# Strategies to Enhance Adherence, Reduce Costs, and Improve Patient Quality of Life

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## ABSTRACT

OBJECTIVES: To (a) analyze recent evidence and research on adherence for human immunodeficiency virus (HIV) and hepatitis B treatment, including discussion on the dynamics and barriers of adherence, and (b) recommend strategies from the patient and clinician perspective to enhance patient adherence.

SUMMARY: Since the widespread use of highly active antiretroviral therapy (HAART) for HIV infection, individuals with HIV are living much longer. A substantial percentage of individuals with HIV also have co-existing medical conditions, including co-infection with hepatitis viruses. While adherence to guidelines does not guarantee success or improved quality of life, 3 key factors affect treatment success: (1) drug resistance and cross-resistance, (2) adverse drug reactions and drug interactions, and (3) the level of adherence, which also affects resistance development.

Adherence to treatment regimens remains 1 of the most important factors related to treatment success. Complete adherence to any medication regimen is difficult. In HIV disease, poor adherence is associated with development of resistance. Health care providers cannot predict patient adherence to therapy, but they can help patients overcome barriers to adherence and take their medication as directed. Simple regimens with once- or twice-daily dosing are preferred. The potential development of side effects depends on the individual patient. Treatment regimens must work with the patient's lifestyle and schedule. Psychosocial issues are also very important. Patient belief that HAART is effective, and a positive relationship between patient and provider can promote adherence.

Strategies to improve patient adherence can be grouped into 3 categories related to the patient: the clinic, the health-care team, and the regimen. Regimens should be simplified as much as possible: reducing the number of pills, their frequency, and dosing restrictions, as well as seeking to minimize drug interactions and side effects. The UCSF Positive Health Program Adherence Support Program is outlined.

CONCLUSION: Adherence is an important aspect of HIV treatment. The key take-home message is that changing the antiretroviral therapy for a non-adherent patient is futile without addressing adherence barriers first.

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Since the widespread use of highly active antiretroviral therapy (HAART) for human immunodeficiency virus (HIV) infection, individuals with HIV live much longer with fewer opportunistic infections.[1] A substantial percentage of individuals with HIV also have coexisting medical conditions, including co-infection with hepatitis B virus (HBV) and/or hepatitis C (HCV).[2-5] HCV co-infection is common, particularly among injection drug users (IDUs).[6] Mental illness and substance abuse are also observed in people with HIV more frequently than in the U.S. population in general.[7] Because of these medical comorbidities, HIV treatment must also consider the use of multiple medications, drug interactions, and the treatment of other illnesses that may impact response to HIV therapy.[2] These considerations are also relevant to patients co-infected with a hepatitis virus.

People infected with HIV today are also likely to die of non-opportunistic illnesses, especially liver disease, pulmonary diseases, cardiovascular disease, and renal problems.[8,9] For example, in the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study that evaluated mortality in 23,441 HIV-infected persons followed for a total of 76,893 patient-years, there were 1,246 deaths, of which 14.5% were liver-related and occurred at higher CD4 cell counts despite antiretroviral therapy (ART).[10]

The U.S. Department of Health and Human Services Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents (DHHS Guidelines)[2] note that the primary goals of antiviral therapy for HIV infection are 4-fold: (1) to reduce HIV-related morbidity and mortality, (2) to improve quality of life, (3) to restore and preserve immunologic function (measured by CD4 cell count), and (4) to maximally and durably suppress viral replication (measured by viral load).

Adherence to guidelines or treatment with any specific therapy does not guarantee success or improved quality of life. However, 3 key factors affect treatment success: (1) drug resistance and cross-resistance, (2) adverse drug reactions and drug interactions, and (3) the level of adherence, which also affects resistance development.

