



HRSACARE ACTION

PROVIDING HIV/AIDS CARE IN A CHANGING ENVIRONMENT

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Adherence and HIV/AIDS

People working in the HIV/AIDS services field have been first-hand witnesses to the incredible power of highly active antiretroviral therapy (HAART). When people living with HIV/AIDS (PLWH/A) are able to meet its challenging adherence requirements, HAART can be a nearly miraculous drug regimen that drastically reduces viral replication and damage to the immune system, and restores daily functioning and well-being.

But there is another part to the story: the challenge of adherence.

Adherence—Both Crucial and Elusive

It's not that patients with HIV/AIDS are adherence "slackers" or "underachievers." They adhere far better than the general population. One often-quoted 1960s study found that only 19 percent of patients in the general population could adhere to a 10-day course of antibiotics.¹ In recent studies, the average adherence rate to treatments for chronic illnesses was about 50 percent. That is far below the self-reported adherence rates of most patients on HAART, which is between 56 and 88 percent.² Unfortunately, even 88 percent is not enough over the long term.

In some studies, adherence of anything less than 95 percent has been linked to treatment failure.³ Adherence at lesser rates fosters development of virus mutations. Some research has found that the risk of developing resistance is highest with adherence in the 80 to 90 percent range.^{4,5} The possibility of quick development of a resistant virus is worrisome because it limits treatment options for the patient. So adherence is something at which patients, ideally, need to be almost flawless for most regimens. That's a hard standard to reach.

Efforts to support adherence are hampered by our present lack of knowledge about what variables predict adherence—and what helps sustain it over time. According to results from the SPNS Adherence Initiative, the only predictor of future adherence is past adherence. That's not encouraging news for patients who have faced adherence problems in the past or for organizations seeking to develop new adherence support models.⁶

Fewer Medications, Fewer Doses—But Is It Enough?

In one sense, adherence to HAART is easier than it ever has been, because today's regimens often have far fewer medications and doses than before. When HAART was introduced in the 1990s, regimens were infamous for their complexity. Consumers were faced with an extraordinary number of pills, most of which had their own dosing schedules and food intake requirements. Adherence required almost constant, around-the-clock attention. No single innovation or adherence support has improved adherence more than the ongoing reductions in medication and dosing requirements.

But challenges still exist. Many patients receive treatments for various other conditions, side effects, and comorbidities. Moreover, HAART still carries a long list of potential side effects, which include nausea, vomiting, diarrhea, exhaustion, lipodystrophy, bone marrow suppression, pancreatitis, and glucose intolerance.

Many other factors can stand in the way of high adherence:^{3,6,7,8,9}

- HAART can make people feel worse, not better

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- Mental illness (which often predates HIV infection) and its symptoms, such as time distortions that interfere with dosing; paranoia; and suspicion about providers
- Continuing or past substance use
- Lack of family and social support
- Comorbid conditions, such as diabetes or tuberculosis
- Patient concerns about the long-term toxic effects of HAART
- A lack of immediate symptoms related to HIV infection
- Poverty-related factors, including homelessness and lack of transportation to medical appointments
- Employment constraints, such as job routines that interfere with dosing requirements and fear of on-the-job disclosure of HIV status
- Lack of patient understanding of HIV illness, of the importance of adherence, and of the specifics of the HAART regimen
- Lack of health insurance or prescription drug coverage.

Adherence: What We Don't Know

Many HIV/AIDS service organizations are dedicating substantial resources to supporting adherence. Yet, their efforts are hampered because of pieces still missing from the adherence support puzzle. The bottom line is that we often know what can inhibit or support adherence, but we don't always know what will.

We don't know who will adhere, and who won't. When it comes to adherence, it may be tempting to believe that we can predict who will adhere to a HAART regimen and who won't. But we can't—and studies show that clinicians' ability to predict adherence is no better than chance. In fact, preliminary data noted in the British HIV Association's guidelines on provision of adherence support indicate that doctors *overestimate* adherence to HIV medications of patients currently on drug regimens.⁹ This tendency to overestimate is exacerbated when patients, out

of a desire to please clinicians, overreport adherence.⁸

Demographics don't predict adherence.

