Retention in Care and Adherence to ART are Critical Elements of HIV Care Interventions

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Abstract Retention in care and adherence to antiretroviral treatment (ART) are critical elements of HIV care interventions and are closely associated with optimal individual and public health outcomes and cost effectiveness. This literature review was conducted to analyse how the roles of clients in HIV care and treatment are discussed, from terminology used to measurement methods to consequences of a wide range of patient-related factors impacting client adherence to ART and retention in care. Unfortunately, data suggests that clients find it hard to follow recommended behaviour. For HIV, the greatest loss to follow-up occurs before starting treatment, though each step of the continuum of care is affected. Measurement approaches can be divided into ‘direct’ and ‘indirect’ methods; in practice, a combination is often considered the best strategy. Inadequate retention and adherence lead to decreased health outcomes (morbidity, mortality, drug resistances, risk of transmission) and cost effectiveness (increased costs and lower productivity).

Keywords Retention · Adherence · HIV/AIDS · Measurement · ART

Introduction

Retention in care and adherence to antiretroviral treatment (ART) are critical elements of HIV care and are closely associated with optimal individual and public health outcomes and cost effectiveness. Despite the significance of retention and adherence, a broad body of evidence suggests that many clients struggle to adopt the appropriate behaviours recommended by their health-care providers. This translates specifically to increased morbidity and mortality through suboptimal viral suppression, increased risk of drug resistance, and increased risk of HIV transmission; and more generally to higher health-care costs and a loss of or reduction in individual income, potentially translating to lower economic productivity at the country level.

Consequently, there is increasing concern about inadequate retention and adherence, due, in no small part, to the amount of financial and human resources investment required to sustain or expand health-care services. Through global effort, ART coverage increased by more than 2,500 % between 2002 and 2011 in low- and middle-income countries, resulting in treatment coverage of just over 8 million people living with HIV (PLHIV), or 54 % of those eligible are receiving treatment [1, 2]. Despite the expansion of HIV services, programme data indicates that PLHIV often encounter multiple challenges to accessing available health-care.

This paper reviews the published literature on retention in HIV care and adherence to treatment and aims to clarify terminology used, provide an overview of retention and adherence research, discuss measurement methods, and

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describe the consequences of inadequate retention and adherence.

Understanding the Concepts of Retention and Adherence

In the last four decades, literature on health care and public health has focused increased attention on the complexities and importance of the patient–health-care provider relationship, also understood as a supply (health-care provider and system)–demand (patient) paradigm [3]. With the steady increase in quality and reach of health services, some experts suggest that efforts to increase client involvement may have a greater impact on health outcomes than any other improvement in specific medical treatments [4].

A review of recent literature reveals a range of terms also used to describe retention in care and adherence to treatment, including: ‘compliance’, ‘concordance’, ‘persistence’, and more simply, ‘retention’ and ‘adherence’ [3, 5–8]. Altogether, they aim to describe the conformity of a person’s behaviour with that recommended by their health-care provider(s). However, each word has a specific meaning and implications for its use. ‘Compliance’ may imply a paternalistic relationship between health-care providers and clients and stigmatize those considered to be not complying with their health-care provider’s advice [3, 7, 9]. Alternatively, some advocate for ‘concordance’, which is meant to more accurately reflect the reciprocal relationship between health-care providers and their clients [10, 11]. The World Health Organization (WHO) uses ‘retention’ (in care) and ‘adherence’ (to treatment) as a preferred terminology, and as such, this article will use the same terms. Simply defined, they are:

- *Retention (in care)* a client’s continued engagement in health services and captures the whole ‘continuum of HIV care’: from enrolment in care to discharge/death of the client;
- *Adherence (to treatment)* signifies the extent a client follows a prescribed medication or treatment regimen [2, 12].

Based on these definitions, a client can be ‘retained in care’ (e.g., attending a clinic appointment according to schedule), but not necessarily ‘adhere to treatment’ (e.g., fail to take medication as prescribed). However, in general, the best outcomes are achieved if a client is retained in care (so that they can be clinically monitored) and adheres to treatment. The above definitions rely on a minimum requirement that ARVs be available. An inadequate supply of ARVs at the facility or country levels can interrupt treatment, leading to poor adherence, and possibly to poor retention.

