically, immunologically or virologically ineffective treatment outcomes (WHO, 2013). Treatment failure in ART depends on various factors including poor level of treatment adherence, inadequate serum drug level to suppress the replication and/or due to the subsequent drug resistance (Bacha, Tilahun, & Worku, 2012; Mossoro-Kpinde et al., 2017). Drug resistance is one of the most significant conditions

resulting in virological failure among children receiving first-line regimens and has been found to increase the need to switch the treatment regimens to second-line regimens. The previous clinical and epidemiological studies indicated that the risk of HIV transmission from HIV-infected person to an infected person is very low when the virus is fully suppressed by ART or the viral copy of HIV in HIV-infected person is below 1000 copies/ml (Loutfy et al., 2013).

Therefore, it is strongly recommended to diagnose and confirm the treatment failure preferably by using the viral load monitoring approach at least six months after treatment initiation and every 12 months thereafter. However, in the absence of routine viral load testing, particularly in resource-limited settings, it is recommended to use the CD4 count and clinical monitoring as an important approach to diagnose treatment failure, with targeted viral load testing to confirm virological failure where possible (WHO, 2013).

Treatment failure can be presenting as one or more forms including clinical, immunological or virological failure. Clinical failure in children is defined as the occurrence of new or recurrent advanced diseases characterized by the child presenting with the clinical condition of WHO stage 3 and 4 with the exception of TB after 6 months of effective treatment. Immunological failure in children is defined based on the level of CD4+ count depending on their age. In children younger than 5 years, immunological failure is determined on the child's persistent CD4 levels below 200 cells/mm3 and in children older than 5 years when the CD4 levels are below 100 cells/mm3. Virological failure is indicated when two consecutive plasma viral load measurements 3 months after treatment initiation rise above the threshold of 1000 copies/ml regardless of adherence support. However, the same first-line regimen of treatment should be continued at least for the first six months to determine treatment failure regardless of the viral load above threshold. (WHO, 2013).

## Children with HIV

According to the Revised Family Code (2002) article 215 in Ethiopia, a child or minor is defined as "a person of either sex who has not attained the full age of eighteen years" (African Child Policy Forum, 2013).

Unlike adults, HIV in children is found to be more complicated related to the nature of late diagnoses of the infection. There is a huge gap in practice of timely HIV diagnosis and proper management in infants, children and adolescents compared to adults. Yet, infants and children die before being confirmed positive for HIV infection because pediatric HIV disease can progress very rapidly (UNICEF, 2016). However, there has been a promising recent scale-up of early infant diagnostic (EID) and treatment services (Vreeman et al., 2015).

It is suggested to improve the treatment of HIV-exposed infants with ART before positive HIV infection is confirmed (FMOH, 2014). On the other hand, lack of or availability of only few child-friendly and safe ARV drug options is a challenge in treating infants and children. So far, from the range of 29 ARV drugs discovered, only 10 of those approved for treating adults with HIV has also been approved to treat children below two years of age. ART in children remains of low quality and is less effective than in adults. Moreover, the ART coverage in infants and children living with HIV is very low compared to adults, although there are huge disparities from region to region, country to country, or city to city (Penazzato, 2016; UNICEF, 2016). A recent report indicates that there is promising progress in producing more effective and child-friendly combinations of ARVs including better fixed-dose ART combinations (Glaser, 2017).

Due to the availability of ART and its efficacy, a large number of children living with HIV who acquired HIV through MTCT are now reaching adolescence (Lowenthal, 2012; UNICEF, 2016). However, it is a great challenge to maintain treatment adherence in adolescents according to previous reports (Lowenthal, 2012). Therefore, provision of quality care and support for pediatric patients is believed to be the pillar to ensure ongoing treatment adherence and retention in care, thus preventing ongoing treatment failure (Lowenthal, 2012) and achieving optimal ART outcomes (Davies et al., 2015).

Children living with HIV face not only decreased physical health, but it also affects the child's psychosocial dimensions such as distress from the loss of parents, economic crises due to high demand of health costs and lack of income source due to loss of parents (Kang, Dunbar, Laver, & Padian, 2008) and mental health problems (Vreeman, McCoy, & Lee, 2017). The psychosocial problems become exacerbated when the child transitions from pediatric age to adolescence due to developmental challenges during this age (Davies et al., 2015). Some of the major challenges include difficulties visiting health facilities and accessing health services on their own. This could be due to the fear of stigma but also due to the lack of a child-friendly conducive environment at the facilities they attend for treatment and care (Davies et al., 2015). In general, their experiences are found to articulate mainly with the struggle of maintaining treatment adherence, ensuring retention in care, resisting stigma, disclosure and getting power to negotiate issues related to sexual relationships (Nachega et al., 2009). The extent of social and structural deprivation in particular settings may exacerbate the aforementioned experiences among children and adolescents (Cluver et al., 2015).

Stigma can affect children either directly when it leads them to active discrimination or status loss, or indirectly when the family caregivers experience stigma and discrimination (courtesy stigma) (Deacon & Stephney, 2007). Active discrimination against the child can exacerbate the existing social marginalization (Deacon & Stephney, 2007). An explorative study through drawings and stories revealed that AIDS-affected children refused to play with other children; they preferred to keep their distance and mistreated others. At school AIDS-affected children often sit at the back

of the classroom as other children do not want to sit close to them, and this affects their learning outcome (Campbell, Skovdal, Mupambireyi, & Gregson, 2010). AIDS-affected children often lack friends, which leads to a negative impact on their psychosocial well-being, leading to loneliness and isolation (Campbell et al., 2010). There is extensive literature on children and HIV/AIDS (Deacon & Stephney, 2007) yet children's stigmatization and its outcomes is an under-researched subject (Campbell et al., 2010; Deacon & Stephney, 2007).

The paucity of strong evidence due to limited research continues to be one of the major barriers to developing high-standard policies and guidelines and thus ensuring the provision of quality of care and treatment for pediatric patients. As a result, the treatment and care of pediatric patients is practiced with less commitment and confidence as most of the recommendations, including the WHO guidelines for pediatric treatment and care, remain conditional to this end (Davies et al., 2015; Vreeman et al., 2015).

## Family caregivers

A family is defined as a social context consisting of at least two persons characterized by caring, mutual attachment, long-term commitment, and responsibility (Craft & Willadsen, 1992). A family caregiver can be defined as anyone who is a family member, a parent, sibling, extended family member, or recognized guardian who is an unpaid for being involved in providing any type of physical and/or emotional care for an ill or disabled individual at home (FCA, 2012). Family caregivers play a fundamental role in ensuring the comprehensive health of a child diagnosed with HIV and enrolled in ART. They are found to bear more than 90 percent of all the HIV-related burdens responding to children below the age of 15 years (Irwin, Adams, & Winter, 2009). These roles include promoting the child's treatment adherence, following and timely reporting child's treatment adverse reactions, and ensuring retention in care (WHO, 2013). Therefore, successful treatment outcomes in children rely on the level of the family caregivers' commitment and involvement (WHO, 2013). However, in most cases they lack adequate knowledge, skill, or resources to tackle it (Irwin et al., 2009).

Regardless of the stage of disease or age of the person, people living with HIV (PLHV) have various and ongoing needs including physical and psychosocial needs. Fulfilling these needs can be more difficult when the HIV-infected person in the family is a child. HIV usually affects the entire family (Irwin et al., 2009). In most cases, the presence of an HIV-positive child in the family means it is likely that the child's biological mother is also living with HIV (Rose & Clark-Alexander, 1998; WHO, 2010a). When family caregivers are biological parents who are living with HIV themselves, the burden of caring for their child becomes intimidating due to the burdens related to their own HIV status and related co-morbidities. This situation further exacerbates the situation

of already poor family caregivers, leaving them physically and mentally overwhelmed (Potterton et al., 2007; Punpanich, Detels, Gorbach, & Leowsrisook, 2008) when they have to fulfill the child's health, economic and social demands (Mathambo & Gibbs, 2009).

When the family caregiver is a biological parent, the range of caregiving is not limited to fulfilling the daily requirements of the child, but also involves preparing the child for how to live their own life without parents in the future (Antle, Wells, Goldie, DeMatteo, & King, 2001). Biological parents are uncertain about their own future due to the devastating health condition related to their own HIV status. The parents assume that preparing the child is important to survive the coming psychosocial and physical health challenges related to the child's own HIV status (Antle et al., 2001). In addition, many children who are infected by HIV have often lost one or both parents at an early age, which makes them highly vulnerable and distressed. This situation in turn leads them to experience economic crises and thus they cannot manage their health service costs and daily basic needs (Kang et al., 2008).

Family caregivers experience considerable stigma and discrimination in the community, which contributes to frustrations in the family (Hamra, Ross, Karuri, Orrs, & D'Agostino, 2005; Surkan et al., 2010; Washington & Oberdorfer, 2013) and eventually may lead to psychosocial catastrophes (Surkan et al., 2010). The family caregivers have also been found to experience high levels of stigmatization and discrimination related to their child-caring process for HIV, which tended to increase their distress levels (Orner, 2006). The family caregivers' experience of stigma and discrimination affects not only the sick child and the family psycho-socially but also the process of healthcare service utilization as a whole (Washington & Oberdorfer, 2013).

## Caring perspectives

The UN Convention on the Rights of the Child (UNCRC) from 1989 (UN 1989) acknowledges children's needs, status, role, and rights. The UNCRC is acknowledged by 196 countries, including Ethiopia. Sixteen of the 54 articles set the standards when caring for children stating that the child's best interest always should be considered. While there is no standard definition of child's best interest, it is proposed that it should imply that the child is an active party in decision making and receives relevant age-appropriate information. Further, decisions made reflect the child's opinions, views, and wishes, while taking into consideration the child's age, maturity and competencies. Earlier research highlights that the child's best interest is reflected when the child knows what is to be expected about their care (Hallström, Runeson, & Elander, 2002; Runeson, Hallström, Elander, & Hermeren, 2002), is respected as having opinions about their care (Hallström et al., 2002; Runeson et al., 2002; Stålberg, Sandberg, &

Söderbäck, 2016), preferences are included (Coyne, 2008; Runeson et al., 2002), is an active recipient of care (Schalkers, Dedding, & Bunders, 2015), offers insights on how care should be delivered (Schalkers et al., 2015), competence is reflected in parents' and healthcare professionals' attitudes (Martenson & Fagerskiold, 2007), and participation is based on principles for child- and family-centered care (Coyne, Hallström, & Soderback, 2016).

In most countries family-centered care (FCC), based on a close and continuous involvement of the child's family has evolved in health care during the last fifty years (Shields et al., 2012). In 2007, Shields et al. defined FCC during a hospital admission as "care that is planned by the health staff around the whole family, not just the individual child" (Shields et al., 2012). Even if FCC has been practiced in many countries and in many contexts the implementation of FCC is problematic (Coyne, O'Neill, Murphy, Costello, & O'Shea, 2011; Coyne, Murphy, Costello, O'Neill, & Donnellan, 2013; Foster, Whitehead, & Maybee, 2010; Harrison, 2010). Two systematic literature reviews show little evidence of its impact and effectiveness for children, families and health care (Shields, Pratt, Davis, & Hunter, 2007; Shields et al., 2012). The dominance of adult family members and professionals in FCC constructs an asymmetric relationship and includes a risk of taking away the focus from the child's perspective (Hallström et al., 2002). This can be problematic when parents' or caregiver's needs are not synchronous with the child's needs. Lately, a discussion about moving from FCC to a child-centered care (CCC) approach and the implications for health care practice has evolved (Coyne et al., 2016). In CCC care is still in the context of family and community but is based on the child's perspective and preferences and reflects the UNCRC standard. CCC implies that the child is involved in healthcare matters affecting them and care is tailored according to the child's needs and preferences (Coyne et al., 2016).

Care at the health facilities in Ethiopia is usually provided for the child through a FCC approach in which the health care providers and family caregivers play the major role in child's caring process. The spectrum of caring practice for the child diagnosed with HIV and enrolled in ART in the health facilities practiced through the task-shifting approach, in which the clinical services such as physical assessment, ART adherence assessment and nutritional assessment are provided by trained health professionals (usually clinical nurses or health officers) at the outpatient department (OPD) (FMOH, 2014). The non-clinical services such as escorting children to OPD services, adherence counseling based on the identified risk of ART non-adherence, facilitating community referral linkage for nutritional and psychosocial support, active tracing of missed appointment children and retention counseling are being done by trained adherence supporters, who are PLHIV themselves (FMOH, 2009a).

Family caregivers are also actively involved in their own and their child's care plan preparation and implementation process (FMOH, 2009b). The FCC approach, with the family involved in all steps of planning, implementation and evaluation of health care delivery, might not be adequate due to lack of a fully functional system that invites

active participation of families in the process. Nevertheless, FCC is suggested to be a feasible and effective approach in providing comprehensive HIV care for pediatric clients as a one-stop model for the family (Luyirika et al., 2013). This is because in resource-limited settings, HIV/AIDS is considered to be a family concern, thus separate service provision for children and adults compromises the process of accessing care, compared to caring for family members together (Tolle, 2009).

The provision of HIV care and treatment services for children has particular implementation challenges such as that children may not know about their HIV and treatment status, pediatric patients are highly dependent on their caregivers and strict follow-up is needed to adjust pediatric medication doses over the time (FMOH, 2014). Therefore, the pediatric ART and care service is intended to practice as child- and family-friendly care as possible (ICAP, 2015). In general, the pediatric ART treatment and care practice is integrated with maternal, newborn, and child health (MNCH) care such as family planning, immunization, growth monitoring and nutrition services in Ethiopian health facilities (ICAP, 2015), aiming to avoid the implementation challenges related to pediatric treatment and care and to ensure continuity of care.