Studies on adherence show that it's impossible to predict, based on patient demographics such as age, gender, ethnicity, and socioeconomic status, which patients will achieve high adherence. There's just no correlation between demographic characteristics and patient adherence levels. Although many factors have been identified as barriers to adherence (including unstable housing, current active substance use of time-distorting binge drugs, depression, severe side effects, and a past history of nonadherence to an antiretroviral drug regimen), research so far reveals a few surprises for anyone who tries to confidently predict adherence.^{3,8} For example, substance abuse with drugs such as heroin (which must be taken at regular intervals) is *not* associated with poor adherence.⁶ Another example: We know from information

About the SPNS Adherence Initiative

The CARE Act Special Projects of National Significance (SPNS) Adherence Initiative assessed innovative interventions to increase adherence to HAART among underserved populations. The 4-year initiative, which ended in 2003, consisted of two components:

- Eleven adherence support programs serving people with HIV receiving HAART
- The Center for Adherence Support Evaluation (CASE) at the New York Academy of Medicine.

The 11 clinic-based programs deliver HIV medical care to underserved populations and have fully operational adherence support programs for their clients receiving HAART. The programs were selected to receive SPNS funding because their adherence interventions were considered innovative. The programs served a variety of populations, but all targeted uninsured or underinsured people with HIV who have difficulty accessing care. They used a range of different adherence interventions, but each program sought to improve the ability of their clients to successfully adhere to HAART.

For more information on the SPNS Adherence Initiative, including a list of journal articles associated with the project, go to www.hab.hrsa.gov/special/spns-adherence.htm.

gathered from the treatment of tuberculosis patients that mental health problems are not always insurmountable impediments to high adherence.⁹

We don't know how to make sure that currently adherent patients will remain adherent. As clinical experience and research indicate, adherence is a "moving target": The longer a patient has been on a HAART regimen, the poorer his or her adherence is likely to be. Adherence significantly drops off at the 6-month and 1-year marks.⁷ This finding reinforces that adherence support needs to be ongoing and offered at key points in time.

We have no way to screen out patients who won't benefit from adherence support in order to concentrate on those who will. Studying adherence, especially in the clinical setting, is a messy science—one that for HAART regimens is still in the early stages. What we do know so far is that adherence is a sometimes baffling composite of more things than we can easily measure. It is idiosyncratic and varies widely at the individual level. Thus, until we know which patients will benefit from adherence support and which won't, we need to offer all patients at least some level of adherence support services on a regular basis.⁸ Of course, because previous good adherence is a predictor of future good adherence, people who have been able to adhere to drug regimens in the past might not need as much adherence support. But the fact is that we don't know—and many variables other than past adherence alone are at play. Therefore, it is critical to monitor adherence for all

clients—and to periodically assess whether adherence support is needed.

There is no "silver bullet." Discouragingly, no study so far has identified an intervention strategy that has shown, on its own, more than a modest effect in promoting adherence. And even those modest effects wane significantly over time.⁷ Just as a variety of factors contribute to nonadherence, so may a variety of factors need to be put in play to encourage high adherence in any given patient. The right approach may turn out to be "both/and" (multiple targeted interventions) rather than "either/or" (a single highly effective strategy for each patient or patient population).⁸

Adherence Interventions: Are They Worth the Costs?

The answer is an unequivocal yes.

The SPNS Adherence Initiative evaluators collected data from initiative grantees on the direct costs of adherence support. Using the average duration of each type of adherence intervention encounter (e.g., counseling, pillbox assembly and distribution) and the national wage rates (as determined by the Bureau of Labor Statistics) for the personnel involved in each encounter, researchers at the New York Academy of Medicine estimated the direct costs of adherence supports.¹¹

Among all interventions, the median number of adherence encounters per year was 16.5 per patient (the low was 4.3 and the high was 104.6); median encounter time was about 25 minutes. The median direct cost per month was

\$35 per patient; for every dollar spent, \$0.66 went to provider costs; \$0.17 paid for incentives; \$0.08 was spent on reminders and other tools; and the remaining \$0.09 was spent on direct administrative time, provider transportation, training, and home delivery. A generally accepted cost-effectiveness threshold for moderately effective adherence interventions is \$100 per month or less; the interventions in the SPNS initiative are well within that limit.

