

Strategies for Optimizing Adherence to Highly Active Antiretroviral Therapy: Lessons from Research and Clinical Practice

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Successful treatment of human immunodeficiency virus infection/acquired immunodeficiency syndrome (HIV/AIDS) with highly active antiretroviral therapy (HAART) requires that patients maintain nearly perfect adherence to the prescribed regimen. Suboptimal adherence to antiretroviral therapy is clearly the most common cause of virologic failure of HAART regimens. Given the critical role of adherence in successful antiretroviral therapy, it is essential that providers of care for patients with HIV infection have a strategy that proactively assists and supports their patients' efforts to adhere to medication regimens. This review endeavors to provide a clinically focused approach to optimizing adherence of patients to HAART.

The widespread use of highly active antiretroviral therapy (HAART) for the treatment of HIV/AIDS has led to dramatic decreases in HIV-related morbidity and mortality in the United States. However, the long-term effectiveness of HAART is dependent upon achieving maximum and durable suppression of HIV plasma virus load [1]. Unfortunately, it has become apparent that, in clinical practice, this therapeutic goal is achieved for as few as 40%–50% of patients [2, 3]. The primary reason for failure to achieve maximum suppression of virus load, particularly among patients receiving initial regimens, is suboptimal adherence to medications [4, 5].

As a result of the pivotal role that adherence plays in the success of HAART, a tremendous amount has been written emphasizing the importance of adherence and the potential consequences of nonadherence [6]. Furthermore, numerous recent studies have examined and documented the correlates and predictors of adherence. Persons living with HIV infection, as well as their care providers, are aware of the importance of adherence and are using a variety of strategies in an effort to

enhance adherence to HAART [7, 8]. However, there are no easy answers regarding how to optimize adherence to HAART in clinical practice. No single study has given us a simple strategy that will work for every patient. In contrast, the more we learn about adherence, the more clear it becomes that an individualized and flexible approach is essential. This review provides an overview of current knowledge regarding adherence to treatment for HIV infection, and it also outlines a strategy, which flows from this knowledge base, for optimizing patients' adherence to HAART.

HOW MUCH ADHERENCE IS ENOUGH?

Although it has been well known that higher levels of adherence correlate with greater suppression of virus load, until recently there was uncertainty about the amount of adherence that was necessary to achieve treatment success in most cases. Several recent studies have shown that >95% adherence is necessary to achieve therapeutic success (a nondetectable virus load) in >80% of treated patients [9, 10]. In this context, the percentage of adherence refers to the percentage of medication doses taken. One of these studies used the Medication Event Monitoring System (MEMS; Aprex), a relatively direct method of measuring medication adherence [9], in which a microprocessor in a special pill-bottle cap records the number of times that the pill bottle is opened. The decrease in the percentage of patients whose virus load becomes nondetectable in association with

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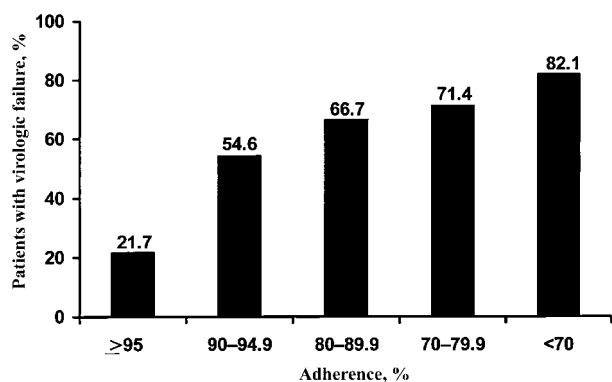


Figure 1. Adherence to antiretroviral therapy in relation to virologic failure (reproduced with permission from [9]).

decreases in adherence is quite steep (only 50% of those with adherence of 80%–90%) [9]. Conversely, this same study documented that the higher the percentage of adherence, the lower the likelihood of virologic failure, as shown in figure 1.

HOW MUCH ADHERENCE IS THE REALITY IN CLINICAL PRACTICE?

Previous research examining patient adherence to medications given for the treatment of other chronic illnesses, particularly hypertension, found that most patients take ~50% of their prescribed doses [11, 12]. One encouraging indication that the message about the importance of adhering to treatment for HIV infection has been heard is that average adherence to HAART is generally much higher than average adherence to treatment for other chronic diseases. In the aforementioned study by Paterson et al. [9], average adherence, as measured by MEMS, was 74.7%. A number of other studies have also found HAART adherence rates of 70%–80% [13–15]. Studies in which investigators have asked about doses missed in the recent past have generally found that ~20% of patients have missed a dose in the past day and that 30%–35% have missed a dose in the past 3 days [16, 17]. All of these results suggest that the average adherence to HAART is greater than the reported average adherence to treatment for other chronic illnesses.