‘Loss to follow-up’ and ‘attrition’ are terms often used in the literature to represent clients who disengaged from care at any stage of the continuum of care. How loss to follow-up is quantified varies greatly in the field, and in some cases, even within some studies. Lamb et al.’s [13] study of the association of adherence support and services in relation to loss to follow-up and attrition, used two types of data analysis and two different definitions for loss to follow-up—cumulative analysis, in which patients were considered loss to follow-up if they had not visited a clinic within the previous three months ‘without documented evidence of death or transfer to another clinic’ and those who returned to care were no longer defined as lost to follow-up; and cohort analysis, in which patients were considered lost to follow-up after six and twelve months, regardless of whether or not they eventually returned to ART care. Loss to follow-up can also be more broadly defined, depending on the context, to consider those who choose not to continue with their treatment or encounter other barriers to continued access to treatment. In that respect, loss to follow-up is not an outcome by itself. The varied definitions of loss to follow-up within Lamb’s study alone, underscores the challenge of comparing research on retention across the field.

Loss to follow-up and attrition are often difficult to quantify, especially in resource-limited settings where unique client identifiers and vital registers may be lacking. Additionally, most studies focus on selected stages, such as the rate of clients initiating treatment after diagnosis, or the rate of clients still on treatment at a specific period in time instead of the entire continuum of care (Exhibit 1).

Monitoring Client Retention and Adherence

A growing body of studies examine client retention and adherence rates, but interpretation needs to be handled with caution. At present, there is no consensus on period definitions for retention or what constitutes ‘adequate’ retention and adherence (e.g., what type or level of client behaviour). Similarly, indicators are not standardized making it difficult to compare across programmes, or differences in retention and adherence over time. In this sense, some studies consider clients to be lost to follow-up as early as one day after missing an appointment, while others begin count as late as 180 days or a year from the last client facility visit. Many programmes report on basis of dichotomous variables, such as in-care versus loss to follow-up or adherent versus non-adherent. There is also a lack of consistency with regard to the inclusion of deceased clients (and thus not following-up) [14, 15]. Other critical issues include self-transferred clients—when people decide to enrol in care at a new health facility without informing staff at their previous clinics—and

Exhibit 1 Continuum of care and contingencies for loss to follow-up

unascertained death where vital registration data is not routinely collected in many resource-limited settings. Due to the high resource demand associated with tracking clients—compounded by the lack of unique client identifiers, especially in resource-limited settings—some studies may not succeed in identifying the true outcome of those who are lost to follow-up, consequently leading to over-reporting of loss to follow-up. Other issues that impair data comparability include the study settings (e.g., formal clinic trials vs. large-scale programmes in resource-limited settings) and the measurement method applied (e.g., self-reporting may be associated with an overestimation of retention in care and treatment adherence) [12, 16–18].

Inadequate retention and adherence affects virtually all client-health-service relationships, independent of the type of disease, however, there are differing observations with regard to client predictors of loss to follow-up and non-adherence, such as ethnicity, age, or gender [19–22]. In general, retention and adherence rates appear to be higher for conditions with short course of illness [23, 24]. Also, there is some evidence that indicates better ART adherence in resource-limited settings compared to some resource-rich settings [25, 26]. Based on a meta-analysis of 569 studies, DiMatteo [27] found an average non-adherence rate of 24.8 % of clients, highest in HIV, arthritis, gastrointestinal disorders, and cancer, and lowest in pulmonary disease, diabetes, and sleep disorders.

Reaching adequate retention in HIV care and ART adherence may be more difficult and may have more complex challenges than for many other diseases. This is due to several factors: (1) HIV is a chronic condition requiring life-long treatment, (2) HIV-related stigma can be a significant barrier, and (3) complex treatment regimens that can also have undesirable adverse effects and drug interactions. Loss to follow-up and poor adherence undermine individual health outcomes, HIV prevention potential and could have implications on the cost effectiveness of HIV treatment.

