Retention in care, viral suppression, treatment adherence and quality of life in a public antiretroviral therapy program in Addis Ababa, Ethiopia
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Chapter 1

General Introduction
Epidemiology of HIV/AIDS Worldwide and in Ethiopia

Globally, the first Acquired Immuno Deficiency Syndrome (AIDS) patients were clinically observed and recognized in 1981 among homosexual men treated for rare types of opportunistic infections and Kaposi’s sarcoma in New York and Los Angeles, USA (1, 2). In 1983, the Human Immuno-deficiency Virus (HIV) that causes AIDS was isolated (3-5). According to the 2015 report of the Joint United Nations Programme on HIV/AIDS (UNAIDS), about 36.9 million people are believed to be infected by the HIV virus worldwide, of whom, 70% are living in sub-Saharan Africa (6). In 2014, sub-Saharan Africa was the region where 66% of all the AIDS-related deaths and 70% of all new HIV infections worldwide occurred (6).

Ethiopia is located in East Africa. In 2014, the total population approximated 90 million and nearly 83% of the inhabitants were living in rural areas (7). Among the sub-Saharan African countries, Ethiopia is greatly affected by the AIDS epidemic. Since its first two cases of HIV were detected in the mid-1980’s in stored serum samples that had been collected in 1984 (8, 9), and its first AIDS cases were hospitalized in 1986 in Addis Ababa (10), the disease has spread rapidly in parallel with the global epidemic. Initially, the epidemic was largely concentrated among key populations such as female sex workers, long-distance truckers, police and military recruits (11-16). Later on, the disease has spread to the general population and the country is now in a state of generalized epidemic, in which people in all walks of life are affected (7, 16, 17). In Ethiopia, the main modes of HIV transmission are heterosexual and via mother to child (17, 18). In general, urban dwellers are more affected than rural inhabitants (7, 16-18, 19). In addition, young women face a higher risk of contracting HIV, because of sexual initiation at early age (usually with high-risk older men), socio-economic reasons, and gender- or culture-related vulnerability (7, 18-21).

According to the “single-point” HIV prevalence estimate of 2007, the national adult HIV prevalence was 2.2% in 2004, while that of Addis Ababa, the capital, was 7.2% (22). In the same year, the new HIV infection rates in Ethiopia and Addis Ababa were estimated at 0.28 and 1.42 per 100 person-years, respectively (22). The latest reports about HIV/AIDS indicated that both AIDS-related morbidity and mortality and the numbers of new HIV infections are declining, primarily due to increased access to combination antiretroviral therapy (cART) and intensified behavioral change and bio-medical interventions (6, 20, 23). For instance, AIDS-related mortality has reduced by more than half within 5 years after cART became widely available in Addis Ababa (24). Also, the estimated national adult HIV incidence has dropped to 3 per 10,000 person-years in 2014 compared to 28 per 10,000 person-years in 2004 - a 90% risk reduction in almost a decade (25). However, HIV infection is still prevalent among most at-risk populations, including commercial sex workers, long-distance truck drivers, prisoners, and migrant or seasonal daily laborers in commercial farming and mega-project work sites like flower plantations, sugar factories, dam/or road construction, and hydro-electric power generation (18, 20).
Antiretroviral (ARV) drugs for the treatment of advanced HIV-1 infection

Less than a decade after HIV/AIDS was discovered, the first Nucleoside Analogue Reverse Transcriptase Inhibitor (NRTI) named azidothymidine (AZT), also called zidovudine (ZDV), was approved in 1987 for monotherapy in patients with advanced HIV infection (26). Then, new ARV drugs from the NRTI class, including didanosine (ddI), zalcitabine (ddC), stavudine (d4T), and lamivudine (3TC) were made available for treatment in short succession (27). Because AZT-monotherapy had benefitted patients only for short-term (28), the introduction of the other new ARV drugs paved the way to treatment with a combination of 2 NRTI drugs. This so-called dual-nucleoside therapy was found to be superior to AZT-monotherapy in terms of patient survival, delay in AIDS-related mortality and disease progression to AIDS (29-31). In 1995 and 1996, three new ARV drugs from a new class called Protease Inhibitor (PI) were introduced: saquinavir (SQV), ritonavir (RTV), and indinavir (IDV) (27). Another new drug named nevirapine (NVP) was approved in 1996 as the first of a third class of ARV drugs called Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) (27).