In resource-constrained settings, care given by family caregivers in the home for chronically ill people is considered to be an efficient and cost-effective substitute for hospital care. It is assumed that the increasing number of children in ART in Ethiopia may mean confronting greater challenges for service providers, family caregivers and the society at large as the demand to follow and meet the holistic needs of the child on treatment would dramatically increase. The very short-term challenges may include ensuring children's treatment adherence as the country has limited experience in this regard. Yet another challenge is family caregivers' long-term challenge of caring for a child with unpredicted needs emerging in relation to the nature of the disease and treatment which is an extra burden far beyond the basic needs of a child under normal circumstances. The major objective of family caregivers' care for a child with HIV is to provide a continuous and holistic care service at home and bridge the referral service linkage with facilities through which to reduce sufferings, complications and eventually to promote health (FMOH, 2007).

However, in resource-limited settings including Ethiopia, the continuity of care practice given by family caregivers obviously may encounter several challenges including fulfilling the basic needs of a child, ensuring access to essential drugs when a child gets sick, regularly following the treatment adherence of the child, dietary restrictions, treatment side effects, and disclosing HIV status to the children themselves (WHO, 2010a). The international AIDS policy makers seem to have overlooked this key issue of HIV status disclosure to children (Dunn, 2005; Hejoaka, 2009). The aforementioned challenges will obviously compromise efforts towards achieving the intended goal of holistically caring for the child through care by the family.

# Theoretical framework

In this thesis stigma theory was used as a theoretical framework, as earlier research has shown that HIV/AIDS-related sigma is one of the major challenges affecting the lives of PLHIV. These challenges originate from stigmatizing behavior leading to stigma-related outcomes including poor social support and health services utilization, violation, poor-quality health, and isolation (Duffy, 2005; Holzemer et al., 2007; Surkan et al., 2010).

When stigma is defined, several authors quote Goffman's traditional definition as a 'significantly discrediting' attribute (Goffman, 1963) p. 3). Based on the Goffman's perspective, Alonzo & Reynolds (1995) further defined stigma as 'a powerful discrediting and spoiling social label that radically changes the way individuals view themselves and are viewed as persons' (p. 304). The concept of stigma is broad and linked to multiple dimensions with the essence of issues related to deviance (Alonzo & Reynolds, 1995). According to social scientists' theory, the existing socio-economic and structural inequalities among already marginalized individuals due to loss of power and social status could be exacerbated by disease-related stigma and its negative outcomes (Daftary & Padayatchi, 2012; Holzemer et al., 2007).

Stigma is a well-known reason to fuel the HIV pandemic and has received huge attention since the 2000 International AIDS Conference in Durban, South Africa. It has become a global agenda to break the silence (Holzemer et al., 2007), which is defined as "the urgent need to break the silence on equal access to treatment and care; prevention of HIV transmission; support of HIV education and resources by the governmental and private sectors; ensure human rights; ensure that all sectors be able to access an appropriate and meaningful information and make sure a supportive environment is created for PLHIV in society" (The Body, 2000). Stigma is found to be a major obstacle to the fight against HIV and its effects as it limits the extent of care and support service utilization as well as treatment adherence among PLHIV (Campbell, Nair, Maimane, & Gibbs, 2009; Weiser et al., 2003). The devastating outcome of the AIDS stigma has been called "the silent killer of AIDS" (Ki-moon, 2008).

It is assumed that there is a need to describe the outcomes of stigma and it is proposed that contextualized and evidence-based stigma reduction interventions should be developed and evaluated in order to promote quality of care and work life (Giddens, 1979).

# Stigma theory

In this thesis the Earnshaw and Chaudoir HIV stigma framework was used to describe the mechanism and outcomes of HIV stigma in PLHIV (Earnshaw, 2009). Earnshaw and Chaudoir (2009) described HIV stigma through mechanisms such as enacted, anticipated, and internalized stigma from the PLHIV perspective. Enacted stigma is described as PLHIV believing they have experienced prejudice and/or discrimination from others in their community; anticipated stigma means that PLHIV expect that they will experience prejudice and discrimination from others in the future; and internalized stigma is when PLHIV develop negative beliefs and feelings about themselves because of their HIV/AIDS (Earnshaw, 2009).

PLHIV can also develop socially devalued status and prejudice, stereotypes and discrimination from HIV-uninfected individuals' perspective, and these stigma mechanisms ultimately harm their psychological, behavioral, and health outcomes (Earnshaw, 2009; Misir, 2015). Stigma can be triggered by an HIV diagnosis or disclosure and lead to stigmatizing behavior that ultimately leads to stigma-related outcomes such as poor health, violence, reduced access to care, and poor quality of work life (Holzemer et al., 2007).

In addition, Giddens's structuration theory of action is used to underline how human action and structure can play an independent role and/or interact to produce HIV stigma as part of a social system (Giddens, 1979). According to Giddens (1979), it is important to understand the power relationship as a form of interaction between the actor and the structure. Giddens explains the duality of structure, where structures can be both the medium and the outcome of practices which ultimately produce a social system. This means that structures produce and shape human action and human action, in return, produces and reproduces structures. This leads to the conclusion that structure and human actions are highly interdependent in supporting each other (Giddens, 1979).

The HIV/AIDS stigma negatively influences an individual's social interactions, ranging from their intimate family to the broader community (Varas-Díaz, Serrano-García, & Toro-Alfonso, 2005). Disease-related stigma is likely to exacerbate the existing social inequalities among already marginalized individuals due to loss of power and social status. The vulnerability to stigma may continue due to the pre-existing socio-economic and structural disparities in the population (Daftary & Padayatchi, 2012).

HIV/AIDS-related stigma is found to affect the child living with HIV and family caregivers in various respects. Fear of stigma may trigger fear of disclosure of HIV status and treatment to the child and/or others in the community due to fear of violence, social rejection and negative attitudes, possibly reflected to the child and caregiver by the community where the child and family caregivers live (Strode & Barrett Grant, 2001). Fear of disclosure of HIV status and treatment to the child is found to cause

high tension and conflict between the family caregiver and the child (Abebe & Teferra, 2012; Brown et al., 2011; Kajubi et al., 2016). These conditions are less common in children with other chronic diseases or malignancies (Kajubi et al., 2016; Vranda & Mothi, 2013). The child and the family caregiver may develop a negative image of themselves, such as feelings of powerlessness and emotional pain (Strode & Barrett Grant, 2001) due to the perceived stigma, which leads them to ill health. In addition, HIV/AIDS-related stigma is likely to hamper ARV treatment adherence, future hope, self-esteem, and empowerment of the PLHIV (Livingston & Boyd, 2010; Nachega et al., 2004; Weiser et al., 2003).

# Aim

The overall aim of this thesis is to contribute to the improvement of care for children living with HIV on antiretroviral therapy in Ethiopia through enhanced knowledge and understanding of the family caregivers' experience and factors of importance for the children's outcomes. The knowledge will serve as basis for further planning of care and informed decision making in the area. Four specific aims were formulated, one for each paper.

## Specific aims

- Illuminate the family caregivers' lived experiences of caring for a child when a child was diagnosed with HIV and enrolled in antiretroviral treatment (Paper I).
- Evaluate family caregiver-reported ART non-adherence and its predictors among children in the early stages of treatment (Paper II).
- Illuminate the family caregivers' lived experiences of caring for a child diagnosed with HIV two years after the child was enrolled in antiretroviral treatment (Paper III).
- Determine rates and predictors of mortality and loss to follow-up among children on ART (Paper IV).

# Methods

## Design

This thesis is based on a mixed methods design aimed to provide a broader picture and a deeper understanding of the family caregivers' lived experience and treatment outcomes of children diagnosed with HIV and enrolled in ART using between-methods triangulation with different perspectives (Johnson, Onwuegbuzie, & Turner, 2007). Four interrelated parts (Papers I–IV) derived from a cohort of children under 14 years of age prospectively enrolled to ART and their respective family caregivers were included.

Both an inductive qualitative design (Papers I and III) and a quantitative prospective cohort design (Papers II and IV) were used. An overview of the studies is shown in Table 3.

**Table 3.** Overview of study design, sample, data collection, time frame, and analysis

| Paper | Design | Sample | Data collection | Time frame | Data analysis |
|---|---|---|---|---|---|
| Paper I | Qualitative inductive | 21 family caregivers | Semi-structured interviews | At the time of enrollment | Hermeneutic phenomenology |
| Paper II | Prospective cohort study | 306 family caregivers | Structured interviews and medical records | One week and one month after the child's enrollment | Descriptive and logistic regression |
| Paper III | Qualitative inductive | 18 family caregivers | Semi-structured interview | Two years after the child's enrollment | Hermeneutic phenomenology |
| Paper IV | Prospective cohort study | 304 children | Medical records | 12 months after the child's enrollment | Survival analysis |

# Mixed methods

Methods triangulation approach was first constructed by Denzin (1978), aimed to obtain a rich information in order to develop a broader understanding of a phenomenon. Based on historical perspectives and new developments, mixed methods is defined as the process of synthesis of methods by using intellectual and practical approaches to combine qualitative and quantitative research to provide the most informative and complete research results (Johnson et al., 2007). Mixed methods is also defined as an "intentionally integrating or combining multiple methods to draw on the strengths of each; and framing the investigation within philosophical and theoretical positions" (Creswell, Klassen, Plano Clark, & Smith, 2011, p. 5).

Denzin (1978) describes four types of triangulation to answer research problems properly: methodological triangulation, investigator triangulation, theory triangulation, and data source triangulation. Methodological triangulation is based on the use of multiple methods to answer the research question by using either within-methods triangulation (the use of either multiple quantitative or multiple qualitative approach) or between-methods triangulation (the use of both quantitative and qualitative approaches) (Denzin, 1978). This is also described by Johnson et al. (2007) as quantitatively driven approaches, qualitatively driven interactive or equal status designs approaches (Johnson et al., 2007). The outcomes of triangulation could be: convergence, inconsistency, or contradiction. Regardless of which outcome, mixed methods give scope to the researcher to uncover the result with comprehensive and rich information with better confidence (Denzin, 1978). This thesis followed the convergence outcome triangulation, and the different parts of the thesis are intentionally merged together to provide a comprehensive understanding of the family caregivers' lived experience and treatment outcomes of children diagnosed with HIV and enrolled in ART.

A hermeneutic phenomenological method advocated by van Manen (1997) was used to gain a deeper understanding of the caregivers' lived experience from the child's diagnosis and two years after. According to van Manen (1997) hermeneutic phenomenological research intends to illuminate and interpret human experience in the way informants themselves describe it. The methodology has roots in both descriptive and interpretative phenomenology and thereby combines lived experience as described phenomena with interpretation of the lived meaning of the phenomena (Dowling, 2007). It seeks to go beyond descriptions in order to discover meanings that are not immediately apparent (Merleau-Ponty, 1996; van Manen, 1997).

According to van Manen (1997) a person's life world covers four existential dimensions: lived body, lived time, lived space, and lived human relations. They are all important when trying to obtain a deeper understanding of phenomena such as caregivers' lived experiences of caring for a child diagnosed with HIV.

In the quantitative studies, a prospective cohort design was used to follow the child's treatment adherence during the early weeks of treatment initiation and determine follow-up outcomes of LTFU and death during the twelve months. Prospective cohort study helps to determine incidence rates and relative risks, and is important for investigating multiple outcomes to the single exposure and it allows survival analyses to be performed (Grimes & Schulz, 2002).

## Study setting

The studies were performed in Ethiopia. Ethiopia is located in eastern Africa and over 99.4 million people were estimated to live there in mid-2017 (World Bank, 2015), making the country the second most populous country in Sub-Saharan Africa. Regardless of the repeated and impressive economic growth, the income per capita in Ethiopia is found to be US$ 590 and a significant proportion, 33.5%, of the population are living below the defined poverty line of $1.90/day (World Bank, 2015).

The studies were conducted in eight selected health facilities in four urban and rural towns (Addis Ababa, Bishoftu, Mojo and Adama) from two big administrative regions (Addis Ababa and Oromia regions) of Ethiopia (Figure 4). The three towns (Bishoftu, Mojo and Adama) from the Oromia region of the East Showa zone are located on the main highway between Addis Ababa and Dijibouti. This highway is known to be the main route for imports and exports to and from the capital, with high traffic and throughput of travelers, thus the risk of HIV transmission is considered to be high in these towns. The health facilities were selected due to their high load of adult and pediatric patients enrolled in HIV treatment and follow-up.

The total population of Addis Ababa is 3.3 million, accounting for 4.4% of the country's population, whereas Oromia has a total population of about 29 million, accounting for 37% of Ethiopia's population projected for 2014–2017 (CSA, 2013). In Oromia a total of 283 health facilities have ART clinics, and in Addis Ababa the corresponding number is 58 (FHAPCO, 2012). Most of the hospitals in Addis Ababa serve patients coming with referral slips from all over the country. The selected health facilities in Oromia also serve a high load of adult and pediatric patients coming from urban and rural peripheries. See the location of the study sites in Figure 4.

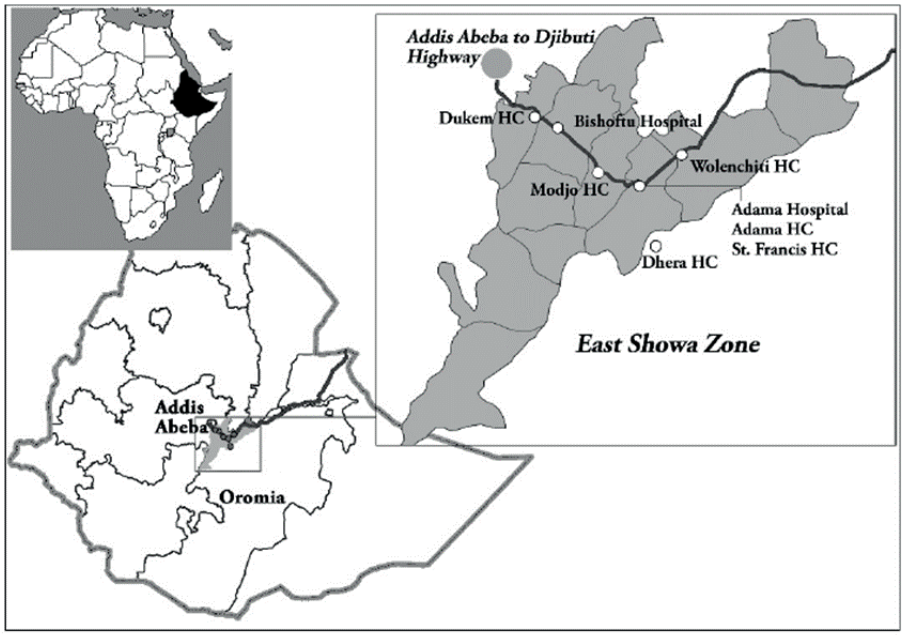


**Figure 4.** Map of Ethiopia with study sites

## Study participants

Different steps were taken during the process of enrolling children and their family caregiver in the study. The first step included a screening log to ensure the participants eligibility. In a second step the eligibility of children and their family caregiver was confirmed in the enrollment log and the caregivers' informed consent/refusal was obtained and documented. Each family caregiver who agreed to participate was assigned a specific participant identification code (SPID) which was recorded in the recruitment log. The structured interviews (appendix III) and the children's' medical records were reviewed by the ART provider using a chart review template (appendix III). Finally, the process of completion of screening log, enrollment log, chart review template was reviewed by the author of this thesis. A description of the enrollment process is presented in Figure 5.