Unfortunately, however, given what we know about the correlation between virologic suppression and adherence, these rates of adherence are still not high enough. In addition, most of these rates are brief cross-sectional measurements of HAART adherence and therefore provide limited information about longitudinal patterns of adherence. It is important to be aware of existing evidence that, for patients with HIV/AIDS, as well as for persons with other diseases, adherence to medication often decreases over time [8, 18, 19]. Patients may experience

“treatment fatigue,” lose their motivation, or simply become complacent.

It may also be instructive to be aware of patients’ reported reasons for missing their doses, since these reasons tend to be fairly consistent from study to study [16, 17]. Figure 2 shows the reasons why doses were missed, as reported by 248 patients with HIV/AIDS who were receiving care in Boston or Rhode Island. Nearly half of the patients reported that the most common reason for missing doses was that they forgot the dose, whereas others reported missing doses because of the side effects of the medication, because they were too busy, or because they did not have their medications on hand when the dose was due to be taken. Of course, patients’ actual reasons for missing doses may often be more complex than they appear. For example, forgetfulness is a product of both cognitive and motivational issues; thus, it cannot be assumed that reminders alone (focusing only on the cognitive aspect) will solve the “forgetfulness” problem. It is also important to be aware of another important reason for missed doses. Some patients report an ongoing, purposeful restructuring of their routines for taking medication, which is undertaken for a variety of reasons ranging from a strategy for reducing side effects to improving the fit between the medication regimen and their daily routine [19, 20].

MEASURING ADHERENCE TO HAART

It is important to use a specific method for measuring adherence to HAART in clinical practice. Ideally, such a measurement strategy should be easily incorporated into clinical care, inexpensive, and helpful in assessing whether adherence interventions are effective. Adherence to HAART can be measured by a variety of methods. The most commonly used methods are pill counts, review of pharmacy records, self-reporting, and use of such electronic medication-monitoring devices as MEMS.

No single method has been established as the “gold standard”

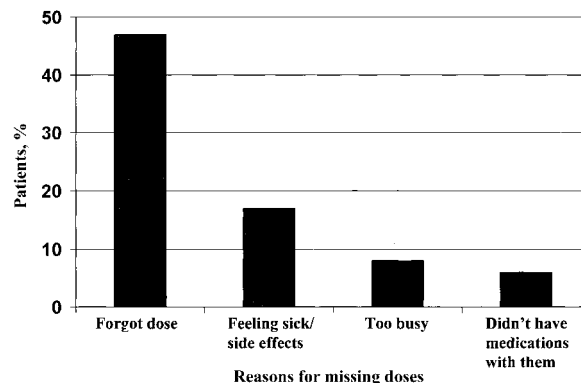


Figure 2. The most frequent reasons for missing doses of highly active antiretroviral therapy [17].

for measuring adherence. All methods have advantages as well as disadvantages. For example, MEMS are advantageous because of the detailed information they provide regarding the patient's pattern of taking medication, the percentage of doses taken, the accuracy of the timing of doses, and so forth. However, MEMS have several important disadvantages: they are quite expensive and thus can be used only on a limited basis or for a limited number of patients. Furthermore, MEMS may be disruptive to the medication-storage systems, such as pill organizers or other special containers, that patients have adopted. Finally, MEMS offer presumptive measures of adherence; removal of a cap does not necessarily mean that the medication in the pill bottle was ingested. In general, pill counts and reviews of pharmacy records are less than ideal, because they provide no information regarding the accuracy of the timing of doses taken and no evidence that the medication doses were actually taken. However, unannounced pill counts have been found to be an accurate measure of adherence, correlating well with such key outcomes as HIV RNA levels and AIDS-free survival [21, 22].

Although self-reporting has been found to overestimate adherence in comparison with adherence measurements made by MEMS [23], increased accuracy is associated with certain methods of assessing adherence by self-report. For example, in a study by Bangsberg et al. [21], structured patient reporting of adherence was strongly associated with adherence measured by unannounced pill counts and MEMS. Similarly, self-administered questionnaires have also been found to measure adherence accurately, on the basis of excellent correlation with virologic response [13]. These and other recent data suggest that it is reasonable to use patient self-reporting to monitor adherence routinely in the clinical setting. To optimize the accuracy of patient self-reports of adherence, (1) consider using a brief [4–6 item] self-administered questionnaire, a format which promotes patients' honesty and candor; (2) approach the subject in a nonjudgmental, matter-of-fact manner, acknowledging how difficult it is to take medication exactly as prescribed; (3) ask about the most recent past, specifically inquiring about the number of doses missed in the past day, 2 days, 3 days, and week; (4) use cues in the patients' daily routine to improve recall; (5) inquire about specific reasons why doses were missed; and (6) use this information to strategize and identify solutions to the adherence problems identified.