Meanwhile, neither AZT-monotherapy nor dual-nucleoside therapy were able to achieve durable virological suppression, with the resulting problem of drug resistance (26, 29, 31). Consequently, a new treatment strategy with a triple combination of antiretroviral drugs from two different classes (usually two NRTIs + one NNRTI, or two NRTIs + one PI) became officially available in the developed countries in 1996 (32-35). The new treatment strategy was first named Highly Active Anti-retroviral Therapy (HAART) and later called combination Antiretroviral Therapy (cART). cART has dramatically shifted HIV care worldwide from the treatment of opportunistic infections, often in the in-patient ward, to a regular follow-up care at the outpatient clinic. From 1996 until 2008, numerous new drugs from existing or new ARV classes became available for treatment, expanding therapeutic options. These drugs included abacavir (ABC), tenofovir (TDF), and emtricitabine (FTC) from the NRTI class; delavirdine (DLV), efavirenz (EFZ), and rilpivirine (RLV) from the NNRTI class; nelfinavir (NFV), amprenavir (APV), ritonavir-boosted lopinavir (LPV/r), atazanavir (ATV), and darunavir (DRV) from the PI class; enfuviritide (T-20) from the Fusion Inhibitor (FI) class; maraviroc (MVC) from the Entry Inhibitor (EI) class; and raltegravir (RLV) from the Integrase Inhibitor (II) class (27). Although many of these newly developed drugs are more potent with less toxicity, they are not widely available in resource limited settings, including Ethiopia.

After cART became the standard treatment protocol for advanced HIV infection, AIDS-related morbidity and mortality have declined substantially and survival has improved progressively worldwide (6, 33, 36-39). Also, the numbers of new HIV infections are declining and patients already infected by HIV are now experiencing a life expectancy approaching that of the general population (40-43). This is primarily the result of the effectiveness of cART in suppressing the viral replication to a minimum level and restoring or maintaining the patients’ immunologic function (44, 45).
Universal access to cART and retention in HIV-care in Ethiopia

In Ethiopia, fee-based cART was first started in 2002 in three hospitals in Addis Ababa (46-48). Thanks to the extraordinary political commitment and special support by the international community and donor agencies, including US President's Emergency Plan for AIDS Relief (PEPFAR), Global Fund, UN agencies and the World Bank, universal free access to cART was launched as of January 2005 (46, 48). To achieve universal access to treatment, Ethiopia has adopted the WHO-recommended public health approach (48, 49). This approach aims at promoting access to cART for free in resource-limited settings where a (sub)specialist physician-oriented model of care with periodic and advanced laboratory monitoring may not be feasible, let alone affordable and sustainable. The WHO-recommended public health approach includes, among others, the following key elements: standardized regimens, decentralized service delivery from hospital-based to lower level primary health care facilities (for example, to health centers) via task-shifting, and periodic laboratory monitoring (48, 49). Task-shifting (also called task-sharing) refers to sharing of patient management responsibilities to the lower cadre of health care providers and into the community (50). The latest Ethiopian ART guideline recommends triple-combination therapy with two NRTIs plus one NNRTI for first-line treatment (51). The second-line regimen encompasses a ritonavir-boosted PI plus two previously unused NRTIs (51).

Currently, the Ethiopian public HIV/AIDS program focuses mainly on HIV prevention including the prevention of mother to child transmission (PMTCT), HIV counseling and testing services, care and support, treatment scale-up, health systems strengthening including leadership, community mobilization, patient information management, decentralizing HIV/AIDS-related services closer to the community and task shifting/sharing to lower level health cadres, such as health officers and nurses (20). In particular, the HIV/AIDS treatment cascade across the continuum begins with the detection of HIV-infected persons via voluntary counseling and testing (VCT), outreach testing campaigns, or provider-initiated testing and counseling (PITC) at the different service-delivery outlets including the outpatient department, antenatal care clinic, tuberculosis clinic, and in-patient ward. Next, persons tested HIV-positive are enrolled into the pre-ART care. After enrolment, patients receive a package of services including information on positive healthy living, safer sexual practices, treatment initiation and adherence, and follow-up medical care via adherence case managers. Patients also receive additional care and support services from community-based organizations or associations of people living with HIV (PLHIV). Then, HIV-infected adults who fulfill the following WHO criteria while in the pre-ART care are automatically eligible to lifelong cART once their readiness to start treatment is assured: WHO clinical stage IV, irrespective of CD4 cell count; WHO clinical stage III with a CD4 cell count of ≤350/mm$^3$; or all WHO clinical stages with CD4 cell counts ≤200/mm$^3$ (51). Based on these criteria, the number of HIV-infected persons ever started cART has rapidly increased from 1,890 patients in 2005 to 521,000 in 2014 (52). Also, the number of health care facilities providing cART has increased from only three hospitals in 2005 to 198 hospitals and 849 health centers as of December 2014 (20). Currently, about 402,000 HIV-infected persons are receiving cART in Ethiopia, among whom, approximately 80,000 (~20%) are living in Addis Ababa (52).
Despite the remarkable achievement in terms of patient enrolment, increasing utilization of cART, patient survival, steep declines in AIDS-related mortality and gradual decreases in new HIV infection rates (6, 20, 46, 23, 24, 46, 52, 53), poor retention in HIV care after patients started cART is recognized as a major challenge in Ethiopia (46, 53, 54). Retention in HIV care generally refers to the proportion of HIV-infected patients who are remaining alive and still receiving HIV care after they started cART, including those stopping ARV medications (because of medical or personal reasons) while remaining in care. Attrition from care is the reverse of retention in care, and is defined as patients’ absence from HIV care for at least 1 month following their most recent planned clinic or pharmacy refill appointment for reasons related to either death or lost to follow-up (LTFU). Poor retention in care, particularly related to lost to follow-up (LTFU), can be devastating for patients’ lives and for society, as it increases the risk of treatment interruption and thereby increases the risk of virological treatment failure, which in turn could lead to an increased chance of HIV transmission (55-59).