### Resistance

Several special issues impact the emergence of resistance to various antiretroviral agents in HIV. First, HIV evolves rapidly because of its high replication and turnover rate combined with a high mutation rate due to error-prone replication. Second, virus diversity is constrained by selective pressures that include the need to evade the host immune system response and by exposure to antiretroviral agents. The key fact is that the evolution rate is proportional to the replication rate. Profound virus suppression achievable with current highly active antiretroviral therapy (HAART) regimens slows or may prevent emergence of resistance, which allows durable virus suppression (low or undetectable viral load) and can lead to immunologic recovery (increased CD4 cell count).

Currently, 2 types of HIV drug resistance assays are commercially available: (1) phenotypic assays directly measure a sensitivity of a patient's virus to specific antiretroviral agents[11] and (2) genotypic assays identify specific genetic mutations that cause resistance to certain drugs or drug classes. With genotypic assays, resistance is inferred through an algorithm or database analysis.[11,12] An advantage of phenotype resistance assays is that they allow quantification of the concentration of a particular drug needed to inhibit HIV replication. For example, the new CCR5 receptor antagonist, maraviroc, requires documentation that a tropotype/tropism assay is completed of the co-receptor used by the patient's virus before initiation of maraviroc therapy.

Resistance testing has been shown to result in short-term improvements in virologic response because ineffective antiretroviral agents may be eliminated from the regimen. However, drug resistance is only detectable by current commercial genotypic or phenotypic assays if resistant virus is present in at least 20% to 30% of the quasi-species (a group of viruses related by a similar mutation or mutations, competing within a highly mutagenic environment). In general, phenotyping should be reserved for complex ART-experienced patients among whom genotyping results may be difficult to interpret.

There are multiple indications for resistance testing, including primary infection, treatment failure, and pregnancy.[2,12] Recommendations about when to use resistance testing vary slightly between the DHHS Guidelines[2] and the International AIDS Society-United States of America (IAS-USA).[12] The IAS-USA recommends use periodically during chronic infection and during pregnancy if the woman is viremic. The DHHS guidelines recommend considering resistance testing during chronic infection. Both guidelines recommend resistance testing in all patients with treatment failure and in primary/acute HIV infection, when it is identified. As early as 1999-2000, more than one fifth (22.7%) of newly-infected HIV patients had evidence of transmitted resistance to at least 1 antiretroviral agent and more than 10% were classified as resistant to multiple antiretroviral agents while still treatment-naive.[13] Rates differ by drug class and other factors, which include risk group and geography.[14,15]

### Adverse Drug Reactions and Drug Interactions

Adverse drug reactions (ADRs) are common, especially for elderly patients, ranging from 1% to 35% in various studies, and occur in about 3% of all hospitalizations, resulting in increased length of stay and other costs. The total costs are estimated at $30 to $130 billion a year, which is several thousand dollars per patient affected. A hospital-related ADR was associated with an almost 2-fold increased risk of death.[16-18]

In HIV disease, the main clinical significance of drug interactions is a decrease in HAART efficacy, and, therefore, an increase in emergence of viral resistance. Drug interactions also increase the rate of ADRs, including QTc prolongation (risk factors include concomitant anti-arrhythmics, certain antibiotics, phenothiazines,

tricyclic antidepressants), rhabdomyolysis (risk factors include use of statins and protease inhibitors), and prolonged sedation and other mental status changes with anxiolytic treatment (for example, diazepam).[19]

In HIV patients, common drug interactions, which may result in additive or synergistic toxicity, include hepatic metabolism changes, drug absorption alterations, and drug displacement.

Drug interactions due to cytochrome P450 3A4 induction are seen with all commonly used nonnucleoside reverse transcriptase inhibitors (NNRTIs), including etravirine, nevirapine, and efavirenz, with rifamycins (rifampin, rifapentine, and rifabutin), and anticonvulsants (phenobarbital, carbamazepine, phenytoin, oxcarbazepine).

