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Why is treatment adherence an important issue?

New antiretroviral therapies (ART) for HIV/AIDS have improved and lengthened the lives of thousands of people fighting the disease. The results have been dramatic, reducing and often eliminating measurable HIV viral load in patients.

Unfortunately, not all HIV patients on these therapies have experienced such lasting treatment benefits. There are several reasons for treatment failure, including individual characteristics (such as gastrointestinal conditions) that interfere with response to the medications, dosing errors by physicians, existing resistance to a medication, or inability to adhere to the treatment regimen. Of these, adherence is the most amenable to change, so efforts to address treatment failure often emphasize improved adherence.

Adherence has both personal and public health implications in the HIV epidemic. Clinicians have determined that adherence to HIV drug regimens is critical for the effectiveness of treatment. There is growing evidence that failure to strictly follow drug regimens may not only compromise the effectiveness of an individual's AIDS therapy, but also leads to development of drug-resistant strains of HIV.

Treatment failure may occur rapidly with poor adherence. Some studies suggest that drug resistance can develop after one week of missed medication or irregular use, or after missing as little as one dose in five. When resistance to a drug develops, it loses its effectiveness forever; in some cases, cross-resistance to other drugs occurs, further limiting treatment options.

Challenges to adherence

Though adherence is an important factor in treatment, it poses significant challenges to many people living with HIV. Newer treatment regimens often include reductions in the frequency of medication dosing, but HIV treatment still frequently requires multiple pills taken at

different times of the day. Many HIV medications also have special requirements, such as being taken with or without meals, and many have significant side effects, including nausea, diarrhea, and headaches. When these new therapies were first introduced, side effects were tolerated as a "cost" of survival. However, as patients have returned to more active lifestyles and as time has worn on, these side effects have increasingly been cited as a cause of intentional non-adherence.

Many people with HIV also have other complicating factors in their lives, including health concerns, economic worries, and difficulties finding safe and affordable housing. Earlier research on adherence to treatment regimens for conditions other than HIV has found an association between poor adherence and the complexity of drug regimens, the number of different medications included in the regimen, and the extent to which the regimen interferes with the patient's daily life. All of these difficulties are present with medications for HIV.

Data on adherence to HIV treatment medications

Studies on AIDS drug adherence completed before the era of combination therapy indicated that significant numbers of HIV patients were not adhering to treatment regimens. Estimates of successful adherence ranged from 42% during the previous month to 67% during the past week.

Several newer studies indicate continued poor rates of treatment adherence among patients using combination therapy for HIV. UCSF's Dr. Steven Deeks and colleagues conducted a chart review of viral load data on clients at the Outpatient AIDS Clinic of San Francisco General Hospital.¹ All patients had been on combination therapy for at least 24 weeks. Deeks found that only 47% of the patients met criteria for "treatment success," meaning undetectable levels of viral load. Fifty-three percent (53%) of the clients had evidence of ongoing viral replication (detectable virus in the blood). The researchers found that non-adher-

ence or dose reduction (as noted in medical records) was the most significant predictor of viral replication.

A second adherence study was reported by UCSF's Chesney and colleagues from the Recruitment, Adherence and Retention, and Patient Care committees of the Adult AIDS Clinical Trials Group (AACTG).² A self-report questionnaire was pilot tested with 75 patients on

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combination therapy who were recruited from ten different AACTG sites around the United States. The survey instrument asked patients to report the number of doses of his/her medication that were missed over the past several days. The survey found that slightly more than 10% of the sample missed at least one dose "yesterday," and that almost 20% had missed at least one dose during the past two days. Over a third of participants (36%) said they had missed at least one dose during the past two weeks.

Another UCSF study conducted at the AIDS Clinic at San Francisco General Hospital³ looked at the association between non-adherence and detectable viremia. In a self-report instrument similar to that used in the AACTG, slightly more than 10% of patients said they had missed at least one dose of their medications the previous day, and approximately one-third acknowledged missing at least one dose over the previous three days. The study found a "highly significant" association between self-report of missed doses and detectable viremia. Other studies have confirmed the association between missed doses and higher levels of detectable virus.^{4,5}

Although several factors make exact measurement of adherence difficult, the body of evidence available indicates that at least 10% of patients on protease inhibitors (one class of antiretroviral drugs) miss a dose each day and at least 20% miss at least one dose over two days. These rates are even higher when the definition of adherence is expanded to include following special instructions for taking medications. One phone survey of individuals being treated for HIV with combination therapy found that 26% reported being non-adherent with dosing or instructions on the previous day.

Factors related to adherence

In studies of HIV treatment prior to combination therapy, patients were most likely to adhere to treatment regimens if they held knowledge or beliefs affirming the efficacy of antiretroviral medications. Patients whose family or friends supported treatment and those who believed they needed treatment were also more likely to follow their treatment regimens.