Supporting Adherence: What We Can Do

Location matters—and it matters a lot. Adherence support appears to work best when offered in the clinical setting. A New York AIDS Institute study found that adherence support is most successful when offered in a clinical care setting, through the clinical care team. In fact, the study determined that the single strongest and most consistent variable affecting adherence was the setting in which support is offered.⁶

Why does adherence support seem to be more effective in a medical rather than a social service setting? The SPNS Adherence Initiative grantees found that a medical care setting helps staff identify and address patient problems with adherence quickly and effectively, because it allows easy contact and case conferencing among various members of the clinical staff. More important, medical care settings have more tools for managing side effects than nonclinical settings do. Clinicians can quickly adjust regimens to fit a client's lifestyle or address other problems such as side effects. When patients' regimens can be

continually adjusted to be more effective and workable, the chance of adherence success has been found to increase. As a result, doctors, AIDS nurses, and other clinical care staff seem best situated to offer adherence support.

What adherence-enhancing tools are available? Evaluation of SPNS Adherence Initiative interventions indicates that several techniques and tools can have at least some effect on adherence:^{3,6}

- Pharmacist- or nurse-provided education and counseling
- Peer counseling and support
- Reminder devices (such as beepers and phone calls)
- Medication pickup (in which the patient comes to the clinical setting to get his or her medications)
- Readiness training (educating the patient about the HAART regimen, purpose, and side effects and perhaps doing a “dry run” with placebos).

Other studies have shown that other interventions can be somewhat helpful:^{6,7,8}

- Directly observed therapy (DOT), in which a health care worker watches the patient take the medications
- Cued-dose timing (in which the patient learns to take his or her doses around daily events, such as mealtimes)
- Electronic reminders, including Internet pagers and programmed wrist watches
- Cash incentives
- Timelines (which involve a nurse or other health care employee sitting down with the patient and creating a daily timeline on which dosing times are marked)
- Pillboxes set up by a clinician.

Each of the adherence strategies listed above has specific limitations. For example, timed reminders are helpful only if the patient misses doses because he or she is actually forgetting them—but if harsh side effects are the real reason a patient shrinks from taking medications, no system centered on reminders is going to succeed.⁶ Another example: DOT works well in controlled settings such as drug rehabilitation facilities or prisons, but its effectiveness immediately ceases once the observation ends.⁶ And DOT is labor intensive, especially when health care professionals must go out into the field to perform it.

Involving service providers or peer counselors outside the clinical care setting is a valuable but limited option. For example, although the SPNS initiative and at least one other study have found that pharmacist-provided education and counseling can be helpful,^{6,7,12} pharmacists cannot directly address many adherence-related barriers. The value of peer support as a primary adherence strategy is also questionable. Some early studies reported success using peers in adherence support programs,⁷ but SPNS found that results from peer programs are not sustained over time: Participants tend to revert to baseline adherence at the 3- to 6-month point.⁶

How Clinicians Can Help

HIV/AIDS care providers know more about barriers to HAART adherence than anyone, and they have responded by trying adherence intervention strategies of all kinds. Yet, as fast as our knowledge about HIV-related adherence is growing,

it's still far from creating a definitive primer on how doctors can help patients win their adherence battles. But some encouraging evidence points to ways in which clinician attitudes and strategies can encourage adherence.

The patient-provider relationship is vital.

For chronic diseases such as HIV, the patient-provider relationship has been shown to be particularly important.¹³ In one study, patients' levels of satisfaction with their medical care correlated with higher adherence to drug regimens;¹⁴ so did patients' perception of their provider as warm and caring.¹⁵ Experts also say that the chances of adherence increase when patients feel that they and the provider are a team that has the shared goals of promoting health and controlling disease (i.e., the “therapeutic alliance”).^{9,16} Clinicians can begin to build a therapeutic alliance by:

- Involving the patient in decision making and regimen selection
- Developing an agreement with the patient about the rights and responsibilities the provider and the patient each will have during ongoing treatment
- Working with the patient to find reasons to adhere that are meaningful to *that particular patient*
- Refraining from using a punitive or lecturing tone when discussing adherence with patients. The literature shows that this approach can be counterproductive because patients resent being “graded” or “punished.”⁸

Readiness: an intervention, not an assessment. The SPNS initiative found a small but real benefit to

Adherence Measurement Tools Are Sometimes Blunt Instruments.

