

What We Know and What We Do Not Know About Factors Associated with and Interventions to Promote Antiretroviral Adherence

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Abstract Antiretroviral therapy (ART) adherence remains critical for achieving successful outcomes. Factors affecting ART adherence can occur at the individual level or be related to the treatment regimen, daily schedule, and/or interpersonal relationships. While treatment-related barriers have diminished with recent simplified ART regimens, guidelines still recommend considering regimen simplicity. ART readiness should be assessed prior to starting ART, with follow-up adherence assessments once ART is initiated, and at all subsequent clinical visits. Adherence interventions work best when multifaceted, targeted for at-risk and nonadherent participants, and tailored to individuals' needs. Successful interventions have included education and counseling, provision of social support, directly observed therapy, and financial incentives. Pillboxes and two-way short-text messaging service (SMS) reminders have been shown to be effective and are widely recommended tools for promoting ART adherence. Further research is needed to determine the optimal combination of adherence interventions, as well as generalizability, implementation, and cost-effectiveness.

Keywords Adherence · HIV · Antiretroviral therapy · Intervention · Predictors

Introduction

Adherence to antiretroviral therapy (ART) is widely recognized to be critical for achieving therapeutic success in the treatment of HIV infection. ART adherence has been shown to strongly correlate with biologic markers of HIV infection, including HIV viral suppression and immunological recovery [1–5], while lower adherence levels and treatment interruptions have been associated with the development of ART resistance [4, 6]. ART adherence also correlates with clinical outcomes, including reductions in hospitalizations [3], HIV disease progression [7] and mortality [8–10], as well as improvements in quality of life [11]. Unfortunately, suboptimal adherence is not uncommon, with an average of only 62 % of individuals reporting adherence rates of 90 % or greater in one meta-analysis [12], and can result in lack of HIV viral suppression. The lack of viral suppression has consequences for the individual as well as the population as a whole because of increased risk of HIV transmission [13, 14].

Significant improvements in HIV therapy have occurred over the past two decades resulting in simpler treatments with fewer side effects. Despite this, suboptimal adherence still persists, with only about 80 % of those prescribed ART achieving undetectable HIV viral load [15–17]. A wide variety of factors related to the individual, the medication, and the disease itself can impact adherence to HIV medication. This article will review recent HIV adherence guidelines, predictors of antiretroviral adherence, and interventions to improve antiretroviral adherence.

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Adherence Guidelines

The realities of the HIV treatment cascade in the USA [15, 16] prompted the International Association of Physicians in AIDS Care (IAPAC) to develop guidelines for improving entry into care, retention, and antiretroviral adherence for persons with HIV [18]. The IAPAC adherence recommendations emphasize the importance of routinely assessing adherence to determine the need for interventions and outline strategies for improving adherence. Suggested types of adherence interventions in the IAPAC guidelines include ART strategies, adherence tools, education and counseling, and interventions related to health systems and service delivery [18].

Additional US and international HIV antiretroviral guidelines also highlight the importance of adherence and make specific recommendations. US guidelines recommend assessing readiness to adhere before initiating ART [19] and consideration of delaying treatment until adherence barriers are addressed [20]. US and international antiretroviral guidelines advocate for routine assessment of adherence by patient self-report [19–21] at every clinical visit [20], as well as conducting other measures of adherence including routine viral load monitoring and assessment of pharmacy refill data if available [19, 21]. A multidisciplinary team approach to adherence is also recommended, including not only providers but also nurses, pharmacists, peer counselors, and caseworkers in order to provide support and also identify and address adherence issues [18, 20]. The WHO HIV guideline recommendations [21] include adherence interventions particularly relevant for populations in developing countries including avoiding out-of-pocket payments at the point of care and strengthening drug supply management systems to ensure adequate supplies of ART. New in the 2013 WHO consolidated guidelines, based on results of studies in developing countries [22, 23], was a strong recommendation to use mobile phone text messages as a reminder tool for promoting ART adherence as part of a package of adherence interventions.

Predictors of Art Adherence

Over the past 30 years, multiple studies have explored factors affecting ART adherence across different populations. Current ART regimens are simpler than in the past, with lower pill burden due to co-formulated medications and with the majority of initial regimens being dosed once daily. Adherence, however, has remained a challenge. While it is difficult to predict whether an individual will adhere to their prescribed ART, several

factors have been found to be associated with adherence. Predictors of adherence have been classified into four groups of related determinants: patient-related, treatment-related, daily schedules, and interpersonal communication. Table 1 summarizes factors that have been found to be barriers and facilitators of ART adherence [12, 24–31].

