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Retention in Care and Medication Adherence: Current Challenges to Antiretroviral Therapy Success

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Abstract

Health behaviors, such as retention in HIV medical care and adherence to antiretroviral therapy (ART), pose major challenges to reducing new HIV infections, addressing health disparities, and improving health outcomes. Andersen's Behavioral Model of Health Service Use provides a conceptual framework for understanding how patient and environmental factors affect health behaviors and outcomes, which can inform the design of intervention strategies. Factors affecting retention and adherence among persons with HIV include patient predisposing factors (e.g. mental illness, substance abuse), patient enabling factors (e.g. social support, reminder strategies, medication characteristics, transportation, housing, insurance), and health care environment factors (e.g. pharmacy services, clinic experiences, provider characteristics). Evidence-based recommendations for improving retention and adherence include 1) systematic monitoring of clinic attendance and ART adherence; 2) use of peer or paraprofessional navigators to re-engage patients in care and help them remain in care; 3) optimization of ART regimens and pharmaceutical supply chain management systems 4) provision of reminder devices and tools; 5) general education and counseling; 6) engagement of peer, family, and community support groups; 7) case management; and 8) targeting patients with substance abuse and mental illness. Further research is needed on effective monitoring strategies and interventions that focus on improving retention and adherence, with specific attention to the health care environment.

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Introduction

The landscape of the HIV epidemic has changed considerably over the past 30 years. Although once considered to be acute and life-threatening, HIV infection can now be chronic and manageable [1]. This transformation is primarily due to advancements in antiretroviral therapy (ART), which has significantly reduced AIDS-related morbidity and mortality and is now being used to prevent new HIV infections [2-5]. Health behaviors, such as retention in HIV medical care and adherence to HIV treatment, pose major challenges to achieving the individual and public health benefits of ART [6-11]. Retention in care is crucial for ART receipt and management of comorbid conditions; while ART adherence is necessary for viral suppression and prevention of HIV resistance and transmission [4, 12-14]. Yet in the U.S., less than half of all people living with HIV (PLWH) are linked to and retained in care and only 25% achieve HIV viral suppression [15].

Retention in care (retention) represents the process of ongoing participation in HIV medical care, while medication adherence (adherence) relates to the "extent to which a person's behavior—taking medications…corresponds with agreed recommendations from a health care provider" [16]. Although retention and adherence are distinct health behaviors and require different sets of actions and tools, they are interrelated. They share similar barriers and facilitators, and are independently associated with HIV outcomes [9, 11, 17, 18]. Therefore, it is necessary to target both retention and adherence in order to reduce new HIV infections, address health disparities, and improve health outcomes.

Barriers and Facilitators to Retention and Adherence

Developing strategies to improve retention and adherence requires an understanding of barriers and facilitators to these behaviors. Andersen's Behavioral Model of Health Service Use (ABM) provides a conceptual framework for understanding how patient and environmental factors affect health behaviors and outcomes (Figure 1) [19-21]. These factors can be categorized into 7 domains: patient factors (predisposing, enabling, perceived need), health care environment factors (system, clinic, provider), and external environment. Predisposing factors are characteristics of the patient that are unlikely to change (e.g. mental illness), enabling factors are resources that encourage health behaviors (e.g. social support), and perceived need relates to beliefs and values affecting subjective acknowledgment of need (e.g. symptoms) [19]. The health care environment includes factors such as clinic experiences, types of pharmacy services, and patient-provider relationships; while the external environment relates to the physical, political, and economic factors unrelated to the health care environment.

ABM has been used to explore factors affecting health care and treatment use among PLWH [22-25]. A qualitative analysis of interview data from 51 PLWH identified 18 barriers/facilitators affecting retention and ART adherence, all of which mapped to ABM [21]. Eleven factors were common to both behaviors (mental illness, substance abuse, stigma, insurance, social support, housing, reminder strategies, competing life activities, symptoms, colocation of services, provider factors), 3 were specific to retention (appointment scheduling, clinic experiences, transportation), and 4 were specific to adherence (pharmacy

services, medication characteristics, health beliefs, health literacy). Several other studies focusing on underserved populations (women, low income) have identified similar factors affecting retention such as patient/provider relationships, social support, transportation, and stigma [26-30]. Therefore, multiple factors, ranging from the patient to the external environment can impact both retention and adherence.

