

ADHERENCE TO POTENT ANTIRETROVIRAL THERAPY

The Panel recommends that certain persons living with HIV, including persons who are asymptomatic, should be treated with HAART for the rest of their lives.

Adherence to the regimen is essential for successful treatment and has been reported to increase sustained virologic control, which is critical in reducing HIV-related morbidity and mortality. Conversely, suboptimal adherence has been reported to decrease virologic control and has been associated with increased morbidity and mortality [1, 2]. Suboptimal adherence also leads to drug resistance, limiting the effectiveness of therapy [3]. The determinants, measurements, and interventions to improve adherence to HAART are insufficiently characterized and understood, and additional research regarding this topic is needed.

Adherence to Therapy During HIV-1 Disease

Adherence is a key determinant in the degree and duration of virologic suppression. Among studies reporting on the association between suboptimal adherence and virologic failure, nonadherence among patients on HAART was the strongest predictor for failure to achieve viral suppression below the level of detection [2, 3]. Other studies have reported that 90%–95% of doses must be taken for optimal suppression, with lesser degrees of adherence being associated with virologic failure [1, 4]. No conclusive evidence exists to show that the degree of adherence required varies with different classes of agents or different medications in the HAART regimen.

Suboptimal adherence is common. Surveys have determined that one third of patients missed doses within <3 days of the survey [5]. Reasons for missed doses were predictable and included forgetting, being too busy, being out of town, being asleep, being depressed, having adverse side effects, and being too ill [6]. One fifth of HIV-infected patients in one urban center never filled their prescriptions. Although homelessness can lead to suboptimal adherence, one program achieved a 70% adherence rate among homeless persons by using flexible clinic hours, accessible clinic staff, and incentives [7].

Predictors of inadequate adherence to HIV medications include

1. lack of trust between clinician and patient;
2. active drug and alcohol use;

3. active mental illness (e.g., depression);
4. lack of patient education and inability of patients to identify their medications [6], and
5. lack of reliable access to primary medical care or medication [8].

Other sources of instability influencing adherence include domestic violence and discrimination [8]. Medication side effects can also cause inadequate adherence as can fear of or experiencing metabolic and morphologic side effects of HAART [9].

Predictors of optimal adherence to HIV medications, and hence, optimal viral suppression, include

1. availability of emotional and practical life supports;
2. a patient's ability to fit medications into his or her daily routine;
3. understanding that suboptimal adherence leads to resistance;
4. recognizing that taking all medication doses is critical;
5. feeling comfortable taking medications in front of others [10]. and
6. keeping clinic appointments [11].

Measurement of adherence is imperfect and lacks established standards. Patient self-reporting is an unreliable predictor of adherence; however, a patient's estimate of suboptimal adherence is a strong predictor and should be strongly considered [10, 12]. A clinician's estimate of the likelihood of a patient's adherence is also an unreliable predictor [13]. Aids for measuring adherence (e.g., pill counts, pharmacy records, "smart" pill bottles with computer chips that record each opening [i.e., medication event monitoring systems or MEMS caps]) might be useful, although each aid requires comparison with patient self-reporting [12, 14]. Clinician and patient estimates of the degree of adherence have been reported to exceed measures that are based on MEMS caps. Because of its complexity and cost, MEMS caps technology might be used as an adjunct to adherence research, but it is not useful in clinical settings.

Self-reporting should include a short-term assessment of each dose that was taken during the recent past (e.g., <3 days) and a general inquiry regarding adherence since the last visit, with explicit attention to the circumstances of missed doses and possible measures to prevent further missed doses. Having patients bring their medications and medication diaries to clinic visits might be helpful also.

Approaching the Patient

Patient-related strategies

The first principle of patient-related strategies is to negotiate a treatment plan that the patient understands and to which he or she commits [15, 16]. Before writing the first prescription, clinicians should assess the patient's readiness to take medication, which might take two or three office visits and patience. Patient education should include the goals of therapy, including a review of expected outcomes that are based on baseline viral load and CD4⁺ T cell counts (e.g., MACS data from the Guidelines [4]), the reason for adherence, and the plan for and mechanics of adherence. Patients must understand that the first HAART regimen has the best chance for long-term success [17]. Clinicians and health teams should develop a plan for the specific regimen, including how medication timing relates to meals and daily routines. Centers have offered practice sessions and have used candy in place of pills to familiarize the patient with the rigors of HAART; however, no data exist to indicate if this exercise improves adherence. Daily or weekly pillboxes, timers with alarms, pagers, and other devices can be useful. Because medication side effects can affect treatment adherence, clinicians should inform patients in advance of possible side effects and when they are likely to occur. Treatment for side effects should be included with the first prescription, as well as instructions on appropriate response to side effects and when to contact the clinician. Low literacy is also associated with suboptimal adherence. Clinicians should assess a patient's literacy level before relying on written information, and they should tailor the adherence intervention for each patient. Visual aids and audio or video information sources can be useful for patients with low literacy [18].

Education of family and friends and their recruitment as participants in the adherence plan can be useful. Community interventions, including adherence support groups or the addition of adherence concerns to other support group agendas, can aid adherence. Community-based case managers and peer educators can assist with adherence education and strategies for each patient.