The UCSF (AACTG and San Francisco General Hospital) studies noted above identified similar reasons for patients missing or skipping doses of combination therapy. The most common reason was simply "forgetting." Second was being engaged with other activities and being away from home or too busy. The third most commonly reported reason was side effects or feeling ill. Depressed mood and related negative affect was the fourth most common reason for poor adherence. Depression, stress, and negative moods have been associated with non-adherence with therapy for many diseases. The AACTG study found that alcohol consumption and "working outside the home" were also both associated with non-adherence.

Adherence literature in general does not find an association between adherence and demographic characteristics. Evidence on adherence rates among "marginalized" populations such as substance users and the poor has been mixed, with some studies finding these populations can effectively adhere to treatment regimens. There is also evidence that adherence among marginally housed and homeless populations with past or current drug and alcohol use is not markedly different from that of other groups of HIV-positive individuals. Indeed, several innovative programs report remarkable success in facilitating treatment adherence with a range of supportive services.

Issues in studying adherence

Adherence is an important area for study, but accurate measurement of adherence presents challenges to researchers. Several measurement strategies exist, including pill counts, electronic monitors on medication dispensers, patient diaries, and interviewer-administered or self-report questionnaires. Each approach has limitations. For example, self-report surveys tend to overestimate adherence. Electronic monitors that record when pill bottles are

opened may underestimate adherence since patients may remove more than one dose at a time.

The UCSF research team, in the AACTG study¹ noted above, piloted two survey instruments. The “Adherence to Antiretroviral Medications” questionnaire requested information on patients’ medications and their adherence to the regimen. The “Baseline Correlates of Adherence” questionnaire asked for information deemed important for pinpointing potential predictors of adherence, including alcohol consumption, self-efficacy to use the medications, and psychological distress. The focus of the questions was on recent adherence, in order to maximize recall and minimize bias.

The pilot study found that the questionnaires each took an average of about ten minutes to complete, a length of time that nine out of ten patients reported was “satisfactory.” Four out of ten patients reported they found questions that were especially important to them or helped them reflect upon important issues. These findings suggest that while self-report instruments may tend to overestimate adherence, they may be helpful tools for the clinical setting. In particular, when a patient reports missed doses, it is reliable information.²

Interventions to improve adherence

Surveys of persons being treated for HIV have found that they emphasize difficulties of integrating medications into their daily lives, rather than the number of pills or dosing schedules, as the major challenge to adherence. Non-adherence to HIV drug regimens should be viewed as a multifaceted problem most effectively addressed with multi-component programs.

With that multifaceted approach in mind, the Center for AIDS Prevention Studies at UCSF developed and implemented the Partnership in AIDS Clinical Trials (PACT) program as a demonstration project to study and model treatment adherence supports. PACT provided patients enrolled in clinical trials with trained facilitators who met individually with patients in person or on the phone. Sessions focused on 1) clarifying the patient’s drug regimen, 2) developing an individualized plan for integrating the regimen into daily life, 3) self-monitoring of adherence, 4) enhancing communication with

treatment staff, and 5) problem solving around episodes of non-adherence.³

Another UCSF demonstration project is Action Point, a storefront drop-in HIV medication adherence program funded by the San Francisco Department of Public Health. The program targets homeless and marginally housed individuals with HIV and operates on the ground floor of a single room occupancy hotel. Action Point offers several kinds of support services, including adherence case management, assistance with accessing a primary care physician, and receipt and dispensing of prescriptions. A \$10 cash incentive is given weekly to clients using the service at least once a week. Clients who have been enrolled in the program for more than one month are also offered a pager that reminds them to take their medications. An assessment of the first five months of Action Point’s operation shows promising results: 76% of clients on ART had improved viral suppression relative to pre-program levels.⁴

Other HIV care clinics are providing services from nurses, social workers, or other health professionals that include sorting pills into daily pill boxes, doing pill counts to help avoid missed doses, and offering telephone-based adherence counseling and support.

Growing availability of HIV treatments in developing countries means that expanded adherence assistance services in these countries is also critically important. Health authorities in developing countries should adapt clinical treatment guidelines, disseminate information on antiretroviral therapies to the public, health professionals, and policy makers, and train medical personnel in the correct use of HIV medications and in culturally appropriate strategies for enhancing adherence.

Reasons patients missed taking medications Adult AIDS Clinical Trials Group (AACTG) Study

	%
Simply forgot	66
Away from home	57
Busy with other things	53
Had a change in daily routine	51
Fell asleep/slept through dose	40
Had problems taking meds at specific times	40
Felt ill or sick	28
Wanted to avoid side effects	24
Felt depressed/overwhelmed	18
Had too many pills to take	14
Did not want others to notice me taking meds	14
Felt drug was toxic/harmful	12

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www.phpartners.com

Materials Available

Further information on adherence is available on the HIVInSite, the UCSF AIDS web site at: hivinsite.ucsf.edu.

Information is also available by contacting: Margaret Chesney, CAPS/UCSF
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