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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Citation for published version (APA):
Chapter 7

Discussion: Lessons Learned
Introduction
The rapid spread of HIV/AIDS in Ethiopia was unprecedented. Shortly after the first seven AIDS cases were identified in 1986 in a Hospital in Addis Ababa (1, 2), HIV/AIDS had become a disease of public health concern. However, the health care system was ill-equipped to respond to the AIDS epidemic as it lacked skilled human power, laboratory and research facilities, drug supplies, training as well as preventive health services.

In 2002, combination antiretroviral therapy (cART) became available in three hospitals in Addis Ababa, but only to patients who could afford it (3, 4). To increase access to cART in low income countries, global initiatives such as the Accelerating Access Initiative by the UN agencies, together with pharmaceutical companies and the World Bank, the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFTAM), the WHO’s “3 by 5” target (3 million treated by 2005), and the Presidents’ Emergency Plan for AIDS Relief (PEPFAR) were designed (5-8). With the help of these initiatives and the generous support from the international community, universal access to cART has been rolled out in Ethiopia since 2005 (3, 4, 9).

According to the report by the Federal HIV/AIDS Prevention and Control Office (HAPCO), the number of health care facilities offering cART has increased from three hospitals in 2005 to 198 hospitals and 849 health centers as of December 2014 (10). The number of persons initiating cART has also increased from 1,890 in 2005 to 521,000 in 2014 (10). As a result, AIDS-related morbidity and mortality have declined by more than half, i.e. 63% (11). The occurrence of new HIV-infections has also reduced gradually from 28 per 10,000 person-years in 2004 to 3 per 10,000 person-years in 2014 (12). This is a remarkable achievement considering the reality a decade earlier.

Between September 2012 and April 2013, we conducted a study among 870 randomly selected HIV-infected adults receiving cART in 10 health-care facilities in Addis Ababa, Ethiopia, with the overall aim of estimating retention in HIV care, viral suppression, medication adherence and patients’ health-related quality of life (HRQoL). An additional aim was to investigate the predictors or associated factors of attrition, detectable viral load, sub-optimal adherence and poor HRQoL. Based on our study results, and the experience we have in HIV/AIDS-related service delivery and research in Africa and Europe, we summarize the lessons learned for future clinical and public health research and practice in other similar settings.

Lessons Learned
1. Retention in care is comparable with, or even higher than estimates in resource-limited or EU/USA settings
The success of cART scale up in Ethiopia is shown by the increase in the numbers of health-care facilities offering cART services and the number of HIV-infected persons receiving cART (3, 4, 13). In 2012/2013, adult cART coverage reached 75% (10). However, because of the expanded eligibility to initiate cART at a higher CD4 cell threshold, adult cART coverage is reported to be around 54% as of
December 2014 (10). This estimate could drop further considering the latest recommendation by the 
World Health Organization (WHO) to treat every person tested HIV positive, also called the “Seek, 
Test and Treat approach” (14). There is an opportunity, however, to increase cART coverage by 
initiating cART immediately among the pool of thousands of patients eligible for cART and currently 
awaiting treatment initiation in pre-ART care.

Despite the initial successful roll out of cART, poor retention in HIV care remains to be a challenge (3, 
15). According to a systematic review of study results in sub-Saharan Africa, the pooled estimate of 
retention in care is reported to be 72% at 36 months (16). Our estimate of 80% retention (17) in the 
first three-and-half years of cART initiation is comparable with, or even better than those achieved in 
resource-limited and EU/USA settings. This achievement could be a result of several ART-program 
initiatives designed by the government with the help of donor support. The case management 
initiative, for example, employs “case managers” (also called adherence counselors) who promote 
positive living and help patients to achieve optimal treatment adherence. Phone-call tracing to LTFU 
patients has been started to re-engage patients back to clinical care, and targeted adherence 
counseling is offered whenever non-adherence (to treatment or to regular drug refill/clinic follow-up 
visits) is detected. Moreover, the community is mobilized at the grass roots level (including 
associations of People Living with HIV and burial societies, also called firdirs) to contribute their own 
share towards HIV prevention, treatment, and care and support services (18). Improving the health 
information management system at the health facility level, and enhancing the supply-chain 
management system to ensure uninterrupted supply of HIV-related commodities and drug supplies 
may also have contributed (19, 20).