Previous studies of retention in HIV care have shown that early attrition due to death shortly after patients started cART is common in many public ART programs in resource-limited settings, including in Ethiopia (46, 60-66). The most frequently mentioned reasons for early death included late presentation with severe immuno-deficiency and poor quality of the health-care services (46, 64-68). Poor retention in HIV care is also a documented problem in developed countries (69-74). However, early attrition shortly after patients started cART is not a characteristic of ART programs in developed countries (61). Also, there is no a gold standard measure of retention in care (75, 76). Consequently, direct and strict comparison of treatment outcomes between the developed and developing countries may sometimes be misleading (77-79).

The Treatment Goals of combination Anti-retroviral Therapy (cART)

Virological suppression: According to the Ethiopian ART guideline, the reduction of the plasma viral load to an undetectable level is described as one of the primary goals of cART (51). Virological suppression allows for immunological recovery, resulting in decreased AIDS-related morbidity and mortality (38, 41, 44, 45). The concept of ‘Treatment as Prevention’ is also related to this primary goal; the HIV Prevention Trial Network (HPTN 052) has proven that by suppressing the viral load to an undetectable level, the HIV transmission rate to uninfected sexual partners is significantly reduced (80, 81). In addition, the level of virological suppression can serve as an important indicator of ART program performance, since it reflects the levels of effort applied to avoid the two most common causes of detectable viremia, i.e. treatment non-adherence and transmitted drug-resistance (82, 83).

Although virological suppression is mentioned as the primary goal of cART in the national ART guidelines (51), measurement of the plasma viral load in patients taking cART is not routinely performed in resource-limited settings, including in Ethiopia. This is because the test is too expensive to routinely carry out in daily clinical practice. Currently, a debate is ongoing whether routine plasma viral load monitoring should be part of the clinical management of HIV-infected patients in resource-
limited settings. Some researchers advocate the routine use of plasma viral load monitoring to detect virological treatment failure at an early stage, to support adherence, to prevent drug resistance and to reduce onward transmission of HIV (84-89). Also, they raise the concern that the present use of the WHO-recommended clinical and immunological criteria to detect virological treatment failure may often be inaccurate or too insensitive (90, 91). Conversely, several other researchers argue that routine plasma viral load monitoring, although clinically important and advantageous for public health, may not be feasible, affordable, cost-effective or sustainable in the developing countries, at least not in the short term (92-95). Instead, they recommend that, for a lasting impact, efforts need to be focused on the unfinished competing priorities, including early detection of HIV, enrolment in HIV care and scale-up of access to cART, tackling early attrition, enhancing retention in HIV care and achieving optimal adherence (93, 96, 97).

**Adherence to combination antiretroviral therapy (cART):** Treatment adherence is a means to achieve and maintain the goal of maximum and durable virological suppression. To achieve this goal, near perfect adherence (usually 95% or higher) is needed for single PI-based regimens (98), although NNRTI- and boosted PI-based cART regimens may require a less stringent adherence level of less than 95% (99-101).

According to the World Health Organization (WHO), adherence is defined as ‘the extent to which a person’s behavior - taking medication, following a diet, and/or executing lifestyle changes - corresponds with agreed recommendations from a health-care provider’ (102). In response, various strategies have been developed to help patients improve their adherence along the course of life-long treatment (103). For example, single tablet or fixed-dose once- or twice-daily combinations of ARVs have been introduced to decrease pill-burden (104-107). Adherence case managers provide routine adherence support before and after patients start cART (51). Moreover, real-time monitoring devices and text-message reminders have been used to enhance adherence in several African countries (108, 109). Despite all these available interventions, maintaining long-term adherence remains a major challenge to both patients and health-care providers. This is because cART is a life-long medication, adverse effects are quite common, there is associated stigma, and patients often loose motivation to take the ARV drugs when they feel better (110, 111).