The following is a brief overview of recent literature on retention and adherence, organized along the different steps of the continuum of care:

- *Diagnosis*—a major challenge in tackling the HIV epidemic is the failure to promptly diagnose HIV infections. In 2010, a median number of 55 tests per 1,000 adult population were conducted (up from 47 in

2009), with the highest number of tests occurring in Sub-Saharan Africa (82 per 1,000) and the lowest in East, South and South-East Asia (22 per 1,000) [2].¹ Despite the increased scale up of HIV tests and testing facilities, the level of testing remains insufficient overall. PLHIV unaware of their status range from approximately 69 % in Congo and 31 % in Kenya [2] to 33 % in Europe [28] and 20 % in the US [29]. Failure to diagnose HIV infection is usually highest among clients who are not perceived to be at risk of HIV infection, or are marginalized (e.g., injecting drug users, men who have sex with men, immigrants) [30].

- *Assessment and initiation of care and treatment*—once clients are diagnosed with HIV, it is crucial to link and enrol them to care and treatment services. Unfortunately, several studies suggest that only a fraction of people diagnosed with HIV actually start treatment. In their systematic review looking at retention in HIV care between HIV testing and counselling (HTC) and initiation of ART, Rosen and Fox [31] found that 59 % of clients are lost between diagnosis and assessment (receipt of CD4 count or clinical staging), 46 % of clients are lost between assessment and eligibility for ART, and 68 % between eligibility and ART initiation. Similarly, data from the Viet Nam Authority for HIV/AIDS Control lists only 31.6 % of (diagnosed) PLHIV as enrolled in care (pre-ART and ART) [2]. In contrast, Gardner et al. [32] estimate that ~75 % of newly diagnosed PLHIV in the United States are linked to HIV care within 6–12 months after diagnosis, and 80–90 % linked within 3–5 years. Measured by the number of days from diagnosis to the start of ART, delays for clients in South Africa were estimated at 78 and 34 days in Free State Province [33] and Cape Town, South Africa [34], respectively, and about 40 days in Cambodia [35].
- *Retention in care and adherence to treatment*—once ART is initiated, clients need to be retained and they need to adhere to treatment. A systematic review of 33 sources describing 39 cohorts and 226,307 clients in sub-Saharan Africa calculated that a median of 86.1 %

¹ Please note that these numbers relate to total number of tests, as opposed to individuals tested. The number of people testing is likely lower as some may take multiple tests over the course of a year.

of clients remained in the programme at 6 months, 80.2 % at 12 months, 70.0 % at 24 months and 64.6 % at 36 months. Of those reported as lost to follow-up, an average of 41 % of clients were identified to be deceased [36]. In 2011, data from 149 low- and middle-income countries indicated an average retention rate of 81 % at 12 months, 75 % at 24 months, and 67 % at 60 months from 92, 73, and 46 countries, respectively [2]. It is noteworthy that loss to follow-up in both studies was highest in the first 12 months, presumably due to early mortality on ART.

In terms of adherence to treatment, i.e., how reliably clients follow the prescribed medication regimen, Ortego et al. [26] found that an average rate of 62 % of clients reported ≥ 90 % adherence. In this meta-analysis, good adherence was more likely in studies with “higher proportions of men who have sex with men (MSM) and lower proportions of injection drug users (IDU), with participants in an earlier stage of HIV infection, [and] in countries characterized by lower Human Development Index (HDI) scores” [26]. Similar results were reported from a meta-analysis conducted by Mills et al. [25], who found that a pooled estimate of 55 % of the populations in North America and 77 % in twelve sub-Saharan African countries achieved adequate levels of adherence. Gardner et al. [32] reports that ~ 60 % of US clients in need of ART and ~ 80 % of those on ART are adherent/achieve viral suppression.

Measuring Retention and Adherence

Health intervention effectiveness is highly dependent on understanding the role of patient/client behaviour and appropriately measuring the levels of both retention and treatment adherence. Health-care providers need to ‘measure what they manage’, in other words, monitor clients’ behaviour during care and treatment to optimize outcomes. It is also crucial to recognize that if the effectiveness of an intervention is evaluated based on outcomes with differing measurement approaches of client retention and adherence, this impairs comparability and consequently the identification of appropriate responses in a given setting [37, 38].