STRATEGIES FOR FACILITATING ADHERENCE TO HAART

What Is Known about the Effectiveness of Interventions to Improve Adherence?

In general, data regarding the effectiveness of interventions to improve adherence to HAART are limited, in part because

many such studies have been small (making generalization difficult) and also because many studies have just gotten under way and are currently collecting data. Two studies of "psychoeducational" interventions to improve adherence to HAART have been reported during the past year [24, 25]. In both studies, the patients who received the psychoeducational interventions demonstrated better adherence than did the patients in the control group. However, the study by Gifford et al. [25] showed that the effect of the educational intervention was not durable. This finding suggests that long-term or repetitive interventions may be required to produce a lasting impact on adherence. Studies of interventions to improve adherence of patients with other chronic diseases have also shown that interventions that are repetitive and multifaceted are most likely to result in improvements in adherence [26, 27].

Thus, there is a rationale for adherence strategies with multiple components, such as the strategies suggested in the sections that follow. Furthermore, the success of any adherence strategy will be enhanced by follow-up, reinforcement, and repetition. Many of the strategies suggested in the sections that follow have been evaluated and have been found to be effective in small studies, reports of which have been presented at scientific meetings but have yet to be published. For cases in which there is compelling and/or published data, this information is presented.

Relevance of Predictors of Adherence and Nonadherence to HAART

As a result of research done in the past 5 years, a great deal has been learned about the many factors that are associated with adherence or nonadherence to HAART. Because medication-taking is a complex behavior that has many determinants, the characteristics of the patient, the HAART regimen, the provider and system of care, and the patient-provider relationship all will influence this behavior. Certain factors in each of these domains have been found to be related to adherence and thus should be considered in the development of a comprehensive strategy for enhancing adherence to HAART. Predictors and correlates of adherence and nonadherence in each of these areas are reviewed here and are followed by recommendations for enhancing adherence within each domain that build upon the information presented.

Patient Characteristics and Adherence to HAART

Demographic characteristics of patients, including race/ethnicity, sex, age, and socioeconomic status, generally have not been found to be predictive of medication adherence [12]. Many recent studies of adherence to HAART have endeavored to determine whether there is a relationship between these patient characteristics and adherence to HAART. Overall, few, if any, demographic characteristics have been found to be consistently

predictive of either increased or decreased levels of adherence. Although several studies have reported lower adherence rates among blacks and women [28–30], the vast majority of studies have found no difference in adherence in relation to either race/ethnicity or sex. Age has not been found to have a consistent association with adherence [17, 28, 30]; in some studies, older patients have better adherence, but, in other studies, they have poorer adherence. However, it is not surprising that patients with higher levels of education have been reported to have better adherence to HAART, whereas those with lower education or limited literacy have poorer rates of adherence [31].

Although demographic characteristics remain inconclusively linked to adherence to HAART, several other factors have been consistently linked to poorer adherence. These factors that consistently predict nonadherence to HAART are heavy alcohol use, active injection drug use, and depression [9, 17, 28, 30, 32]. It should be noted that depression has been found to be among the strongest correlates of poor adherence to treatment for other medical illnesses as well [33]. In contrast to active injection drug users, former substance abusers appear to have rates of adherence to HAART that are similar to those of individuals with no history of substance abuse [19, 23].

The patient's social situation can have a tremendous impact on his or her ability to consistently access care and adhere to medication regimens. For those individuals whose lives are chaotic or who have unstable housing situations, adherence will be much more of a challenge and will frequently be suboptimal. Research by Bangsberg et al. [5, 21] has documented that adherence can be quite good among homeless or marginally housed individuals, so homelessness should not be seen as a reason for withholding HAART from a motivated patient. In addition, family members' support and knowledge of the patient's disease and treatment are critical to successful adherence; when a patient is hiding a diagnosis of HIV infection from loved ones while trying to take HAART, adherence suffers [20].

Patients' health beliefs and attitudes about their treatment for HIV infection have also been found to be predictive of adherence [8, 17, 28, 34]. Patients' perceptions that antiretrovirals are ineffective or harmful have been associated with poorer adherence [34]. In contrast, those who have positive perceptions of HAART tend to have better adherence [8, 17, 28]. The latter group includes those who report that the drug regimen works well with their schedules, those who perceive that HAART is effective, those who believe that protease inhibitors will extend their life, and those who have friends or peers who have had a positive experience with HAART.

