For patients with HIV, strict adherence with antiretroviral therapy (ART) is critical in restoring immune function, reducing rates of drug resistance, and preventing progression of HIV to AIDS. Although adherence with highly active ART has generally improved over the years, it remains a challenge today with increasing life expectancy of the HIV population. This article defines the current state of adherence, with regard to assessment techniques, barriers, and counseling strategies. Although many formal adherence tracking methods are available (eg, electronic devices or medication event monitoring system caps, pharmacy records, and biologic markers), the most efficient method is simply asking the patient. Causes of nonadherence are multifactorial and commonly include mental illness, unstable housing, active substance abuse, low socioeconomic or education status, and major life crises. Other important factors that negatively affect adherence include adverse effects, increased duration of therapy, frequency of drug administration, dietary restrictions, and pill burden. Determinants of successful adherence with HIV therapy involve the program, the healthcare provider, the patient, and the regimen. Because the patient is ultimately the most important determinant of adherence, he or she should be properly evaluated for any one of the many issues that may prevent adherence and counseled intensively regarding medication schedules, dietary restrictions, and adverse effects.


THE ROLE OF THE PHARMACIST IN IMPROVING ADHERENCE TO HIV THERAPY

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The success of antiretroviral therapy (ART) is certainly evident, based on numerous studies highlighting the decreased incidence of progression from HIV to AIDS and a general improvement in survival among individuals with HIV. But in achieving these milestones, many patients will be initiating or have initiated therapy when asymptomatic and must be adherent to lifetime treatment in order to maximize their odds of sustained viral suppression and reduced rates of resistance. Considering the fact that the very success of ART has increased life expectancy for people living with HIV, medication adherence has become an even greater challenge in this current day.

To ensure continued improvement of clinical outcomes in HIV, clinicians must identify and develop methods to overcome the many barriers to adherence that are inherent to ART and the HIV population. As former Surgeon General Everett Koop, MD, stated, “drugs don’t work in patients who don’t take them.” Very few disease states does this statement apply to as much as it does to HIV.

ADHERENCE: IMPORTANCE AND ASSESSMENT STRATEGIES

At this point, the association between adherence and critical outcomes, such as restoration of immune function and reduced rates of resistance and transmission, is well documented. Likewise, the link between the lack of adherence and drug resistance is also well established. Suboptimal administration of antiretroviral agents allows HIV to replicate at an accelerated rate, selecting for viral mutations, which leads to drug resistance and therapeutic failure. Once resistance develops to one antiretroviral agent, extensive cross-resistance to other agents within the same class may develop rapidly, severely limiting therapy for adherent and nonadherent patients.

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Unfortunately, nonadherence is ubiquitous in medicine, with 50% of patients taking their medication (as prescribed) 80% of the time. Although antiretroviral medications are associated with a relatively higher rate of adherence (70%), compared with other medications such as antihypertensives (47%) and antistatics (54%), this rate still does not appear to be sufficient. Although the exact degree of adherence needed to ensure successful outcomes from ART is not fully known, one early study found that patients must take 95% of their doses to maintain drug levels that will achieve viral suppression, prevent drug resistance, and avert treatment failure. This study, which examined the correlation between different levels of adherence to unboosted protease inhibitors (PIs) and clinical outcomes, found that patients with an adherence rate of 95% or greater had a 22% incidence of virologic failure, fewer days in the hospital, and no opportunistic infections or deaths. Dropping the adherence rate to 80% or less raised the incidence of virologic failure to 80%. This demand for near-perfect adherence with HIV therapy is considerably higher than that required for other chronic diseases, such as hypertension, in which the very same adherence rate of 80% is considered sufficient to achieve therapeutic goals. The adherence rate that is required varies based on the type of regimen that is taken (ie, non-nucleoside reverse transcriptase inhibitor based, unboosted PI, or boosted PI). Although the 95% rate of adherence has been widely cited in HIV literature, it is somewhat dated because it mostly applies to unboosted PIs and is not reflective of today’s newer regimens, which likely require somewhat less stringent adherence rates. Also, adherence patterns, which may change over time, greatly impact the amount of adherence necessary to maintain viral control. Thus, although adherence remains the single most important determinant of virologic success, it may not be as exact as it used to be.