Drug interactions due to P450 3A4 inhibition include antifungal azoles (ketoconazole, itraconazole, voriconazole, and fluconazole) and macrolides (erythromycin, clarithromycin, and azithromycin). Protease inhibitors (PIs) affect the metabolism of the phosphodiesterase type 5 (PDE5) inhibitors sildenafil, vardenafil, and tadalafil. High-dose ritonavir (widely used as a pharmacologic enhancer with other protease inhibitors) causes the largest effect, while saquinavir causes the smallest. Tipranavir, atazanavir, loprinavir, fosamprenavir/amprenavir have an intermediate effect.[2]

Grapefruit and grapefruit juice consumed concurrently with antiretrovirals is known to affect levels of other pharmaceuticals and should be used with caution by HIV patients.[20]

Atazanavir interacts with both proton pump inhibitors (PPIs) and $H_2$-blockers. Several commonly used pharmaceuticals (simvastatin, rifampin, PDE5 inhibitors, warfarin, and fluticasone) are known to interact with at least some antiretrovirals. Tipranavir, as well as the newer drugs darunavir and etravirine, are characterized by interactions with other antiretroviral agents.
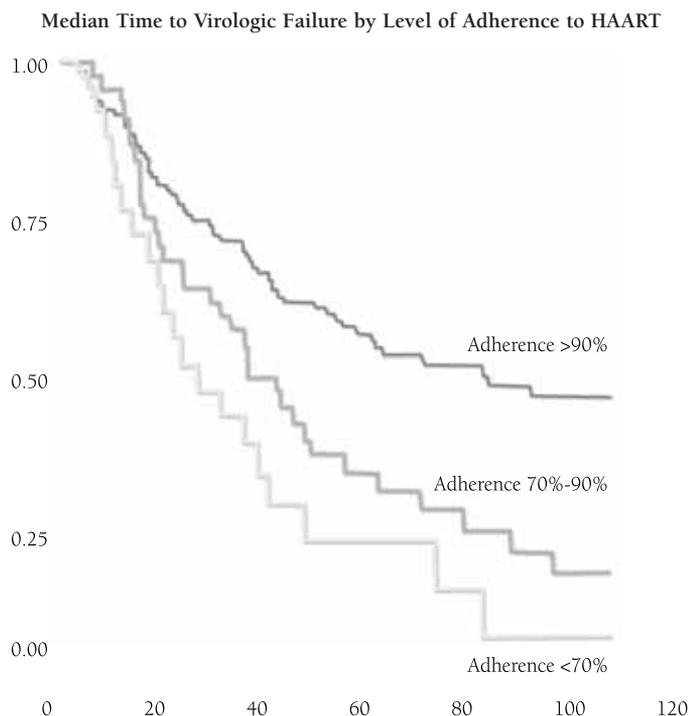
### Adherence

Adherence to treatment regimens remains 1 of the most important factors related to treatment success. Complete adherence to any medication regimen is rarely achieved. In HIV disease, various levels of adherence correspond to treatment success and are associated with development of resistance. Key predictors of long-term virologic success of antiretroviral therapy are listed in Table 1.[2]

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**TABLE 1**  *Predictors of Long-Term Virologic Success[2]*

- **Potency of antiretroviral regimen**
- **Adherence to treatment regimen**
- **Low baseline viremia**
- **Higher baseline CD4 cell count**
- **Rapid (≥1 log in 1 to 4 months) reduction of viremia in response to treatment**

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**FIGURE** Relationship Among Non-Adherence, Virologic Failure, and Progression to AIDS[21]

**Median Time to Virologic Failure by Level of Adherence to HAART**

Adherence >90%

Adherence 70%-90%

Adherence <70%

**Time from First Undetectable HIV-1 RNA (Weeks)**
Kitahata M, et al. *Int J STD AIDS.* 2004;15:803-810.

**Adjusted Hazard Ratio of Progression to Clinical AIDS or Death by Levels of Adherence**

| Level of Adherence | Hazard Ratio (95% CI) | P |
|---|---|---|
| >90% | 1 (REF) | $P<0.007$ |
| 70%–90% | 0.52 (0.14–2.03) | >0.2 |
| <70% | 5.71 (2.01–16.2) | 0.0001 |