Temporary postponement of HAART initiation has been proposed for patients with identified risks for suboptimal adherence [19, 20]. For example, a patient with active substance abuse or mental illness might benefit from psychiatric treatment or treatment for chemical dependency before initiating HAART. During the 1–2 months needed for treatment of these conditions, appropriate HIV therapy might be limited

to OI prophylaxis, if indicated, and therapy for drug withdrawal, detoxification, or the underlying mental illness. In addition, readiness for HAART can be assessed and adherence education can be initiated during this period. Other sources of patient instability (e.g., homelessness) can be addressed during this time. Patients should be informed and in agreement with plans for future treatment and time-limited treatment deferral.

Selected factors (e.g., sex, race, low socioeconomic status or education level, and past drug use) are not reliable predictors of suboptimal adherence. Conversely, higher socioeconomic status and education level and a lack of past drug abuse do not predict optimal adherence [21]. No patient should automatically be excluded from antiretroviral therapy simply because he or she exhibits a behavior or characteristic judged by the clinician to indicate a likelihood of nonadherence.

Clinician and health team-related strategies

Trusting relationships among the patient, clinician, and health team are essential. Clinicians should commit to communication between clinic visits, ongoing adherence monitoring, and timely response to adverse events or interim illness. Interim management during clinician vacations or other absences must be clarified with the patient.

Optimal adherence requires full participation by the health-care team, with goal reinforcement by more than 2 team members. Supportive and nonjudgmental attitudes and behaviors will encourage patient honesty regarding adherence and problems. Improved adherence is associated with interventions that include pharmacist-based adherence clinics [21], street-level drop-in centers with medication storage and flexible hours for homeless persons [22], adolescent-specific training programs [23], and medication counseling and behavioral intervention [24]. For all health-care team members, specific training regarding HAART and adherence should be offered and updated periodically.

Monitoring can identify periods of inadequate adherence. Evidence indicates that adherence wanes as time progresses, even among patients whose adherence has been optimal, a phenomenon described as pill fatigue or treatment fatigue [19, 25]. Thus, monitoring adherence at every clinic encounter is essential. Reasonable responses to decreasing adherence include increasing the intensity of clinical follow-up, shortening the follow-up interval, and recruiting

additional health team members, depending on the problem [20]. Certain patients (e.g., chemically dependent patients, mentally retarded patients in the care of another person, children and adolescents, or patients in crisis) might require ongoing assistance from support team members from the outset.

New diagnoses or symptoms can influence adherence. For example, depression might require referral, management, and consideration of the short- and long-term impact on adherence. Cessation of all medications at the same time might be more desirable than uncertain adherence during a 2-month exacerbation of chronic depression.

Responses to adherence interventions among specific groups have not been well-studied. Evidence exists that programs designed specifically for adolescents, women and families, injection-drug users, and homeless persons increase the likelihood of medication adherence [21, 23, 26, 27]. The incorporation of adherence interventions into convenient primary care settings; training and deployment of peer educators, pharmacists, nurses, and other health-care personnel in adherence interventions; and monitoring of clinician and patient performance regarding adherence are beneficial adherence [22, 28, 29]. In the absence of data, a reasonable response is to address and monitor adherence during all HIV primary care encounters and incorporates adherence goals in all patient treatment plans and interventions. This might require the full use of a support team, including bilingual providers and peer educators for non-English-speaking populations, incorporation of adherence into support group agendas and community forums, and inclusion of adherence goals and interventions in the work of chemical-dependency counselors and programs.

Regimen-related strategies

Regimens should be simplified as much as possible by reducing the number of pills and therapy frequency and by minimizing drug interactions and side effects. For certain patients, problems with complex regimens are of lesser importance, but evidence supports simplified regimens with reduced pill numbers and dose frequencies [30, 31]. With the effective options for initial therapy noted in this report and the observed benefit of less frequent dosing, twice-daily dosing of HAART regimens is feasible for the majority of patients. Regimens should be chosen after review and discussion of specific food requirements and patient understanding of and agreement to such restrictions. Regimens requiring an empty stomach multiple times daily might be difficult for patients with a wasting disorder, just as regimens requiring high fat intake might be difficult for patients with lactose intolerance

or fat aversion. However, an increasing number of effective regimens do not have specific food requirements.

Directly observed therapy

Directly observed therapy (DOT), in which a health-care provider observes the ingestion of medication, has been successful in tuberculosis management, specifically among patients whose adherence has been suboptimal. DOT, however, is labor-intensive, expensive, intrusive, and programmatically complex to initiate and complete; and unlike tuberculosis, HIV requires lifelong therapy. Pilot programs have studied DOT among HIV patients with preliminary success. These programs have studied once-daily regimens among prison inmates, methadone program participants, and other patient cohorts with a record of repeated suboptimal adherence. Modified DOT programs have also been studied in which the morning dose is observed and evening and weekend doses were self-administered. The goal of these programs is to improve patient education and medication self-administration during a limited period (e.g., 3–6 months); however, the outcome of these programs, including long-term adherence after DOT completion, has not been determined [32–35].

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