Generally, barriers and facilitators to ART adherence are consistent across multiple settings and countries [25]. Fear of disclosure, simply forgetting, a lack of understanding of treatment benefits, complicated regimens, and being away from their medications were consistent barriers to adherence across developed and developing nations. More common barriers in developing settings were issues of access, including financial constraints and a disruption in access to medications. In the US, race has emerged as an important predictor of nonadherence, with Blacks having significantly lower ART adherence compared to other race/ethnicities [32–34]. This racial disparity is likely multifactorial, possibly related to poverty and other psychosocial patient factors, poor health literacy, mistrust, and provider bias. Past studies have shown higher ART adherence rates among men who have sex with men (MSM) [12]; however, more recent studies have shown Black MSM are less likely to be virally suppressed than White MSM, suggesting lower ART adherence [35].

Special Populations

HIV is a stigmatized condition requiring lifelong treatment. As seen in Table 1, challenges to ART adherence are many in general but are even more daunting for certain populations, who may require specialized interventions.

Pregnant and Postpartum Women

Optimal ART adherence during pregnancy and the postpartum period remains a significant challenge. Many women are first diagnosed during pregnancy and may be dealing with the HIV diagnosis, issues of disclosure, and concerns about how it might affect the health of the fetus. Pill burden, number of clinic visits during pregnancy, long waiting times at clinics, and lack of follow-up and transfer to other clinics after delivery present additional challenges. Moreover, pregnancy-related symptoms may negatively affect ART adherence [36–38].

Children and Adolescents

ART adherence among perinatally infected infants and children is determined largely by their caregivers, who are often infected themselves. Unique medication-related factors

Table 1 Barriers and facilitators of ART adherence

	Barriers	Facilitators
Patient-related	<ul style="list-style-type: none"> • Feeling depressed, overwhelmed, hopeless, psychological symptoms • Concurrent addiction/substance use/IDU • Low levels of health literacy or numeracy • Financial and access constraints • Fear of disclosure and wanting to avoid taking medications in public places • Being suspicious of treatment/medical establishment • Wanting to be free of medications or preferring a natural approach • Feeling that treatment is reminder of HIV • Wanting to be in control • Doubting or not accepting HIV status • Lack of self-worth/self-efficacy • Homelessness • Cognitive impairment • Other concurrent illnesses/comorbidities • Stigma • Young age 	<ul style="list-style-type: none"> • Medication taking priority over substance use • Seeing positive results when adhering to ART • Acceptance of seropositivity • Clinical HIV infection stage A
Treatment-related	<ul style="list-style-type: none"> • Side effects (real or anticipated) • Lower baseline CD4+ count • Use of PI-based regimen • Complex regimens • Bigger size, higher dosing frequency, higher pill burden • Dietary restrictions of medication • Doubting efficacy of ART • Poor quality of life • Unwanted changes in body image • Treatment fatigue 	<ul style="list-style-type: none"> • Having a simple regimen • Belief in efficacy of ART • Treatment optimism • Understanding treatment benefits • Understanding the need for strict adherence • Lower pill burden
Daily schedules	<ul style="list-style-type: none"> • Conflicts with routines, disruptions in routine, or having a chaotic schedule • Finding ART too inconvenient or difficult to incorporate • Difficulties coordinating adherence with work, family, caregiving responsibilities • Difficulties with ART dietary requirements • Sleeping through a dose • Away from home and not bringing medication • Too distracted or busy • No time to refill prescriptions, or other pharmacy-related problems • Difficulties with a particular dose, especially midday or early morning dose 	
Interpersonal relationships	<ul style="list-style-type: none"> • Lack of trust or a dislike of a patient's health-care provider • Social isolation • Negative publicity regarding ART or the medical establishment • Discouraging social network • Low social support 	<ul style="list-style-type: none"> • Trusting relationship with a healthcare provider • Openly disclosing HIV status to family/friends • Strong social support • Living for someone, especially, children • Sharing treatment decision • Using friends/family as reminders

associated with nonadherence for infants and children include limited choice of pediatric formulations, bad taste of medications, difficulty swallowing pills, dietary restrictions, and frequent dosing requirements [38–40].

Adolescence is another challenging period for those who are perinatally infected and are transitioning into adult care, which means possible interruptions due to inability to navigate the system, insurance changes, and assuming responsibility for their own care [41]. Adolescents deal with peer pressure to conform, and may have issues with not remembering to take medications, inconsistent daily routines, disclosure, as well as depression and substance use [41, 42].

Incarcerated Populations

HIV prevalence is higher among incarcerated populations in both developed and developing countries [43]. Incarceration negatively affects continuity of care and development of trust, which ultimately may result in suboptimal adherence. Incarceration provides a public health opportunity to provide ART to HIV-infected persons; however, barriers to ART delivery and adherence exist [44–46], and unintended ART interruptions sometimes occur after release [47]. Key challenges to ART adherence among incarcerated populations include identifying successful strategies for medication distribution that

preserve confidentiality and avoid stigma [48–51] and maintaining ART use during transitions from correctional facilities to the community [52–54].