*Patients were characterized into 3 levels of adherence:*
*High (>90%); Moderate (70%-90%); Low (<70%)*
*CI=confidence interval*

Relationship among non-adherence, virologic failure, and progression to AIDS is shown (Figure).[21] In this study, patients were characterized into 3 levels of adherence: high (>90%), moderate (70%-90%), and low (<70%). Increasing level of adherence to HAART was significantly associated with longer time to virologic failure ($P<0.001$). The median time to virologic failure was 89 weeks among patients with a high level of adherence compared with 42 weeks among patients with moderate adherence, and 30 weeks among patients with a low level of adherence to HAART ($P<0.001$). Patients with low adherence were almost 6 times more likely to progress to clinical AIDS or die than the high-adherence reference group, and this was statistically significant. Also, half of the high-adherence group achieved undetectable viral HIV-1 RNA compared with about 10% in the low-adherence group.[21] Viral rebound has been linked with clinically significant resistance.[22,23]

High-adherence levels are required for success of PI-based regimens.[24] In a 2000 study that has remained the benchmark for adherence aspirations, only one fifth (21.7%) of patients with adherence of 95% or greater had virologic failure. Virologic failure (54.6%) was significantly lower than in patients with 90% to 94.9% adherence. Lower levels of adherence were associated with higher failure rates (up to 82.1% for patient with <70% adherence).[24]

*Provider Perspectives on Adherence*
First, health care providers cannot accurately predict patient adherence to therapy.[24] In an adherence study using Medication Events Monitoring System (MEMS), physicians misjudged adherence (taking greater than 80% of the prescribed doses of antiretroviral medications) in 41% of patients. Nurses misjudged adherence in 30% of patients. While overestimation of adherence occurred in 28% of cases, 51% of patients that clinicians predicted to be less than 80% adherent, in fact, had adherence levels >80%, and 21% had adherence level >95%.[24]

The patient factors that physicians said affected adherence[24] were gender, socioeconomic level, psychiatric morbidity, age, employment status, HIV risk factors, race, and substance abuse. However, in multivariate analysis, older age, and lack of psychiatric morbidity are associated with adherence >95%. Univariate analysis also identified substance abuse as affecting a patient's ability to achieve 95% adherence.

Data from the AIDS Clinical Trials Group (ACTG) indicated that 25% of participants admitted not understanding how to follow their regimens.[25] Several factors have been found to be barriers to patient adherence to medication. Reducing regimen complexity with once- or twice-daily dosing is preferred. While pill burden is important, dosing schedules and food restrictions appear to have a more pervasive influence on adherence. The effect of side effects—transient (diarrhea, nausea) or longer lasting (lipodystrophy, dyslipidemia, neuropathy)—depends on the individual patient. Regimens must work with the patient's lifestyle and schedule. Difficulty understanding medication schedules is a barrier to adherence. Psychosocial issues are very important. Substance abuse, depression, stress, hopelessness, and negative feelings each reduce motivation for self-care. Patient belief that HAART is effective, and a positive relationship between patient and provider can promote adherence.[25] Predictors of poor adherence are listed in Table 2.[25]

Patient perspectives on adherence include factors related to the

**TABLE 2** Predictors of Poor Adherence[25]

- Lack of trust between patient and provider
- Active drug/alcohol use
- Active mental illness
- Lack of patient education
- Lack of patient being able to identify meds
- Lack of reliable health care access
- Medication ADRs
- Domestic violence

**TABLE 3** Patient-Related Strategies to Improve Adherence

- Establish readiness to start therapy
- Provide education on medication dosing
- Review potential side effects
- Anticipate and treat side effects
- Utilize educational aids
- Engage family, friends
- Simplify regimens, dosing, and food requirements
- Utilize team approach with pharmacists, nurses, etc.
- Provide accessible, trusting health care team
- Assess literacy level
- Involve patient in regimen selection