While it is clear that measuring retention to care and adherence to treatment is critical, doing so accurately is complex and, at present, no globally agreed on ‘gold-standard’ of measurement exists. Measuring adherence objectively in routine-care settings is often a challenge because of potential issues related to approaches originating from feasibility, cost, and health-care providers’ time. Programmes and research use different methods to measure adherence to treatment, each with specific advantages and

disadvantages. Approaches are usually divided into direct and indirect methods [9, 39]: ‘direct’ refers to monitoring of the implementation of the intervention or its immediate outcomes; and ‘indirect’ refers to the use of proxy indicators that are associated with adherence. Consequently, direct approaches are often regarded as more accurate, while indirect methods may be more feasible to implement (and thus also more commonly used) [16].

Direct approaches to measuring adherence include: directly-observed treatment and biochemical analysis of compounds in bodily fluids. An example for direct observation would be handing out and taking drugs in the presence of health care staff. Alternatively, biochemical analysis of compounds in bodily fluids measures drug adherence through detection of either the medication itself (or its metabolites) or non-toxic markers that have been added to the regimen.

Indirect approaches to measuring ART adherence include viral load monitoring, client self-reporting (i.e., client interviews, questionnaires and diaries), pill-counting, prescription claims/pill refill, electronic monitoring devices, client clinic attendance, and provider reporting. Client self-reports are widely employed, however, they are inherently subjective, prone to recall bias, and often over-estimate adherence if patients shy from reporting any lapses in adherence due to fear of criticism from their care providers [12, 16–18]. Another, widely employed indirect measurement method is pill-counting, which is usually performed during clinical appointments and, if the date of the last refill is known, allows calculation of drug adherence. However, pill counting at the clinic may lead to ‘pill dumping’ if a client knows that this may be routinely assessed. Unannounced home visits for pill counting have also been employed as part of adherence monitoring in clinical trial settings. The downside of this method is that it is time consuming and clients may perceive it as ‘policing’, thus posing a challenge to client-provider trust. Additionally, it can be difficult to ascertain whether the client has followed the prescribed frequency and/or dosage through pill counting alone. Prescription claims/pill refills follow a similar logic, using the timing and/or frequency of these as indicators, and is potentially immune to social desirability or reporting bias. A comparison of different adherence monitoring approaches indicates that pharmacy records more accurately correlate with ART adherence compared to self-reporting. Electronic monitoring devices are a relatively new but expensive measurement method that records the date and time the drug container is opened—providing detailed information on patterns of medication taking. This method is not commonly used in routine care settings due to high costs associated with it. Client intervention outcomes may also be used as indicators of adherence, as clinical (e.g., return to health) and biological

outcomes (e.g., suppressed viral load), in certain cases, can only be achieved with adequate adherence. Client clinic attendance monitors timing and frequency of clinic visits, and is the most common measurement method to assess retention in care. However, most programmes do not routinely monitor retention in care, and routine programme cohort analysis needs to be strengthened in several settings.

The selection of the most appropriate measurement approach needs to be at least reliable (i.e., consistent across time and settings) and valid (i.e., measures what it purports to measure) [40, 41]. It also needs to take into account: goal of measurement (i.e., research/documentation vs. routine care), type of intervention (e.g., drug intervention vs. life-style changes), length of intervention, number of and access to clients, available resources, and ethical and legal considerations. In practice, combining more than one measurement method, e.g., subjective client self-reporting with more objective pharmacy-based pill refills, is often considered the most feasible approach in resource-limited settings [12, 40, 42], or reflecting the impact of the intervention, as in viral load suppression. With regard to the latter, for those taking ART, viral suppression is usually an indication that they are adhering effectively to prescribed medicines. The converse may not always be true as someone may be adhering to their ART but if they had been given a regimen which was effective against their viral strain this would not result in viral suppression.