Full exploration of all these factors is beyond the scope of this article, but several are worth further description as they represent potential key areas for intervention. These include patient predisposing factors (mental illness and substance abuse), patient enabling factors (social support, reminder strategies, medication characteristics, transportation, housing, insurance), and health care environment factors (pharmacy services, clinic experiences, provider characteristics).

PLWH are at increased risk for having mental illness and substance abuse as co-occurring conditions [31]. These predisposing factors can be significant barriers to health behaviors because patients may struggle with their own health during these active periods. In a cohort study of 773 HIV-infected patients in Uganda, 47% (95% CI: 39-55%) of those with severe mental illness remained in care 12 months after ART initiation, compared to 65% (95% CI: 61-69%) of those without severe mental illness [32]. In an analysis of 85 HIV-infected patients with active or former drug use, median adherence of those with active cocaine was significantly lower compared to non-users (27% vs. 68%) [33].

Social support from family, friends, and neighbors who are aware of patients' HIV status can help patients maintain clinic visits and medication adherence, as these supports often provide moral encouragement and health care assistance through transportation and reminders [21]. Based on survey data from a representative sample of PLWH in New York City between 1994 and 1997, social support was associated with improved adherence to ART among those who disclosed their HIV status to household members or friends and acquaintance networks [34].

Patients who adopt reminder strategies such as using alarms, calendars, and pillboxes are less likely to forget appointments and medication doses [21, 35]. Having a medication regimen with low pill burden, small pill sizes, and minimal adverse effects facilitates adherence because these characteristics are more pleasant to patients, especially those who have difficulty swallowing pills [21]. In a meta-analysis of randomized controlled trials comparing once-daily versus twice-daily ART regimens, lower pill burdens and once-daily regimens were independently associated with improved adherence [36].

Structural factors such as transportation, housing, and insurance, can influence a patient's ability to attend appointments and adhere to treatment. Lack of affordable transportation is often cited as a major reason for missing clinic appointments [26-28]. With unstable housing comes lack of privacy and increased vulnerability to theft and loss of medications. Patients may fear status disclosure by taking medications in the presence of others, and are therefore more likely to skip doses if they cannot secure a private space [21]. In a systematic review of the impact of housing status on health-related outcomes among PLWH, a positive association was found between increased housing stability and outcomes such as medication

adherence, use of health and social services, health status, and HIV risk behaviors in all included studies [37]. Finally, the cost of medical care and medications can be major barriers for patients, compromising clinic attendance and prescription fills [21].

The health care environment such as pharmacy services, clinic experiences, and patient/provider relationships can significantly impact retention and adherence. Pharmacy characteristics such as unprofessional staff and limited hours can discourage patients from refilling medications promptly [21]. However, special services such as home delivery and reminder calls can improve convenience for patients and facilitate adherence [38, 39]. Furthermore, provision of medication management by an HIV clinical pharmacist has been shown to improve adherence and clinical outcomes [40]. In a retrospective cohort study involving 75 patients where pharmacists provided recommendations on ARV regimen changes, medication adherence (measured by pharmacy refill records) increased from 81% to 89% with pharmacist intervention ($p=0.003$). Clinical outcomes, such CD4+ count and viral suppression, also improved statistically when pharmacists intervened [40]. Clinics with discourteous staff and complicated appointment scheduling and referral processes may deter patients from returning [21]. While, providers who gain patients' trust, are responsive, display empathy, and provide individualized care can encourage both retention and adherence among patients [21, 41, 42]. In an analysis of patient perceptions of provider attitudes, those with a gap in care of more than one year were more likely to perceive that the provider didn't listen carefully to them or disliked caring for HIV-infected people [43].