*Source: Adapted from U.S. Department of Health and Human Services, Panel on Clinical Practices for Treatment of HIV Infection. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Washington, DC: U.S. Department of Health and Human Services; January 29, 2008.*

**TABLE 4** Clinic and Health Team Strategies to Improve Adherence

1. Establish trusting relationship
2. Commit to
   - Communication between clinic visits
   - Ongoing adherence monitoring
   - Timely response to adverse events or interim illness
3. Establish interventions
   - Pharmacist-based adherence clinics
   - Street-level drop-in centers with medication storage/flexible hours for homeless persons
   - Adolescent-specific training programs
   - Medication counseling
   - Behavioral intervention
   - Directly observed therapy
4. Monitor adherence
5. Be aware of the effect of new diagnoses or symptoms on adherence

*Source: Adapted from U.S. Department of Health and Human Services, Panel on Clinical Practices for Treatment of HIV Infection. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Washington, DC: U.S. Department of Health and Human Services; January 29, 2008.*

patient and to the regimen. The 3 most important reasons patients give for missing doses are: too busy/forgot (52%), away from home (46%), and a change in daily routine (45%). The next most common reason was feeling depressed or overwhelmed (27%).[26]

Based on scores for the impact of regimen attributes on adherence, the ideal regimen would be 2 small pills dosed once daily at the same time with an acceptable adverse event profile, and no dietary restrictions. This regimen should also come with a single prescription, as single refill, a single medication bottle, and a single insurance copayment.[27] Although once daily was the preferred dosing frequency, once-daily regimens did not score better than other regimens in this study. Limitations in the study include the fact that patient perception is not necessarily reflective of actual patient behavior in clinical practice.

### Strategies to Improve Adherence
While health care professionals may not be able to predict adherence, they can take steps to improve it. Strategies to improve patient adherence can be grouped into 3 categories related to the patient (Table 3), the clinic and health care team (Table 4), and the regimen.

### The UCSF Positive Health Program to Improve Adherence
The approach to improving adherence taken at the University of California-San Francisco Positive Health Program includes many structured interactions between patients and members of the health care team.

Before initiating ART, patient readiness is assessed using the ACTG Readiness Questions:
How sure are you that:
❑ you will be able to take all or most of your medications as directed?
❑ the medication will have a positive effect on your health?
❑ if you don't take this mediation exactly as instructed, the HIV in your body will become resistant to HIV medications?
At each visit, patients are asked about depression.
Since your last visit:
❑ have you felt depressed, sad, or blue much of the time?
❑ have you often felt helpless about the future?
❑ have you had little interest or pleasure in doing things?
❑ have you had trouble sleeping many nights?

During front-line counseling, drug-drug interactions are evaluated and then determined for that patient. An important factor to consider is whether restrictions related to taking medications with food or while fasting is important to the patient

and consistent with his or her lifestyle. Therapeutic duplication and prescribing errors, such as tenofovir disoproxil fumarate/emtricitabine (Truvada) and tenofovir disoproxil fumarte (Viread), which both contain tenofovir; abacavir sulfate/lamivudine (Epzicom) and abacavir sulfate (Ziagen), which both contain abacavir; stavudine (d4T) and zidovudine (AZT), which are both thymidine analogs; zidovudine (Retrovir) and ritonavir (Norvir), which have similar names and have been confused, are corrected as are any duplicate prescriptions. Creation of rapport and asking open-ended questions is important and does not take any more time.

Other patient-related strategies to improve adherence are listed in the DHHS guidelines (see Table 17 in the current version available at www.aidsinfo.org).[2]

## ■ Summary

In summary, adherence is an important aspect of HIV treatment. Factors that affect adherence include regimen complexity, side effects, patient-related factors (such as psychosocial issues, the patient's belief system regarding antiretroviral medication and the health care system), and the relationship between the patients and the provider. Of importance to managed care is consideration of the development and implementation strategies to improve adherence and outcomes. The key take-home message is that changing the antiretroviral therapy for a non-adherent patient is futile without addressing adherence barriers first.

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