Currently, measurement of adherence with ART is imperfect and lacks established standards. Although patient self-reporting has been an unreliable predictor of adherence, a patient’s estimate of suboptimal adherence is a strong predictor and should be taken seriously. A healthcare professional’s assessment of a patient’s adherence is a notoriously poor predictor of actual adherence. In a study examining the rate of discordance between patient-reported and physician-estimated adherence with ART, investigators found that of the 111 studied patients, physicians did not correctly estimate patient-reported adherence to ART in more than 33% of patients. In another study, physicians and nurses predicted adherence incorrectly for 41% and 30% of patients with HIV, respectively. Due to this discrepancy, it is critical to have a systematic way of assessing and monitoring adherence among patients with HIV in place.

Many formal tracking methods are available, including electronic devices or medication event monitoring system caps (eg, MEMS or "smart" pill bottles with computer chips that record each opening); pill counts, pharmacy records, biologic markers, and drug assays. The latter are most useful when patients professing adherence are not responding well to therapy; however, low drug levels may also be the result of poor absorption or drug interactions. In examining pharmacy records, time-to-prescription-refills appears to be a valid measure of antiretroviral adherence, as evidenced by one study linking a viral load decrease of 0.12 log copies/mL for each 10% increase in time-to-refill.

Computer-assisted self-interviewing technology, which may improve disclosure of medication nonadherence by providing a neutral and seemingly private interview, is increasingly used to assess adherence, as well as to collect information on side effects and high-risk behaviors that might be missed in a less structured patient-clinician interaction. In one study, more than 50% of 110 patients who completed a computer program assessing their understanding of and adherence to HIV treatment made at least 1 error in reporting their medication regimen.

In clinical practice, the most efficient method to measure adherence is simply to ask the patient in a nonjudgmental way. Allowing patients to be open in their responses, inquiring about the most immediate past, and asking appropriate questions (eg, number of missed doses in the last 2 days, causes of missed doses, and regimens that are easiest to adhere to) are all useful in assessing adherence during patient interviews. To get the most reliable information, patients should be given permission to have missed doses. For example, one may ask, “Everyone misses doses some of the time; in the last 2 weeks, how many doses have you missed?” Past studies have found that when patients are approached in this type of a nonjudgmental way, the majority (80%) are truthful about their medication taking. Although the most frequent reasons offered for missing ART doses appear simple and obvi-
ous (eg, forgetting, feeling sick, or being too busy), the underlying causes are much more complex and encompassing.

**IDENTIFYING BARRIERS TO ADHERENCE**

Causes of nonadherence are multifactorial and commonly include mental illness (particularly untreated depression), unstable housing, active substance abuse, low socioeconomic or education status, major life crises, and other factors included in Table 1.\(^{12,19,20}\) One study found a direct correlation between the number of lifetime traumatic events, including physical and sexual abuse, and antiretroviral nonadherence.\(^{21}\) In examining a potential association between demographic characteristics and adherence, investigators have found that women, African Americans, Hispanics, younger adults, and those with higher CD4 counts reported lower rates of adherence.\(^{16}\) Although these factors have been linked with nonadherence, they are not reliable predictors of it. Likewise, a lack of past drug use or higher socioeconomic status does not predict optimal adherence.

Considering the many adverse effects associated with ART and the necessity for lifelong treatment, it is not surprising that many patients infected with HIV stop or reduce the dose of medication because of adverse effects.\(^{6}\) A study examining the types of reported side effects that are predictive of nonadherence found that nausea, anxiety, confusion, vision problems, anorexia, insomnia, taste perversion, and abnormal fat distribution were significantly associated with nonadherence.\(^{22}\) Another study found that those who experienced at least 1 severe medication-related symptom were more than twice as likely to report intentional nonadherence.\(^{23}\) Each additional symptom that required clinical action was associated with a 25% increase in the risk of intentional nonadherence.

Other important factors that negatively affect adherence include increased duration of therapy, frequency of drug administration, dietary restrictions, and pill burden.\(^{6,24}\) Researchers have found that twice-a-day versus 3-times-daily dosing frequency, taking more than 1 drug on an empty stomach, and increased medication complexity with less patient understanding are all associated with lower adherence.\(^{25-27}\) Regimen complexity and pill burden were actually the most common reasons for nonadherence when combination therapy was first introduced, but advances over the last several years, such as development of coformulated antiretroviral combinations pills with once-daily dosing, have dramatically simplified regimens. Many other measures, some of which are discussed below, have been researched and implemented in an effort to optimize adherence among patients with HIV.