Finally, for PLWH, transitioning between various healthcare settings, providers, or levels of care can be a significant barrier to linkage to care, retention, and ART adherence [44]. These include transitions from correctional institutions to community-based care, inpatient to outpatient care, and pediatric/adolescent to adult clinics. A study evaluating 1,359 newly diagnosed HIV-infected patients found that, compared to medical clinics, diagnosis at correctional facilities, counseling and testing centers, and inpatient settings resulted in a 75%, 46%, and 33% decrease in the probability of linkage, respectively [45]. In a retrospective cohort study of 2,215 HIV-infected patients who were receiving ART at a Texas prison, only 30% filled their first ART prescription within 60 days after their release [46]. Therefore, in order to help PLWH maintain treatment success, further understanding of why they are lost to follow-up or develop gaps in ART treatment during transitions in care is needed.

Measuring retention and adherence

Systematic monitoring of clinic attendance is crucial for identifying individuals poorly engaged in care and those who have fallen out of care. Multiple measures of retention exist, with no clear gold standard (Table 1) [47, 48]. Studies have shown that all of these measures are related, but have their own strengths and limitations [47-49]. Use of a specific retention measure can be dependent on multiple factors, such as type of data available, scheduling practices of the clinic, and purpose for measuring retention [48]. Overall, selection of retention measures should be guided by the needs of the clinic or agency, patient population, as well as local standards of care. Measures to monitor national retention in HIV care include the Institute of Medicine (IOM) (proportion of patients with ≥ 2 visits separated by ≥

90 days within a 12-month interval) and the U.S. Department of Health and Human Services (HHS) (proportion of patients with ≥ 1 visit within each 6-month time period over 24 months, with ≥ 60 days between the first visit in one 6-month time period and the last visit in the subsequent 6-month time period) core indicators [50, 51]. Although these are different indicators, a recent study has shown agreement using clinical cohort data from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) [49].

Medication adherence among patients should also be monitored periodically. Similar to retention, there is no gold standard to adherence measures. HIV viral load, patient self-report, and pharmacy refill data can be used as tools for monitoring adherence [52]. Other adherence measures such as directly administered ART (DAART) and use of electronic drug monitors (EDMs) and biological samples should not be performed in the general clinic setting as they have not been validated, are labor and resource intensive, or inconvenient for patients.

The WHO and CDC recommend using HIV viral load as a tool to monitor ART effectiveness that may be impacted by adherence [52, 53]. In a meta-analysis of 6 retrospective and 2 prospective observational studies, pooled data from 5 studies showed that using viral load to monitor adherence among patients who had already begun ART resulted in an estimate of 70.5% (95% confidence Interval: 56.6% to 84.4%) resuppression [54]. However, this method does not allow for providers to detect non-adherence in real time. Therefore, other methods, such as pharmacy refill records and self-report should be used in combination with viral load monitoring for measuring adherence.

Although patient self-report data often overestimate adherence due to recall bias, it is an easy method that has been shown to be valid using electronic drug monitors and virologic failure as reference measures [55-57]. However, the type of adherence information to be elicited from the patient is crucial. Questionnaires that are simple and qualitative, gathering patient's personal estimates of adherence over 1 month, such as the Visual Analogue Scale [57] or the Swiss HIV Cohort Study Adherence Questionaire [58], provide more accurate assessments of adherence compared to ones that require patients to state the number of missed doses within specific time intervals [56].

Pharmacy refill data is another adherence measure that has been validated and should be used in conjunction with self-reported data to assess patients' adherence to ART [59]. Using pharmacy refill records, the medication possession ratio (MPR) or the proportion of days covered (PDC) can be calculated in order to determine the proportion of days the patient had access to medications over a period of time. This type of information can be extremely useful for detecting non-adherence if patients are consistently late with refills or have gaps. However, high MPRs or PDCs do not confirm adherence since patients can be stockpiling, rather than taking them. This is especially the case when patients have minimal to no co-pays and pharmacies provide automatic refills or free delivery services.