Homeless and Marginally Housed

In developed countries where stable housing is a societal norm, homeless persons face multiple and often interrelated adherence challenges, such as unstable housing, mental illness, substance use disorders, food insecurity, mistrust of the health-care system, incarceration, and inconsistent provider–patient relationships [18]. In developed countries, many homeless people have concomitant mental illness or substance use disorders that are associated with incomplete adherence [55]. Homelessness itself often disrupts daily routines, including medication taking, and can make medication storage difficult. The homeless have competing survival needs, including food access, which have been associated with incomplete adherence and poor viral suppression [56]. Excellent adherence and reliable viral suppression can, however, be achieved despite these multiple barriers [57, 58].

Other Key Populations

Key populations, including sex workers, MSM, transgender people, and people who inject drugs, face multiple challenges to accessing health services, mainly owing to deep stigma related to these behaviors. Service delivery approaches to improve continuity of care and maintain adherence for key populations remain a critical gap in both developed and developing settings.

Interventions to Promote Adherence to Antiretroviral Therapy

A wide variety of interventions to promote ART adherence have been tested individually and in combination with mixed results; benefits, when achieved, are often small and short lived. In general, targeted interventions tailored to individuals' needs have had the greatest success [59]. Limited data exist on the cost-effectiveness of adherence interventions for persons with HIV infection, though reviews suggest a potential for being cost-effective, particularly for patients with low baseline adherence [60]. Recent evidence-based successful interventions or intervention components for promoting adherence are described below.

In order to intervene to improve ART adherence, it is critical to be able to identify suboptimal adherence in real-time and avoid consequences such as virologic failure, deterioration in immune function, antiretroviral resistance, as well as morbidity and mortality related to complications of HIV. A variety of methods have been evaluated to assess adherence,

but self-report has been most widely recommended given its ease of use in clinical settings and the lack of additional costs to administer. Self-report is known to overestimate actual adherence, but when obtained in a nonjudgmental manner can yield useful information and has been shown to correlate with immunologic and virologic outcomes [1, 2]. A discussion of nonadherence can also yield information on the reason(s) for missed doses or barriers to adherence. The use of pharmacy refill data is another adherence measure that has been implemented in a variety of settings in both high and low income countries and also been shown to correlate with virologic and clinical outcomes in HIV [61]. This measure may be more feasible in settings with a centralized pharmacy.

Readiness

Antiretroviral guidelines advocate addressing adherence even before starting ART by assessing treatment readiness [20, 21]. Interventions addressing readiness have included education about HIV, medications, and side effects; development of an adherence plan; identifying and addressing potential barriers to adherence, including depression; and having patients undergo placebo pill taking trials [62–64]. A small pilot study involving pre-treatment ART practice trials as well as adherence counseling and tailored adherence support showed a benefit with a higher proportion of participants having optimal dose timing and undetectable viral load compared to patients receiving usual care [63].

Education and Counseling

Providing education about HIV, the medication regimen, side effects, and the importance of adherence is an important component of adherence support [18, 59]. This, along with specific counseling and the promotion of problem-solving skills, often utilizing a cognitive-behavioral component, such as developing an adherence plan and a medication side effect plan, and working to fit medication dosing into one's lifestyle and daily routine, have all been used as components of successful adherence interventions [18, 31, 62, 64–66].

Social Support

Social support has been shown to be a facilitator of adherence. Many adherence interventions have utilized social support, by enlisting the support of patients' partners, family members, or others in their social network, to promote ART adherence [31, 59, 65, 66]. In addition, others have used support provided by peer educators to promote trust and ART adherence for those with limited social support specifically for HIV [18, 59]. Evidence regarding the efficacy of peer support for ART adherence is limited, though peer support has been successfully used to promote HIV knowledge and behavior change related

to sexual risk and substance use [67]. Data from resource-limited settings also show the benefit of community health workers in promoting ART adherence, resulting in reduced viral load levels and improvements in CD4 cell counts [68]. Professional staff has also been successful in providing support as medication managers [62].