Adherence support is complicated by the fact that tools for measuring adherence—self-reporting, pill counts, blood tests for viral load and ARV plasma levels, and MEMS (Medical Event Monitoring Systems) caps—are only rough instruments at best. An example: If a patient's blood test doesn't show HIV viral load reduction, that doesn't necessarily mean the patient hasn't been adhering, because nonadherence is just one of several possible causes for virologic failure.⁶

Self-reporting has shown some accuracy, but it is clouded by factors such as patients' desire to please the health care provider and difficulty in recalling missed doses. Research shows that patients tend to overreport adherence.^{18,19} (Self-reporting of missed doses within a recent time framework, however, *has* been shown to correlate with viral load levels and is a useful tool.)^{20,21} Pill counts are sometimes thwarted by the fact that patients can easily dump pills. Pharmacy record monitoring is tangled in privacy restrictions and complicated by patients' use of multiple pharmacies for refills. Blood or urine tests that indicate either the presence of a medication or of a marker added to the medication are only snapshots. They can measure only whether the patient took his or her most recent dose, and they don't necessarily say anything about the patient's adherence levels over a long period. Some studies have shown some reliability for measuring plasma protease inhibitor markers in conjunction with composite scores from self-administered questionnaires.^{22,23} Electronic monitoring devices such as MEMS caps can be expensive, don't work with blister packs, and record only the opening and closing of a medication container—an inaccurate measurement for patients who decant an entire day's or week's supply of pills at one time.

Here's another complication in measuring true adherence to complex HAART regimens: the challenge of figuring out whether patients are taking doses within prescribed time limits and while following dietary restrictions. A 1999 study of the first 2 months of HAART treatment found that even within a subgroup of patients who took more than 90 percent of doses, the *timing* of dosing fluctuated in 50 percent of the patients. Dosing fluctuations ranged from taking the medications within 2 hours of the prescribed dose time to in excess of 2 hours of the prescribed time.²⁴

In short, no gold standard exists for measuring adherence. In the years to come, however, it's possible that more precise measurement tools can be designed to assist doctors in targeting adherence support strategies.

readiness programs for patients about to go on HAART.⁶ The initiative defined readiness as a series of specific steps designed to prepare clients for the daily realities of adhering to HAART. An effective readiness program requires that doctors or health care staff:

- Assess the patient's current mental and physical health, support system, and possible barriers to success on HAART
- Educate the patient about how HAART works, the importance of adherence, and the possible consequences of nonadherence (including the risk for failure with subsequent medications or of developing resistance to entire drug classes)
- Familiarize the patient with the lab values and other techniques that will be used to measure the regimen's success
- Prepare the patient for possible side effects in advance (this builds trust and helps "inoculate" patients who might be otherwise be discouraged by unexpected side effects)
- Give the patient ways to quickly access information about and treatment for side effects, both during and outside office hours
- As one option, carry out a mock trial in which the patient tries to follow a HAART regimen using placebos instead of the actual medications (the British HIV Association recommends that patients should actually see the medications they will be taking).

Ongoing adherence support is crucial. Adherence is both the challenge of a lifetime and a challenge for a lifetime. Research shows that patients who attain

high levels of adherence early in treatment may not maintain it over time in the face of pill fatigue, failure of a specific regimen despite high adherence, severe side effects, and other setbacks. Whether the patient is treatment naïve or treatment experienced, the chance that he or she will remain adherent diminishes over time.^{7,8}

Add to this reality the fact that numerous randomized controlled trials have shown that one-time interventions don't have a lasting benefit.⁸ Then factor in the snag that patients may tell physicians that they understand the ins and outs of their regimen even when that's not the case. (One study found that 13 percent of study participants were not taking their HAART medication correctly but *believed*

that they were.)¹⁷ It's clear that providers need to do "adherence check-ups" and offer ongoing adherence support to *all* patients (even those they think of as high adherers), especially at key points: at treatment start-up, when regimens are changed or adjusted, and when viral loads rebound.

Clinicians need to aggressively treat side effects before discouragement or distrust sets in. In study after study (as any clinician would guess), side effects emerge as a primary reason patients stop taking their HAART medication.^{3,8,9} Thus, it's vital to aggressively and promptly treat side effects. Medical advice and treatments for side effects (such as antiemetics for drugs

that commonly cause vomiting) should be easily available to patients both during and outside office hours. Also, managing side effects will be easier for patients if, as said earlier, they know the possible side effects in advance and have been coached in how to deal with them.

