



Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

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Limitations to Treatment Safety and Efficacy

Adherence to Antiretroviral Therapy (Last updated May 1, 2014; last reviewed May 1, 2014)

Strict adherence to antiretroviral therapy (ART) is key to sustained HIV suppression, reduced risk of drug resistance, improved overall health, quality of life, and survival,^{1,2} as well as decreased risk of HIV transmission.³ Conversely, poor adherence is the major cause of therapeutic failure. Achieving adherence to ART is a critical determinant of long-term outcome in HIV infected patients. For many chronic diseases, such as diabetes or hypertension, drug regimens remain effective even after treatment is resumed following a period of interruption. In the case of HIV infection, however, loss of virologic control as a consequence of non-adherence to ART may lead to emergence of drug resistance and loss of future treatment options. Many patients initiating ART or already on therapy are able to maintain consistent levels of adherence with resultant viral suppression, CD4+ T-lymphocyte (CD4) count recovery, and improved clinical outcomes. Others, however, have poor adherence from the outset of ART and/or experience periodic lapses in adherence over the lifelong course of treatment. Identifying those with adherence-related challenges that require attention and implementing appropriate strategies to enhance adherence are essential roles for all members of the treatment team.

Recent data underscore the importance of conceptualizing treatment adherence broadly to include early engagement in care and sustained retention in care. The concept of an HIV “treatment cascade” has been used to describe the process of HIV testing, linkage to care, initiation of effective ART, adherence to treatment, and retention in care. The U.S. Centers for Disease Control and Prevention estimates that only 36% of the people living with HIV in the United States are prescribed ART and that among these individuals, only 76% have suppressed viral loads.⁴ Thus, to achieve optimal clinical outcomes and to realize the potential public health benefit of treatment as prevention, attention to each step in the treatment cascade is critical.⁵ Therefore, provider skill and involvement to retain patients in care and help them achieve high levels of medication adherence are crucial.

This section provides updated guidance on assessing and monitoring adherence and outlines strategies to help patients maintain high levels of adherence.

Factors Associated with Adherence Success and Failure

Adherence to ART can be influenced by a number of factors, including the patient’s social situation and clinical condition; the prescribed regimen; and the patient-provider relationship.⁶ It is critical that each patient receives and understands information about HIV disease including the goals of therapy (achieving and maintaining viral suppression, decreasing HIV-associated morbidity and mortality, and preventing sexual transmission of HIV), the prescribed regimen (including dosing schedule and potential side effects), the importance of strict adherence to ART, and the potential for the development of drug resistance as a consequence of suboptimal adherence. However, information alone is not sufficient to assure high levels of adherence; patients must also be positively motivated to initiate and maintain therapy.

From a patient perspective, nonadherence is often a consequence of one or more behavioral, structural, and psychosocial barriers (e.g., depression and other mental illnesses, neurocognitive impairment, low health literacy, low levels of social support, stressful life events, high levels of alcohol consumption and active substance use, homelessness, poverty, nondisclosure of HIV serostatus, denial, stigma, and inconsistent access to medications).⁷⁻⁹ Furthermore, patient age may affect adherence. For example, some adolescent and young adult HIV patients, in particular, have substantial challenges in achieving levels of adherence necessary for successful therapeutic outcomes (see [HIV-Infected Adolescents](#) section).^{10,11} In addition, failure to adopt practices that facilitate adherence, such as linking medication taking to daily activities or using a medication reminder system or a pill organizer, is also associated with treatment failure.¹²

Characteristics of one or more components of the prescribed regimen can affect adherence. Simple, once-daily regimens,¹³ including those with low pill burden, without a food requirement, and few side effects or toxicities, are associated with higher levels of adherence.^{14,15} Many currently available ARV regimens are much easier to take and better tolerated than older regimens. Studies have shown that patients taking once-daily regimens have higher rates of adherence than those taking twice-daily dosing regimens.¹⁵ However, data to support or refute the superiority of fixed-dose combination product of 1-pill versus 3-pills (of individual drug products), once-daily regimens—as might be required for the use of some soon-to-be-available generic-based ARV regimens—are limited.

