To Switch or Not to Switch—When is it a Question?

When the first official guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents were published by the Department of Health and Human Services (DHHS) on April 24, 1998, the HIV treatment landscape was a different world: hitting the virus early still seemed like a logical idea, an apparent never-ending supply of protease inhibitors was flowing out of the drug-development pipeline, non-nucleoside reverse transcriptase inhibitors were coming into vogue as potent backbone options, nucleoside analogues did not appear to suffer much in the way of cross resistance, and an extraordinary percentage of HIV-positive individuals were still doing well on their first triple-drug regimens. In short, treatment options were plentiful and the DHHS was confident in its endorsement of pushing viral load to undetectable levels and keeping it there, using a succession of seemingly endless regimen switches to maintain this goal.

Five years later, it has become increasingly clear that antiretroviral regimen switches are by no means endless. Significant cross-resistance among all of the currently available drug classes can and does occur, drastically reducing the number of switch options that are feasibly available to the patient. The most recent incarnation of the Guidelines, published on July 14, 2003, recognizes this and acknowledges that an undetectable viral load is not the end-all, be-all goal of therapy in patients with limited options to choose from. As clearly stated, “Viral suppression is often difficult to achieve in patients with extensive prior treatment. Thus, the goal is to preserve immunologic function and prevent clinical progression, even with ongoing viremia. Even partial virologic suppression of HIV-RNA >0.5 log copies/mL below pretreatment baseline correlates with clinical benefits...It is reasonable to observe a patient on the same regimen, rather than changing the regimen, if there are few or no treatment options.” And this is, precisely, what many clinicians are now doing.

Of course, many clinicians will likely have difficulty getting their heads around the idea of maintaining their patients on an antiretroviral drug regimen that is no longer proving to be maximally suppressive. To help demystify this option — and to discuss a relatively new concept known as partial treatment interruptions — Dr. Steven Deeks recently visited PRN to share some of his more recent intriguing clinical experiences involving HIV-positive individuals at the end of their treatment rope.

Undetectable or Bust?

Dr. Deeks explained why a sustained undetectable viral load is still considered to be the best possible outcome of antiretroviral treatment. “We have been following a cohort of 200 to 300 individuals with multiple-drug-resistant virus who, for whatever reason, have chosen to remain on a stable regimen,” he said. “Some of the earliest patients in the study have been followed very carefully now for up to four years. Their viral loads have remained detectable and we’ve seen the level of phenotypic resistance to the drugs they’re taking increase over time. The longer these patients remain on therapy, the more resistant and cross-resistant their viruses are becoming. Ideally, we’d switch the regimen in order to bring the viral load back down to undetectable in order to prevent the accumulation of additional mutations. But this isn’t always possible, not easily anyway. In turn, is it acceptable for clinicians to stop being so aggressive and to stop modifying treatment in the face of virologic failure?”

For many HIV-positive patients who have exhausted two or three different regimens, the most plausible treatment option is mega-haart, a “kitchen sink” approach in which five to nine drugs are combined to conjure up as much antiviral firepower as possible. However, the risks of these salvage regimens sometimes outweigh the potential benefits they may provide. “In my experience, following 100 or so patients in my own clinic, many of whom are heavily pretreated and have been taking medications for at least ten years, I have found a great deal of pill fatigue that is limiting my patients’ abilities to commit to yet another switch,” Dr. Deeks said.

Aside from pill fatigue, another issue that potentially stands in the way of multiple-drug combinations is cost. For example, enfuvirtide (Fuzeon), one of the most important treatments developed and approved for the treatment of HIV-infected people with limited treatment options, is currently priced at $15,000 to $20,000 a year. “Because of the complexities involved in manufacturing this drug, it will remain a high-cost treatment,” Dr. Deeks explained. “This is having a dramatic impact on AIDS Drug Assistance Programs, many of which are simply unable to cover the cost of this drug. Some clinicians who want to prescribe this drug simply might not be able to do so because of cost.”