Where Do We Go From Here?

Since the advent of HAART, adherence has received considerable attention from the CARE Act community. Today, CARE Act funded grantees and providers are supporting adherence among their clients in many ways. Complementing local efforts are projects such as the SPNS Adherence Initiative and the training activities supported by the CARE Act

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Adherence: Provider ABCs

- A. Don't guess who can adhere.** Research shows that clinicians' ability to predict adherence carries exactly the same odds as random chance. Study after study of chronic illnesses and of HIV proves that demographics such as age, gender, ethnicity, and socioeconomic status won't tell us who can adhere and who can't. The only somewhat reliable indicator of a patient's future adherence is his or her current and past adherence—and even that data can't predict adherence at the individual, idiosyncratic patient level.
- B. Adherence support should involve everyone on your clinical care team.** Even in the best circumstances, clinicians' time with patients is limited. Thus, adherence support must become something that your entire clinical care team provides. It's helpful for your office to have a written adherence support strategy to help all employees understand their roles. For example, patient adherence counseling and education can be provided effectively by nurses. Physician assistants can also be helpful in this area. Staff should be aware that patient inquiries regarding side effects and dosing need prompt responses, and your practice should have a system in place whereby patients can quickly access advice and treatment for side effects, both during and outside office hours. Prompt referrals for treating comorbid conditions should be provided. Finally, it's important for the clinical staff to identify and improve strategies for working in tandem with case managers, social workers, pharmacists, and mental health professionals to solve patients' adherence problems.
- C. Offer adherence support to every patient, even those you think don't need it.** A "good adherer" can become a "poor adherer" over time as a result of pill fatigue, discouragement over regimen failure, or persistent or emerging side effects. And a patient who seems unlikely to adhere might surprise you—for example, he or she might stop drinking and find a new determination to adhere, or the emergence of symptoms might be a wake-up call. Because any patient, given specific circumstances, can demonstrate low or high adherence, adherence support should be offered to all patients at every point in the HAART process.

AIDS Education and Training Centers (AETCs). The regional AETCs have incorporated adherence into their curricula, and they provide course participants with a variety of informational, training, and support materials on the topic. In addition, the AETC National Resource Center provides guidelines, articles, and other publications that can help clinicians better address adherence. These range from training modules such as *Behavior Management in Clinical HIV Care: Part I-Treatment Adherence*²⁵ to treatment guidelines published by the U.S. Department of Health and Human Services and the HIV Medicine Association of the Infectious Diseases Society of America. Readers are urged to visit the resource center at www.aids-etc.org/ for a complete review of available materials.

But much work remains to be done. Because the study of adherence to HIV medications is still in its early days, it often raises more questions than it answers. It's a given that further study is needed to evaluate specific adherence interventions: how well they work; how long their effects last; and which strategies work best on specific populations such as children, pregnant women, and substance abusers. Experts also suggest that medical professionals may find it useful to have access to specific professional development programs on adherence. And all HIV/AIDS clinicians need model adherence strategies that address the practical issues that separate people living with HIV/AIDS from the power of HAART.



The Three Questions: Adherence Self-Reporting Made Easier

The SPNS Adherence Initiative included an in-depth analysis of different adherence measures used at 11 clinical sites. Measures examined in the study were missed dose in past 3 days, self-reported adherence, and viral load. The SPNS study found that an index based on a score of three simple questions was as good a predictor of undetectable viral load as—or better than—a longer self-report measure commonly in use.

The SPNS self-report questions are as follows:

(circle the number that corresponds with your answer to each question and add together to get score)

1. How often do you feel that you have difficulty taking your HIV medications on time? By "on time" we mean no more than 2 hours before or 2 hours after the time your doctor told you to take it.

1. All of the time
2. Most of the time
3. Rarely
4. Never

2. On average, how many days PER WEEK would you say that you missed at least one dose of your HIV medications?

1. Every day
2. 4 to 6 days/week
3. 2 or 3 days/week
4. Once a week
5. Less than once a week
6. Never

3. When was the last time you missed at least one dose of your HIV medications?

1. Within the past week
2. 1 to 2 weeks ago
3. 3 to 4 weeks ago
4. Between 1 and 3 months ago
5. More than 3 months ago
6. Never

Scoring

- >10 equals good adherence
- <10 = poor adherence

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