Characteristics of the clinical setting can also have important structural influences on the success or failure of medication adherence. Settings that provide comprehensive multidisciplinary care (e.g., with case managers, pharmacists, social workers, psychiatric care providers) are often more successful in supporting patients' complex needs, including their medication adherence-related needs. Further, specific settings, such as prisons and other institutional settings, may thwart or support medication adherence. Drug abuse treatment programs are often best suited to address substance use that may confound adherence and may offer services, such as directly observed therapy, that promote adherence.

Finally, a patient-provider relationship that enhances patient trust through non-judgmental and supportive care and use of motivational strategies can positively influence medication adherence.

Routine Monitoring of Adherence and Retention in Care

Although there is no gold standard for assessing adherence,¹ properly implemented validated tools and assessment strategies can prove valuable in most clinical settings. Viral load suppression is one of the most reliable indicators of adherence and can be used as positive reinforcement to encourage continuous adherence. When patients initiating ART fail to achieve viral suppression by 24 weeks of treatment, the possibility of suboptimal adherence and other factors must be assessed. Similarly, treatment failure as measured by detectable viral load during chronic care is most likely the result of non-adherence. Patient self-report, the most frequently used method for evaluating medication adherence, remains a useful tool for assessing adherence over time. However, self-reports must be properly and carefully assessed as patients may overestimate adherence. While carefully assessed patient self report of high-level adherence to ART has been associated with favorable viral load responses,^{16,17} patient admission of suboptimal adherence is highly correlated with poor therapeutic response. The reliability of self report often depends on how the clinician elicits the information. It is most reliable when ascertained in a simple, nonjudgmental, routine, and structured format that normalizes less-than-perfect adherence and minimizes socially desirable or “white coat adherence” responses. Some patients may selectively adhere to components of a regimen believed to have the fewest side effects or the lowest dosing frequency or pill burden. To allow patients to more accurately disclose lapses in adherence, some experts suggest that providers inquire about the number of missed doses during a defined time period rather than directly asking “Are you taking your medicines?” Others advocate simply asking patients to rate their adherence during the last 4 weeks on a 5- or 6-point Likert scale.^{18,19} Regardless of how obtained, patient self-report, in contrast to other measures of adherence, allows for immediate patient-provider discussion to identify reasons for missed doses and to explore corrective strategies.

Other measures of adherence include pharmacy records and pill counts. Pharmacy records can be valuable when medications are obtained exclusively from a single source so that refills can be traced. Pill counts are commonly used but can be altered by patients. Other methods of assessing adherence include the use of therapeutic drug monitoring and electronic measurement devices (e.g., MEMS bottle caps and dispensing systems). However, these methods are costly and are usually done primarily in research settings.

Interventions to Improve Adherence and Retention in Care

A continuum of ART adherence support services is necessary to meet individual patient needs. All health care

team members, including physicians, physician assistants, nurse practitioners, nurse midwives, nurses, pharmacists, medication managers, and social workers play integral roles in successful adherence programs.^{17,20-22}

Effective adherence interventions vary in modality and duration, and by clinical setting, provider, and patient. There are many options that can be customized to suit a range of needs and settings (see [Table 13](#)). An increasing number of interventions have proven effective in improving adherence to ART. For descriptions of the interventions, see: <http://www.cdc.gov/hiv/topics/research/prs/ma-good-evidence-interventions.htm>.²³

Clinicians should provide all patients with a basic level of adherence-related information and support. Before writing the first prescription(s) for patients initiating or reinitiating ART, clinicians should assess the patient's adherence readiness. Clinicians should evaluate patients' knowledge about HIV disease, treatment, and prevention and provide basic information about ART, viral load and CD4 count and the expected outcome of ART based on these parameters, the importance of strict adherence to ART, and the consequences of non-adherence. In addition, clinicians should assess patients' motivation to successfully adhere to ART and identify and support facilitating factors and address potential barriers to adherence. Finally, clinicians should be assured that patients have the necessary medication taking skills to follow the regimen as prescribed.

