

The Importance of Treatment Adherence in HIV

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Introduction: The Consequences of Poor Adherence in HIV

In addition to the primary objective of reducing the risk of morbidity and mortality, the secondary goal of treatment for HIV is viral suppression. Numerous effective therapeutic agents for viral suppression in HIV have been developed. Their efficacy, however, requires that patients with HIV be adherent to their prescribed regimens. Effective use of antiretroviral agents requires not only good adherence to therapy on the part of patients but sustained adherence over time (persistence) if viral suppression is to be successful.¹ For HIV therapeutic regimens in which an unboosted protease inhibitor is a component, there exists a substantial risk of failed viral suppression with treatment adherence less than 95%.²

High levels of treatment adherence in HIV have been shown to predict better viral suppression outcomes, whereas poor treatment adherence in HIV is associated not only with less effective viral suppression but also with drug resistance and reduced survival.^{3,4} The **Figure**³ shows the relationship between levels of adherence to nonnucleoside reverse-transcriptase inhibitors (NNRTIs) and viral suppression in an observational cohort study involving 2821 adults infected with HIV. The differences in effect on viral suppression of 80% to 89% versus 100% adherence, and even 90% to 99% versus 100% adherence, are notable.

Different classes of antiretroviral therapy (ART) are associated with different thresholds of adherence needed to achieve viral suppression and avoid resistance mutations. Each class of agents has a unique relationship between adherence rates and these 2 key outcome variables. For example, highly active antiretroviral therapy (HAART) based around an NNRTI needs a very high level of adherence to limit the risk of resistance mutations. A study by Maggiolo et al found a 4.9% risk of resistance mutations in patients receiving NNRTI-based HAART who dropped below a 75% rate of treatment adherence, while patients treated with HAART with an unboosted protease inhibitor (PI) as its backbone had a very low mutation risk at that level of adherence. Boosted PIs were associated with a mutation risk between unboosted PIs and NNRTIs at the same adherence rate. By comparison, the risk of viral rebound after the cessation of an unboosted PI HAART regime was approximately 5-fold the

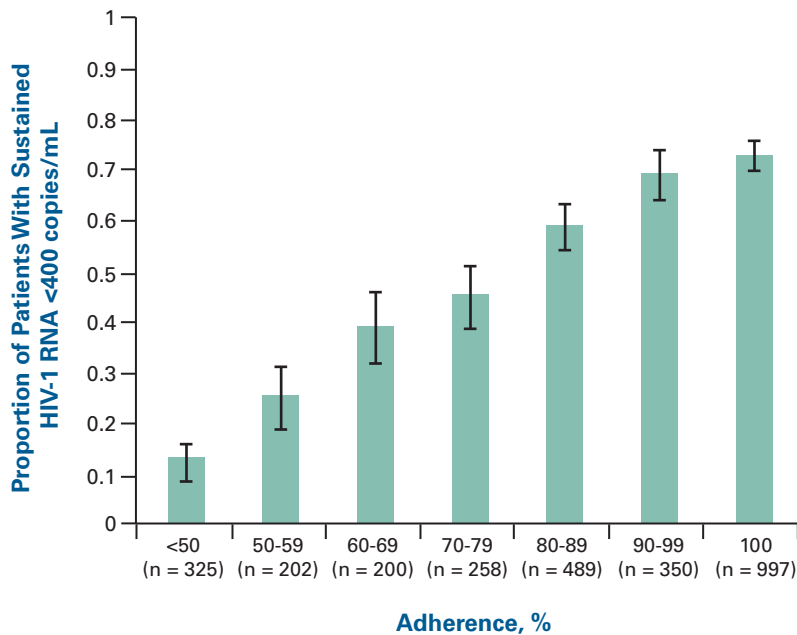
Abstract

Treatment adherence is generally regarded as an important factor in achieving optimal outcomes across many disease states; in the treatment of HIV, poor adherence to treatment has the potential to impact outcomes on multiple levels. Poor adherence to antiretroviral therapy (ART) is associated with less effective viral suppression, which risks the immediate health of the patient, but also risks creating permanent treatment resistance to that particular agent or group of agents within a given combination therapy regimen. This may have downstream effects on treatment costs as well as therapeutic options. The causes of poor adherence to ART are extremely diverse, and include complexity of therapeutic regimens (eg, pill burden and dosing frequency), treatment side effects, poor health literacy, poor patient-physician relationship, and limited access to ART as a result of formulary restrictions or copayment costs. Treatment approaches, such as the use of fixed-dose combinations of ART agents to reduce dosing complexity, as well as educational interventions, such as medication therapy management initiatives, have been shown to improve adherence to therapy in HIV. It is important that all members of the healthcare team address potential barriers to adherence in order to achieve viral suppression and optimize outcomes in patients with HIV.