However, cautious interpretation and comparison of retention-in-care estimates within and across the 
different settings is needed. First, the duration of follow-up after cART initiation may not be the same 
for all patients in a particular study or in different studies. The longer the duration of follow-up, the 
lower by definition the probability of a patient being retained in clinical care. Second, retention-in-care 
in EU/USA is measured along the full cascade of care, from HIV testing to enrollment in care, and then 
to viral suppression (21-23). This is one potential reason that most retention-in-care estimates in 
EU/USA settings might appear low. Third, most studies measure retention as a fraction of patients 
retained in clinical care at a particular time period, and is often expressed in percentages. This can 
potentially overestimate retention-in-care, as attrition (due to LTFU) may have occurred more than 
one in the same patient over the course of treatment. Fourth, the definition of LTFU and the time 
frame to classify a patient as lost or dropped is not uniform across the studies, affecting the retention 
in care estimate in either direction (24, 25). For example, some studies use a time frame of one month, 
while others use three, six or even twelve months (26-32). The longer the time frame to classify a 
patient as lost to follow-up, the higher would be the retention-in-care estimate, and vice versa. Fifth, 
follow-up time is not uniformly distributed, as censoring time (due to LTFU or untimely death) is mostly 
clustered in the first few weeks or months of cART initiation in the developing countries (33, 34). This 
is one of the major reasons that comparison of ART-program outcomes between developed and 
developing countries that are based mainly on results from patients currently receiving cART can be
quite misleading (35-37). Other issues, such as formal transfer-out of the patients to another ART-clinic or informal “self-transfers” by the patients themselves, the definition of stopped cases, late presentation and initiation of cART with severe immunodeficiency, could also affect retention-in-care estimates either directly or indirectly. In general, retention-in-care estimates using data from observational studies need cautious interpretation. If feasible, longitudinal measurement of retention along the full cascade of HIV-care and using a ‘person-time’ approach could solve some of the problems we mentioned above.

2. Early attrition from care shortly after cART initiation is evident

Conceptually, attrition from care complements retention in HIV care. Because HIV is a chronic infection, its clinical management requires that patients should come to the ART-clinic for regular and scheduled follow-up visits (usually every one-to-three months). However, some patients enrolled in HIV care become absent, mainly due to LTFU or death. Although retention in care in our study may appear high, early attrition due to LTFU and death was evident (17). Nearly one-fifth (152/836) of the patients were not retained-in clinical care in the first three-and-half years of cART initiation. The median time to attrition was 5 (IQR, 0-10) months, and nearly one-third (50/152) of the patients had died (n=33) or had become LTFU (n=17) in the first one month of cART initiation (17). This problem of early attrition was already recognized in the early periods of cART expansion in the resource constrained settings (33, 34, 38). Unfortunately, it is still a prevailing reality nearly a decade after cART roll-out has started in Ethiopia (17).

In our study, all-cause mortality accounted for 46% (70/152) of attrition after a phone call tracing was made to ascertain the current status of LTFU patients (17). Close to half (33/70) of the patients had died before celebrating their first month of cART initiation. Historically, HIV/AIDS was a deadly infectious disease. However, the introduction of cART has transformed HIV-infection into a chronic manageable, but incurable disease (39, 40). Despite cART being widely available, early death is still a reality in most resource-limited settings, such as Ethiopia. Previously done studies in sub-Saharan Africa have reported mycobacterial and neurologic infections, malnutrition/anemia, drug toxicity, immune reconstitution inflammatory syndrome (IRIS), and septicemia as the immediate causes of early mortality (38, 41, 42). The most credible underlined cause, however, is that patients start treatment late, with severe immunodeficiency, and often present with symptomatic diseases (38, 43). In addition, the poor quality of health-care services to diagnose and treat AIDS-related co-morbidities and ARV drug adverse effects may contribute significantly to the early mortality (38).