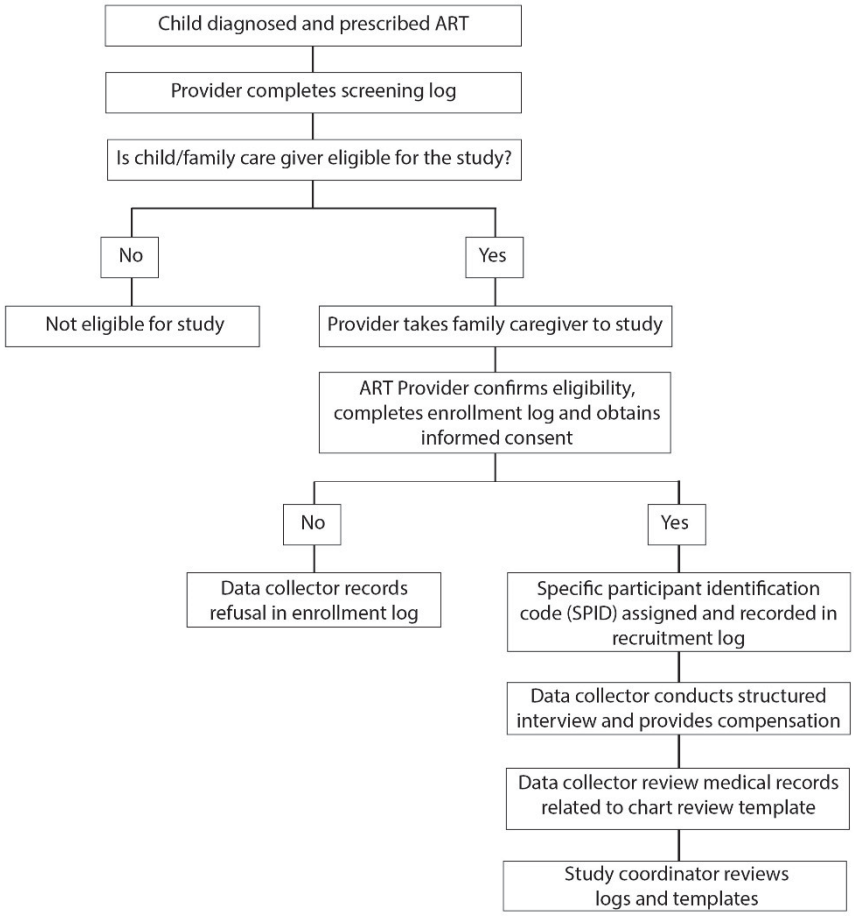


**Figure 5.** Description of the child's/family caregivers' enrollment process.

## Description of children and family caregivers in the cohort

In total 309 children, newly diagnosed with HIV and enrolled in ART, and 309 family caregivers from eight health facilities were eligible for inclusion in the study between 20 December 2014 and 20 April 2015.

The inclusion criteria were:

- Family caregiver or responsible guardian older than 18 years.
- The child between the age of 3 weeks and 14 years diagnosed with HIV and enrolled in ART not more than a month duration.

The exclusion criteria were:

- The child has already been on ART for more than a month
- The child has other severe illnesses or is terminally ill

After the child's diagnosis and enrollment to ART the family caregiver was approached by the ART provider. Three caregivers refused to allow their children to participate in the study, making the response rate 99%. Three hundred and six family caregivers (250 females and 56 males) to 306 (158 males and 148 females) children were consecutively included in the study (Figure 6), comprising 184 biological mothers, 40 biological fathers, 18 grandmothers, 12 sisters, 5 brothers, 4 legal guardians, and 43 other relatives (Paper II). During ART initiation, the median age of children (both girls and boys) was 9 years with interquartile range, IQR, 6–13 and 5–12 respectively. At ART initiation, the median BMI for age z-scores for girls and boys were –0.86 (IQR –1.8–0.005) and –0.75 (IQR –1.4–0.1) respectively. Most (82%) family caregivers were females and 73% of them were biological parents or legal guardians of the children (Paper II). Two children were found to have the same unique code and were excluded from the follow-up pool, resulting in 304 children on follow-up (Paper IV). A description of the cohort of family caregivers' and children is shown in Figure 6.

At the time of child enrollment to ART (Paper I), 21 family caregivers to 21 children consecutively enrolled to ART from seven of the health facilities were purposively selected (Shenton, 2004) from the list of family caregivers enrolled to be interviewed. The selected family caregivers comprised 13 biological mothers, four biological fathers, one uncle, one grandmother and two other relatives.

Two years after the child's enrollment in ART (Paper III), two of the 21 caregivers had withdrawn from their regular appointments and could not be contacted. One caregiver was critically ill and the child died during the data collection period. In total, 18 family caregivers of 18 children were interviewed (Paper III), comprising 12 biological mothers, three biological fathers, one uncle, and two other relatives. All biological parents participating in the study were HIV-positive and were on ART. The other caregivers' HIV status was unknown. A description of the family caregivers is shown in Figure 7.

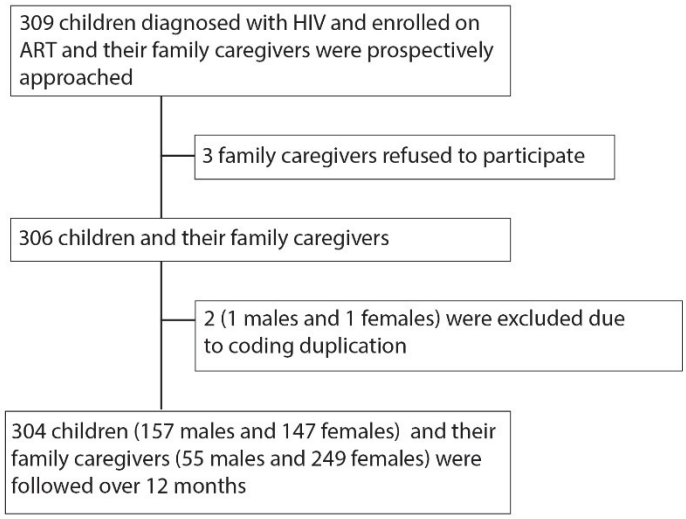


**Figure 6.** Family caregivers and children diagnosed with HIV.

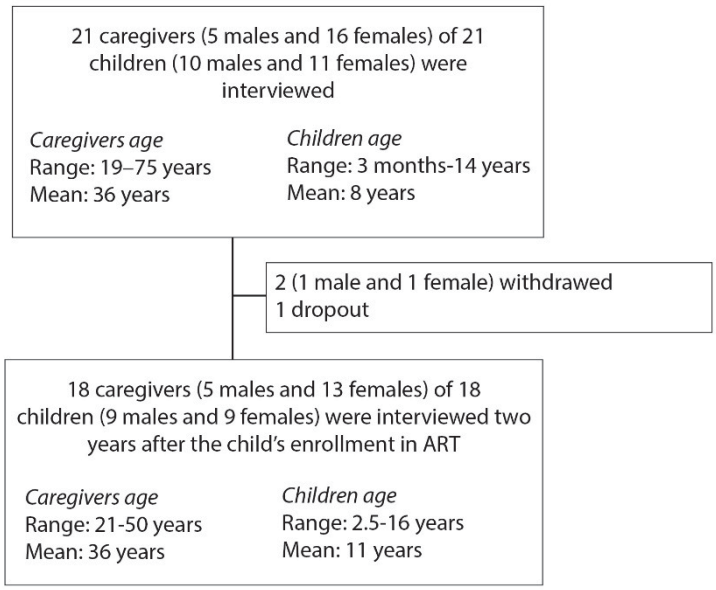


**Figure** 7. Family caregivers and children diagnosed enrolled in ART at baseline and after two years.

## Qualitative data collection

In Paper I, a semi-structured interview guide (Appendix I) developed by the author of this thesis and discussed with four senior researchers was used as a guide during the interviews. Two pilot interviews were carried out to evaluate the flow of the interview, to identify sensitive areas, and to get further emerging ideas and direction. Based on the pilot interview findings, the interview guide was further modified with some new insights and the flow of the questions was slightly changed. The pilot interviews were not included in the analysis due to the modifications made.

Conversational individual interviews were conducted between January and September 2014 by the author of this thesis, speaking Amharic with each family caregiver to illuminate their experiences, perceptions, feelings, and challenges caring for the child enrolled to ART (Paper I), and two years after (Paper III). Before starting the interviews (Papers I and III), the interviewer spent some time with the caregivers and conversed informally in order to establish a good atmosphere so that the caregivers felt comfortable. The caregivers were then asked to narrate, in their own words, their experiences of caring for a child living with HIV. In Paper I, each interview lasted between 30 and 60 minutes with an average time of 40 minutes. Each interview started with the initial question: "Can we discuss what it means for you to care for a child living with HIV?" Follow-up questions such as, ''Can you explain further?'' and ''Can you tell more about it?'' were then posed by the interviewer.

In a second interview, two years after the child's enrollment to ART between April and September 2016 (Paper III), the family caregivers were reminded about the first interview two years ago and thereafter asked to narrate their experiences of caring for a child diagnosed with HIV and enrolled in ART. Each interview started with the initial question: "Do you remember how you felt when we met two years ago?" and "Can you tell me about your experiences of caring for your child with HIV since we met two years ago?" Follow-up questions included, "Tell me about good or/and bad experiences"; "Did you experience any challenging events?", "Can you tell me more about it?" An interview guide (Appendix II) made sure that specific topics were covered in all interviews. The second interviews lasted between 40 and 60 minutes with an average time of 50 minutes.

All interviews (Papers I and III) were conducted in a private room at the ART clinic of the health facility to ensure the participants' confidentiality. The interviews were audio-taped with permission from the participants'. Written notes were taken by the interviewer for two of the participants as they declined to be recorded (Paper I). In addition, notes were taken (Papers I and III) to complement participants' non-verbal expressions, such as emotions and silences.

## Quantitative data collection

Data were collected seven and 30 days after initiation of ART to the child newly diagnosed with HIV between 20 December 2014 and 20 April 2015 (Paper II). Children were followed for 12 months where the second data collection was performed (Paper IV). Before starting the study, the data collection materials were piloted in two sites on 20 caregivers and their children. Accordingly, minor modifications were made to the instrument.

A study-specific, Self-Reported Adherence questionnaire (Appendix III) and follow-up data capturing template (Appendix IV) (Papers II and IV) was adopted based on the instruments used in similar studies (Arage, Tessema, & Kassa, 2014; Ebissa, Deyessa, & Biadgilign, 2015). In addition, the child's medical records pertinent to assess children's treatment adherence in terms of baseline CD4 count and WHO staging, and variables concerning the child's treatment regimen during treatment initiation were documented using the standardized protocol (Arage et al., 2014; Ebissa et al., 2015).

Data were collected by an ART provider assisted by a data clerk using Self-Reported Adherence questionnaire (Appendix III) (Paper II) and follow-up data collection template with periodical and regular scheduled visits to the clinic (Paper IV). The instrument was suggested to be a useful instrument for assessing ART adherence in an earlier study (Munoz-Moreno et al., 2007). The child's regular visits followed the national guidelines that children returned for their first follow-up visit two weeks after ART initiation and every month thereafter for treatment refill and adherence assessment. Then after every three months for clinical examination and toxicity assessment (FMOH, 2007).

Independent variables included in the questionnaire were: socio-demographic, socioeconomic, and disclosure variables of caregivers and children as well as the child's adherence to treatment and clinical data of the child including baseline and progressive assessment of CD4 count, baseline WHO clinical staging; child's baseline treatment regimen. Additional explanatory variables were: change of the child's treatment over the time, child's anthropometric measurements at baseline and after 12 months. The structured questionnaire and template for data collection was developed in line with the national data capturing and documentation system. Attrition (Paper IV), defined as a combination of death and LTFU, was considered to be the main outcome variable as reported in patient records. The ART provider and assistant data clerk received training on how to collect data and they were supervised twice monthly and provided with regular on-site support by the author of this thesis.

# Data Analysis

## Qualitative data analysis

The transcribed interviews in Papers I and III were analyzed using a hermeneutic phenomenological approach inspired by van Manen (1997). First the interviews were transcribed in the local language, Amharic, and thereafter translated to English. This process was conducted by the author of this thesis in collaboration with a native speaking co-author fluent in English and with extensive experience in qualitative research. In Paper I all the transcribed interviews were read by all authors to develop an overall sense of the participants' descriptions. Then the author of this thesis looked at every single sentence, asking what each sentence showed about the caregivers' lived experience and key phrases from the sentence were highlighted. With all four authors' consensus, substantial statements were organized and interpreted, based on their similarities and differences.

In Paper III the interviews were read by three of the authors (MB, DJ, IH) to obtain an overall picture of the caregivers' lived experience as described in their own words. Then the interviews were separately read line-by-line by four of the authors (MB, DJ, IH, PL). Thereafter, the clusters of sentences with key phrases illuminating the caregivers' lived experiences were highlighted using different colors to reflect the four fundamental lifeworld existentials (van Manen, 1997).