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■ **Figure.** Relationship of Adherence to NNRTIs and Viral Suppression in 2821 HIV-Positive Patients^{3,a}



NNRTI indicates non-nucleoside reverse-transcriptase inhibitor.

^aError bars represent 95% confidence intervals.

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viral rebound risk observed with an NNRTI-based HAART, while a boosted PI HAART regime had a rebound risk approximately two-thirds greater than NNRTI.⁵ The data on integrase inhibitors is much more limited at present, and it remains uncertain where these agents sit on the HAART spectrum with regard to adherence requirements.

In the United States, the rate of adherence to HIV therapy is generally low. A meta-analysis of adherence studies—the durations of which ranged from a few days to 1 year—observed a rate of 55% who “achieved adherence” among a pooled group of 17,573 patients. The definition of “achieving adherence” in the studies ranged from above 80% adherence to 100% adherence. By comparison, in sub-Saharan Africa, the pooled adherence rate in studies comprising 12,116 patients was 77%.⁶

The causes of poor adherence in HIV treatment are extremely varied (Table 1),⁷ including patient challenges related to age, health literacy, psychosocial and neurocognitive issues, and substance abuse, among other factors. Adherence is also impacted by medication-related barriers, such as complexity of regimens and treatment side effects; and healthcare system challenges, such as drug costs and coverage issues, can also reduce the likelihood of a patient taking his or her medications as appropriate. The purpose of this article is to review the nature and impact of several key adherence-related factors in HIV.

The Influence of Dosing and Formulations on Adherence

As with many diseases requiring complex treatment regimens, adherence to therapy in HIV is strongly affected by how difficult it is to follow the prescribed treatment. Pill burden—the number of pills a patient needs to take in a given period—is one important factor in the relationship between dosing and adherence in HIV, and the medical literature shows significantly greater rates of adherence when the pill burden is low.⁸

The influence of pill burden on adherence and outcomes was observed in a study published in 2012 by Sax et al, in which 7073 commercially insured HIV-infected patients (selected from the LifeLink database) were evaluated for adherence and risk of hospitalization, with medication possession ratio (MPR) being used to measure adherence. The study subjects were stratified into 3 groups: those taking 3 plus pills per day (60.8%), 2 pills per day (5.8%), or 1 pill per day (33.4%). A treatment adherence rate of 95% or higher was observed in approximately 47% of patients taking 1 pill a day versus 41% in patients taking 2 pills a day versus 34% taking 3 pills or more a day ($P = .019$ for 1 pill vs 2 pills; $P < .001$ for 1 pill vs ≥ 3 pills). After logistic regression analysis, hospitalization risk was found to be significantly lower for patients taking 1 pill a day versus those taking 2 or 3 plus pills a day ($P = .003$), although

■ **Table 1. Common Factors Associated With Poor Treatment Adherence to ART⁷**

- Low levels of health literacy
- Age-related challenges (eg, polypharmacy, vision loss, cognitive impairment)
- Younger age
- Psychosocial issues (eg, depression, homelessness, low social support, stressful life events, psychosis)
- Nondisclosure of HIV serostatus
- Neurocognitive issues (eg, cognitive impairment, dementia)
- Active (but not history of) substance abuse, particularly for patients who have experienced recent relapse
- Stigma
- Difficulty with taking medication (eg, trouble swallowing pills, daily schedule issues)
- Complex regimens (eg, high pill burden, high-frequency dosing, food requirements)
- Adverse drug effects
- Nonadherence to clinic appointments
- Cost and insurance coverage issues
- Treatment fatigue

ART indicates antiretroviral therapy.

there was no difference in risk between the 2 pills and 3 plus pills groups.⁹

Dosing frequency can also play a significant role in treatment adherence for HIV, as evidenced by the NOCTE study, a 48-week randomized controlled trial in which 87 patients received the same HAART either on a once-nightly or twice-daily dosing schedule. Persistence—which, along with proper execution of a prescribed regimen, is one of the 2 components of adherence—was the main driver of adherence in the study, with 81% of those dosing once nightly persisting with treatment for the full 48 weeks compared with 62% of those dosing twice daily. At the end of the trial period, patients in the once-nightly dosing group were significantly more likely to have been adherent compared with patients in the twice-daily dosing group ($P = .03$).¹⁰

Because ART regimens commonly involve taking multiple drugs at the same time, fixed-dose ART combinations (FDCs), which combine 2 or more drugs in a single formulation, have been developed to increase the likelihood of treatment adherence. The emergence of generic versions of some antiretroviral drugs has, however, caused some third-party payers to consider disallowing FDCs when a generic equivalent is available, in order to lower treatment costs.