In principle, all of the above measurement methods may be applied in HIV care. However, from a programmatic perspective, especially in resource-limited settings, direct approaches are usually considered less feasible given the comparatively high amount of resources associated with it (especially for life-long treatment) [17, 43–45]. For measuring the impact/effectiveness of a programme measuring viral suppression is key (Exhibit 2).

Retention and Adherence in the Response to HIV

Retention and adherence play a critical role in the response to HIV, spanning across the whole continuum of care: from diagnosis and assessment to the initiation and continuation of treatment. Retention in care and adherence to antiretroviral therapy (ART) need to be maintained for life—presenting significant challenges for clients and health-care providers alike as the epidemic evolves from one requiring an emergency response to one necessitating long-term comprehensive care.

Several factors underscore the importance of retention and adherence in the response to HIV. UNAIDS and WHO estimate that the rate of new HIV infections are decreasing—by 19 % between 2002 and 2011—indicating that prevention efforts have been successful in many settings

(although 2.5 million new HIV infections occurred in 2011) [1, 2]. This success is due in part to the significant expansion of access to HIV related-health services in low- and middle-income countries where ART coverage increased more than 2,500 % during 2002–2011 [1, 2]. For the 34 million people presently living with HIV, most will reach CD4 cell count levels requiring treatment initiation within this decade (as of 2011, approximately 8 million PLHIV were receiving ART, with 6.8 million still eligible) [1]. In addition, the effectiveness of ARVs is improving, substantially reducing morbidity and mortality [46–49], and simpler, less toxic ARV regimens are gradually being introduced in low-income countries.

Consequences of Inadequate Retention in Care and Adherence to ART

Inadequate retention in care and adherence to treatment are widely associated with significant negative implications—such as reduced programme effectiveness and increased morbidity and mortality—for the client and population as a whole [12]. Amongst other things, the development of drug resistance is related to suboptimal adherence [50], reducing treatment effectiveness. Suboptimal adherence may also bear population-level implications, specifically through increased risks of transmission, including transmission of drug-resistant strains (Exhibit 3).

As a consequence of suboptimal health outcomes, insufficient retention and adherence also negatively affect cost effectiveness of health interventions (i.e., increases direct health-care costs and indirect loss of income/productivity). In the case of health-care costs, these are largely dependent on the health-care financing systems of a country. For loss of income/productivity, the implications may be greater if the consequences of reduced productivity on an individual level and its effects on other, healthy, individuals are taken into consideration (i.e., reduced productivity of one individual may impair productivity for other individuals).

Retention in care and adherence to ART have significant implications on health outcomes and cost effectiveness of HIV interventions for both PLHIV and society as a whole. Failure to diagnose HIV and/or delayed care and treatment initiation ('late presentation') are associated with higher rates of on-going HIV transmission, greater risk of opportunistic infections, reduced treatment effectiveness, and significantly increased short-term mortality in 'late presenters' compared with clients who are diagnosed and start treatment earlier [51–53]. Several studies have identified poor treatment adherence, second only to CD4 cell count, as a strong predictor of HIV progression to AIDS and ultimately death [54–56].