In both papers (Papers I and III) all authors looked at the highlighted text to evaluate it, and in discussions among all authors, its meaning was interpreted to reflect the caregivers' lived experience. After extensive discussions among the authors, preliminary themes emerged. These were compared and a thematic meaning structure of main themes and sub-themes was formulated. During the writing process, the text evolved through a continuous back-and-forth process of parts between the emerging themes and the transcribed interviews to ensure that the caregivers' lived experience was deeply rooted in the text (van Manen, 1997)

Quotes from the interviews were used to illustrate the caregivers' lived experience. Different code numbers and letters after the quotations indicate different health facilities and references to the participants; Mother (M), Father (F), and other relative (OR) (Papers I and III).

## Quantitative data analysis

OpenEpi statistical software (http://www.openepi.com/Menu/OE_Menu.htm). was used for calculation of the sample size. The following assumptions were used to calculate sample size: Lost to follow-up (LTFU) as the main outcome variable;

inadequate family and heath care support as the exposure category (dichotomized as adequate or inadequate); percentage of exposed and unexposed groups with outcome as 30.6% and 15% respectively; Odds Ratio (OR) of 2.5; and power of 80% at 95% CI. The minimum sample size was expected to be 300 children including a 20% non-response rate (Papers II and IV).

In Paper I descriptive analysis was applied to describe the baseline information of the child and family including: socio-demographic, treatment and clinical markers in proportion. In addition, logistic multivariate regression was applied to determine independent predicting factors of ART non-adherence among children in their early weeks of treatment initiation. Similarly, in Paper IV a descriptive analysis was performed to describe child's person time contribution in follow-up, incidence rates of LTFU and death, and the changes in treatment regimen. Furthermore, survival analysis was done using multivariate Cox proportional hazards models to assess independent predicting factors of an outcome. The frequencies and proportions of caregiver and child characteristics were described using descriptive statistics. Levels of ART adherence was dichotomized and measured as non-adherent versus adherent in the first week and first month after the child's enrollment in ART. The dichotomized ART adherence was the main outcome variable in Paper II. The explanatory variables with $p<0.25$ in the bivariate analysis were included in the multivariate analysis. Multivariate analysis was performed using the binary logistic regression method and statistical association was described as adjusted odds ratios with 95% CI. Statistical significance was set at $p<.05$.

In Paper IV time duration on follow-up was adjusted for the child's heterogeneous enrolment in treatment. The main outcome was attrition due to death and/or loss to follow-up. Outcomes in the time period up to the end point of the 12-month follow-up were assessed by categorizing as under follow-up, LTFU, dead (as recorded in the treatment register) or transferred out (TO) and these outcomes during the follow-up were estimated using Kaplan–Meier methods. The explanatory baseline variables included in the Cox proportional hazards models were: caregiver's and child's socio-demographic variables (age, sex, residence, vital status), child's clinical markers such as baseline hemoglobin (Hgb) levels in g/dl, severe immunodeficiency based on immunological or clinical definitions, body mass index for age (BAZ), CD4 counts and WHO clinical staging.

In Paper IV a multivariable model was used to adjust for age, sex, residence (rural, urban), CD4 cell count, WHO stage, and Hgb g/dl. Variables with $p<0.25$ in the univariate analyses were included in the multivariate analyses. The IBM statistical package for social sciences version 22.0 for data entry and analysis (IBM Corporation, Armonk; NY, USA) was used (Papers II and IV). Statistical significance was described as adjusted hazard ratio (HR) with 95% CI and statistical significance was set at $p<0.05$.

# Preunderstanding

Preunderstanding is considered as the knowledge that is based on our previous, non-critical, taken-for-granted exposure that is important to understand a specific phenomenon (Dahlberg, Nyström, & Dahlberg, 2007; van Manen, 1997). According to van Manen (1997) a person's understanding might influence the person to reflect the lived experience prematurely before achieving the level of understanding to describe the phenomenological question. It is therefore important to make your own understanding and beliefs explicit and hold it at bay, but not to ignore it.

The author of this thesis has a professional background in clinical nursing and public health and has worked in the areas of HIV prevention, treatment, care, and support programs and has more than fifteen years of experience at both local and national levels in Ethiopia. Furthermore, he is the father of two children. This means that he has long experience of the researched area and of being a family caregiver himself. During the research process, the preunderstanding was continuously discussed and reflected on to minimize the risk of bias and making premature interpretations. The other participants in the research team had other clinical and research experiences which enhanced and broadened the research perspective.

# Ethical considerations

The Swedish Regional Ethics Board (Ref. no. 2013/85) as well as the Institutional Review Board of Addis Ababa University (Protocol no. 045/13/sph), Oromia Regional Health Bureau (Ref. no. HIV-AIDS/sup-10/379), Addis Ababa City Administration Health Bureau (Ref. no AAH13/2084/227) and the National Research Ethical Review Committee in Ethiopia (Ref. no. 3.10/322/05) provided formal ethical approval. The studies strictly followed the international principles of research ethics outlined in the Declaration of Helsinki (World Medical Association (WMA, 2013).

In clinical research which includes human subjects, the principles of ethics need to be strictly followed with respect to the participants included in the study. In general, children are considered to be vulnerable as they cannot speak for themselves or who are unable to protect their own interests (Beauchamp & Childress, 2015). Conducting research on children diagnosed with HIV and enrolled in treatment and their family caregivers is challenging (Beauchamp & Childress, 2001) due to the risk of disclosure of the child's HIV status to others and the related fear of stigma and discrimination.

The four ethical principles for autonomy, beneficence, non-maleficence, and justice (Beauchamp & Childress, 2015) were strictly followed. In the studies, respect for participants' autonomy was assured by minimizing the risk of influence either from the researcher or the health care provider (Beauchamp & Childress, 2015). Adequate oral and written information was provided to the family caregiver about the purpose of the study and data collection process. This was demonstrated to promote caregiver freedom of choice to have a self-determined and independent decision to participate or not. Written consent was obtained from all family caregivers. For those who could not read and write, the consent statement was read to the participant and their consent was given by their fingerprint. In addition, the ART clinic focal person was asked to add his/her signature as an impartial witness. Confidentiality was assured and explanations of the purpose and possible benefits and disadvantages of the study were provided to the participants. They were told that they could withdraw from the study at any time without affecting the child's treatment. The ART provider explained the difference from the regular clinical care practice and they told the family caregivers that being enrolled in the research project did not affect their care or their child's clinical care. They were also told that they could withdraw from the study at any time without affecting the child's treatment; the duration of follow-up and the necessary information that was being collected during the follow-up was explained.

The principle of beneficence and non-maleficence was underlined to carefully evaluate any possible harm versus the benefit that may possibly be obtained from the research (Beauchamp & Childress, 2015). Conducting interviews with family caregivers about their HIV-diagnosed child enrolled in ART is challenging as the family caregivers' life situation is vulnerable. During the interview, the caregivers were assumed to be mentally and emotionally affected due to their child's disease and treatment status. The interview could exacerbate their emotional distress, and a careful approach and respect for them was shown during the interview. Most of the family caregivers said that they were happy and felt relieved with the opportunity to discuss their experience with the interviewer.

To ensure the principle of justice (Beauchamp & Childress, 2015), during the entire data collection period participants had adequate communication and were provided with the full address of the researcher. Both female and male family caregivers were invited to participate in the study regardless of their socio-economic status.

During the data collection time points family caregivers and children were offered drinks and fruits and compensation for travels. After the data collection period was ended children received school materials and bags. These gifts were not considered to compensate for the time and efforts the caregivers had contributed, but it was a small token of appreciation for their commitment.

# Findings

The findings about the family caregivers' lived experience when their child was diagnosed with HIV and enrolled to ART and the child's treatment outcomes are merged under the headings; *Caring perspectives at the time of diagnosis and treatment initiation through early weeks of follow-up* (Paper I and Paper II) *and Caring perspectives during the two years subsequent to the child's diagnosis and initiation of ART* (Paper III and IV).

## Caring perspectives at the time of diagnosis and treatment initiation through the early weeks of follow-up

The family caregivers experienced an overwhelming turmoil when their child was diagnosed with HIV and enrolled to ART. Their lived space, described as their normal family life, vanished since the attention in the family was diverted to the sick child and their previous family life pattern was totally altered. When the family caregivers were informed that their child had to start the treatment it was difficult for them to accept that their child had to be on lifelong treatment and they felt uncertain about their child's future life. Biological parents, especially mothers, felt that they were responsible for the HIV transmission to their child and they expressed that they felt guilty of being the one that caused the child's disease. Fathers accused themselves of being the reason for the HIV transmission to their partner and thereby to their child. This affected their own health and well-being, described as their lived body as well as their feelings and behaviors originating from negative images about themselves and their child due to the HIV status, described as their lived space. Not every child was cared for by a biological parent; about 27% of the children in the cohort study were taken care of by non-biological parents (Paper II) including brothers, sisters, grandmothers or fathers, uncles, other relatives, and legal guardians. In terms of non-adherence or missing doses during the first month after the child's ART initiation, the children whose caregivers were non-biological parents had better ART adherence than children with biological parents, 87 and 80% respectively (Paper II).

The family caregivers experienced a tension due to their child's situation and described many needs emerging from their child's HIV status. The child's condition was stressful for the caregivers regardless of being close to the child at home or away at a time. The family caregivers wanted to be close to their child to provide good care all the time.

However, this was not possible because they had to provide for the entire family, which required their engagement at work. The family caregivers also experienced a strain due to the HIV-related opportunistic diseases that might affect their child. This further affected the caregivers both physically and mentally as they thought that their child's situation required them to observe the child all the time. The family caregivers' strain was exacerbated when the child was critically ill and weak. Their stress could also be increased when they were enrolled to ART. This was observed among 65% of the caregivers in the cohort study (Paper II).

The family caregivers worried about and feared that their child's HIV and treatment status would be disclosed to the child or to other family members, who were not actively involved in the child's care, for example people in the village or friends at school, described as their lived human relations. They worried as they lived in communities where people lived close to each other and they shared activities in their daily life (Paper I). The results revealed that among children from 6 years of age and enrolled in ART, only 37% (n= 85) knew they were HIV positive (Paper II). Family caregivers felt that both the child and they were at risk of facing stigma and discrimination in the community where they lived which gave them much worry.

After the treatment started, the child became curious and asked the family caregivers about the regular clinic visits, the treatment and the reason for taking it. Due to the questions being raised, some caregivers disclosed the child's HIV and treatment status, which led the child to become committed to take responsible for their own treatment. When the family caregivers did not answer the child's question, it sometimes resulted in the child refusing to take the treatment (Paper I). Refusal to take the medication contributed to 20% of the reason for missing ART doses during the first month of the child's treatment (Paper II).

During the child's treatment initiation, the family caregivers also experienced that their child was unhappy about taking the medication due to medication-related side effects and unpleasant tastes of the syrup preparation. Medication side effect was found to contribute to 3.3% (n=10) of the missing prescribed doses during the first month after the child's treatment initiation. The extent of this problem was further examined and children receiving the combination therapy of protease inhibitor (PI) (LPV/r) or abacavir (ABC)-based treatment regimen were more likely to be non-adherent (aOR = 12.32, 95% CI: 3.25, 46.67). In addition, about 31% out of 306 children were also found to miss taking the prescribed doses due to other reasons including child sleeping, child illness, drug ran out, lack of food, transportation problem and other unknown reasons (Paper II).

The family caregivers had different religions beliefs, with the majority (80%) being Orthodox Christian, 11% Protestant Christian, (9% Muslims (Paper II). Their religious beliefs were found to be important and they were empowered in their strong belief in God. In addition, the benefits of the child's treatment and the counseling and support from the health workers was felt to be important. This further strengthened

their commitment to provide the regular care for their child and for themselves (Paper I). The family caregivers hoped that the treatment would possibly cure their child, which helped them to believe in a future for their child, described as their lived time. They were committed to allocating a significant amount of time to follow the child's health conditions on a regular basis, and some of the family caregivers used alarms to ensure 100% treatment adherence. (Paper I).

The findings revealed that the children whose family caregivers did not use a medication reminder were more likely to be non-adherent (aOR=5.21, 95% CI: 2.23, 12.16). In addition, the family caregivers' forgetfulness about the child's treatment contributed to 46% of the major reasons for missing ARV doses during the first month of the child's treatment. We also found that ART non-adherence decreased among children whose caregivers were not undergoing HIV care and treatment themselves (aOR=0.17, 95% CI: 0.04, 0.71) during the first week of treatment. However, during the first seven days and the first month after the child's treatment initiation, the overwhelming majority, about 93% and 94% of the children respectively were adhering to their ART. The caregivers' strong commitment and the close follow-up of the child's treatment was also found to be important for the child's adherence to ART.

## Caring perspectives during the two years following the child's diagnosis and initiation of ART

Two years after treatment initiation, the family caregivers felt that they were secured and happy due to the promising and positive effect of the treatment which improved their child's health. They found that their child was healthy and happy like the other children in the family and that they were able to attend school without interruption. As a result, the caregivers felt that their lived space, their normal life was restored and they could perform their daily activities again and their burden eased.

The initial burden of visiting health facilities for their child's frequent illness ceased. As treatment progressed, family caregivers' visits to health facilities were replaced by visits for the child's regular check-ups and medication refills instead of visiting the health facility when their child got sick. Due to this, family caregivers felt empowered, happy, and believed in their child's future. They also hoped that their child would further benefit in the future as the advancement of medical technologies continued. The family caregivers became aware that they could treat their child like any other healthy child in the family, nevertheless keeping the child's treatment adherence as the most important thing to practice all the time as they knew that their child's survival depended on it.

As time progressed, the caregivers observed that their child became more and more responsible for taking the medication due to the child's increased awareness of the importance of medication. The family caregivers noticed that the child's treatment adherence was ensured further due to their true love and close follow-up of their child's medication time in their daily life routines. In addition, family caregivers experienced

that the level of ART adherence in children also depended on the type of the medication regimen the child was taking. They preferred a fixed dose treatment to other regimens to be prescribed for their child. The challenge of a child refusing to take the medication was often solved after the medication was changed, particularly for the children to whom the initial numerous tablets were switched to one single tablet (Paper III).