A cost-utility study sought to evaluate the validity of this approach by comparing cost and utility scores of 70 patients with HIV/AIDS receiving ART as an FDC regimen with a matched group of 70 patients with HIV/AIDS receiving ART as separate pills. Mean annual costs were \$15,766 for patients receiving FDC compared with \$11,895 in the sepa-

rate-pill group. Utility, measured by the SF-6D health instrument, was higher in the FDC group, but not significantly so. However, the incremental cost-utility ratio was shown to favor the FDC regimen above the \$40,000 threshold.¹¹

An additional benefit of FDCs for the personal health of patients, as well as for public health, is that these formulations limit the possibility of selective noncompliance, or covert monotherapy, which can increase the risk of drug resistance.¹²

ART-Related Adverse Events

ART is associated with a number of adverse events (AEs) that may negatively impact adherence to therapy. The association between adherence and specific AEs was the subject of a recently published meta-analysis of studies of adherence to ART in adults with HIV. The authors identified 19 studies from which pooled odds ratios for the risk of reduced adherence with specific AEs were derived. Among those AEs associated with statistically significant reduced adherence were anxiety, confusion, nausea, fatigue, taste disturbances, and loss of appetite (**Table 2**).¹³

These results are consistent with a French survey that examined factors contributing to nonadherence in 1010 patients with HIV who were treated with HAART for up to 10 years (follow-up period range: 12-120 months). Nonadherence was strictly defined as taking less than 100% of prescribed HAART medications in the 4 weeks prior to the survey. Adherence behavior was determined via a questionnaire that sought to identify nonadherent behav-

Table 2. Pooled Odds Ratios for Risk of Reduced Adherence Associated With Antiretroviral-Related Adverse Events¹³

Adverse Event	Pooled OR (95% CI)	P
Fatigue	0.63 (0.43-0.92)	.016
Anxiety	0.63 (0.41-0.95)	.028
Confusion	0.35 (0.18-0.66)	.001
Taste disturbances	0.49 (0.30-0.77)	.003
Loss of appetite	0.54 (0.32-0.93)	.027
Nausea	0.57 (0.43-0.77)	<.001

CI indicates confidence interval; OR, odds ratio. Adapted from Al-Dakkak I, Patel S, McCann E, et al. *AIDS Care*. 2013; 25(4):400-414.

iors, including skipping a dose, altering the dosing schedule at least once, and taking all of a day’s medications at once instead of at planned intervals. The authors observed that a higher number of self-reported treatment side effects (from a list that included diarrhea, nausea, stomach pain, headache, change in taste, skin itching, muscle pain, heartburn, sore mouth, vomiting, fever, kidney stones, and fatigue) was one factor contributing to nonadherence. Other factors associated with reduced adherence were younger age, daily ART dosing 3 or more times per day, depressive symptoms, alcohol consumption, and poor partner support.¹⁴

Of those ART-related AEs that contribute to poor adherence, gastrointestinal AEs may, ultimately, be the most consequential. According to a recently published study in which 1096 patients with HIV were retrospectively followed up to determine those factors most likely to cause discontinuation of treatment (which may be regarded as a form of total treatment nonadherence), gastrointestinal AEs were the primary culprit, accounting for nearly 29% of all discontinuations due to AEs.¹⁵

Healthcare System Factors Impacting Adherence to Treatment

Osterberg and Blaschke have described a series of related interactions between patients, physicians, and the healthcare system that have a negative influence on treatment adherence. On the patient side, several common types of barriers to adherence prevail, including gaps in knowledge about: a) the disease, b) the rationale for a given treatment, and c) how that treatment should be implemented. These areas of poor understanding combine patient limitations and, perhaps, insufficient guidance and education from providers and/or the healthcare system in which the patient is a participant. The complexity of a treatment regimen—as pre-

scribed by a provider—is also a potentially serious barrier to adherence that should be addressed by patient and provider. Forgetfulness is the most common patient factor leading to poor adherence, while personal or emotional issues can also affect adherence.¹⁶

Providers may unintentionally influence adherence due to limited familiarity with drug costs and/or limited knowledge of insurance coverage and formularies. A physician may select a treatment regimen optimized for a given patient based on clinical trial data and personal clinical knowledge without taking into account patient cost and access to treatment, factors which may ultimately influence patient adherence.¹⁶