		Advantages	Disadvantages
Direct	1 Observation of intervention execution	<ul style="list-style-type: none"> Allows holistic monitoring of actual intervention (e.g., timing, 'quality' of adherence) Avoids client recall (e.g., reporting of socially expected behaviour) 	<ul style="list-style-type: none"> Potential strong Hawthorne effect Resource-intensive, thus limited applicability (e.g., clinic settings)
	2 Biochemical analysis of compounds in bodily fluids	<ul style="list-style-type: none"> Avoids client and provider recall or bias (e.g., reporting of socially expected behaviour) issues Standardized, quantified measurement outcomes 	<ul style="list-style-type: none"> Results influenced by metabolism and/or other external factors Resource-intensive Limited breadth of information (e.g., reasons for non-adherence) Potential strong Hawthorne effect
Indirect	3 Client interviews	<ul style="list-style-type: none"> Flexibility on data gathering depending on client responses 	<ul style="list-style-type: none"> Relatively resource intensive Potential client/prescriber bias and recall issues
	4 Client questionnaires	<ul style="list-style-type: none"> Low resource requirements Standardized, partially quantitative measurement outcomes 	<ul style="list-style-type: none"> Potential client bias and recall issues Requires client literacy
	5 Client diaries	<ul style="list-style-type: none"> Low resource requirements Avoids client recall issues 	<ul style="list-style-type: none"> Potential client bias issues Low levels of standardization Potential high effort for client
	6 Pill-counting	<ul style="list-style-type: none"> Standardized, quantified measurement outcomes 	<ul style="list-style-type: none"> Potential data distortion (e.g., pill dumping, refill from other channels) Limited breadth of information
	7 Prescription claims/pill refill	<ul style="list-style-type: none"> Objective Low resource requirements 	<ul style="list-style-type: none"> Potential data distortion (e.g., pill dumping, refill from other channels) Limited breadth of information
	8 Electronic monitoring devices	<ul style="list-style-type: none"> Avoids client bias or recall issues Standardized, quantified measurement outcomes Analysis of timing of drug intake 	<ul style="list-style-type: none"> Potential data distortion (e.g., pill dumping, refill from other channels) Resource-intensive
	9 Client intervention outcomes	<ul style="list-style-type: none"> Avoids client and provider bias or recall issues 	<ul style="list-style-type: none"> Results may be influenced by other factors (e.g., client diet) Resource-intensive Limited breadth of information
	10 Client clinic attendance	<ul style="list-style-type: none"> Objective Low resource requirements 	<ul style="list-style-type: none"> Potential weak relationship with adherence to treatment Client transfers to other facilities Limited breadth of information
	11 Provider reporting	<ul style="list-style-type: none"> Avoids client bias or recall issues Low resource requirements 	<ul style="list-style-type: none"> Limited prescriber insight in actual client behaviour

Exhibit 2 Retention and adherence measurement methods and respective advantages and disadvantages

	Health outcomes	Cost effectiveness
Client-level implications	<ul style="list-style-type: none"> • Increased morbidity • Increased mortality • Development of drug resistances 	<ul style="list-style-type: none"> • Increased health-care costs borne by client • Reduced income
Population-level implications	<ul style="list-style-type: none"> • Increased risk of disease transmission* • Increased risk of transmission of disease drug resistances* 	<ul style="list-style-type: none"> • Increased health-care costs borne by society • Reduced economic productivity

** In the case of communicable diseases*

Exhibit 3 Potential consequences of inadequate retention in care and adherence to treatment

Relatively small differences in medication intake can trigger major differences in viral suppression. Using different methods of measuring data, several studies analysed the relationship between adherence and viral load and/or mortality. Grossberg et al. [57] found that a 10 % increased adherence rate was associated with viral load decreases of 0.12 log c/mL (adherence measured through drug refills). Similarly, Paterson et al. [58] found that virologic failure occurred in only 22 % of clients with 95 % or greater adherence compared to clients with 80–94.9 % adherence (61 %) and those with under 80 % adherence (80 %) (adherence was measured through electronic intervention monitors). In terms of mortality, adherence has also been shown to be a critical determinant of client survival. A population-based analysis of 1,282 ART-naïve HIV-positive individuals in British Columbia found that clients who used antiretroviral drugs intermittently (adherence level < 75 %) were 2.97 times more likely to die (after adjustment for other prognostic factors, measuring adherence through drug refills) [56]. Similarly, Nachega et al. [59] analysed survival among 6,288 HIV-1-infected South African adults enrolled in a private-sector AIDS management program and found that adherence levels below 80 % were associated with a 3.23 higher mortality. When drug adherence was divided into quintiles (20 % each), each quintile had lower survival rate than the next higher one (adherence measured through prescription claims). Using clinic visits as the predictor, Giordano et al. [60] also come to comparable findings: based on a total of 2,619 men followed for a mean of more than 4 years, clients with visits in three quarters, two quarters, and one quarter in the first year had a 1.42, 1.67 and 1.95 higher mortality respectively compared with clients with visits in all four quarters.