Given the wide array of treatment options, individualizing treatment with patient involvement in decision making is the cornerstone of treatment planning and therapeutic success. The first principle of successful treatment is to design an understandable plan to which the patient can commit.^{24,25} It is important to consider the patient's daily schedule; patient tolerance of pill number, size and frequency; and any issues affecting absorption (e.g., use of acid reducing therapy and food requirements). With the patient's input, a medication choice and administration schedule should be tailored to his/her routine daily activities. If necessary, soliciting help from family members may also improve adherence. Patients who are naive to ART should understand that their first regimen usually offers the best chance for taking a simple regimen that affords long-term treatment success and prevention of drug resistance. Establishing a trusting patient-provider relationship over time and maintaining good communication will help to improve adherence and long-term outcomes. Medication taking can also be enhanced by the use of pill organizers and medication reminder aids (e.g., alarm clock, pager, calendar).

Positive reinforcement can greatly help patients maintain high levels of adherence. This technique to foster adherence includes informing patients of their low or suppressed HIV viral load levels and increases in CD4 cell counts. Motivational interviewing has also been used with some successes. Recognizing high levels of adherence with incentives and rewards can facilitate treatment success in some patients. Adherence-contingent reward incentives such as meal tickets, grocery bags, lotto tickets, and cash have been used in the treatment of HIV and other chronic diseases. The effectiveness of using cash incentives to promote HIV testing, entry to care, and adherence to ART is currently being studied in the multi-site HPTN 065 trial. Other effective interventions include nurse home visits, a five-session group intervention, pager messaging, and couples or family-based interventions. To maintain high levels of adherence in some patients, it is critically important to provide substance abuse therapy and to strengthen social support. Directly observed therapy (DOT) has been effective in providing ART to active drug users²⁶ but not to patients in a general clinic population.²⁷

To determine whether additional adherence or retention interventions are warranted, assessments should be done at each clinical encounter and should be the responsibility of the entire health care team. Routine monitoring of HIV viral load, pharmacy records, and indicators that measure retention in care are useful to determine if more intense efforts are needed to improve adherence. Patients with a history of non-adherence to ART are at risk for poor adherence when re-starting therapy with the same or new drugs. Special attention should be given to identify and address any reason for previous poor adherence. Preferential use of ritonavir-boosted protease inhibitor-(PI/r)-based ART, which has a higher barrier to the development of resistance than

other treatment options, should be considered if poor adherence is predicted.

The critical elements of adherence go hand in hand with linkage-to-care and retention in care. A recently released guideline provides a number of strategies to improve entry and retention in care and adherence to therapy for HIV infected patients.⁵ As with adherence monitoring, research advances offer many options for systematic monitoring of retention in care that may be used in accordance with local resources and standards. The options include surveillance of visit adherence, gaps in care, and the number of visits during a specified period of time.²⁸

Conclusion

Adherence to ART is central to therapeutic success. Given the many available assessment strategies and interventions, the challenge for the treatment team is to select the techniques that best fit each patient and patient population, and, according to available resources, the treatment setting. In addition to maintaining high levels of medication adherence, attention to effective linkage to care, engagement in care, and retention in care is critical for successful treatment outcomes. To foster treatment success, there are interventions to support each step in the cascade of care, as well as guidance on systematic monitoring of each step in the cascade.⁵