Another player, the healthcare system, can have a very large influence on treatment adherence by instituting cost savings policies—such as limiting patient access to healthcare resources, restricting formularies, or increasing copayments—that may be counterproductive if they negatively impact adherence, leading to poor outcomes and, consequently, higher treatment costs. Limitations in access may, in some cases, be incidental rather than intentional, as when a change in formulary not aimed at restricting access produces an additional obstacle for patients who are unable to navigate the healthcare system.¹⁶

Physician-Patient Relationship

The relationship between patient and provider may influence whether a patient will be adherent to treatment. Nevertheless, while the relationships between patients and their providers are widely assumed to impact treatment adherence, this assumption is not always supported by reliable data. To address this need in the context of HIV treatment, Schneider et al undertook a study to quantify the impact of different aspects of the physician-patient relationship on adherence. The authors surveyed 554 patients with HIV being treated at 22 outpatient practices in Boston, Massachusetts, evaluating adherence through targeted and confirmatory questions, and patient perceptions of their relationship with their physicians primarily through established multi-item patient satisfaction scales. After adjusting for age, gender, education, race, physical health, and mental health, 6 out of 7 physician-patient relationship factors were significantly associated with adherence: 1) general communication, 2) adherence dialogue (ie, perceptions regarding a doctor’s skills at providing treatment-related information), 3) physician trust, 4) satisfaction with physician, 5) willingness to recommend physician, and 6) (provision of) HIV-specific information. The only factor that did not achieve statistical significance was “participatory decision making.”¹⁷

A study from Johns Hopkins evaluated the importance of the physician-patient relationship in a somewhat different way by determining whether patients felt “known as a person” by their provider. The study included 1743 patients with HIV who were interviewed an average of 2.7 times to determine not only whether the patient felt their HIV provider knew them, but whether they had received a prescription for HAART, if they were adherent to their regimen, and the status of their viral suppression. Subjects who had a positive response to the “known” question were found to be significantly more likely to have been prescribed HAART (60% vs 47%; $P < .001$), to be adherent to their prescribed treatment (76% vs 67%; $P = .007$), and to have undetectable serum HIV RNA (49% vs 39%; $P < .001$).¹⁸

Access to ART

The relationship between access to HIV therapies and treatment adherence is an important one. In the absence of a cure for HIV/AIDS, it is vitally important that patients be able to access antiretroviral therapies for managing HIV infection. This has become a more important issue because ART has allowed people with HIV to live much longer today compared with the time of HIV’s first widespread emergence. Because of the lifetime duration of ART treatment, patients with HIV will sometimes need to make changes to their drug regimen as issues of diminishing efficacy and drug resistance arise. Consequently, it is important that patients with HIV have access to the maximum number of treatment options in order to receive treatment that is optimally effective, while having the option of switching if that treatment loses its efficacy. This need for broad access to HIV medications has a significant bearing on adherence as both treatment efficacy, in terms of viral suppression, and patient confidence in the efficacy of ART in general constitute major factors influencing patients’ adherence to treatment.^{8,17}

There are many potential barriers to access to treatment. Mechanisms such as formulary restrictions and higher copayments are often employed to limit costs; however, these approaches may have unintended consequences. This tension between apparent cost savings and long-term consequences, both in terms of costs and patient outcomes, may be observed in the effect on adherence of increasing copayments.

Johnston et al conducted an observational study employing data from a major US claims database of commercially insured individuals (Thomson Reuters MarketScan Commercial Database) during the period 2003 to 2008; from a pool of nearly 57 million insured individuals, a cohort of 3731 patients with HIV fulfilled the study inclusion criteria. The study examined the effect of 3 different cost-sharing

levels for a 30-day supply of ART—\$25, \$75, \$144—on 2 different thresholds of treatment adherence, 78% and 95%. The authors found that, after sensitivity analyses, an increase in cost sharing amount was associated with a significant reduction in the likelihood of achieving either the higher or lower treatment adherence threshold (all $P \leq .029$).¹⁹

Certainly, this study does not answer the question of what long-term effects increased copayments have on treatment costs in HIV; that remains an area for future study. However, by demonstrating an association between increased copayments and reduced adherence, these data point to the risk of precipitating undesirable longer-term consequences associated with poor adherence, including increased risk of the development of drug resistance, and less effective viral suppression leading to higher treatment costs arising from, among other things, the costs of treating a sicker patient, who may also be at increased risk of comorbidities. Similarly, reducing the efficacy of available treatments due to poor adherence could result in increased treatment costs if the patient is less responsive to available drugs, thus leaving the patient in a state of poorer health, while those drugs that remain effective may also be more expensive.

