Recent trends in treatment: HAART

One of the most important advances in the field of HIV disease in the past few years has been greatly improved therapeutic efficacy. In 1995-1996, with the approval of the first protease inhibitors (PIs), it became possible to treat HIV infection with combinations of agents that targeted two of the virus's essential enzymes, protease and reverse transcriptase (RT). Use of three-drug combinations, called highly active antiretroviral therapy (HAART) because they can reduce viral replication by more than 99.9%, resulted in measurable improvements in the outcomes of HIV disease. For instance, AIDS mortality nationwide dropped by 42% from 1996 to 1997 and a further 20% in 1998.1-4

Moreover, it has been determined that patients being treated with HAART who experience a rise in CD4 cells to 200/µL or greater (which appears to be a threshold level of immunity against infection by opportunistic pathogens) may safely stop prophylaxis for Pneumocystis carinii pneumonia (PCP).5,6 Prophylaxis against M. avium infection can also be stopped in patients who have a response to HAART.7

As one AIDS clinician recently wrote, "[W]e are now capable of turning HIV disease into a chronic, manageable condition through informed and judicious use of drug therapy."8

Some clinical investigators have suggested that even greater benefits, such as retention of HIV-specific immune responses, could be obtained by treating very early, during the acute phase of HIV infection.9-12 However, most experts believe that treatment during the acute phase should still be done in the setting of clinical trials.

Very recent data show that the benefits of HAART on survival continue to be seen, but that many patients lose this benefit over time, underscoring the need for additional treatment options.13,14

New classes of drugs are still being developed; in particular, inhibitors of the third essential HIV enzyme, integrase, are being explored. Integrase inserts a copy of HIV's nucleic acid into the host genome, a critical step in the production of new virus. Although promising, integrase inhibitors are still in the research phase.15

During the last few years, three new antiretroviral drugs have been approved, one in each of the three main classes currently being employed: amprenavir, a PI; abacavir, a nucleoside reverse transcriptase inhibitor (NRTI); and efavirenz, a nonnucleoside reverse transcriptase inhibitor (NNRTI). Additional approvals are likely in the near future. From the 14 currently available therapeutic agents against HIV, a large number of drug combinations can be designed to meet the needs of the wide variety of HIV-infected persons.

While having a greater number of potent drugs available offers greater treatment options, it has created a dilemma for clinicians—how to choose the best regimen for each patient. Obtaining the greatest benefit from these expanded treatment choices requires expert disease management.

Selecting an initial regimen

Both major guideline panels focused on two types of combination regimens—either a PI combined with 2 NRTIs, or an NNRTI combined with 2 NRTIs.9,16 Although both

panels acknowledged regimens composed of 3 NRTIs, the International Aids Society (IAS) panel referred to this combination as being "under evaluation."

Because it is difficult to devise a highly potent second regimen when the first regimen fails, it is always advisable to start with the best possible regimen.17,18 In a randomized trial in which a PI was added to 2 NRTIs either at the start of therapy or at a later time, more extensive and longer durability of viral suppression occurred with the more potent initial regimen. The authors attributed these results to the more potent regimen's greater ability to suppress emergence of drug-resistant HIV variants.18

What makes the "best possible" regimen? One way to define it would be a regimen that is both potent and durable—one that suppresses viral replication to a very low level and that continues to maintain viral suppression for a long time, preferably for years. Few head-to-head comparisons of the efficacy and durability of various regimens have been published. But the guideline panels noted that NNRTI-based regimens have "limited long-term data"9 and that their comparability to PI-containing regimens with regard to clinical endpoints is "unknown."16

By considering what properties might increase the durability of an antiretroviral drug (ARV), we can create a profile of an optimal anti-HIV agent. Factors that influence ARV durability can be grouped into three categories—viral variability, patient variability, and ARV variability.

