

## Antiretroviral Therapy: Time To Think Strategically

Highly active antiretroviral therapy (HAART), the use of combinations of antiretroviral drugs that can profoundly suppress HIV replication for prolonged periods, has substantially decreased AIDS-related morbidity and mortality in the United States and western Europe (1). However, the optimal use of antiretroviral drugs remains a rapidly evolving field and numerous obstacles need to be addressed. Many HAART regimens are associated with substantial toxicity, large pill burdens, and high cost. In addition, it has become clear that currently available HAART regimens cannot completely suppress HIV replication (2).

Guidelines for the optimal use of antiretroviral therapy have been issued by several panels of experts (3). Recommendations on the best time to initiate antiretroviral therapy are based on studies of the relation between surrogate markers of HIV disease progression and risk for clinical progression to AIDS (4). On the basis of these data, antiretroviral therapy is usually recommended for asymptomatic patients with CD4<sup>+</sup> counts less than 500 cells/mm<sup>3</sup> or plasma viral levels less than 10 000 HIV RNA copies/mL. Decisions about which antiretroviral agents to use in these circumstances and when to switch therapy are guided by published data and expert opinion. To keep pace with rapidly evolving concepts, the guidelines issued by the U.S. Department of Health and Human Services (DHHS) and the Henry J. Kaiser Family Foundation (3) are updated frequently on the World Wide Web (<http://www.hivatis.org>).

In this issue, Henry (5) argues for a more conservative, individualized approach to antiretroviral therapy and challenges some of the foundations on which guidelines have been based. An important point of Henry's article is that the goals of antiretroviral therapy must extend beyond simply suppressing plasma viremia as much as possible for as long as possible. In fact, the DHHS/Kaiser Foundation guidelines are being revised to emphasize this point. Additional goals of therapy include reduction in HIV-related morbidity and mortality; restoration and preservation of immune function; minimization of toxicity, disruption of lifestyle, and the frequency

with which drug-resistant virus strains emerge; and preservation of future treatment options.

Cogent arguments can be made for both early and delayed therapy in HIV-infected persons. The rapid dynamics of viral replication (6, 7), the recognition that high levels of viral replication occur in lymphoid tissue at all stages of disease (8), and the early appearance of immune system dysfunction support early therapy. Recent data, however, suggest that at least some degree of immune reconstitution occurs after initiation of HAART, even in patients with late-stage disease (9, 10). Restoration of in vitro responses to antigens associated with opportunistic infections (for example, cytomegalovirus) are frequently restored during HAART (11); most important, it may be safe to discontinue primary prophylaxis against *Pneumocystis carinii* pneumonia and maintenance therapy for cytomegalovirus retinitis in the setting of increasing CD4<sup>+</sup> T-cell counts (12, 13). In addition, HAART may be able to partially reverse some HIV-induced disruptions of lymphoid tissue architecture (14).

The encouraging data on immune reconstitution during HAART support initiation of antiretroviral therapy at a later stage of disease than is currently recommended. Later initiation of therapy may also spare associated toxicity and cost. However, clinicians and patients opting for this approach should consider several concerns. First, there is probably a threshold for loss of CD4<sup>+</sup> T cells and thymic function beyond which immune reconstitution is severely impaired (15). Furthermore, reconstitution of HIV-specific CD4<sup>+</sup> T-cell responses may be possible only when HAART is initiated in the very early stages of HIV infection (16), although the clinical significance of this observation remains uncertain.

Another caveat regarding delayed initiation of antiretroviral therapy concerns the goal of minimizing the emergence of drug-resistant strains of HIV. Henry argues that the only guarantee against drug resistance is delaying therapy and thereby avoiding exposure to the selective pressure of the antiretroviral agents. Such a strategy, however, would result in far more viral replication cycles than early, successful HAART. Because of the stochastic nature of mutations in the HIV genome, the greater number

**Table. Strategic Approaches to Antiretroviral Therapy**

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Early compared with delayed initiation of antiretroviral therapy
Rational sequencing of agents based on toxicity and resistance profiles
Initiation of therapy with protease inhibitor-containing compared with protease inhibitor-sparing regimens
Induction with a protease inhibitor-containing regimen followed by simplification with a protease inhibitor-sparing regimen
Simplification of dosing regimens to improve adherence and tolerability
Use of drug levels to guide dosing
Exploitation of pharmacokinetic interactions to optimize exposure to antiretroviral agents (for example, inhibition of cytochrome P450 by one protease inhibitor to boost levels of a second protease inhibitor)
Intensification with additional agents for viral breakthrough in the absence of resistance
Use of resistance assays to choose agents in an antiretroviral regimen
Use of treatment interruption to restimulate immune responses or to spare toxicity and cost
Use of immune-based therapies in conjunction with antiretroviral therapy to target latent reservoirs of HIV or to stimulate certain antiviral immune responses