There are several approaches to assess medication adherence, with each method having strengths and weaknesses (112-114). Self-reported adherence, for example, is the easiest and most commonly used measure, but it tends to overestimate adherence and is susceptible to recall bias (112, 115). Treating clinicians may assess patients’ adherence at each follow-up clinic visit. But, their ability to assess patients’ medication taking behavior is quite limited (116-118). Pharmacy-refill is used to estimate adherence based on the patients’ refill visit history at the ART pharmacy. However, it only tells drug possession, not consumption (119-121). More objective adherence measures are measuring drug levels in blood or urine and the use of the medication event monitoring system (MEMS). However, measuring drug levels in biological samples of patients does not distinguish non-adherence
from malabsorption or drug-drug interactions. In the case of MEMS, patients may not actually take the drug or take a higher dose of ARV drugs during each bottle opening (112, 122). Therefore, it is usually recommended to use a combination of methods for a better estimate, since there is no single gold standard adherence measure (112, 123, 124).

**Health Related Quality of Life (HRQoL) enhancement**: Because the clinical management of chronic HIV-1 infection is lifelong and the disease and its treatment can cause adverse effects (111, 125, 126), HRQoL has become an important outcome and its enhancement is one of the primary goals of cART (51). In addition, the tendency to expand the scope of medical/health care to encompass the spiritual, psychological, and socio-economic aspects of health increased the importance of HRQoL as an outcome measure (127). To date, there is no universally agreed upon definition of HRQoL. However, many would agree that it is a multi-dimensional concept encompassing at least three aspects of health: physical, psychological, and social wellbeing and functioning (128). According to the World Health Organization (WHO), HRQoL is defined as ‘individuals’ perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns’ (129). In this regard, HIV/AIDS may affect all HRQoL domains (125, 126).

Despite the improvement in survival and HRQoL of HIV-infected persons after the introduction and rapid scale-up of cART (36-39), their HRQoL is still lower compared to that of the general population (130). Previous research findings of poorer HRQoL in HIV-infected persons pointed out that particularly depressive symptoms and stigma can adversely impact HRQoL, either directly or indirectly (mainly via medication non-adherence) (131). Inadequate social support and both short-term and long-term adverse effects of cART can also negatively affect patients’ physical and psycho-social wellbeing and daily functioning (111, 132). In Ethiopia, enhancing HRQoL is acknowledged as one of the primary goals of cART (51). However, it has not yet received adequate attention. The implication is that HIV-infected persons may continue to experience disproportionately poor HRQoL.

**Outline of the thesis**

In this thesis, we present the results of a PhD study which was undertaken between September 2012 and April 2013 in 10 health-care facilities in Addis Ababa, Ethiopia. The overall aim is to estimate the levels of retention in HIV-care, virological suppression, medication adherence and health related quality of life among HIV-infected adults who have received at least six months of cART. An additional aim is to investigate the predictors of attrition from HIV care, detectable viral load, sub-optimal adherence and poor HRQoL. Knowledge about the predictors or correlates can help to design interventions aimed at tackling the problems.

A total of 870 patients who initiated cART between May 2009 and April 2012 were randomly selected from the ART-register. Six hundred sixty four (76.3%) patients, who were alive, were retained in HIV care and using cART underwent a face-to-face interview to assess their level of medication adherence and HRQoL. HRQoL was measured by the WHOQoL-HIV BREF, depressive symptoms by the
Kessler-6 scale, and stigma by the Kalichman internalized AIDS stigma scale. The level of medication adherence for the same 664 patients was estimated using the self-report adherence questions, clinician-recorded and pharmacy-refill measures. In addition, plasma HIV-1 RNA concentration was measured in the 642 patients who provided a blood sample.

In chapter one, a general introduction about the epidemiology of HIV/AIDS and the evolution of its treatment is presented in the global and Ethiopian context. In chapter two, the aim is to investigate retention in HIV-care after patients started cART and to describe the predictors of attrition from care. In chapter three, we investigate the level of virological suppression and identify the predictors of detectable viremia among 642 HIV-infected adults who are still using cART. In chapter four, we assess the levels of adherence to cART according to self-report, clinician-recorded and pharmacy-refill measures, and examine the adherence measure best able to distinguish between patients with a plasma viral load below or above 400 RNA copies/mL. In chapter five, we identify factors associated with sub-optimal adherence as assessed with each of these methods. In chapter six, we present the findings on the level of health related quality of life and its predictors or correlates among the 664 HIV-infected adults who are receiving at least 6 months of cART. In chapter seven, we describe the lessons learned for future clinical and public health practices related to cART in Ethiopia and other similar settings.
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