Under variability of the virus, we need to consider its degree of resistance to the ARV. As we will discuss in detail later, the genetic material of HIV is constantly undergoing mutation as part of its normal replication.19 As a result, in the body of any given HIV-infected individual, "[R]eplication-competent virus with every possible single drug-resistance mutation is likely to be generated daily."19 A small fraction of these viral variants will harbor a mutation that will give them some level of resistance to any ARV that is available to us. How important this will be in determining the outcome of treatment will depend on the degree of resistance conferred by the existing mutations, the proportion of the viral population that contains such a mutation, and whether the other drugs in the combination can overcome the level of resistance to any one ARV.

A particularly important form of viral variability is the recent emergence of primary resistance—the finding that virus tested within a few months after a person becomes infected with HIV already has some level of resistance to various ARVs, even before the patient has been treated.20-22 Most likely, primary resistance reflects transmission of resistant virus from a person who had been treated. The rise of primary resistance makes it even more imperative to use ARVs that have a wide margin of efficacy—ARVs whose serum concentration is much higher than the concentration needed to block HIV replication.

Turning to the patient factors that influence durability, some important considerations are how well the patient absorbs the agent, the patient's ability to tolerate the regimen, and the patient's degree of adherence to the regimen.9 Adherence is particularly important. As Clumeck wrote, "With respect to the successful long-term control of viral replication, the issue of compliance is crucial."17 Results from a clinical trial led the investigators to a similar conclusion: "In patients failing triple-drug therapy, diminished antiviral potency

(as a result of suboptimal adherence or drug delivery) undoubtedly contributed to rebound."23

Of course, the patient factors are interrelated. An editorial commenting on the Havlir study noted, "These studies indicate that virologic failure is indeed multifactorial and not solely the result of multidrug resistance. Undoubtedly, adherence to a treatment regimen is essential … Less toxic, simpler and more patient-friendly regimens are urgently needed, but as these studies point out, not at the expense of the regimen potency."24

All of these "patient" factors are influenced by characteristics of the ARV as well. For instance, if a drug reaches very high levels in plasma relative to the concentration needed to block viral replication, then minor patient-to-patient variability in absorption will not greatly affect efficacy. Adherence, in turn, is dependent on a number of characteristics of the drugs included in the regimen, such as frequency of dosing and whether the drugs have to be taken with meals or with fluids.25-27 Tolerability, too, is a consequence of an interaction between the patient and the ARV, with different drugs having different propensities to cause severe adverse effects.

But one critical element in determining durability of viral suppression is an intrinsic property of the ARV—the degree of genetic barrier that it presents to the virus. Genetic barrier refers simply to the number of mutations that a virus needs to contain to become highly resistant to the ARV. Viral strains with one mutation conferring resistance to a particular ARV will arise spontaneously. But if it takes 2 or 3 or more mutations against an ARV, all in the same viral variant, for that virus strain to be able to escape suppression, then it is much less probable that such a variant will arise. In fact, the probability of a highly resistant variant becomes exponentially smaller with each mutation required. In this context, it is important to note that there is wide variation among ARVs in the number of mutations required for the virus to escape their suppression.

Havlir et al23 make this point clearly in discussing the results of their study on viral rebound. "For lamivudine or non-nucleoside reverse transcriptase inhibitors (RTIs) such as nevirapine or efavirenz," they write, "a single nucleotide change can confer a 20- to 1,000-fold reduction in susceptibility. In the presence of drugs, the mutant virus is so much more fit that it will predominate. Clinical data confirm that when antiviral potency of a regimen containing one of these drugs is insufficient to suppress replication, drug-resistant virus rapidly emerges." One kind of evidence for this assertion is the finding that "In a study of isolates from patients with rebound when taking an efavirenz and indinavir combination, most isolates were resistant to efavirenz."

So we can say that lamivudine, nevirapine, and efavirenz present a low genetic barrier to the virus. In contrast, PIs have a higher genetic barrier. As the same authors write, "[D]evelopment of high-level resistance to PIs and zidovudine requires the accumulation of multiple mutations. For PIs, the first mutation confers only limited reduction in susceptibility, usually less than 10-fold."23 For these drugs, the genetic barrier presented to the virus is of a moderate height. For at least one drug now under review, the genetic barrier is even higher, with effective viral suppression being lost only after the virus accumulates 8 to 10 mutations.