Lost to follow-up accounted for 54% (82/152) of attrition by the time of the study (17). Thirty-three (40%) patients were lost to follow-up in the first 6 months, while 56 (68.3%) were lost in the first 12 months after cART initiation. The median time between patients’ last known clinic/refill visit and date of tracing was 16 (IQR, 8.3-26) months. The most frequently reported reasons for being LTFU, among others, were being away from home for various reasons and searching for religious cure. Fifty-one LTFU patients were untraceable due to absence of a contact address, a non-functioning telephone number, or they had given a wrong telephone number (17). The implication of all these is that patients
may need to be prescribed with the amount of ARV drugs sufficient to cover the time period during which they will be away from home. Also, contact addresses (if possible, with alternatives) must be recorded correctly and tracing of LTFU patients to ascertain their current status need to be strengthened as part of the daily clinical care.

3. High on-treatment viral suppression: implications for routine plasma viral load monitoring and achieving the UNAIDS 90-90-90 target

Combination antiretroviral therapy is primarily used to suppress viral replication to an undetectable level (44, 45). To monitor whether patients achieved viral suppression after cART initiation the plasma viral load is measured. Although routine plasma viral load measurement is part of the daily clinical management of treated HIV infection in resource-rich settings, it is usually unavailable in most resource-limited settings, as the test is too costly (45, 46). As an alternative, patient monitoring based on CD4 cell count or clinical criteria is recommended by the WHO in these settings (47). However, many researchers have reported that the WHO-recommended criteria are poorly predictive of virological treatment failure (48-50).

In our study, nearly 95% of the patients achieved viral suppression of <400 HIV-1 RNA copies/mL in on-treatment analyses (51). This result was remarkable in the sense that patients retained in HIV care can achieve such a high viral suppression level even if adherence support via routine plasma viral load monitoring is unavailable. Most importantly, this result would mean that resource-limited settings can achieve the recent UNAIDS 90-90-90 target provided that they could retain patients for a longer time (52). However, assuming that LTFU, dead, or stopped patients had a detectable viremia, the proportion of patients with undetectable viral load would decrease to 71.6%. This latter estimate is clearly an underachievement considering the latest UNAIDS 90-90-90 target mentioned above (52). Therefore, efforts should be galvanized to prevent early attrition (and thus promote retention) along the cascade of HIV care in order to achieve the UNAIDS target.

Considering the high viral suppression result, we suggest that routine plasma viral load monitoring of all patients may not be preferred over the existing CD4 cell and clinical driven monitoring, at least not until affordable viral load tests become widely available. Currently, a debate is ongoing whether routine plasma viral load monitoring at its current cost should be part of the daily clinical management of HIV infection in resource-limited settings (53-58). Researchers debating for and against routine viral load testing both agree that viral load testing is useful to detect virological treatment failure early, to support medication adherence, to guide clinical decisions, to prevent drug resistance, and thereby to reduce onward transmission of HIV (54, 57). Both sides also understand that viral load testing is advantageous for public health (57, 59, 60). However, they differ in what to prioritize at this moment. Researchers advocating routine viral load testing argue that it should be part of the daily clinical care as quickly as possible to avoid costly outcomes (60, 61). Conversely, those against it suggest that priority should be given to unfinished tasks such as increasing cART coverage by reaching out to key populations for HIV testing, enrolling HIV-positives in care and initiate cART before they are severely immuno-compromised, tackling early attrition, and improving retention in care and treatment
We also believe that priority should be given to these unfinished tasks for a sustainable result.