Strategies for Improving Retention and Adherence

The World Health Organization, International Association of Providers of AIDS Care (IAPAC) and U.S. Centers for Disease Control and Prevention have provided evidence-

based recommendations for improving retention in care and ART adherence for PLWH (Table 2) [52, 53, 60]. With respect to retention strategies, majority of evidence focuses on the use of peer or paraprofessional navigators to re-engage patients in care and help them remain in care. Patient navigators are trained health care workers who provide guidance and support to patients and help facilitate interactions between them and various components of the health care system. Depending on resources, patient navigators can perform outreach with telephone calls, written letters, or home visits, and reinforce the importance of regular HIV care. A study examining the effects of patient navigation among those who were not fully engaged in HIV medical care at 4 sites from the U.S. Special Projects of National Significance Outreach Initiative showed reduction in barriers to care and improvement in retention measures (proportion of patients with >2 visits in the last 6 months increased from 64% at baseline to 79% at 12 months) [61]. Regarding more specific measures, CDC recommends the provision of reminders for all visits and expansion of appointment availability, such as evening hours [53, 62].

Evidence-based recommendations for improving medication adherence include optimization of ART regimens that are consistent with patient preferences, optimization of pharmaceutical supply chain management systems, provision of reminder devices and tools, general education and counseling, engagement of peer, family, and community support groups, case management to address food and housing instability, transportation, insurance problems, and any other high direct or indirect health care costs [60]. Adherence challenges among those with substance abuse and mental illness are unique, and strategies (e.g. methadone or buprenorphine treatment programs) targeting these populations should also be considered.

Prior to initiating ART, the provider should evaluate the patient's readiness to start and the potential barriers (e.g. structural and psychosocial) to sustained high adherence [53]. Selection of ART regimens should take into account patient co-occurring conditions (drug-disease interactions), concomitant non-ART medications (drug-drug interactions), adverse event profiles, toxicities, resistance patterns, and patient preferences regarding regimen frequency, pill burden, and pill [63]. Self-reported medication adverse effects and symptoms have been associated with non-adherence to ART [64]. Therefore, it is crucial to select ART regimens that are tolerable and acceptable to patients. Drug-drug and drug-disease interactions should also be minimized as these have the potential to create additional adverse effects. Majority of studies show that ART regimens requiring lower dosing frequencies (e.g. once daily versus twice daily) [65, 66] and consisting of fixed dose combinations [67, 68], which lower pill burden, improve adherence without compromising efficacy. Providers should also consider patient preferences when selecting an ART regimen—patients who have difficulty swallowing pills may prefer the higher pill burden or dosing frequency in exchange for smaller pill sizes or the availability of alternative formulations (liquid, ability to crush, etc).

In resource-limited settings, optimization of pharmaceutical supply chain management systems to prevent stock-outs of ARV drugs is crucial to ensuring adherence among PLWH [52]. In a cohort study of 1,554 patients in Cote d'Ivoire, 170 patients (11%) discontinued treatment or modified their ARV regimen because of drug stock-outs. Among patients

experiencing ARV discontinuations related to stock-out, the risk of death or interruption in care more than doubled (adjusted hazard ratio [HR], 2.83; 95% CI, 1.25-6.44) [69].

One common reason patients cite for missing medication doses is forgetfulness. Reminder strategies such as pillboxes, calendars, or other medication planners can help improve adherence [35, 70, 71]. In an observational study, use of pillboxes improved adherence as well as increased the likelihood for viral suppression among a cohort of 245 HIV-infected patients [35]. These strategies require minimal resources and are simple to adopt. Some pharmacies can provide medication blister packages, which are essentially pre-filled pillboxes, as a free service. Providers should consider directing their patients to these pharmacies. However, blister-packages may not be available in certain areas due to safety concerns for small children (i.e. not child-proof). Other reminder strategies such as use of communication technologies (e.g. short message services [SMS]) have also been shown to improve adherence and viral outcomes and may be cost-effective [72-78]. Depending on resources, these can involve one-way reminder text messages or pages [73, 76], text messages requiring patient response [74, 77], or phone calls allowing for interactive conversations about adherence [75]. Interventions requiring some form of patient response may be more effective compared to one-way reminders [77].