Directly Observed Therapy

Directly observed therapy (DOT) is a labor-intensive and costly adherence intervention known to be of benefit for a finite treatment course, such as therapy for tuberculosis. DOT, however, would not necessarily be cost-effective for conditions requiring life-long therapy such as HIV. While some meta-analysis studies suggest a short-term beneficial effect of DOT for ART on virologic, immunologic, and adherence outcomes, conflicting results have been reported and sustained improvements have not been seen post-intervention [66, 69, 70]. Consensus has been building that an intensive adherence strategy such as DOT might not be necessary or pragmatic for most individuals who start ART; however, DOT or some modified version of it is more appropriate for individuals in whom the therapy would have the greatest effect: those at highest risk of nonadherence [26, 70]. Ford et al. reported that DOT might be marginally superior to self-administered therapy in their sub-group analysis of active drug users and homeless individuals [69]. The IAPAC guidelines recommend DOT for ART for individuals with substance use disorders, during incarceration, and in limited cases in pediatric and adolescent patients [18]. DOT has also been shown to be effective in improving adherence and viral load suppression among depressed individuals [71]. While a posttreatment intervention effect was not observed in a limited number of studies [72–74], it may be useful for short-term benefits in critical periods (e.g., during pregnancy, incarceration, or when starting ART). In a study utilizing mathematical modeling, DOT in the third trimester of pregnancy was found to be associated with significantly lower HIV transmission rates and was highly cost-effective [75].

Regimen

Factors related to the medication regimen have been shown to be associated with adherence, with regimen simplicity (i.e., low pill burden and low dosing frequency) being an adherence facilitator as described above [26, 29, 57, 65]. Guidelines recommend tailoring the regimen to the individual's needs, in addition to considering ease of administration in terms of low pill burden, low dosing frequency, no food requirements, and low incidence and severity of adverse effects [18, 19].

Pillboxes

HIV medication and adherence guidelines and reviews widely recommend the use of pillboxes as a tool for promoting ART adherence [18, 19, 59, 65]. In observational studies, pillbox use was associated with significant improvements in adherence and virologic suppression [76, 77].

Text Messaging (Reminders)

Mobile phone technology, including short-text messaging service (SMS), has been used in HIV care and other chronic-disease management to improve patient-provider communication and for patient tracking and medication adherence [78, 79]. SMS reminders serve as practical aids to attendance at scheduled appointments and medication adherence. They may also function to communicate health-care providers' commitment to patient well-being and can thus reinforce a constructive patient-provider relationship, which has been associated with increased engagement in HIV care [80, 81]. High quality evidence of efficacy in interventions using short weekly messages has been found [78] and WHO guidelines include a strong recommendation to consider text messaging for promoting adherence to ART as part of a package of adherence interventions [21]. A recent meta-analysis has shown that text-messaging interventions yielded significantly higher adherence than control conditions and were associated with improved viral load and/or CD4 cell count [82]. Larger intervention effects were seen when interventions (1) were sent less frequently than daily, (2) supported bidirectional communication, (3) included personalized message content, and (4) were matched to participants' ART dosing schedule [82].

Conditional Economic Incentives

Appropriately implemented conditional economic incentives (CEI), a form of financial incentives, have been found to significantly increase ART adherence while incentives are in place, but adherence returned to pre-intervention levels once the incentives were removed [83]. A major challenge for CEI interventions is how to promote longer intervention effects. CEI have been tested in vulnerable populations, which may be part of the reason that optimal adherence did not persist after removal of incentives. However, despite the short-lived effects of CEI on ART adherence, there may still be cases where incentives could be used with key populations [83]. Food assistance or food transfers, conditional upon clinic or pharmacy visits, also may improve adherence to HIV and TB treatment and clinic visits in resource-limited settings [84].

Conclusions

While antiretroviral therapy has improved dramatically since the onset of the HIV epidemic, adherence remains critical for achieving successful outcomes from treatment. It is difficult to predict an individual's adherence, though many factors have been identified, as summarized above, which can act as either barriers or facilitators of ART adherence to antiretroviral medication. Factors affecting ART adherence can occur at the individual patient level or can be related to the treatment regimen, the individuals' daily schedule, and/or their interpersonal relationships. ART adherence readiness should be assessed prior to starting ART, with follow-up assessment of ART adherence at all clinical visits once ART is initiated. Interventions for promoting ART adherence work best when multifaceted, targeted for nonadherent participants (or those at risk based on adherence barriers), and tailored to individuals' needs. Successful ART adherence interventions have included education and counseling, provision of social support, directly observed therapy, and financial incentives. While treatment-related barriers have diminished with recent simplified ART regimens, guidelines still recommend considering regimens with a low pill burden, once daily dosing, few side effects, and minimal dietary requirements, while still considering individual preferences, contraindications, and drug–drug interactions. Adherence tools including pillboxes have been shown to be effective and are widely recommended. Two-way SMS texting is a newer strategy that has been successful in promoting ART adherence. The benefits from some adherence interventions can diminish once the intervention has been completed, leading to recommendations for some short-term interventions such as DOT to be limited to high risk groups such as active substance users or during pregnancy. Further research is needed to determine the optimal combination of adherence interventions, as well as their generalizability and implementation, and their cost-effectiveness.

Compliance with Ethics Guidelines

Conflict of Interest Yael Hirsch-Moverman and Sharon Mannheimer have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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