At baseline, 12.5% received triple fixed-dose combination (FDC) TDF-3TC-NVP/EFV (Paper IV). However, at twelve months of follow-up compared to baseline (Paper IV), a slightly increased number of children (n=38 to n=48) received triple fixed-dose combination (FDC) TDF-3TC-NVP/EFV. The details are shown in Table 4.

**Table 4.** Children ART regimen at base line and during 12 months of follow-up

| Characteristics | Number | % |
|---|---|---|
| Child's base line treatment regimen | | |
| AZT-3TC-NVP/EFV | 212 | 70 |
| D4T-3TC-NVP/EFV | 31 | 10 |
| ABC-3TC-NVP/EFV/KAL | 23 | 7.6 |
| TDF-3TC-NVP/EFV | 38 | 12.5 |
| Child treatment regimen during 12 months of follow-up | | |
| AZT-3TC-NVP/EFV/KAL | 208 | 68 |
| ABC-3TC-NV/EFV/KAL | 48 | 16 |
| TDF-3TC-NVP/EFV | 48 | 16 |

The family caregivers' lived human relations were influenced by the lack of transparency and their inability to tell the truth to their child, which caused them suffering. Some family caregivers disclosed the child's HIV diagnosis and treatment status at an early age as they feared that lying to their child might result in an untrusting relationship. When the HIV and treatment status was revealed the family caregivers found it facilitated better communication between them and their child, causing less confusion and fewer conflicts between them. But due to lack of appropriate planning and communication between the family caregivers and health care workers, family caregivers sometimes experienced a challenge of an inadvertent disclosure of diagnosis and treatment to their child, which led the child to feel depressed and caused frustration to the caregivers.

As the treatment progressed the family caregivers experienced changes in their child's behavior. Family caregivers felt that children could become unhappy, depressed, or

mentally absent. The family caregivers felt that taking the medication for a long time might contribute to their child's changed behavior. Some of the children still struggled to take their medication even after their status was disclosed. The family caregivers expressed severe conflicts when the child did not want to take the medication or did not want to be responsible for their medication. These conflicts made the caregivers frustrated and they became angry at their child. However, they tried their best to control their emotions in front of the child and tried to continue their daily struggle to convince the child to take the medication. The results also indicated that the child's refusal to take ART was due to the conflict between some family caregivers and their child, and this was found to be the reason for the child's LTFU (n=5). At the end of follow-up (Paper IV), 91% of the children were under active follow-up while 24 attritions were recorded, yielding an attrition rate of 8.3 per 100 person-years' observation (PYO) (95% CI 5.4–12.1) and most of the attrition 14 (58%) occurred during the first six months of treatment. Eighteen cases (75%) of attrition were due to LTFU. The overall LTFU rate was thus 9.12 per 100 PYO. Higher rates of attrition documented among children with both biological parents alive and close biological relation of the family caregiver (mother, father, brother, or sister) compared to their counterparts.

On the other hand, family caregivers felt that the presence of peer support groups in the health facilities was most important since it helped their child to have a positive behavioral development and they became responsible for their own medication management. Children who joined the peer support groups in the health facilities became happy, empowered and had strong friendship with peers regardless of HIV status. This alleviated the family caregivers' stress and they felt happy. Meeting peers frequently in their living environment had lightened the family caregivers' caring burden and related stresses, described as their lived body, because the child became responsible for managing their own medication and follow-up schedules. However, the findings indicated that younger children aged below three years were associated with a five-fold increase in attrition. Similarly, a three-fold increase in attrition was found among children with baseline Hgb <10 g/dl compared to those with higher Hgb values at baseline. Also, LTFU was about 3.8-fold among children aged below three years (Paper IV).

At the time of follow-up, the family caregivers experienced HIV-related discrimination, described as their lived human relations. They felt that people in their neighborhood did not want to meet and talk to them. They observed that some individuals were pointing fingers at them and talking in secret about them because they and their child were HIV positive. Because their and their child's HIV status was discovered, some family caregivers lost their job or feared to apply for jobs, while others were forced to leave their rental houses by the landlords. Due to these experiences, family caregivers felt hated and rejected by the community. The stigma and discrimination that originated from the caregivers' own community aggravated the negative feelings of themselves which led them continue to keep their HIV status and treatment, as well as

that of their child, a secret. Our findings also indicated that the majority, n= 12/18 (66.6%) of LTF children were unreachable due to wrong telephone and residence address documented in child's record (Paper IV).

Because of the fear of society-triggered stigma and discrimination, most of the family caregivers preferred to travel to a location far from their living environment when it was time for their child to receive treatment. It became a challenge for the caregivers to keep the child's follow-up schedule when the health facility was located far from their actual place of residence. The 12 months of child's treatment follow-up (Paper IV) also revealed that children coming from rural areas were about four times more likely to experience attrition. Similarly, LTFU was about 3.6-fold higher among children from rural areas. Variables predicting higher mortality rates included baseline Hgb <10 g/dl (16-fold increase) and WHO stage III & IV (12-fold increase). Possible underlying causes of death were ascertained for three out of six deaths; two died after hospital admission due to opportunistic infection and one child died due to severe anemia. The cause of death for the remaining three was not recorded as these deaths occurred at home.

# Discussion

## Methodological considerations

This thesis is carried out using a longitudinal prospective cohort method through mixed methods design aimed to provide a broader picture and a deeper understanding about the family caregivers' lived experience and treatment outcomes of children diagnosed with HIV and enrolled in ART. Both children and their family caregivers were followed during two years. This approach is believed to encompass multiple viewpoints, perspectives, positions, and standpoints (Johnson et al., 2007). In terms of integrating different forms of data in mixed methods, three approaches have been discussed, including merging data in which the researcher combines both quantitative and qualitative data to gain the best understanding of the study participants' experiences, connecting data, which is also said to be an explanatory sequential design used to have one dataset build on the results from the other and embedding data used to supplement one another to reveal new insights (Creswell et al., 2011). The research approach followed the perspective of "between-methods" triangulation (Johnson et al., 2007), merging an inductive qualitative design (Papers I and III) and a quantitative prospective cohort design (Papers II and IV). Intentionally merging of the quantitative and qualitative results is believed to provide a more complete understanding of the phenomenon of the study (Creswell et al., 2011; Zhang & Watanabe-Galloway, 2014). The use of between-methods triangulation is therefore suggested to be the best approach as it utilizes mixed methods, which is believed to avoid the bias that likely arises from one data source, investigator and/or the use of one particular method.

## Longitudinal perspectives

### Inductive qualitative design

One of the major merits of qualitative longitudinal design is that it gives room for prolonged engagement and trustful relationships between researcher and participants. Emerging findings will therefore likely express the true phenomenon (Sterling & Peterson, 2005). In addition, it also facilitates insights into how phenomena possibly

change over time. This is believed to be an appropriate way of understanding the behavior and experience of a particular illness (Carduff, Murray, & Kendall, 2015). However, qualitative research needs to be evaluated according to trustworthiness throughout the research process according to the four suggested criteria: credibility, confirmability, dependability, and transferability (Guba & Lincoln, 1989; Lincoln & Guba, 1985). Credibility evaluates the extent of true value created from the participants' reality and not from the researchers' subjective view (Lincoln & Guba, 1985). Van Manen (1997) also suggests that for a hermeneutic phenomenological study to be convincing, the findings need to harmonize with the reality. The true value of the study therefore depends on the data collection, analysis, and interpretation (Guba & Lincoln, 1989) and the extent of respondents' ability to give rich descriptions of the phenomenon they are asked to describe (van Manen, 1997). In our longitudinal study, the family caregivers were selected consecutively from four different sites and they differed in terms of their cultural features, family structure, geographic and sociodemographic position, ensuring the variety of informants recommended by van Manen (1997). However, no other family members than the family caregiver were interviewed, unlike previous studies of children with other long-term illness such as cancer (Björk, Nordstrom, Wiebe, & Hallström, 2011; Björk, Wiebe, & Hallström, 2005, 2009) and diabetes (Wennick & Hallström, 2006, 2007), showing that all family members' experiences are important. Including other family members would provide an understanding of the entire family's experience in terms of caring for a child with HIV and on ART. Three of the caregivers during the second interview in Paper III did not participate due to severe illness or death; their lived experience might differ from those described.

After careful development of data collection tools, a pilot study was conducted aiming to test the interview guide, to let the interviewer practice interview skills, and to ensure that it was possible for the respondent to respond comfortably without any difficulty during a vulnerable and stressful time. All interviews were conducted by the author of this thesis who has prolonged engagement in the field and who is skilled and experienced in caring for people with HIV. A good relationship was built between interviewer and participants during the two different interviews. Having such an exposure is believed to increase the true value in the description of the findings (Lincoln & Guba, 1985; Morse, 2015; van Manen, 1997).

The interviews were first transcribed in the local language and then translated to English by the interviewer and assisted by a native-speaker researcher, fluent in English and with extensive experience of qualitative research. During the interpretation and description of the findings, several steps were followed through systematic arrangement of the data aiming to ensure that the descriptions of the findings were deeply embedded in the caregivers' own narrative. These steps included that each transcribed interview was read line-by-line by the four authors to develop an overall picture of the interviews (van Manen, 1997), to generate meaning units and emerging subthemes and themes from the transcribed narratives. To ensure dependability, researchers with different

backgrounds and preunderstanding participated in different steps of the analysis process. In addition, the findings were discussed at research seminars and collaborative meetings aiming to deepen the understanding of the family caregivers' lived experience according to van Manen's (1997) recommendations.

Conformability refers to the extent to which the findings could be verified by others and that the findings correspond to the data material. To strengthen the conformability, the stages in the analysis process were clearly described and quotations were used to ensure that the findings were embedded in the caregivers' own descriptions (Lincoln & Guba, 1985; van Manen, 1997).

Researchers with different preunderstanding, competence and cultural background participated in the analysis process, which strengthened the dependability. Furthermore, the findings were discussed during several collaborative meetings aiming to deepen the insight into the caregivers' lived experiences according to van Manen's (1997) recommendations.

Van Manen (1997) suggests that the only generalization that can be made from phenomenological studies is that they should never be generalized. Dahlberg et al. (2007) also underline that qualitative research is contextual and that findings, therefore, never can be assumed to be general. However, transferability to other contexts with similar conditions is possible (Dahlberg et al., 2007; Krefting, 1991). Transferability is enhanced as the family caregivers' experiences were similar to other results from low socio-economic settings regardless of differences in gender, age, sex and cultural features (Bejane, 2013; Gyamfi, Okyere, Enoch, & Appiah-Brempong, 2017; Potterton et al., 2007; Punpanich et al., 2008; Washington & Oberdorfer, 2013). Hence, the findings may also be used to develop hypotheses for other studies.

## Prospective cohort study

In Papers II and IV data were collected prospectively in regular child clinical HIV care and treatment settings. Prospective cohort studies have several advantages over other methods (Grimes & Schulz, 2002). They are useful to determine incidence rates and relative risks, to investigate multiple outcomes to the single exposure, and to perform survival analyses. These attributes of prospective cohort design are directly relevant to our study.

On the other hand, a prospective cohort study has disadvantages as well, including possibilities of selection bias, loss to follow-up, and it is not an appropriate approach to observe rare events. This cohort study was not vulnerable to a high loss to follow-up rate, as is very common when investigating diseases with long latency periods (Song & Chung, 2010). A follow-up period of 12 months is relatively short and we used an individual survival time (person-time contribution) to estimate predictors and rates of LTFU and death. As each unit of person-time contributed to an individual follow-up

time, a person keeps his or her own classification in terms of exposure. In cohort studies in any other epidemiological study, there is a need to achieve adequate sample size to determine the power of a study and consequently to determine valid statistical association. In this prospective cohort study, we used adequate sample size, which enabled us to make precise estimates of predictors of important outcomes as evidenced by narrow confidence intervals of hazard ratios. Moreover, we achieved the predetermined sample size and power. Thus, we did not observe any compromise of results in multiple comparisons. In quantitative research, the concepts of validity and reliability are used to evaluate strengths and weaknesses (Creswell, 2014).

*Validity*

The concept of validity concerns the degree to which a measurement or study reaches a true conclusion. It is classified into internal validity and external validity (Greenberg, 2005).

*Internal validity*

Internal validity concerns the extent to which findings reflect the true relationship between the exposure and the outcome whether of an investigation accurately reflects the true situation of the study population. There are three types of bias in observational studies: selection bias, information bias, and confounding (Dawson, 2004; Greenberg, 2005).

Selection bias is one of the three major types of systematic errors that can happen when subjects are identified in a way that gives rise to non-comparability between the groups. In our cohort study, all of the HIV-diagnosed children enrolled in ART were invited to the study through their caregivers during the given study duration. Thus, selection bias is unlikely in this study.

Information or observation bias occurs because inaccurate information is collected on either the exposure or the disease or both. The most common types of information bias include: non-differential (random) misclassification, differential misclassification, and recall bias. Both differential misclassification and recall bias are often basic problem of case-control and retrospective cohort studies. However, in our study these are unlikely to occur as the causal relation to the outcome was independently determined to all participants and observer bias is also unlikely to occur as the exposure data were collected prior to the onset of outcomes.

Confounding bias occurs when the effect of an extraneous variable is mixed with the effects of the exposure on the disease of interest (Greenberg, 2005). Confounding is known to distort the outcome of a study either by overestimating, underestimating or changing the direction of the observed association. In the cohort study, some family caregiver-and-child pairs came from rural areas, which might affect the adherence and attrition; educated caregivers may have better understanding of health care uptake; and child age differences may affect the extent of health service utilization. However,

confounding was controlled for mainly by using multivariable models to adjust for age, sex, residence (rural, urban), CD4 cell count, WHO stage, and Hgb g/dl.