4. High level of adherence to cART, but there is a room for improvement as sub-optimal adherence is present

Sufficiently high level of adherence is the cornerstone to achieve the therapeutic goals of cART (63, 64). Previous studies have reported that treatment adherence is generally high in resource-limited settings (65, 66). Our study result of nearly 96% average adherence according to pharmacy refill is in support of this claim (67), and probably explains the high degree of viral load suppression. However, maintaining high adherence level for a long term remains to be a challenge for patients and healthcare providers. For example, up to a quarter of the same patients in our study had sub-optimal adherence according to self-report, clinician-recorded and pharmacy-refill measurements (68). Therefore, ART-programs should not be lenient with the high adherence claim, but should work harder to maintain long-term adherence (69). Maintaining high levels of adherence will not only benefit individual patients, but also preserves the long-term effectiveness of first-line cART regimens in settings where therapeutic choices are limited.

Because routine viral load monitoring is unavailable in most resource-limited settings (45, 46), clinicians need to rely on detecting non-adherence to diagnose virological treatment failure or to carry out important clinical decisions. Given the absence of a single gold-standard adherence measure (70), however, it would be commendable to identify the adherence measure most predictive of detectable viral load in a public ART-program where there is no routine viral load testing. In our study, non-adherence as measured with each of the self-report, clinician-recorded, and pharmacy-refill methods had a likelihood of more than 80% to correctly identify patients with a plasma viral load below or above 400 HIV-1 RNA copies/mL (67). Therefore, we suggest that clinicians in resource constrained settings use either of these assessment methods alone or in combination to measure adherence in their respective resource-constrained settings.

5. High levels of depressive symptoms and HIV stigma were most strongly and most consistently associated with a low Health Related Quality of Life (HRQoL)

In recent years, being alive is not enough for a clinical care being considered successful. Other patient-reported outcomes such as HRQoL should also be considered (71, 72). In our study, the level of patients’ HRQoL was comparable with that in previous studies in resource-poor settings (73). Nearly 15% of the patients had depressive symptoms based on the scale’s previously validated cut-off score. In general, higher levels of depressive symptoms and HIV-stigma were most strongly and consistently associated with a lower level of HRQoL. Conversely, obtaining sufficient nutritious food and access to jobs were significantly associated with better HRQoL. Therefore, interventions aimed at improving the HRQoL should focus on reducing depressive symptoms and HIV-stigma, and on enhancing food security and job opportunities.
6. Late presentation with low CD4 cell count at cART initiation appears the underlined cause for poor cART outcomes

The CD4 cell count is an objective measure and key indicator of patients’ immunological function and disease severity or progression (46). It is currently being used to assess patients’ eligibility for cART initiation and to monitor therapeutic responses thereafter in resource-limited settings (45, 46). The WHO and national guidelines have been revised several times to raise the CD4 cell threshold of cART initiation. The initiation of treatment based on a certain CD4 cell threshold was meant to balance the benefits of cART with possible occurrences of non-adherence or adverse drug effects. Recently, the WHO has recommended treating every person tested HIV-positive irrespective of the CD4 cell count, once patients’ readiness to initiate cART is assured (14). Unfortunately, nearly two-thirds (65.3%) and little more than one-third (34.1%) of the patients we studied had already been in a state of severe immunodeficiency below, 200 and 100 cells/μL, respectively, when tested HIV positive or when enrolled in HIV care (17). Therefore, our study results suggest that raising the CD4 cell threshold or treating every person testing HIV-positive should be preceded or supported by earlier detection of asymptomatic cases with far less advanced diseases.

The value of the CD4 cell count at enrollment in HIV care as a cART-program performance indicator remains crucial. It indicates the intensity of our efforts to detect and enroll HIV-infected persons in care as early as possible. In our study, the median CD4 cell count at enrollment in HIV care and at start of cART were 141 (IQR, 73-239) and 133 (IQR, 72-203) cells/μL, respectively (17). There is very little change in the CD4 cell count at enrollment in HIV care between 5 or 8 years ago (3). This is an indication that early identification of asymptomatic cases should receive equal, or even more attention than raising the CD4 cell threshold of cART initiation or treating patients shortly after they get tested HIV-positive.