Suggested patient-focused adherence strategies:

1. Screen all patients for depression prior to initiation of HAART; if depression is found, treat and stabilize depression before initiating HAART.

2. Screen patients for substance abuse and alcohol abuse, and encourage treatment. If a patient is unwilling to receive treatment for substance abuse but is committed to beginning HAART, use a variety of strategies to enhance his or her ability to successfully adhere to treatment. You may want to consider placing the patient either in a directly observed therapy (DOT) program, if available, or in a setting in which medications will be directly administered, such as a halfway house.

3. Do all that you can to assist in stabilizing the patient's living situation and social support system. Begin by establishing a clear understanding of his or her housing arrangement, the stability of that situation, and the patient's significant others. Collaborate with a case manager or social worker to effectively address these issues.

4. Assess the patient's beliefs and perceptions about HAART. Consider the use of a support group, peer educator, or "treatment buddy" if the patient has negative perceptions of HAART or does not believe that the medications will work.

5. Assess the patient's commitment and readiness for starting to receive HAART, and provide education and sufficient time to address any concerns. Be mindful that there rarely is a need to begin HAART urgently. Rather, it is usually more prudent to delay initiation of HAART until the patient is ready.

6. Get the patient involved in choosing and individualizing the regimen. Encourage the patient to help you choose a regimen that will be easy to incorporate into his or her daily routine.

7. When providing educational materials for patients, be mindful of their reading skills and primary language. Whenever possible, provide dosing schedules that maximize the use of pictures, especially photographs of the medications. Remember to ask about the patients' primary-language reading skills before giving materials in that language.

8. Structured individualized or group educational sessions about antiretrovirals, how they work, the importance of adherence, and strategies for adherence have been found to be effective in a number of studies and settings. These can be administered by a nurse, health educator, pharmacist, or other staff member, either on a one-on-one basis or in a group setting.

9. With the patient's help, identify a family member, friend, or partner who will assist with and help take responsibility for the patient's medication-taking and adherence. This will serve to enhance social support while enhancing adherence.

10. Focus on potentially modifiable patient factors in an effort to enhance the patients' likelihood of adherence. Never use personal characteristics that patients are unable to change (such as their race or the fact that they have young children at home) as a reason for withholding HAART. Instead, use

any such factors that cause concern as a reason to provide even more intensive adherence-related supports.

Medication Regimen Characteristics and Adherence to HAART

Research on treatment adherence among most patients with chronic diseases suggests that increased complexity of medication regimens is associated with decreased adherence [35]. In this context, regimen complexity refers to the number of doses taken per day, the number of pills per dose, the number of different medications taken, the presence of any food-dosing restrictions or requirements, and the presence of any special fluid-intake requirements. Clearly, HAART regimens can, at times, be extremely complex, involving many doses, many pills, and, often, one or more medications that cannot be taken with food. The complexity of HAART regimens sometimes requires patients to alter their eating and sleeping patterns and to change their daily routine. This level of lifestyle change and accommodation may ultimately result in frustration and treatment fatigue [8].

At least one recent study has documented that adherence is, in fact, poorer among those treated with more complex antiretroviral regimens [36]. In addition, a study examining virologic response to triple regimens in clinical trials found that a greater percentage of patients reached a nondetectable virus load when taking regimens that involved taking fewer pills per day [37], a finding that is most likely mediated by better adherence to regimens with a lower pill burden. On the basis of a recent survey of 550 HIV-infected individuals, it appears that total number of pills taken per day, dietary restrictions, and dosing frequency are all regimen characteristics that patients believe are likely to influence their adherence [38].

Side effects are another regimen characteristic that can be a major obstacle to adherence. Patients who are experiencing >2 side effects are less likely to adhere to their HAART regimen than are other patients [23]. A number of other investigators have also reported finding an association between the occurrence of side effects during treatment with HAART and decreased adherence to HAART [12, 16, 17].

Suggested regimen-focused adherence strategies:

1. Simplify the regimen as much as possible while incorporating the necessary potency. Focus on constructing regimens that involve fewer pills and fewer doses and that minimize food-dosing restrictions.
2. Individualize HAART regimens; work with each patient to choose a regimen that is tailored to his or her lifestyle and schedule. Avoid adopting a "one-regimen-fits-all" philosophy.
3. Choose regimens with fewer side effects. Whenever possible, avoid medications known to commonly cause extremely unpleasant side effects.

4. Proactively manage side effects. Let patients know what side effects may be experienced and how each side effect will be managed.