Table 13. Strategies to Improve Adherence to Antiretroviral Therapy and Retention in Care
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Strategies	Examples
Use a multidisciplinary team approach. Provide an accessible, trustworthy health care team.	<ul style="list-style-type: none"> • Nonjudgmental providers, nurses, social workers, pharmacists, and medication managers
Strengthen early linkage to care and retention in care.	<ul style="list-style-type: none"> • Encourage healthcare team participation in linkage to and retention in care.
Assess patient readiness to start ART.	
Evaluate patient's knowledge about HIV disease, prevention and treatment and, on the basis of the assessment, provide HIV-related information.	<ul style="list-style-type: none"> • Considering the patient's current knowledge base, provide information about HIV, including the natural history of the disease, HIV viral load and CD4 count and expected clinical outcomes according to these parameters, and therapeutic and prevention consequences of non-adherence.
Identify facilitators, potential barriers to adherence, and necessary medication management skills before starting ART medication.	<ul style="list-style-type: none"> • Assess patient's cognitive competence and impairment. • Assess behavioral and psychosocial challenges including depression, mental illnesses, levels of social support, high levels of alcohol consumption and active substance use, non-disclosure of HIV serostatus and stigma. • Identify and address language and literacy barriers. • Assess beliefs, perceptions, and expectations about taking ART (e.g., impact on health, side effects, disclosure issues, consequences of non-adherence). • Ask about medication taking skills and foreseeable challenges with adherence (e.g., past difficulty keeping appointments, adverse effects from previous medications, issues managing other chronic medications, need for medication reminders and organizers). • Assess structural issues including unstable housing, lack of income, unpredictable daily schedule, lack of prescription drug coverage, lack of continuous access to medications.
Provide needed resources.	<ul style="list-style-type: none"> • Provide or refer for mental health and/or substance abuse treatment. • Provide resources to obtain prescription drug coverage, stable housing, social support, and income and food security.

Table 13. Strategies to Improve Adherence to Antiretroviral Therapy and Retention in Care
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Strategies	Examples
Involve the patient in ARV regimen selection.	<ul style="list-style-type: none"> • Review regimen potency, potential side effects, dosing frequency, pill burden, storage requirements, food requirements, and consequences of nonadherence. • Assess daily activities and tailor regimen to predictable and routine daily events. • Consider preferential use of PI/r-based ART if poor adherence is predicted. • Consider use of fixed-dose combination formulation. • Assess if cost/co-payment for drugs can affect access to medications and adherence.
Assess adherence at every clinic visit.	<ul style="list-style-type: none"> • Monitor viral load as a strong biologic measure of adherence. • Use a simple behavioral rating scale. • Employ a structured format that normalizes or assumes less-than-perfect adherence and minimizes socially desirable or “white coat adherence” responses. • Ensure that other members of the health care team also assess adherence.
Use positive reinforcement to foster adherence success.	<ul style="list-style-type: none"> • Inform patients of low or non-detectable levels of HIV viral load and increases in CD4 cell counts. • When needed, consider providing incentives and rewards for achieving high levels of adherence and treatment success.
Identify the type of and reasons for nonadherence.	<ul style="list-style-type: none"> • Failure to fill the prescription(s) • Failure to understand dosing instructions • Complexity of regimen (e.g., pill burden, size, dosing schedule, food requirements) • Pill aversion • Pill fatigue • Adverse effects • Inadequate understanding of drug resistance and its relationship to adherence • Cost-related issues • Depression, drug and alcohol use, homelessness, poverty • Stigma • Non-disclosure • Other potential barriers
Select from among available effective treatment adherence interventions.	<ul style="list-style-type: none"> • See http://www.cdc.gov/hiv/topics/research/prs/ma-good-evidence-interventions.htm. • Use adherence-related tools to complement education and counseling interventions (e.g., pill boxes, dose planners, reminder devices). • Use community resources to support adherence (e.g., visiting nurses, community workers, family, peer advocates). • Use patient prescription assistance programs. • Use motivational interviews.

Table 13. Strategies to Improve Adherence to Antiretroviral Therapy and Retention in Care

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Strategies	Examples
Systematically monitor retention in care.	<ul style="list-style-type: none"> • Record and follow up on missed visits.
On the basis of any problems identified through systematic monitoring, consider options to enhance retention in care given resources available.	<ul style="list-style-type: none"> • Provide outreach for those patients who drop out of care. • Use peer or paraprofessional treatment navigators. • Employ incentives to encourage clinic attendance or recognize positive clinical outcomes resulting from good adherence. • Arrange for directly observed therapy (if feasible).

Key to Acronyms: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; PI = protease inhibitor; PI/r = ritonavir-boosted protease inhibitor

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