*External validity*

External validity refers to whether the findings can be generalized to outside of the study populations (Greenberg, 2005; Shadish, Cook, & Campbell, 2002). The cohort study was conducted in urban and rural settings of two regional states (Addis Ababa and Oromia), Ethiopia, where there is high load of pediatric and adult patients visiting the study health facilities to obtain ART treatment and care services. It is likely that it may be applicable to other contexts with similar conditions since participants often have similar experiences despite their age, sex, and cultural differences (Bhattacharya & Dubey, 2011; Nyogea et al., 2015; Ugwu & Eneh, 2013) in terms of ART adherence (Alvarez-Uria, Naik, Midde, & Pakam, 2014; Sutcliffe, van Dijk, Bolton, Persaud, & Moss, 2008) and ART outcomes including attrition. However, larger full-scale study is needed to verify whether rates, predictors of attrition, and factors affecting treatment adherence can be generalized.

# General discussion and clinical implications

The family caregivers lived experience in terms of body, space, human relations, and time showed that the child's HIV diagnosis and enrollment into ART influenced the caregivers significantly. The most important challenges during the two-year timeframe were influences on the family caregivers' health and wellbeing, disrupted family and social networks, as well as challenging relations with the child, their partner, family and friends, in work and with health care professionals, and in society. The challenges were reduced over time but often their fear of stigma remained.

The family caregivers felt that the child's survival was dependent on lifelong treatment and that created a feeling of uncertainty and fear for the child's future among the parents. This finding is in line with Nelms (2005) who pointed out that family caregivers were uncertain about the child's future, the continuation of treatment with ART and its short- and long-term effects. Nevertheless, the caregivers participated voluntarily in the longitudinal study with a response rate of 99%. This could be due to the caregivers trust and confidence in health care providers and the compassionate care being provided by the health care providers. However, it could also be that the family caregivers did not understand that they could say no to participate in the research project or the fact that they were dependent upon the health care provider even though great efforts were made to explain this.

Child ART non-adherence was one of the prominent challenges along child caring process. The poorer ART adherence was mainly associated with children receiving PI-based treatment regimens, which is in line with a study report that poor palatability

and adverse effects of PI-based regimens are known to contribute to poor adherence (Chandwani & Shuter, 2008; WHO, 2013). Changes to the child's ART medication by simplifying dosing regimens such as a once-daily single-tablet formulation were found crucial to the child's recovery; this has shown significant benefit in terms of adherence and taking of the medication consistently among pediatric HIV patients (Schlatter, Deathe, & Vreeman, 2016). In addition, a higher rate of non-adherence was documented among the children whose caregivers did not use a medication reminder. This confirms the well-recognized role of medication reminders for enhancing treatment adherence through behavioral change (WHO, 2013). Medication reminder is found to be a relevant tool to be used in a setting where forgetfulness is the most common reason for non-adherence (Biadgilign, Deribew, Amberbir, & Deribe, 2008; Biressaw, Abegaz, Abebe, Taye, & Belay, 2013).

Poorer ART adherence was also documented among children whose caregivers were undergoing HIV treatment and care themselves together with their child. The possible contributing factors for this could be the existing stigma and discrimination against people with HIV in the studied areas and related missed appointments or failure to collect new medication (Reda & Biadgilign, 2012). This could also be due to sub-optimal care being provided to the family caregivers from the facility and related decreased level of family caregivers' commitment towards the child's ART treatment (WHO, 2013). In addition, the experience of high levels of stigmatization and discrimination among family caregivers was found to affect the process of healthcare service utilization negatively (Bejane, 2013; Surkan, 2010; Washington, 2013).

When the family caregivers observed that it was easier for the child to take the medication, the children also became more responsible and engaged, the family caregivers were empowered and hoped that the treatment would cure their child in the future. Other studies in children living with HIV (Potterton et al., 2007) and children with cancer (Björk, 2008) also showed that the parents' level of stress decreased when the child's health improved and their hope increased. The good relations with the health care providers and the healthcare services including healthcare providers' empathy, regular counseling provided in their health facilities, and the peer support groups for their child were found to be pillars to empower them and their child. This is in line with Potterton et al. (2007), who explored parental stress among caregivers of children diagnosed with HIV.

Tensions and conflicts between the caregiver and the child was exacerbated by the family caregivers' fear of stigma. The fear of HIV stigma was prominent for the caregivers, which was described as enacted or received prejudice, stereotypes, or discrimination by HIV-uninfected people. The other forms of stigma experienced by the family caregivers also include internalized and anticipated stigma. Due to high burden of fear of being stigmatized, some of the family caregivers felt that they ought not to disclose their and their child's diagnosis to the child, the family, and the community. Other studies also report that the fear of stigma is a major reason for not disclosing a child's HIV status (Biadgilign, Deribew, Amberbir, Escudero, & Deribe,

2011) and an individual's social interactions with their intimate family or the broader community can be negatively influenced (Varas-Díaz et al., 2005). Researchers (Abebe & Teferra, 2012; Brown et al., 2011; Murnane et al., 2016) in Ethiopia, Nigeria, and South Africa have also reported that lack of child HIV status and treatment disclosure to their child, deception about the child's HIV and treatment status or lack of knowledge on how to start and when to make full disclosure to their child were the main reasons for conflict between the caregiver and the child.

Child care at the health facilities of Ethiopia is usually provided through a FCC approach in which the health care providers and family caregivers play the major role in the child's caring process and the child's perspective seems overlooked (FMOH, 2014). It is suggested that the pediatric ART and care service should practice as child- and family-friendly care as possible (ICAP, 2015). In the child-caring process including all communications, the child's best interest should always be considered and a child needs to take part in decision making and receive relevant age-appropriate information (UN, 1989). This can be problematic when parents' or family caregivers' needs are not synchronous with the child's needs (in this case disclosure of HIV and ART status to the child). A recent study in Uganda reported that lack of adequate communication and not letting children discuss their own HIV condition resulted in that the family caregiver and the child remained in a tensed relationship (Kajubi et al., 2016). It is also suggested that in sub-Saharan Africa, the child care process needs to incorporate the perspectives of HIV infected children and promote child participation so they will be able to manage their challenges in the community (Skovdal and Daniel, 2012). The results of this thesis indicate that the established peer support groups in some of the health facilities are found to be a good way to include children in their own care, facilitate disclosure of their HIV and ART status, and make them aware and prepare to be primarily responsible for their own treatment. Children who joined the peer group in the health facilities were empowered to connect with each other, meet, and play in their living environment, which was also a relief for the family caregivers. Joining the peer support groups and meeting peers with HIV in the health facilities and related service provisions allowed the child to share feelings and burdens in a good atmosphere.

Some family caregivers chose to arrange their follow-up visits at the health facility located far away so neither their nor their child's diagnosis would be revealed in their neighborhood. This resulted in long travel distances for their child's ART follow-up. Children enrolled in ART in the study facilities and coming from rural areas had greater risk of attrition than those from urban settings. Attrition due to either LTFU or death was another challenge in ensuring quality health care for the child enrolled in ART. Younger children, those from rural areas, at advanced stage of disease at baseline, and those with anemia were at significantly higher risk of attrition. Furthermore, higher rates of attrition were documented among children with both biological parents alive and biologically related close family caregivers. The result (Paper IV) confirms that the child's age being below 3 years (Abuogi, Smith, & McFarland, 2016; Asfawesen et al., 2011; Melaku et al., 2017) and the presence of baseline anemia (Abuogi et al., 2016;

Koye, Ayele, & Zeleke, 2012) were predictors of attrition from HIV care in a setting with limited resources.

In our cohort, we were able to ascertain the vital status of five of the 18 children reported to have been lost to follow-up and all the five were alive but not taking their medications. The status of the remaining 13 was unknown. In earlier reports among adult patients in sub-Saharan Africa, it was noted that 46% of those reported to have been LTFU were found to be dead (Brinkhof et al., 2009). Similarly, in an earlier report from Ethiopia it was further confirmed that 40.6% of adult patients reported to be LTFU were actually dead but this was over a long-term follow up period (Mulissa et al., 2010). Subsequent studies among paediatirc populations used higher mortality estimates for patients LTFU and therefore adjusted mortality estimates for the entire cohort based on these assumptions. However, they also acknowledged the limitations of extrapolating mortality estimates from adult cohorts to those of children (Fenner et al., 2010). In our cohort, even if we assumed that about 50% of those who had been LTFU were dead (disregarding the fact that all the five we traced were alive), the mortality rate would still be low at 5.2 per 100 PYO.

The caregivers feared for anticipated stigma due to their daily life situation in society as both the caregiver and the child were HIV-positive. Among children lost to follow-up, most of them about 67% were unreachable due to incorrect home address or telephone number provided by their family caregivers during the child's enrollment to ART. This could be due to fear of anticipated stigma associated with HIV. The fear of anticipated stigma further affected the family caregivers in getting psychosocial support from donating agencies in their community and job opportunities, as well as their life in society. Other researchers have reported that HIV contributed to a greater burden of stigma and create boundaries between PLHIV and others in the community (Stevelink, van Brakel, & Augustine, 2011) compared to other infectious diseases, e.g. leprosy (Kaur & Ramesh, 1994; Stevelink et al., 2011). According to a previous study (Kidman & Heymann, 2016), the family caregivers' needs are best meet through social protections and policies.

Studies indicate that stigmatizing behavior which leads to stigma-related outcomes such as poor health, violence, reduced access to care, and poor quality of work life can be triggered as a result of HIV diagnosis or disclosure (Holzemer et al., 2007). According to HIV/AIDS stigma conceptual frameworks, the most common stigma mechanisms are those in which PLHIV believe they have actually experienced prejudice and discrimination from others in their community, or PLHIV expect that they will experience prejudice and discrimination from others in the future, or have internalized stigma in which PLHIV develops the negative beliefs and feelings about themselves associated with HIV/AIDS (Earnshaw, 2009). They describe the internalized stigma from the perspective of PLHIV and prejudice refers to negative emotions and feelings, stereotypes refers to group-based beliefs about PLHIV, and discrimination refers to behavioral expressions of prejudice from the HIV-uninfected individuals' perspectives and explained how these stigma mechanisms ultimately harm the psychological,

behavioral, and health outcomes of both (Earnshaw, 2009; Misir, 2015). The pre-existing socio-economic and structural disparities in the population may exacerbate the family caregivers' vulnerability to stigma (Daftary & Padayatchi, 2012). Internalized stigma in PLHIV (Holzemer et al., 2007) was found to have a negative impact on treatment adherence and psychosocial variables such as hope, self-esteem, and empowerment (Livingston & Boyd, 2010). The internalized or insider's view of stigma often leads individuals to experience that they withdraw from social services, develop fear of disclosure and self-exclusion (Weiss et al., 1992).

According to Giddens's (1979) structuration theory of action, human action and structure can play an independent role and/or their interaction to produce HIV stigma as part of social system, thus there is a need to have appropriate interventions in human action and structure which produce stigma. Ethiopia has adopted a guideline which focuses on involvement of PLHIV on HIV prevention, care and treatment activities (FMOH, 2009a). However, there is a lack of a clear guiding strategy and practice to empower PLHIV individuals and family in how to resist HIV stigma in their community. To reduce HIV/AIDS-related stigma and related negative outcomes to the child and family caregiver, it is crucial to develop a contextualized stigma framework in a way that might be able to influence stigma-triggering attitudes and practices of the actors, structure and the social system at large. It is equally important to consider the stepwise empowerment plan for the child living with HIV and family caregiver so that they may be able to resist and fight against both external and perceived stigma. Having these interventions in place is believed to facilitate the improvement of the health and social outcomes of children and caregivers. Moreover, this practice is believed to help them to lead quality healthy life in the community where they live.

The result revealed that about 78% of LTFU happen at an early stage, especially during the first six months after the child's treatment initiation. This suggests the need to give greater attention and create a conducive environment at health facilities for children. Enhancing children's ART adherence by issuing an electronic reminder for caregivers, establishing a joint network and two-way referral system between health facility and community adherence support workers to perform active and early tracing of children should be implemented to ensure adequate retention of children in care. Evidence from other studies suggests that the use of tailored text message alerts for mothers or family caregivers of the child promotes child retention in HIV care among HIV-exposed infants (Finocchario-Kessler et al., 2014). Having such a practice is believed to promote retention on treatment and improves treatment outcome among all children in HIV care (Melaku et al., 2017). The finding in this thesis also highlights that children with advanced clinical stage during ART initiation were at the highest risk of death, underlining the need for early treatment initiation (Abuogi et al., 2016; Koye et al., 2012) regardless of immunological markers such as CD4 count. This is already part of the national guidelines in Ethiopia which needs to be reinforced.

The findings of this thesis can deepen the understanding of what it means to become a family caregiver for a child diagnosed with HIV and enrolled in ART. In addition, the

results also deepen our understanding of ART outcomes in children. Having such understanding is believed to contribute to the improvement of care for children living with HIV on antiretroviral therapy. The knowledge will serve as a basis for further planning of care and informed decision making to strengthen the family caregiver and child's ART follow-up so as to ensure the quality of care. The results also may have a potential to develop further study hypotheses in the research area. The findings led to some reflections when caring for children diagnosed with HIV and enrolled in ART and their family caregivers. These include:

- Establish adequate support to family caregivers at the child's HIV diagnosis and ART initiation as these are the critical points. Emphasize the empowerment of family caregivers through detailed and continuous family-centered discussions prior to the child's initial treatment.
- Intervention modalities and strategies such as ways to empower the family caregivers economically and protect them from HIV-related violence in the community need to be incorporated within the existing policy and guidelines to support family caregivers during the child's HIV care.
- The development of strategies for increased family-centered care in the healthcare organization to increase the involvement of the child and not only the family caregiver in the care of the child with HIV.
- Strategies for addressing stigma should be incorporated in the clinicians' formal training, at least as part of their on-the-job capacity building
- Mainstreaming existing good practice of supporting the family caregivers and their child at health facilities to be practiced on a wider scale in the community and health care organizations, for example compassionate care and empathetic counseling.
- Enhancing the practice of organizing peer support groups for older children and their impact on the long-term outcomes on children should be studied.
- Make medication reminders available for family caregivers and children, careful selection of ART regimens and improving child–caregiver communication with regard to disclosure of HIV status should be emphasized in HIV programs.
- With further scale-up of the universal ART initiation approach, there is great need for focused interventions to ensure retention and minimize attrition caused by death or LTFU.