In addition to increases in morbidity and mortality, inadequate adherence reduces treatment effectiveness due to drug resistances, and also limits ARV options. There has

been extensive discussion on the relationship between client adherence levels and the prevalence of drug resistance [61, 62]. Earlier studies indicate a bell-shaped curve (i.e., suppression of drug resistances is best at medium–high levels, less at low- and near-perfect adherence). More recently, studies have shown that each regimen class may have different adherence-resistance relationships [63, 64]. Gardner et al. [65] have found that ‘differential’ adherence—defined as any difference in self-reported adherence levels to individual antiretroviral drugs at the same time (when on a multiple-pill drug regimen)—is associated with increased antiretroviral resistance. HIV treatment guidelines from both WHO and the US Department of Health and Human Services stress the importance of adherence to suppress drug resistances and improve health outcomes [66, 67].

While inadequate retention and adherence negatively impact individual health outcomes, evidence suggests that it also has population-level implications. Transmission of drug resistances following poor treatment adherence can lead to suboptimal response to first-line therapy in newly diagnosed PLHIV [68]. However, the prevalence of transmitted drug resistances is increasing, but at lower rates than some had feared based on the significant expansion of ART coverage [69]. Treatment adherence has also a critical role in prevention of HIV transmission. Knowledge of HIV status allows PLHIV to adopt risk-reduction behaviours. Evidence from the randomised control trial HPTN 052 confirmed findings from previous cohort studies that by reducing virus levels in bodily fluids, ART has the potential to significantly reduce HIV transmission [70–72]. However, in order to harness the prevention benefits of ART, clients need to adhere to medication.

Retention and adherence are also critical determinants of programme cost effectiveness: due to higher morbidity, client health-care needs increase, and potential drug

resistance makes more expensive second-/third-line treatment necessary. In a study on cost implications from sub-optimal medication adherence, Nachega et al. [73] followed 6,833 HIV-infected adults in South Africa between August 2000 and April 2006, monitoring ART, hospitalizations, consultations, investigations and non-ART medications. Clients were grouped in four adherence quartiles, with total mean costs ranging from \$313 for highest adherence to \$376 for lowest adherence per month (adherence was measured through prescription claims). Although ART costs alone were higher in clients with better adherence, the total mean costs were offset by significantly reduced hospitalization costs. Comparable results were found in two earlier studies: Knobel et al. [74], examining the influence of treatment adherence on hospital admissions in patients on HAART in Barcelona, calculated mean hospital days per admission of 3.73 for adherent clients (>90 % adherence), as opposed to 14.75 days for non-adherent clients (adherence was measured through client interviews and pill counts); and Paterson et al. [58], looking at combination ART with protease inhibitors in patients in Pittsburgh, found that clients with above 95 % adherence had fewer hospital days (2.6 days per 1,000 days of follow-up) and developed fewer opportunist infections than less adherent clients (12.9 days per 1,000 days of follow-up) (adherence was measured through electronic interventions monitors).

Drug resistances resulting in the need to start more costly treatment regimens earlier is emphasized by the significant price differences between first- and second-line ARV regimens. In 2010, the most commonly used adult first-line ART regimens in low- and middle-income countries cost on average \$124 per person per year, compared with \$554 for second-line drugs (price difference of 347 %) [2]. In this regard, Long et al. [75] calculated that total second-line outpatient health-care costs are 2.4 times higher than first-line. Predictably, the biggest increase came from higher costs of second-line drugs, with limited additional expenditure for laboratory services and clinic visits. Because of cost implications, Long et al. stress the importance of limiting or delaying the number of clients requiring second-line therapy. Furthermore, second-line treatment is often not widely available in resource-limited settings.