**REMOVING BARRIERS TO ADHERENCE**

One working group of clinicians convened to evaluate the medical literature on HIV-related clinical outcomes and identified the following determinants of success in adherence with HIV therapy: the program, the healthcare provider, the patient, and the regimen.\(^{28}\) An effective HIV program should use an interdisciplinary approach; have accessible resources; exhibit cultural, educational, social, and linguistic sensitivity; and have standardized patient evaluation and commitment (written collaborative agreement). HIV programs should establish a trusting relationship with patients, commit to communication between visits, be flexible with visits, and have goal reinforcement by more than 2 team members. Healthcare providers involved in HIV care should have ample expertise and interpersonal characteristics that foster continued patient relationships and consistent interactions with patients and other providers. Building trust, maintaining confidentiality, being accessible, and using appropriate lay language are all helpful in establishing an effective and ongoing patient dialogue.\(^{29}\)

The patient is ultimately the most important deter-

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**Table 1. Patient Factors Predictive of Nonadherence**

- Active substance or alcohol abuse
  - Strongest predictor is cocaine use, less with alcohol and heroin
- Mental illness/depression
- Low functional literacy
- Young age
- Chaotic lifestyle or living situation
- Hiding HIV status
- Lack of trust with providers
- Lack of patient education/ability to identify medications
- Lack of reliable access to care or medications
- Adverse medication effects
ominant of adherence and should, therefore, be scrutinized for any one of the many issues that may prevent him or her from adhering to complex regimens. Evaluating environmental (access to transportation, food, and shelter), social (ties to family and friends), psychological (substance abuse and mental health), and personality (coping strategies and treatment beliefs) factors may offer some insight into the probability of adherence. If, for example, patients are marginally housed (or homeless), have little social support, or are depressed, they are less likely to comply with therapy. Linking these individuals with housing resources, support groups, and psychological services is sometimes the first step in HIV care. Early patient discussions should be focused on past experiences with taking medications, ability to cope with side effects, attitudes and cultural beliefs about “pills,” and trust in and beliefs about the medical system. Another critical step is assessing whether the patient is ready to make the lifelong commitment to therapy. Clinicians should be relatively assured that patients realize the value of therapy and will be able to take their medication despite cost and potential side effects. Because those who are educated about the risks, benefits, and rationale of complex treatments are more likely to adhere, all patients should be taught a body of HIV-specific knowledge before beginning therapy (Table 2).

Another major determinant of adherence is the regimen itself, which may be virologically effective yet too difficult to comply with. Simplicity of a regimen may be as important as antiviral potency, because virologically highly active regimens have been known to fail solely because they are too difficult to take correctly or are intolerable. Choosing the right regimen requires balancing antiretroviral potency with the immunologic, physiologic, and psychosocial characteristics of that individual. Some patients who work cannot take medication 3 times daily and many cannot tolerate diarrhea or nausea, even with treatment. Assessment of patient biases, daily routines, and support systems is, therefore, necessary before deciding on a specific regimen. Simplified regimens, with minimal number of pills and doses, are preferred and increasingly possible with availability of coformulated products containing 2 or 3 antiretroviral agents.

**Pharmacist Interventions**

For pharmacists working with patients with HIV, medication counseling is perhaps the most important intervention and is particularly critical during the first few months of therapy, when patients are adjusting to taking medication and potential side effects. When treatment-naïve patients are asked how they feel about starting ART, the most common response is fear and anxiety surrounding adverse effects. Therefore, ample counseling should be provided regarding management of potential side effects. Treatment for side effects should be included with the first prescription, in addition to instructions on appropriate response to side effects and when to contact the clinician (see article by Jennifer Cocohoba, PharmD, for more information on antiretroviral adverse effects).

When starting therapy, patients should be given a schedule of medications that includes brand, generic, and colloquial (eg, zidovudine/AZT) names, and shows which pills need to be taken at each time each day. Educational material should be tailored to patients’ appropriate literacy level and be available in

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**Table 2. Suggested Body of Knowledge that Patients Should Be Taught Before Beginning Antiretroviral Therapy**

- How HIV is transmitted
- How HIV replicates and weakens the immune system
- How immunosuppression is gauged by the degree of CD4+ cell depletion
- How the rate of disease progression can be gauged by the viral load and CD4+ cell count
- The effect of antiretroviral therapy on viral load, CD4+ cells, and therefore, disease progression and survival
- The common laboratory tests and their meaning
- The need to have laboratory tests done on time, and the time necessary to have the tests processed by laboratory
- The need for 100% medication adherence
- The fact that minor lapses in adherence can lead to emergence of drug resistance mutations that may cause the current regimen to fail and limit future treatment options
- That many medication adverse effects are time-limited and manageable
- What to do if a patient misses a dose or cannot access medication
- How to obtain medications if the pharmacy or the healthcare professional on call will not provide a refill