# Future perspectives

The findings identified important areas for further research:

- Further studies are recommended to address family caregivers' needs in the family, community, and health facility (using a model for developing and evaluating complex interventions to improve health outcomes).
- Large-scale study using a combination of adherence measuring methods at the beginning of treatment initiation is needed to bring forward a more convincing report in resource-limited settings.
- The design and assessment of child-friendly strategies of stigma reduction and development of need-specific modalities to support caregivers in the community.
- Further studies with long-term follow-up of the cohort of children enrolled in ART are needed to better understand the underlying reasons for the attrition.

# Summary in Amharic

ማጠቃለያ በአማርኛ

መግቢያ

ይህ ጥናት ‘‘የፀረ-ኤች አይ ቪ ህክምና በመውሰድ ላይ ያሉ ህፃናትና ተንከባካቢ ቤተሰቦቻቸውን የሚያጋጥሙ ተግዳሮቶችና መልካም አጋጣሚዎች እንዲሁም የፀረ-ኤች አይ ቪ ህክምና ዉጤቶች በኢትዮጵያ’’ በሚል ርዕስ የተሰራ ነዉ፡፡ የፀረ-ኤች አይ ቪ ህክምና፣ ኤች አይ ቪ በደማቸዉ ዉስጥ ያለባቸዉን ህፃናት ጤንነት ከመሻሻሉም አልፎ ህፃናት በለጋ ዕድሜያቸዉ አንዳይሞቱና ረጅም እድሜ እንዲኖሩ ከፍተኛ አስተዋፅኦ አበርክቷል፡፡ ይሁን እንጂ ኢትዮጵያን ጨምሮ በማደግ ላይ ባሉት ሀገራት፣ የፀረ-ኤች አይ ቪ ህክምና የተፈለገዉን ያህል ዉጤታማ እንዳይሆን የተለያዩ ምክንያቶች አሉታዊ አስተዋፅኦ አበርክተዋል፡፡ ከነዚህም ምክንያቶች መካከል ለህፃናት የፀረ-ኤች አይ ቪ ህክምና እና ክትትል ተገቢ አያያዝ አለመኖር፣ ኢኮኖሚያዊ ዉስንነቶች፣ ያሉት የጤና እና ማህበራዊ ስርዓቶች ያልተስተካከሉ መሆናቸዉ፣ የቤተሰብ ተንከባካቢዎች ማህበራዊ እና ኢኮኖሚያዊ ተግዳሮቶች፣ግንባር ቀደም ተጠቃሽ ምክንያቶች ናቸዉ፡፡

የጥናቱ ዓላማ፡- ኤች አይ ቫይረስ በደማቸዉ ዉስጥ ያለባቸዉና የረጅም ጊዜ ፀረ-ኤች አይ ቪ ህክምና እየወሰዱ ያሉትን ህፃናት እንክብካቤ ከመሻሻል ረገድ ጉልህ አስተዋጽኦ ማድረግ ነዉ፡፡ ይህም ህፃናትን የሚንከባከቡ የቤተሰብ አባላት ከህክምና ጎን ለ ጎን ስለሚገጥማቸዉ የህይወት ገጠመኞቻቸዉና ልምዶቻቸዉ የተሻለ እውቀትና ግንዛቤ በማንፃበራቅ ነዉ፡፡ ዝርዝር ዓላማዎቹም፤የቤተሰብ አባላት ለህፃናቱ በቤት ዉስጥ በየቀኑ በሚሰጡት እንክብካቤ ሂደት ዉስጥ የኤች አይ ቪ እና የህክምና ሁኔታ ይፋ ማድረግ፣ ህፃናት የፀረ-ኤች አይ ቪ ህክምና በጀመሩበት የመጀመሪያ ሳምንታት ዉስጥ የሚኖራቸዉን የህክምና ዘለቄታዊ ቁርኝት እንዲሁም ከአንድ ዓመት በኋላ የክትትሉን ዉጤት ምን እንደሚሆን መከታታል ነዉ፡፡ ከዚህ ጥናታዊ ጽሑፍ የተገኘዉ እውቀት ለተጨማሪ የእንክብካቤ ዕቅድና በመረጃ ላይ የተመሰረተ ውሳኔ ለመስጣት መሠረት ሆኖ ያገለግላል ተብሎ ይታመናል፡፡

የጥናቱ ዘዴ፡-ይህ ጥናት የተካሄደዉ ድብልቅ ዘዴ (A mixed method design) በመከተል ነዉ፡፡ ይህም ከቤተሰብ ተንከባካቢዎቻቸዉ ጋር አንድ ለአንድ የሚደረግ ጥልቅ መጠይቅና ዉይይት እንዲሁም የህፃናትን የህክምና ክትትልንና ዉጤትን አስመልክቶ የተዘጋጁ ወጥ የሆኑ መጠይቆችንና የክትትል ቅጾችን በመሙላት ነዉ፡፡ጥናቱ የተካሄደዉ በአዲስ አባባና ኦሮሚያ ክልል ዉስጥ በሚገኙ ስምንት የመንግስት ጤና ድርጅቶች ዉስጥ ነዉ፡፡

ይህ ጥናት ትኩረት ያደረገዉ ዕድሜያቸዉ ከ ሦስት ሳምንት እስከ 14 ዓመት ዕድሜ ክልል ዉስጥ ባሉት ህፃናትና የቤተሰብ ተንከባካቢዎቻቸዉ ላይ ነዉ፡፡ የመረጃዉ አሰባሰብ ሂደትን አስመልክቶ በጠቅላላው 306 አዳዲስ የፀረ-ኤች አይ ቪ ህክምና የጀመሩ ህፃናት እና 306 የቤተሰብ ተንከባካቢዎች በ 8 የጤና ተቋማት ዉስጥ ከተህሣስ 11, 2007 እስከ ሚያዚያ 12, 2007 መካከል ባለው ጊዜ ጥናት ውስጥ እንዲካተቱ ተደርገዋል፡፡ በጥናቱም በ 7 እና 30 ቀናት ውስጥ ህክምናዉን የጀመሩ ህፃናት የነበረባቸዉን የፀረ-ኤች አይ ቪ ህክምና ዘለቄታዊ ቁርኝት፣ የቤተሰብ ተንከባካቢዎችን በራስ ሪፖርት የተደረገ የተሳትፎ መጠይቅ በመጠቀም ደሰሳ ተደርጓል (ጥናት 2)፡፡ ከእነዚህም 304 ህፃናት ለ 12 ወራት የህክምናቸዉ ክትትል

ከተደረገለቸዉ በኋላ ከህክምና ክትትል የጠፉትን ህፃናት ልጠፉ የቻሉበትን የተለያዩ አስተዋፅኦ ልያበረክቱ የሚችሉ ሁኔታዎችን ጥናቱ ለክቷል (ጥናት 4)።

በሌለ በኩል ደግሞ በሁለት የተለያዩ ጊዜያት ማለትም ህፃኑ የፀረ-ኤች አይ ቪ ህክምና በጀመረበት ወቅት ጥናት 1 (21 የቤተሰብ ተንከባካቢዎች) እና ከሁለት ዓመት በኋላ ጥናት 3 (18 የቤተሰብ ተንከባካቢዎች) ጥልቅ ቃለ-መጠይቆችን በመጠቀም፣ ህፃናትን ከሚንከባከቡ የቤተሰብ ተንከባካቢዎች ጋር ዉይይት ተደርጓል።

መረጃ የማቀናበርና የመተንተን ሂደትን ለመተግበር በጥናት አንድ እና ሶስት hermeneutic phenomenological approach በመባል የሚታወቀዉን የጥናት ስልት በመጠቀም ሲሆን በጥናት ሁለት እና አራት ደግሞ SPSS የተሰኘዉን የኮምፕዉተር የስራ ስልት በመጠቀም ነበር።

የጥናቱ ዉጤት እንደሚያሳየው ህፃናት የፀረ-ኤች አይ ቪ ህክምና በጀመሩበት ወቅት የህፃናት አሳዳጊዎችና ቤተሰቦቻቸዉ የሕይወት ልምምድ ልጅን ከመንከባከብ አኳያ በተለያዩ ፈተናዎችና ተግዳሮቶች የተሞላ ነበር፡ ሆኖም ለልጆቻቸዉ ካለቸዉ ብርቱ ፍቅርና ስስት የተነሳ፣ እጅግ ፈታኝ በሆኑ ሁኔታዎች ዉስጥ በቁርጠኝነት ማለፍ ችለዋል። የፀረ-ኤች አይ ቪ ህክምና እየወሰዱ ያሉትን ህፃናት ከመንከባከብ አንጻር የቤተሰብ ተንከባካቢዎች በርካታ አሳሳቢ ሽክሞች በመኖረቸዉ ምክንያት በጣም ከመጨነቃቸዉ የተነሳ ስለልጆቻቸው ኤች አይ ቪ እና ህክምና ሁኔታ ስያስቡት ምቾት አይሰማቸውም ነበር። ይሁን እንጂ ልጆቻቸውን ለመንከባከብ ያላቸው ቁርጠኝነት፣ በአምላክ ላይ ያላቸው ፅኑ እምነት፣ ጠንከራ የህክምና አገልግሎት እና ከጤና ባለሙያዎች የሚያገኙት ርህራሄ የተሞላ ድጋፍ ችግሮቻቸውን እንዲቋቋሙትና በጽናት እንዲያልፉት ረድቷቸዋል።

ከጥቂት ጊዜ ቆይታ በኋላ የቤተሰብ ተንከባካቢዎች ህፃኑን ከመንከባከብ አኳያ የነበረባቸዉ ጫና የህፃኑ የጤንነት ሁኔታ ከመስተካከሉ የተነሳ ተቀርፎላቸዋል። ለዚሁም ከሚጠቀሱት ምክንያቶች ዋናኞቹ፤ በጤና ተቋማት የሚሰጡ የፀረ-ኤች አይ ቪ ህክምና እና ከጤና በለሙያዎች የሚያገኙት እገዛ ግንባር ቀደም ተጠቃሾች ናቸዉ። ከሁለት ዓመታት ቆይታ በኋላ የቤተሰብ ተንከባካቢዎች በህይወታቸው እንደገና መሻሻል ከመታየቱ የተነሳ ስለልጆቻቸዉ የወደፊት ህይወት ተስፋ ማድረግ ችለዋል። ይሁን እንጂ በሚኖሩበት ማህበረሰብ መካከል ካለዉ ከፍተኛ አድሎና መገለል እንዲሁም ለሚንከባከቡት ህፃን የራሱን ኤች አይ ቪ እና ህክምና ሁኔታ ይፋ ካለማድራግ ጋር የሚፈጠሩ ግብግቦች ከፍተኛ ተግዳሮት ሆኖባቸዋል።

በሌለ በኩል ለራሳቸዉ የፀረ-ኤች አይ ቪ ህክምና እና ክትትል የማያደርጉ የቤተሰብ ተንከባካቢዎች፣ የልጆቻቸዉ የፀረ-ኤች አይ ቪ ህክምና ዘለቄታዊ ቁርኝት፣ ህክምናቸዉን በጀመሩበት የመጀመሪያ ሳምንት ላይ የተሸላ ሆኖ ተገኝቷል። ለልጆቻቸዉ የፀረ-ኤች አይ ቪ ህክምና መድኃኒት ማስታወሻ ዘዴን የማይጠቀሙ የቤተሰብ ተንከባካቢዎች ልጆቻቸዉ ህክምናቸዉን በጀመሩበት የመጀመርያ ወር ላይ የታዘዘላቸዉን የፀረ-ኤች አይ ቪ ህክምና በአግባቡ የመዉሰድ እድላቸዉ ዝቅተኛ ሆኖ ተይቷል። የፀረ-ኤች አይ ቪ ሕክምናው ከተጀመረ ከአንድ ወር በኋላ ፕሮቴስ እንህብተርስ (PIs) ወይም ABC-ምድብ የተሰኘዉን የፀረ-ኤች አይ ቪ ህክምና የሚወስዱ ህፃናት የፀረ-ኤች አይ ቪ ህክምና ዘለቄታዉ ቁርኝት ዝቅተኛ ሆኖ ተይቷል።

በ 12 ወራት ክትትል ወቅት ከህክምና ክትትል የጠፉት ህፃናት በአጠቃለይ 24 ነበሩ። ከነዚህም ዉስጥ 18 የጠፉ ሲሆን 6 ሞተዋል። በሌላ በኩል አምስት ህፃናት ደግሞ ወደ ሌላ የጤና ተቋም ተላልፈዋል። እድሜያቸዉ ከሶስት አመት በታች የሆኑ እና የፀረ-ኤች አይ ቪ ህክምና በጀመሩበት ወቅት የደም ማነስ የነበረባቸዉ ህፃናት ከክትትል የመጥፋት ተጋለጭነታቸዉ ከፍተኛ ሆኖ ተመዝግቧል። እንዲሁም የፀረ-ኤች አይ ቪ ህክምና በጀመሩበት ወቅት የደም ማነስ የነበረባቸዉ እና በሽታን የመቋቋም አቅማቸዉ አነሳ ሆኖ ህክምና የጀመሩት ህፃናት ለሞት ተጋለጭነታቸዉ ከፍተኛ ሆኖ ተመዝግቧል (ጥናት 4)።

የዚህ ጥናት ግኝት ኤች አይ ቪ በደማቸዉ ዉስጥ ያለባቸዉና የፀረ- ኤች አይ ቪ ህክምና በመዉሰድ ላይ ያሉ ህፃናት የቤተሰብ ተንከባካቢ መሆን ምን ማለት እንደሆነ የበለጠ ለመረዳት ያስችላል፡፡ በተጨማሪም የጥናቱ ውጤት ስለ ፀረ-ኤች አይ ቪ ህክምና በልጆች ላይ ያለንን ግንዛቤ ያጠናክርልናል፡፡ እንዲህ ዓይነቱ ግንዛቤ ኤች አይ ቪ በደማቸዉ ዉስጥ ያለባቸዉ ልጆች እየወሰዱ ያለዉን የፀረ-ኤች አይ ቪ ሕክምና ለማሻሻል አስተዋጽኦ እንደሚያደርግ ይታመናል;፡፡ በመሆኑም ከጥናቱ የተገኘዉ እዉቀት የሕክምና እንክብካቤ ጥራት ለማረጋገጥ፣ የቤተሰብ እንክብካቤ ሰጪውን እና የህፃናት የፀረ-ኤች አይ ቪ ሕክምና ክትትልን ለማጠናከር ጠቃሚታ አለዉ፡፡ እንዲሁም የቤተሰብ አባላት ህፃናቱን ከመንከባከብ አኳያ የተሻለ የእንክብካቤ እቅድ እና በመረጃ ላይ የተደገፉ ውሳኔዎችን ማድራግ እንዲችሉ ከፍተኛ ጠቃሚታ ይኖረዋል፡፡ የጥናቱ ውጤት በጥናት ምርምር መስክ ተጨማሪ የጥናት መላምቶችን ለማቅረብም እድል ይፈጥራል ተብሎም ይታመነል፡፡

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# Appendix

# Appendix I

## Semi-structured interview guide - Paper I

Can we discuss what it means for you to care for a child living with HIV?