Treatment Approaches and Overcoming Adherence Barriers

Several strategies have demonstrated positive effects on treatment adherence in patients with HIV both in terms of managing the disease and in terms of directly addressing barriers to adherence.

Multidisciplinary Care

Multidisciplinary care has become an increasingly popular approach to treatment across a variety of disease states; however, what exactly constitutes an optimal care team is often not discussed in the medical literature. A recent study by Horberg et al sought to answer this question in the context of treatment for HIV by analyzing the impact of multidisciplinary care teams (MDCTs) on adherence, specifically focusing on the composition of different MDCTs (ie, different clinician specialties). The study, which was conducted within the Kaiser Permanente California healthcare system, included 9669 patients treated from 1996 to 2006 and covering 10,801 regimen starts, approximately two-thirds of which were first-time ART regimens in ART-naïve patients. Marked differences were observed between differently composed MDCTs, and when compared with treatment by an HIV specialist alone, 5 MDCTs demonstrated significantly greater association with 12-month patient adherence to treatment after linear regression modeling (Table 3).

Table 3. Multidisciplinary Care Team Combinations Associated With Increased 12-Month Adherence Compared With Single HIV/ID-Specialist Care²⁰

Team Composition	Mean Adjusted % Increased Adherence	P
HIV/ID specialist	Reference	—
Pharmacist + non-nurse care coordinator + non-HIV primary care	+8.1%	.003
Nurse + social work/benefits coordinator + non-HIV primary care	+7.5%	<.001
HIV specialist + mental health	+6.5%	.001
Pharmacist + social work/benefits + non-HIV primary care	+5.7%	<.001
Pharmacist + non-HIV primary care	+3.3%	.01

ID indicates infectious disease.
Adapted from Horberg MA, Hurley LB, Towner WJ, et al. *J Acquir Immune Defic Syndr.* 2012;60(2):183-190.

Clinical pharmacists were found to be the only allied health-care professionals, in collaboration with physicians, associated with increased adherence.²⁰

Educational and Medication Management Initiatives

As previously discussed, the side effects of ART can have a detrimental effect on adherence. Educational initiatives aimed at improving patients’ knowledge of, and ability to manage, ART side effects may have a beneficial effect on adherence. A study by Hirsch et al (2009) evaluated the impact of education and management initiatives on adherence among HIV/AIDS patients in the Medi-Cal system participating in a pharmacist-provided medication therapy management (MTM) program. The aim of the intervention, which extended beyond the purely educational, was: a) to help patients understand and manage AEs and medication side effects, b) evaluate patients’ ability to adhere to prescribed regimens, and c) provide suggestions for optimal drug regimens to accommodate specific patient needs. This 3-year study used pharmacy and medical claims data from Medi-Cal to compare adherence rates in patients who filled their prescriptions at pharmacies participating in the MTM study—“pilot” pharmacies—with those who filled their prescriptions at non-pilot pharmacies.²¹ Adherence, measured by MPR, was found to be significantly higher for patients using pilot pharmacies for each of the 3 years of the study. In 2005, adherence for patients using pilot pharmacies was 66% compared with 43% in non-pilot pharmacies; in 2006 it was 72% versus 45%, and in 2007 it was 69% versus 47% (all *P* <.001).²² Although health outcomes of patients in the study by Hirsch et al were not tracked, higher levels of adherence would be expected to result in improved viral suppression, as demonstrated in a study by Fairley et al (2005).²³

The specific relevance of health literacy to adherence was the subject of a small study from the University of

Connecticut, which included 145 people with HIV/AIDS. Study subjects were assessed for health literacy using the Test of Functional Health Literacy in Adults (TOFHLA) instrument, and were evaluated for adherence using unannounced telephone-based pill counts. Using a cutoff point of 90% correct answers on the TOFHLA to define higher and lower health literacy, the authors found that those with higher health literacy were significantly more likely than those with lower health literacy to be 80% adherent (*P* <.05), 85% adherent (*P* <.05), and 90% adherent (*P* <.01) to ART therapy.²⁴

Summary

Poor adherence to treatment in HIV is extremely complex both in its myriad causes and in its capacity to negatively affect patient outcomes, treatment options, and healthcare costs. Although the potential negative effects of poor adherence are known, in patients with HIV, adherence takes on particular importance as adherence may impact not only viral suppression, but also the emergence of permanent treatment resistance. Treatment-related factors, patient-related factors, provider-related factors, and healthcare system-related factors may all impact adherence. Consequently, it is important that all participants involved in the management of HIV infection—from patients to clinicians to third-party payers—recognize and address factors that may potentially reduce treatment adherence.

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