The overall body of evidence suggests that one-on-one education and counseling of individuals can improve medication adherence and possibly viral outcomes [60]. However, specifics as to the content or model of the educational and counseling sessions and the overall structure in terms of frequency, duration, and interactive modality (in-person, telephone calls, home visits, or combination) are unknown. These interventions have consisted of various health care workers (e.g. nurses, pharmacists, therapists, social workers) providing individualized educational and counseling sessions that were based on a variety of behavioral (e.g. information, motivation, behavior Skills [1MB]) and educational models, and psychotherapeutic strategies (e.g. motivational interviewing [Ml]) [60]. Overall, these patient-centered strategies were used to increase adherence by enhancing self-efficacy and promoting problem-solving skills. More specifically, CDC recommends the provision of information regarding the patient's ART regimen, such as side effects, drug interactions, and dietary restrictions, as well as the benefits of sustained adherence and risks of low adherence [53]. Regardless of the specifics, ongoing attempts to provide some form of education and counseling for patients should be made based on needs and resources of the clinic.

Peer, family, and community support can be engaged to improve patient knowledge and beliefs related to HIV infection and to improve medication adherence [52]. In a study involving 499 HIV-infected adults in Nigeria starting first-line ART who were randomized to either standard of care or patient-selected treatment partner-assisted therapy (TPA), use of patient-selected treatment partners showed improved drug pickup adherence. There was also a statistically significant higher proportion of patients in the TPA arm achieving viral suppression at week 24 (61.7 vs. 50.2%), but not at week 48 [79].

Strategies to improve retention and adherence shouldn't only focus on the patient, but also on the health care environment. Provision of case management to address housing and transportation problems, as well as any high direct and indirect health care costs, has been

shown to improve retention and adherence, and is therefore recommended [52, 80, 81]. Ancillary services targeting those with substance abuse and mental illness should also be provided as these populations are at increased risk for non-adherence [82, 83]. Clinic-based methadone and buprenorphine maintenance treatment programs, with or without DAART, can improve adherence as well as retention among patients with opioid dependence [84-86]. However, general provision of DAART among patients with substance abuse cannot be recommended despite positive outcomes due to lack of sustainability of effects once DAART is discontinued and would require substantial additional resources [87]. Finally, on-site services for the screening, management and treatment of patients with mental health disorders should be adopted. Cognitive behavioral therapy in conjunction with ART adherence counseling can significantly improve adherence and immunologic and viral outcomes among depressed patients [88, 89]. If resources are limited for such services, providers should at least screen patients and provide pharmacological treatment since this intervention alone has been shown to increase ART adherence [90-92].

Although we have described some potentially effective strategies for improving retention and ART adherence, much is still unknown, particularly regarding retention. More research is needed on effective monitoring strategies, comparison of retention measures with the goal of standardization, interventions using various modalities or combinations to help patients remain in care, and the role of the multidisciplinary care team to improve adherence at a system level [93]. In addition, strategies to increase both retention and ART adherence should focus on improving the health care environment, such as clinic and provider characteristics. Little is known about whether simple interventions such as shortening clinic wait times, expanding appointment availability, or training of staff and providers to enhance relationships with patients can improve retention and adherence. Research is needed on the impact of ancillary services such as peer navigators and programs that can provide various forms of social support to patients. The impact of mobile health technology (mheath) should be continually evaluated since it is rapidly evolving and can be expanded to a broad range of initiatives, including improving medication and appointment adherence. Finally, implementation and cost-effectiveness studies are needed to inform decisions about programs and policies that would ultimately make a public health impact.

Conclusions

While ART has made it possible to significantly decrease HIV-related morbidity and mortality, its true potential cannot be fully realized without addressing barriers related to retention in care and medication adherence. Many of these patient-related and environmental factors have been mapped to ABM, which can be used to help develop new intervention strategies. Systematic monitoring for poor retention and adherence is crucial for identifying targets for interventions. Currently, strategies to improve retention include outreach and use of patient navigators. Strategies to improve adherence may include optimization of ART regimens and pharmaceutical supply chain management systems; provision of reminder devices and tools; education and counseling; engagement of peer, family, and community support groups; case management; and addressing substance abuse and mental illness. However, choice of strategies would be dependent on the local context and acceptability to the patient. Interventions focusing on the healthcare environment, particularly clinic and

pharmacy services and provider characteristics, may help to further improve retention and adherence and reduce new HIV infections, address health disparities, and improve health outcomes.