- Probe for the hope the caregiver has for the future of the baby
- Probe for the strong/good feelings the caregiver has at times (ask the mother to tell you a peculiar moment when she felt bad and when she felt good/has hope)
- Probe for the bad/weak feelings the caregiver has at times

What did you feel when your physician told you that your child is eligible and should have to start to take lifelong antiretroviral therapy (ART)?

- How long did it take you to accept and decide that your child should start to take the treatment?
- What was your first feeling when a child has started to take ART medication?
- Probe for a story again

How would you explain taking care of a child living with HIV/AIDS while taking antiretroviral therapy (ART)? Ask for particular events to tell you like a story

Can we talk about your experience and problems faced while caring for a child on ART?

Let's talk about disclosure of the fact to your child, do you believe that you should disclose?

Did your child know about his/her HIV and treatment status?

- If yes who disclosed to him?
- At what age?
- How?
- Feeling of the child
- How a child benefited from knowing his/her HIV and treatment status

If the answer is no, can you share with me why you decided not to disclose his/her HIV and or treatment status?

Do you get any external socio-economic support?

- If the answer is yes what was it?

Wrap-up questions

1. Do you have anything to add?
2. Is there anything I should have asked?
3. How did the interview feel for you?

# Appendix II

## Semi-structured interview guide - Paper III

Start with a short introduction

We met almost two years ago when your child was diagnosed with HIV. Do you remember? You told me about your experiences at that time. At this interview I would like to ask you to tell me about your experiences since we last met.

1. Do you remember how you felt when we met two years ago?

2. Can you tell me about your experiences of caring for your child with HIV since the time we met two years ago?
   - Good experiences
   - Bad experiences

3. How would you explain what it is taking care of a child living with HIV/AIDS while taking antiretroviral therapy (ART)?
   - Ask for experiences and problems faced
   - Ask for challenging events
   - Ask the parents to describe an event

4. Do you have experiences that are particularly good or bad due to your child's ART?
   - Can you give me an example of such a situation?
   - Can you tell me how the experience affected you?

5. Have you disclosed the HIV and treatment status to the child?

   If yes,
   - Who disclosed to him/her?
   - When was the disclosure?
   -- Age of the child at disclosure?
   - What was the reason for disclosure?
   - How did it happen?
   - What was the reaction from your child?
   - What have been the consequences for the child? Benefits/challenges from knowing his/her HIV and treatment status?
   - What was the trigger for disclosure?

If the answer is no,

- Can you share with me why you decided not to disclose his/her HIV and or treatment status?
- Do you think your child should be informed? If yes, when? If no, why?

6. What do you feel about the care you and your child are getting here at the health facility?
   - Can you describeSome examples of good care for the child and for yourself - Some examples of bad care for the child and for yourself

7. Is the child illness affecting you/family/siblings?
   - How? Can you give me an example? How you deal with it?

8. Do you get any external socio-economic support?
   - If the answer is yes, what are those?
   - What is the impact of this support on your child caring process?

Wrap-up questions

1. Do you have anything to add?
2. Is there anything I should have asked?
3. How did the interview feel for you?

# Appendix III

## Structured questionnaire - Paper II

Part I. Socio-demographic and economic characteristics of family caregiver

Facility Identification Code (FID): _____ Study Participant Identification (SPID):_____

| No | Question | Category |
|---|---|---|
| 101 | How old are you? | _____years |
| 102 | What is your religion? | 1. Orthodox<br>2. Muslim<br>3. Protestant<br>4. Catholic<br>5. Other (specify)------- |
| 103 | What is your educational level? | 1. College/university graduated<br>2. High school (grades 9–12)<br>3. Grades 1–8<br>4. Able to read and write<br>5. Unable to read and write<br>6. No response<br>7. Other (specify)---------- |
| 104 | Marital status | 1. Currently married<br>2. Never married partner<br>3. Widowed/widower<br>4. Divorced/ Separated<br>5. Cohabitated/ living together |
| 105 | Residence | 1. Urban<br>2. Rural |
| 106 | Caregiver relationship with child | 1. Biological mother<br>2. Biological father<br>3. Brother<br>4. Sister<br>5. Grandmother/father<br>6. Legal guardian<br>7. Other (specify)_____<br>8. Other relatives |

| | | |
|---|---|---|
| 107 | Number of children the mother/father has | _____(children) |
| 108 | Mother/father enrolled in HIV/ART care | 1. Yes<br>2. No |
| 109 | HIV disclosure status of child's mother/father | 1. Disclosed<br>2. Not disclosed |
| 110 | Where the mother/father enrolled for care | 1. In the same facility where her/his child is enrolled<br>2. Out of the facility<br>3. Unknown |
| 111 | Parent's vital status | 1. Both father and father are alive<br>2. Father dead<br>3. Mother dead<br>4. Both dead<br>5. Other (specify)--------- |
| 112 | What is your current occupation? | 1. Unemployed<br>2. Student<br>3. Housewife<br>4. Daily laborer<br>5. Government employee<br>6. Non-governmental organization (NGO) employee<br>7. Merchant<br>8. Private employ<br>9. House servant<br>10. No response<br>11. Other (specify)---------- |
| 113 | How much do you expend monthly? | 1. _____ETH birr<br>2. No income<br>3. No response<br>4. Other (specify)_____ |
| 114 | Is there any external financial support for the child? | 1. No<br>2. Yes----------ETH birr |
| 115 | If there is external support, where do you get it from? | 1. ----------<br>2. ----------<br>3. ----------<br>4. ---------- |

Part II. Socio-demographic and HIV disclosure characteristics of a child on ART

| | | |
|---|---|---|
| **116** | At what age did the child start to take ART? (dd/mm/yy) | _____dd/_____month/_____year |
| **117** | Sex of the child | 1. Male<br>**2.** Female |
| **118** | Does your child have schooling? | 1. Yes<br>**2.** No |
| **119** | How long ago was your child found to be tested HIV-positive? | _____year/_____months/_____weeks |
| **120** | HIV and treatment disclosure status of the child | 1. Child HIV and treatment status disclosed<br>2. Child HIV and treatment status not disclosed<br>**3.** Other (specify)---------- |
| **121** | If the answer for Q 120 is 1, please mention the person who disclosed | 1. Mother<br>2. Father<br>3. Grandmother<br>4. Other relatives<br>5. Health provider |
| **122** | Age at HIV & treatment disclosure | <6 years<br>6–10 years<br>>11 years |
| **123** | Time since disclosure was made | _____year/s/_____months/_____weeks |

Part III. Caregiver responses regarding future intentions to disclose the HIV diagnosis to children

| | | |
|---|---|---|
| 124 | Appropriate time to disclose | _____year/s/_____months |
| 125 | Person responsible for disclosing the child's HIV and treatment status | 1. Mother<br>2. Father<br>3. Grandmother<br>4. Other relatives<br>5. Health provider |

Part IV. Caregivers' response regarding child's ARV treatment adherence and missed doses

| | | |
|---|---|---|
| 126 | How many doses has your child missed in the last month? | 1. One dose<br>2. Two doses<br>3. Three doses<br>4. Four doses<br>5. More than four doses<br>6. None |
| 127 | Is there a history of your child ever missing the treatment doses? | 1. Yes<br>2. No |
| 128 | How was your child taking the drug in the last 7 days? | 1. Exactly on time<br>2. Occasionally a few minutes late<br>3. 1 hour late<br>4. 1–2 hours late<br>5. 3 or more hours late |
| 129 | How many doses has your child missed in the last seven days? | 1. One dose<br>2. Two doses<br>3. Three doses<br>4. Four doses<br>5. More than four doses<br>6. None |
| 130 | What was the reason for your child missing a dose or not taking it timely in the last seven days? | 1. Child refusal<br>2. Lack of food<br>3. Caregiver's forgetfulness<br>4. Drug finished<br>5. Child illness<br>6. Child slept<br>7. Transportation problem<br>8. Drug adverse reaction<br>9. Other (specify)---------- |
| 131 | Do you have a medication reminder strategy for your child? | 1. Yes<br>2. No |
| 132 | Does the child have other illness (co-morbidity)? Say yes if the child has one or more co-morbidity on the list (TB, cardiac illness, diabetes, mental illness or any form of cancer) | 1. Yes<br>2. No |

Part V. Document review of the child at the beginning of the ART initiation

| | | |
|---|---|---|
| **133** | Child HIV/ART enrollment | 1. Enrolled within the facility<br>2. Referred from other facility |
| **134** | WHO clinical stage when a child starts ART | 1. WHO stage I<br>2. WHO stage II<br>3. WHO stage III<br>**4.** WHO stage IV |
| **135** | Type of ART regimen initiated | 1. 1st line regimen<br>2. 2nd line regimen |
| **136** | Child's weight | _____Kg (Day_____month_____year_____) |
| 137 | Child's length/height | _____cm (Day_____month_____year_____) |
| | **Lab value** | |
| **138** | CD4 cell count/$mm^3$, CD4 % and TLC | CD4 number<br>_____(Day_____month_____year_____)<br>CD4 %<br>_____(Day_____month_____year_____)<br>TLC<br>_____(Day_____month_____year_____) |
| **139** | Hgb | _____(Day_____month_____year_____) |
| **140** | OI Prophylaxis taken | CPT (Day_____month_____year_____)<br>IPT (Day_____month_____year_____) |

Data collector name and signature_____

Date_____

Collected data verified by (PI): _____

Date_____

# Appendix IV

## Cohort Study follow-up template – Paper IV

**Children with HIV on ART Cohort Study in Ethiopia (CCS-E): Follow-up outcome at 6 months, 12 months, 18 months and 24 months of ART initiation**

**A. Follow-up outcome observed at (please mark " ✓ " at the appropriate one)**

1. At 6 months_____ 2. At 12 months: _____ 3. At 18 months_____

4. At 24 months_____

**B. Identification profile (traceable from the baseline information)**

1. Name of Health Facility: _____
2. Study site identification code:_____
3. Specific participant identification code (SPID)_____
4. Unique ART code_____

**C. Events during follow-up after ART initiation**

1. Total number of visits after ART (including initiation visit): _____
2. Number of unscheduled visits_____
3. Number of scheduled visits_____

**Children with HIV on ART Cohort Study in Ethiopia (CCS-E): Follow-up outcome at 6 months, 12 months, 18 months and 24 months of ART initiation**

| Variable | Visits by value & date (DD/MM/YY) | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| 1. Height/length (DD/MM/YY) | | | | | | | | | | | | | |
| 2. Weight (DD/MM/YY) | | | | | | | | | | | | | |
| 3. WHO stage/T-stage (DD/MM/YY) | | | | | | | | | | | | | |
| 4. CD4 count (DD/MM/YY) | | | | | | | | | | | | | |
| 5. CD4 % (DD/MM/YY) | | | | | | | | | | | | | |
| 6. Viral load (DD/MM/YY) | | | | | | | | | | | | | |
| 7. Hgb (DD/MM/YY) | | | | | | | | | | | | | |
| 8. Functional status (Studying (S), Ambulatory (A), Bedridden (BR) or Not recorded (NR) (DD/MM/YY) | | | | | | | | | | | | | |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 9. Developmental Milestone Appropriate (A), Retrieve (R) Delay (D) | | | | | | | | | | | | | |
| 10. Adherence (G, F, P) (DD/MM/YY) | | | | | | | | | | | | | |
| 11. Develop any OI (Y/N) (DD/MM/YY) | | | | | | | | | | | | | |
| 12. IPT (Continued/stopped) (DD/MM/YY) | | | | | | | | | | | | | |
| 13. CPT Continued/stopped) (DD/MM/YY) | | | | | | | | | | | | | |
| 14. Disclosure (Y/N) (DD/MM/YY) | | | | | | | | | | | | | |
| 15. Anti-TB (Y/N) (DD/MM/YY) | | | | | | | | | | | | | |

16. Change in drug regimen: 1. Yes 2. No
    a. Date of last drug regimen change:---/---/--- (dd/mm/yy)
    b. Reasons for the last regimen change: 1. Treatment failure 2. Side effect 3. Infections 4. Other specify_____
17. Any switching to second line 1. Yes 2. No
18. Reason for switching_____

Any 2nd line treatment failure 1. Yes 2. No

Action taken after 2nd line treatment failure:
_____

Current drug regimen: _____

End point event 1. Under follow-up 2. Transferred out (TO) 3. Lost to follow-up (LTFU) 4. Died

Date of endpoint event ---/---/--- (dd/mm/yy)

Reason for TO, STOP or LTFU_____

If died, cause of death_____

25.1. Place of death 1. Health facility 2. Home

Information recorded by----------Date ----------

Approved by ----------Date ----------

Data entered by----------Date ----------