Another situation that often stands in the way of clinicians switching to a newly minted drug is the lack of effective drugs to combine with it. For example, the success of enfuvirtide in patients enrolled in the phase III clinical trial program was highly dependent on the sensitivity of HIV to the optimized background regimens used. An analysis of TORO 1—the phase III study conducted in North America and Brazil—used genotypic sensitivity scoring (gss) and phenotypic sensitivity scoring (pss) to evaluate the effectiveness of enfuvirtide-based regimens on 24-week virologic results (Sista, 2003). A patient with either a phenotypic or genotypic score of zero had high-level resistance to all of the antiretrovirals used in their optimized regimen. Patients with a gss or pss of one or two had virus sensitive to one or two of the drugs used in their optimized regimen, and so on.

Patients with a pss of one or two in the enfuvirtide group saw their viral loads drop by approximately 1.8 log copies/mL after 24 weeks, compared to a 0.8 log copies/mL drop in the optimized regimen group. Similarly, patients with a pss of three or four in the enfuvirtide group saw their viral loads drop by approximately 2.4 log copies/mL after 24 weeks, compared to a 1.5 log copies/mL drop in the optimized regimen group. “These data show us that we can quickly turn a three-class failure into a four-class failure by adding Fuzeron to a combination of ineffective drugs,” Dr. Deeks commented. “For this reason, many clinicians...
have become a bit more conservative in how they approach treatment, delaying a switch until a new drug like Fuzeon can be combined with at least one, or preferably two, other effective drugs.”

Getting to the heart of his discussion, Dr. Deeks discussed what is likely the most important factor to be considered in deciding to delay a regimen switch in patients with limited treatment options—the fact that many patients continue to do well clinically, despite ongoing replication while on a failing regimen.

In one study reviewed by Dr. Deeks, he and his colleagues examined the relationship between HIV RNA levels and CD4+ cell counts in 380 HIV-positive adults receiving long-term therapy with a protease inhibitor-based regimen (Deeks, 2000). Generally speaking, patients experiencing virologic failure—defined as persistent HIV RNA levels above 500 copies/mL—had CD4+ cell counts that remained greater than pre-therapy baseline levels, at least through 96 weeks of follow-up (see Figure 1). The CD4+ cell response was directly and independently related to the degree of viral suppression below the pretreatment baseline. “What is most interesting,” Dr. Deeks explained, “is that a large number of individuals, approximately 17% of our entire treated cohort, achieved what we call a transient response while on a failing regimen.”

Helping to confirm these findings are new data from a study conducted by Dr. Bruno Lederberger of the Zurich University Hospital and a team of international collaborators (Lederberger, 2003). This prospective, observational study included patients from 13 cohorts in Europe, North America, and Australia with triple-class failure—multiple-drug resistance—and viral loads >1000 copies/mL for at least four months while on a stable antiretroviral regimen. A total of 628 patients were evaluated. Among patients who were able to maintain a viral load below 10,000 copies/mL, there was actually an increase in the CD4+ cell count over time. Once the viral load approached 30,000 copies/mL, there was some evidence that viral replication had a negative impact on CD4+ cell counts over time. On average, the CD4+ cell decline in these patients was on the order of 20 cells/mm3 a year, compared to a much more severe slope in untreated patients with viral loads above 30,000 copies/mL.

“These studies do not prove or even suggest that it’s always okay to keep our HIV-infected patients on a failing drug regimen,” offered Dr. Deeks. “What they do say is that, for individuals with limited treatment options, remaining on a regimen that is no longer completely suppressive will likely result in stable, or at worst, slower progressive HIV disease.”

**What’s Good for the Goose...**

**Understanding why viral load often remains suppressed below pretreatment levels despite the presence of high-level drug resistance is still being explored. While it’s likely that residual drug activity is partly responsible for this observation, there’s emerging evidence to suggest that impairment of replication capacity, caused by drug-resistance mutations, is also a factor.**

Technically speaking, HIV’s “fitness” is defined as its ability to multiply in a given environment. Fitness also generally refers to a situation in which one species competes against a second species. Thus, wild-type HIV is often more fit than drug-resistant HIV when measured in the absence of drug, but wild-type HIV is always less fit than drug-resistant HIV when measured in the presence of drug. In contrast, “replication capacity” (RC) refers to inherent replicative efficiency of a given HIV strain, and is often measured ex vivo in the absence of drug. Finally, “virulence” refers to capacity of a given viral strain to cause disease (e.g., by causing progressive CD4+ cell depletion).