Low CD4 cell count at enrollment in care or at start of cART also means that screening for opportunistic infections (OIs) and prophylactic treatment is necessary until patients’ immunologic function is sufficiently improved to protect them against common adulthood infections (74). In Ethiopia, OI screening and cotrimoxazole prophylactic treatment is part of the routine clinical management of HIV-infection in patients with severe immune deficiency (45, 75). However, there have been reports of frequent stock-out of these drugs.

Different strategies are already put in place, and new ones can still be designed at various levels to detect asymptomatic cases and to facilitate entry in to clinical care as early as possible. In clinical settings, patients at high risk of having HIV such as tuberculosis patients, patients with sexually transmitted diseases (STDs), antenatal care (ANC) attendants, and laboring mothers are already provided an opt-out HIV-testing and counseling service (10, 45). However, targeted interventions are still needed to reach out to key populations driving the epidemic, including female sex workers, heavy truck drivers, prisoners, daily laborers in commercial farming and construction sites, police and military recruits, and sexually active in-school or out-of school youth. The role of private health-care facilities and clinics run by non-governmental organizations (NGOs) to diagnose HIV infection among their
clients, including key populations, and immediate linkage of HIV positives to clinical care should be strengthened (76, 77). Moreover, the feasibility of new HIV testing approaches, such as self-testing and home-based HIV testing using urban or rural community health workers (also called health extension workers in Ethiopia), may need to be considered to detect HIV-infected persons early in the community or in working places (such as brothels) (78-82). All these can help to best use our limited resources for a lasting impact. Also, early identification and treatment initiation will not only be beneficial to individual patients (83), but is also advantageous to reduce HIV transmission to the wider community (84, 85).

7. Younger age is potentially predictive of detectable viremia and non-adherence to cART

Many researchers have reported that younger patients are not benefitting optimally from cART, partly because they adhere to it less well compared to older patients (86-90). Poor adherence to cART among young patients may occur due to various reasons including HIV stigma, lack of friendly services, socio-economic barriers, and field/migratory labour work (86-90). In our study, young patients were at greater likelihood of having sub-optimal adherence (68). This finding was consistent with the higher likelihood of having a detectable viral load among these same young patients, even after adjustment for medication non-adherence (51). The implication is that further investigations may be required whether transmitted drug resistance has played any role. In addition, special programs with a comprehensive package of services are needed, specifically for young people, to reduce HIV infection, to promote testing for HIV, to enroll patients in HIV care immediately after being tested positive, to improve treatment adherence and retention in care, and finally to prevent detectable viral load. For example, young-friendly services during extended and weekend clinic hours, can be offered at the health facility level (91). Family-focused and home-based approaches can be designed to create an enabling environment for social support and treatment adherence. In addition, young patients themselves can be trained about self-management skills to improve their medication taking behaviour (91).

Conclusions and the way forward

The rapid scale-up of cART in Addis Ababa was generally successful in terms of increasing the numbers of health care facilities offering cART services, the numbers of patients accessing cART, reductions in AIDS-related morbidity and mortality, and a decreasing incidence of new HIV infections. In addition, high levels of on-treatment viral suppression and medication adherence are apparent, and retention in care appears comparable with, or even higher than estimates in other settings. However, early attrition from care should receive close attention. Its underlying causes, such as late presentation with severe immunodeficiency, should be programmatically addressed. The quality of health care services to manage symptomatic AIDS illnesses, AIDS-related co-morbidities, and ARV drug adverse effects may also need to be checked. Although average adherence appears high, it should be understood that there is room for improvement, as sub-optimal adherence occurred in up to a quarter of the patients. Younger patients should be closely monitored for treatment adherence and therapeutic responses. Additional research may be required to check whether transmitted drug resistance has played any role in developing detectable viremia, particularly among young people.
References


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