5. No matter how simple or complex the regimen is, make sure patients understand exactly how to take their medications. Confusion is a major cause of suboptimal adherence. Providing a dosing schedule with photographs of the medications can be very helpful in this regard. In addition, consider helping patients to correctly fill a medication organizer (e.g., 7-day pill box) with their new medications.

6. Be open to patients' requests to change their HAART regimen because of side effects.

Clinical Care Setting, the Patient-Provider Relationship, and Adherence to HAART

A good patient-provider relationship appears to be strongly associated with better adherence to HAART [8, 17, 39]. The quality of this relationship is generally measured in terms of the support, trust, and caring that the patient perceives. It has been found, in numerous studies, that outcomes are better for patients whose providers have greater experience caring for persons with HIV disease; most recently, it has been found that such patients also have better adherence to HAART [30]. This may be because the aforementioned providers are more likely to be actively working to enhance their patients' adherence. In a 1998 survey, providers who were highly experienced in caring for persons with HIV infection were more likely to have incorporated new activities into their practices in order to enhance their patients' adherence to HAART [7].

DOT has been used for decades as a successful strategy for ensuring adherence to tuberculosis treatment. Given the many commonalities between HIV disease and tuberculosis, and given the commonalities of their respective multidrug therapies [40], there is growing interest in the use of DOT as a programmatic strategy for enhancing adherence to antiretroviral therapy. The increasing availability of once-a-day HAART regimens has made the use of DOT for HIV infection appear more feasible now than ever before [41–43]. A number of HIV clinic programs have already developed DOT programs to enhance adherence, and many are studying the effectiveness of DOT among selected subsets of patients [44–46]. Most often, these programs have been targeted toward "special populations," such as injection drug users, persons in methadone maintenance programs or other special settings, homeless persons, prisoners, or persons with persistently poor adherence [44–46]. Some use a modified DOT strategy in which patients are observed taking a subset of their prescribed doses (usually one dose a day, 5 days a week) [44]. Several studies now document that DOT (and modified DOT) significantly improve patients' adherence to HAART [44–46].

Furthermore, a study by Fischl et al. [47] showed that those

who received their medications via DOT also had significantly better short- and long-term virologic responses to treatment, in comparison with those who self-administered the same medication regimen. Given these compelling data, it is likely that DOT will become more widely used for HIV infection during the next several years. Nonetheless, many important questions regarding the use of DOT for HIV infection—including the optimal duration of DOT, the most appropriate candidates, how to implement DOT yet respect a patient's autonomy, and its cost-effectiveness—need better answers before broad implementation occurs.

Suggested clinical care setting and provider-focused adherence strategies:

1. Develop a set of adherence-focused activities that are provided for each patient, including an assessment of readiness for HAART, education regarding importance of adherence and consequences of nonadherence, an individualized dosing-instruction sheet with photographs of medications, structured follow-up assessment of adherence, and problem-solving for adherence-related difficulties that are identified.
2. Give patients the time and opportunity to develop a warm, caring patient-provider relationship with you, even if they are not yet receiving HAART or do not feel ready to begin receiving HAART.
3. Consider referral to a DOT program for patients with special adherence challenges, such as active substance abuse or homelessness, who are committed to starting and continuing to receive HAART.
4. Try to make your clinical site as user-friendly as possible. Make sure it is easy for patients to call and obtain answers to their questions and to come in at short notice if problems develop.
5. Utilize a multidisciplinary care team, if possible, so that other providers, such as nurses, case managers, pharmacists, and peer counselors, will be available to coordinate some of the adherence-related activities. This also increases the likelihood that patients will find someone on the care team to whom they can comfortably relate and from whom they can get needed information about their medications.
6. Schedule intensive and frequent visits during the month after initiation of HAART. Focus on identifying and solving adherence problems and difficulties with medication tolerance. These visits can also be used to obtain early measures of adherence and to reinforce the correct dosing schedule.
7. Provide access to reminder devices, such as beepers, watches with alarms, or medication organizers (pill boxes) for patients who believe that they may benefit from their use. Remember to instruct patients in their use.
8. Keep assessing adherence at each visit and use each visit as an opportunity to discuss adherence with every patient.

Remember that treatment fatigue may develop after long periods of successful treatment with HAART. In light of this, it is wise to be vigilant and inquisitive regarding adherence throughout the course of your patients' HAART regimen.

SUMMARY

There is a broad array of strategies that providers can use to enhance their patients' adherence to HAART. It is important for each provider and HIV-focused practice to have an adherence strategy that consists of core interventions for all patients and optional components that are based on the needs of individual patients. Routinely intervening to enhance the adherence of all patients before problems develop will increase the likelihood of early treatment success for our patients who receive HAART.

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