

# ADHERENCE: THE ACHILLES' HEEL OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY

*At the recent New York course, Gerald H. Friedland, MD, from the Yale University School of Medicine in New Haven, Connecticut, discussed adherence as a key factor in extending the benefits observed with aggressive combination therapy in clinical trials to the practice setting.*

**A**dvances in HIV pathogenesis and viral dynamics, and the availability of viral load assays and potent antiretroviral drug regimens have provided new opportunities to treat patients with HIV disease. Combined aggressive antiretroviral therapy has enormous potential to delay disease progression and death. However, achieving this potential in the practice setting involves addressing the complex behavioral issue of compliance/adherence. Despite different connotations, the terms "compliance" and "adherence" are currently used interchangeably. Adherence is perhaps the more accurate term in that it indicates patient choice in medication taking, but compliance is in more common usage.

## **Efficacy vs Effectiveness**

The term efficacy is used to characterize the definable benefits from a drug or a combination of drugs; measures of efficacy are specific, clearly defined, and usually derived from a controlled clinical

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trial. Effectiveness, however, refers to how a drug or combination of drugs works in the real world. For many reasons, including methodological issues, wide variations in responses to drug, pharmacologic variability, and the influence of licensing and regulatory goals on

the structure of clinical trials, information derived from clinical trials may not necessarily translate well to clinical practice.

Clinical trials are designed to enroll highly-selected populations and the findings are often difficult to generalize to the larger, more diverse patient population in clinical practice. Patients with medical issues such as liver function abnormalities, renal failure, alcoholism, and substance abuse, while common in clinical practice, are excluded from most drug trials. In part due to the maturity of the HIV epidemic, patients presenting in the clinical setting are often heavily pretreated, and have advanced disease. In addition, the behavioral characteristics of patients who enroll in clinical trials differ from those of patients who do not. In a study conducted by Ethier and colleagues at Yale, investigators assessed characteristics of patients in clinical trials, those interested in participating in clinical trials, and those declining participation. Patients choosing to enroll in clinical trials were more likely to be able to keep track of time, to be able to adapt their lifestyle to treatment regimens, and to believe that the value of the drug outweighed the inconvenience of the number of pills involved, and were less fearful of potential of side effects.

## **Adherence to Treatment Regimens**

Studies in the disease areas of hypertension, epilepsy, tuberculosis, and in the geriatric population have demonstrated 1) adherence to drug regimens is poor across populations and diseases; 2) providers cannot predict who will or will not adhere to drug regimens; and 3) providers consistently overestimate patients' adherence to recommended drug regimens.

Clearly, the degree of adherence to therapy affects treatment outcome; low adherence reduces both efficacy and toxicity. Importantly, in the field of HIV disease poor adherence promotes the opportunity for the development of viral resistance. If a patient takes very little or no drug, the likelihood of resistance is relatively low because there is little or no pressure to se-

lect a resistant mutant. In theory, if adherence is complete (100%) with potent combination therapy, viral replication will most likely be halted and resistant viral mutants are unlikely. However, in patients who intermittently or irregularly take drugs (the majority of patients in clinical practice setting), the likelihood of selection of mutants that are resistant to the drug(s) increases, a consequence of both continuing viral replication and selective antimicrobial pressure.

## **Determinants of Adherence**

As shown in Table 1, adherence to medication has multiple, overlapping determinants. In terms of patient characteristics, social support is probably the most important factor. The literature on adherence strongly and consistently demonstrates that adherence cannot be predicted based

**Table 1. Factors That Affect Adherence**

### **Patient characteristics**

- Knowledge
- Social support
- Beliefs
- Trust in provider
- Demographic characteristics

### **Treatment regimen**

- Number of medications
- Frequency of dosing
- Complexity
- Duration
- Side effects
- Degree of behavioral change required

### **Patient-provider relationship**

- Trust
- Consistency
- Level of supervision
- Similar demographic characteristics