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Key Points

- Barriers related to HIV retention in care and medication adherence need to be addressed in order to reduce new HIV infections, address health disparities, and improve health outcomes.
- Many of these barriers have been mapped to Andersen's Behavioral Model of Health Service Use, which can inform the design of intervention strategies.
- The World Health Organization, International Association of Physicians in AIDS Care, and Centers for Disease Control and Prevention have provided evidence-based recommendations for improving retention in care and ART adherence for people living with HIV

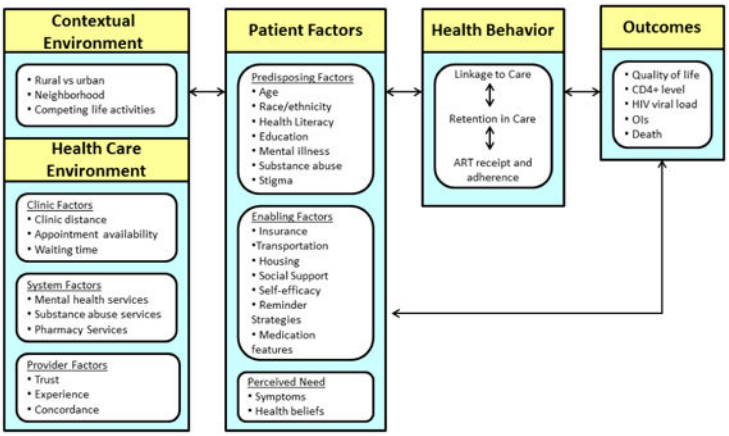

Figure 1. Andersen's Behavioral Model (adapted) [19-21]

Table 1
Measures of Retention and Medication Adherence

Measures	Description
Retention [48, 50, 51]	
Missed Visits	Number of “no shows” within an observation period
Appointment Adherence	Proportion of completed visits (numerator) out of all scheduled visits (denominator) within an observation period
Visit Constancy	Proportion of time intervals (usually 3-6 months) with ≥ 1 completed visit within an observation period.
Gaps in Care	Time interval (usually months) between completed visits
Hybrid Measures (Visit Constancy and Gaps in Care)	
Institute of Medicine (IOM) Core Indicator	Proportion of patients with ≥ 2 visits separated by ≥ 90 days within a 12-month interval
U.S. Department of Health and Human Services (HHS) Core Indicator	Proportion of patients with ≥ 1 visit within each 6-month time period over 24 months, with ≥ 60 days between the first visit in one 6-month time period and the last visit in the subsequent 6-month time period
Adherence	
Patient Self-Report	Personal estimates of adherence over 1 month using validated questionnaires such as the Visual Analog Scale or the Swiss HIV Cohort Study Adherence Questionnaire
Pharmacy Refill data	Dates on which medications were dispensed. Refills that aren't obtained in a timely fashion suggest missed doses, which allow the refill to last longer than it should.
Pill Counting	Number of remaining doses of medications, representing the number of missed doses
Directly Administered ART (DAART)	Direct observation of patient taking the medication dose
Electronic Drug Monitor (EDM)	Pill bottles with a computer chip embedded in the cap that records the time and duration of each opening
Biological Samples	Plasma concentrations of medications

Table 2

Selected Recommendations for Improving Retention in Care and ART Adherence for PLWH [52, 53, 60]

Retention in Care
Systematic monitoring of retention
Use of peer or paraprofessional navigators to re-engage patients in care and help them to remain in care
Provision of reminders for all visits and expansion of appointment availability
ART Adherence
Periodic monitoring of medication adherence among patients using HIV viral load, patient self-report, and pharmacy refill data
Optimization of ART regimens that are consistent with patient preferences
Optimization of pharmaceutical supply chain management systems to prevent ARV drug stock-outs
Provision of reminder devices and tools
Provision of general education and counseling
Engagement of peer, family, and community support to improve patient knowledge and beliefs about HIV infection and to improve medication adherence
Provision of case management to address food and housing instability, transportation, insurance problems, and any other high direct or indirect health care costs.
Provision of ancillary services targeting those with substance abuse and mental illness