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of replication cycles that occur in the setting of delayed therapy could serve to increase the frequency of preexisting resistance mutations and shorten the time to treatment failure after therapy is initiated (17). This scenario may explain the observation that high baseline viral levels and low baseline CD4<sup>+</sup> T-cell counts are independent predictors of failure during HAART (18). In fact, Richman and colleagues (19) demonstrated in 1990 that viral isolates taken from patients with fewer signs and symptoms or high CD4<sup>+</sup> T-lymphocyte counts developed reduced susceptibility to zidovudine at slower rates than isolates taken from patients with AIDS or AIDS-related complex. It is reasonable to assume that the persistent, low-level HIV replication that occurs during HAART (2) would lead to the emergence of drug resistance; however, such replication seems to occur often even in the absence of detectable drug-resistant mutations (2).

The optimal time to initiate antiretroviral therapy and the optimal regimen to use are determined by myriad factors and may vary considerably among individual persons. The DHHS/Kaiser Foundation guidelines can provide useful suggestions to facilitate these decisions (3); however, these same guidelines clearly state that patients and physicians must jointly make such decisions after carefully weighing the risks and benefits as well as the patient's readiness to commit to a complex medical regimen (3). Indeed, a discussion of therapeutically aggressive and conservative approaches is included in the guidelines (3).

Henry advocates a long-term strategic approach to antiretroviral therapy. This is undoubtedly where the field must go. Although most of the 14 antiretroviral agents have become available only within the past 3 years, encouraging developments have already been seen in strategic approaches to antiretroviral therapy. The request for applications for the

National Institute of Allergy and Infectious Diseases' Adult Therapeutic Clinical Trials Program for AIDS (AI-98-013; <http://www.niaid.nih.gov/daids/adulttrialsrfa.htm>) calls for study designs that evaluate strategic approaches to antiretroviral therapy, including when to initiate therapy, which agents to use, when to switch therapy, and how to maximize immune reconstitution. Studies that evaluate long-term outcomes of antiretroviral therapy are also called for, and studies that address many strategic issues in antiretroviral therapy are already in progress (Table).

Today's studies help formulate tomorrow's guidelines. The rapid expansion of the antiretroviral armamentarium over the past few years is a welcome change for HIV-infected persons. However, many studies must be conducted over an extended period to determine the best ways to use the wide range of available antiretroviral regimens.

*Oren J. Cohen, MD*

National Institute of Allergy and Infectious Diseases  
Bethesda, MD 20892-2520

*Note:* Dr. Cohen is Executive Secretary for the Department of Health and Human Services (DHHS)/Kaiser Family Foundation Panel on Clinical Practices for the Treatment of HIV Infection. The opinions in this article are those of the author and are not official policy positions of the U.S. government or the DHHS/Kaiser Foundation panel.

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*Requests for Single Reprints:* Oren J. Cohen, MD, National Institute of Allergy and Infectious Diseases, 31 Center Drive MSC 2520, Building 31, Room 7A05, Bethesda, MD 20892.

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It is a curious thing . . . that a man who knows perfectly well that in decency he must not practise on his friends has not the slightest hesitation in doing so when it comes to medicine. We give strongly-coloured, strongly-flavored, physically inoperative draughts, pills, boluses in order to profit by the patient's belief that having been dosed he now feels much better—a belief whose invaluable physical effects you have often seen. In this case I exhibited the tincture in the unusually powerful dose of five and thirty drops, disguising it with asafetida and a little musk and suppressing its name, since the patient has a horror of opium, while at the same time, to deal with the initial stimulation that often accompanies the ingestion of narcotics by those unaccustomed to them, I provided four pills of our usual pink-tinted chalk, to be taken in the event of wakefulness. The patient, comforted by the thought of this resource, will pass the first ten minutes or so in placid contemplation, ignoring the slight excitement, and then he will plunge into an oblivion as deep as that of the Seven Sleepers, or deeper. I flatter myself that this deep peace, this absence of vexation and irascibility, will allow the organs to carry on with their usual task unhindered, responding to my cholagogues, eliminating the vicious humors and restoring the former equilibrium.

Patrick O'Brian  
*The Truelove*  
 New York: W. W. Norton; 1992:35-6

Submitted by:  
 Joel E. Gallant, MD, MPH  
 Johns Hopkins University  
 Baltimore, MD 21287

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