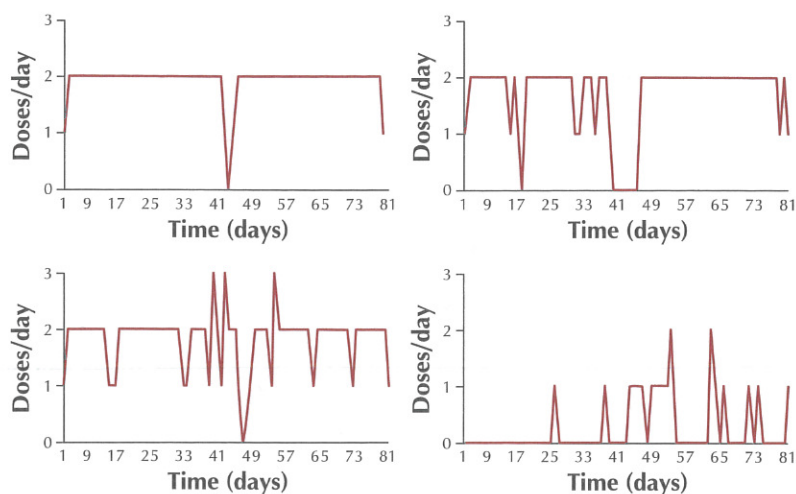
solely on age, race, sex, or educational status. Addressing individual health beliefs, and understanding the individuals risk-benefit equation is a key in influencing adherence. Aspects of the patient-provider relationship, including trust, consistency, and continued interaction are also important determinants of adherence. In a study by Altice and colleagues conducted among prison inmates with HIV disease, a scale designed to measure trust in physician was used to demonstrate that increased trust was associated with both increased acceptance of and adherence to antiretroviral medication. Characteristics of the treatment regimen also predict adherence. Increasing number of pills, frequency of dosing, duration of therapy, and frequency of side effects all decrease the likelihood of adherence.

### Measuring Adherence

Four methods are commonly used to measure adherence: self-report (questionnaire/interviews/diary), pill count, drug assay, and electronic monitoring. Pill counts have been used extensively but are not believed to be accurate; patients may empty the pill box, or take all of the remaining pills before their clinic visit. The accuracy of drug assays depends in part on the half-life of the drug; longer-acting indicators have been used, but testing will show only past ingestion and not frequency or dosing interval.

### Table 2. Interventions to Enhance Adherence

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| <ul style="list-style-type: none"> <li>• Provide peer education and support</li> <li>• Involve family members and partners</li> <li>• Provide substance abuse treatment</li> <li>• Provide financial support/ensure drug availability</li> <li>• Build trust and offer consistency</li> <li>• Provide appropriate and persistent information and reinforcement</li> <li>• Do medication checks</li> <li>• Link adherence to treatment goals (ie, viral load)</li> </ul> | <ul style="list-style-type: none"> <li>• Use existing lifestyles</li> <li>• Pay attention to food/no food requirements</li> <li>• Avoid unnecessary medications</li> <li>• Simplify regimens (bid v tid)</li> <li>• Monitor and manage side effects proactively</li> <li>• Involve nonphysician providers</li> <li>• Elicit health beliefs</li> <li>• Use modified directly observed therapy (DOT)</li> </ul> |
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**Figure 1. Individual patterns of adherence as measured by the MEMS in four patients given didanosine therapy.** Adapted from Blatschke T. Presented at the 4th Conference on Retroviruses and Opportunistic Infections. Abstract No. S43.

The Medication Event Monitoring System (MEMS) provides a computer chip in the cap of the medicinal bottle; information is recorded each time the bottle is opened. Figure 1 is an example of MEMS data, and shows the wide variation in adherence patterns for four patients given didanosine therapy. Data from the MEMS allows calculation of 1) the adherence rate, or percentage of pills taken; 2) prescribed frequency; and 3) prescribed interval. A small study of adherence in patients taking antiretroviral therapy revealed that while the overall adherence rate (fraction of doses taken) was 82% to 86%, more detailed

measures of the fraction of doses taken at the prescribed daily interval (55%-76%) and fraction of doses taken at the prescribed dosing interval (27%) were lower.

### Interventions to Improve Adherence

Table 2 lists strategies for improving adherence to drug therapy. As noted earlier, social and technical support from partners, family members, and health care providers are important elements for enhancing adherence.

### Conclusion

Impressive gains have been made in the ability of antiretroviral therapy to suppress viral replication and delay disease progression in patients with HIV. However, given the current recommendations to use highly aggressive combination therapy, drug options remain limited. In order to replicate the findings observed in clinical trials of these combinations, and to maximize the potential of each drug, targeted efforts to increase adherence in the real world clinical setting are essential.

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## Suggested Readings

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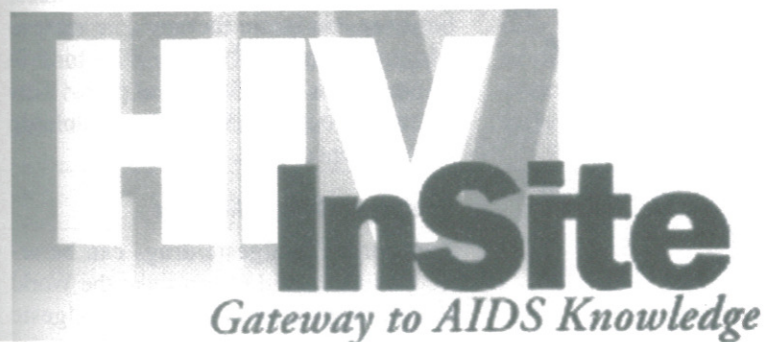
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