Treatment 2.0

WHO and UNAIDS have also put increasing emphasis on the need to support retention in care and adherence to ART for PLHIV. The Treatment 2.0 Framework, an initiative launched in 2010 seeking to address the financial and technical challenges in achieving universal access, defines five priority areas for future efforts in HIV—each is

interlinked with retention in care and adherence to treatment [76]:

1. ‘*Optimize drug regimens*’ calls for “effective, affordable, one pill, once daily potent ARV regimens with minimal toxicities or drug interactions”. This can be expected to have significant positive impact on adherence, as several studies validate the relationship between ease of drug use, such as pill burden, and actual intake [77–80].
2. ‘*Provide access to point-of-care and other simplified diagnostics and monitoring tools*’ addresses the insufficient level of HIV testing and counselling and CD4 testing and monitoring leading to late start of HIV treatment, which in turn is associated with increased morbidity and mortality [81, 82]. A recent study from Mozambique indicates that availability of point of care CD4 testing enables clinics to stage clients quickly on-site, reducing risks for pre-treatment loss to follow-up among those who are eligible for ART at time of assessment [83].
3. ‘*Reduce costs*’ emphasizes that it is necessary to ensure the most effective use of limited available resources (e.g., through pooled-drug procurement and diagnostics) [84]. While such activities would likely not directly affect retention and adherence, it is obvious that retention and adherence can maximise programme efficiency.
4. ‘*Adapt delivery systems*’ emphasizes the need for a decentralized HIV response, integrated with other health services. Recent studies from Zambia suggest that the provision of ART integrated with maternal and child health services significantly increased treatment initiation [85, 86]. Similarly, a study from South Africa indicates that integrating ART with tuberculosis care improves treatment coverage among co-infected clients [87]. Factors such as transport costs and waiting time have been identified as major barriers to retention and adherence [88, 89], indicating that proximity as well as convenience of service delivery are critical.
5. ‘*Mobilize communities*’ calls for a better integration and linkages of the ‘informal’ community sector in the response to HIV. Engaging communities in the creation, development, and implementation of programmes and services can provide a more enabling environment that supports quality of care, retention in care, and treatment adherence for their populations. While the health-care sector can strive to improve the availability and quality of HIV services, many barriers to retention in care and adherence to treatment exist outside their purview (e.g., disability, stigma, poverty). Unfortunately, the health-care sector is often not well positioned to address many of these issues. However,

by actively involving communities—through coordination with and strengthening of health-care and other key sectors—significant improvements can occur at both the individual- and community-levels to overcome these barriers, resulting in increased access to HIV services, stigma reduction, retention in care, and treatment adherence [90–92].

The importance of retention and adherence is also reflected in the 2011 General Assembly Political Declaration on HIV/AIDS, which emphasizes the need to “address factors that limit treatment uptake and contribute...to poor adherence” and calls for the “mobilization and capacity-building of communities to support treatment scale-up and patient retention” as well as “programmes that support improved treatment adherence” [93]. A focus on the client side was also underscored by UNAIDS in their 2011–2015 strategy, which stated that “the demand side of treatment—the factors that make people enrol for treatment and adhere to it—has not received enough attention” [94].

Conclusions and Areas for Further Research

Retention in care and adherence to treatment are critical for health outcomes and cost effectiveness of health interventions. Disease-generic as well as HIV-specific data suggest, for a variety of reasons, that clients often face challenges following the behaviour recommended by their health-care providers. This holds true for both resource-rich and resource-limited settings.

Major challenges to the response to HIV include: prompt diagnosis of HIV infection, poor linkage to care, delayed treatment initiation, and insufficient adherence to treatment. Historically, attention was focused primarily on the latter stage (continuation of treatment); however, it becomes apparent when examining the continuum of HIV care that most client loss to follow-up happens following testing and before start of ART. On both the client- and population-levels, failure to link clients to care following testing and inadequate retention and adherence to ART, once in care, result in significant increases in morbidity and mortality and are associated with on-going transmission of HIV infection. Additionally, suboptimal viral suppression may result a higher risk of developing drug resistances, as well as the transmission of drug resistance. From a cost-effectiveness perspective, inadequate retention and adherence may lead to an increase of health-care costs.

Current suboptimal retention in care and adherence to ART threaten the benefits of the on-going scale up of HIV care and treatment, and may result in a failure to capitalise on the treatment and prevention benefits of ART. Therefore, it is crucial that retention and adherence are put at the

heart of the HIV response: to better understand barriers to retention and adherence; to identify, design, and implement programmes to overcome these barriers; and to monitor and evaluate their impact and acceptability.

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