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their native language (if possible). Many tools are available to assist patients in becoming familiar with and adhering to dosing schedules, including pillboxes, printed schedules, various alarms (eg, pagers, timers, and watches), visual clues (eg, bottles and magnets), diaries, Internet, life-size color pictures of pills, and support (eg, family, friends, and clinic). One strategy used in familiarizing patients with medications and ensuring that they go home with proper dosages, involves having them fill a 7-day pillbox with actual medications before starting therapy.

Because the activity of antiretrovirals is based on drug levels above the minimum inhibitory concentration, around-the-clock dosing is required. Therefore, prescriptions ordered for once daily or twice daily should always be written and conveyed to the patient as every 24 hours or 12 hours, respectively. Antiretrovirals with longer half-lives (eg, boosted PIs, nevirapine, efavirenz, tenofovir, didanosine, and emtricitabine) provide a larger pharmacologic cushion and are, therefore, somewhat more “forgiving” regarding late doses or variations in absorption or metabolism.

Counseling on medication administration in relation to food is vital, because certain antiretrovirals require food for absorption in order to reach critical therapeutic concentrations, whereas others require empty stomach dosing or fluid requirements in order to minimize side effects. During this discussion, it is important to inquire about underlying conditions, such as heartburn, which precludes the use of certain antiretrovirals. Patients with lactose intolerance or fat aversion may have difficulty complying with regimens that require high-fat intake for absorption. In regard to drug accessibility, pharmacists can be helpful by making certain that the prescription quantity is appropriate, sufficient refills are provided, refill reminders are in place, and availability of various financial assistance programs are disclosed to patients. Because some pharmacies may only carry a portion of a given regimen, patients should be instructed not to pick up their medication until all components are available.

Counseling sessions should be focused on adherence early on in therapy, as well as later when patients’ adherence tends to wane (ie, pill fatigue). Patients should be asked open-ended questions, such as “are there times when you find it hard to take your medication?” More detailed inquiries about timing of doses, number of pills, and impediments to taking medications can follow. Patients should be encour-

aged to bring medications with them to counseling sessions, so that pillboxes may be checked for missed doses and prescription dates.

Because frequent and intensive follow-up allows clinicians to ascertain adherence and identify medication problems early on in therapy, it is critical in the HIV population. One report suggests that patients should be contacted within 24 to 48 hours of beginning therapy. If they are not taking medication correctly, experiencing significant side effects, or have not yet taken medication, they should be recontacted within 24 to 48 hours. Additional follow-up 5 to 14 days after starting a new regimen is recommended to reinforce adherence and manage adverse effects.

STRATEGIES FOR MANAGING SUBOPTIMAL ADHERENCE

For patients with identified risks of suboptimal adherence (eg, active substance abuse), temporary postponement of ART may be a viable option, if possible. Patients on therapy who develop new diagnoses (eg, severe depression) that significantly influence adherence may require temporary cessation of therapy, which may be more desirable than uncertain adherence. In the interim, appropriate referrals and prophylaxis therapy for opportunistic infections may be offered. One way of assuring adherence in problematic patients is to use directly observed therapy (DOT), in which a healthcare provider directly observes ingestion of medication. Although DOT is known to be successful in the management of tuberculosis in poorly complying patients, it is labor-intensive, expensive, and complex, especially in the context of lifelong HIV therapy. Modified DOT programs, in which only the weekday morning doses are observed, have been studied in various HIV populations (eg, pregnant women) with positive outcomes, but long-term adherence after completion of such programs has not been determined.

Adherence case management programs are another option for poorly compliant patients. Designed to be maintained over an extended period of time, these programs consist of intensive adherence education and collaborative multidisciplinary planning. One such program, which included weekly medication organization sessions using pillboxes (medi-sets) and monthly individualized adherence counseling, was shown to significantly improve medication adherence, as measured by pharmacy refill data and fewer hospitalizations.
CONCLUSIONS

The task of meticulously adhering to complex multidrug regimens for life is a daunting one for any individual. Unfortunately, asking anything less of patients with HIV will be in sacrifice of the many positive outcomes that have been achieved with ART. By helping physicians individualize regimens and manage side effects, and offering patients education and support, pharmacists can make it that much more feasible for patients with HIV to comply with their lifelong treatment.

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