“Replicative capacity is the term we should use more often,” Dr. Deeks said. “It refers to the inherent efficiency of a virus and its capacity to replicate.” To measure RC of a given patient’s HIV, it is compared to a reference, usually wild-type virus. Decreased RC may be intrinsic to the virus strain or may result from mutations selected by pressure and resistance. There is an assumption that a virus with low RC will be less fit in vivo and less virulent.

To gain some insight into the connection between evolving drug resistance and RC, investigators at the University of California—including Dr. Deeks—teamed up with investigators at the Gladstone Institute of Virology and Immunology and at ViroLogic to conduct a longitudinal observational study of 20 HIV-infected individuals who remained on a stable protease inhibitor-based regimen despite ongoing viral replication (HIV RNA levels consistently above 500 copies/mL) (Barbour, 2002). Patients were seen every three to six months, up to the time therapy was suspended. And this benefit persists in our hands indefinitely, as long as their viral load remains at least .7 or .8 log below the pretreatment viral load. As long as treatment can maintain some degree of viral suppression, CD4+ cell counts are also maintained.”

**Figure 1. Complete, incomplete and transient responses to HAART.**

The relationship between HIV RNA levels and CD4+ cell counts in 380 HIV-positive adults receiving long-term therapy with a protease inhibitor-based regimen. The magenta lines reflect the median HIV RNA values and CD4+ cell counts for patients achieving “complete” viral suppression for 96 weeks; the orange lines reflect median values for “partial” virologic responders, characterized as patients with detectable viremia, but with a viral load >1 log below pretreatment levels; the dark red lines reflect the median values for patients dubbed “transient” virologic responders, defined as patients who experienced a transient decrease in viral load >1 log with subsequent rebounds in HIV RNA toward pretreatment values. Approximately 17% of the patients in this University of California, San Francisco cohort were transient virologic responders. These patients had high levels of viral replication but also had sustained CD4+ cell increases for at least 96 weeks. This benefit persisted in all patients who maintained HIV RNA levels at least .7 or .8 log below pretreatment viral load.

The change in viral load (A), phenotypic susceptibility (B), and replicative capacity (C) for 13 patients treated with a protease inhibitor-based regimen are shown. Patients who experienced virologic failure and remained on a stable regimen were identified retrospectively from an ongoing study of individuals followed in the UCSF SCOPE cohort. Each thin line represents the treatment response for a single patient. Month zero reflects the time virologic failure of a protease inhibitor-based regimen was confirmed. A smooth line reflecting the cohort’s treatment outcomes over time was generated using the locally weighted scatter-plot smoothing technique (bold red line).


Modified or discontinued. After two years of follow-up, the investigators had amassed 248 samples from the 20 patients, all of which were assayed for phenotypic drug susceptibility and viral rc, using a single-cycle recombiant-virus assay developed by ViroLogic. The initial treatment-mediated decrease in HIV-rc was directly proportional to a reduction in rc. Early virologic rebound was associated with the emergence of HIV exhibiting increased protease inhibitor phenotypic resistance, while rc remained low. During long-term virologic failure, HIV-rc levels often remained stable or increased slowly, while phenotypic resistance continued to increase and rc decreased slowly (see Figure 2). The emergence of primary genotypic mutations within the protease gene—most notably V82A, V82M, and I90M—was temporally associated with increasing phenotypic resistance and decreasing rc, while the emergence of secondary mutations within protease was associated with more-gradual changes in both phenotypic resistance and rc. Based on these findings, the investigators concluded that “HIV may be constrained in its ability to become both highly resistant and highly fit and this may contribute to the continued partial suppression of plasma HIV-rc levels that is observed in some patients with drug-resistant viremia.”

“The bottom line,” Dr. Deeks explained further, “is that you end up with a viral load setpoint while on a failed regimen that is below the pretreatment setpoint. This, however, is a complicated issue. Virologic failure is associated with increasing resistance over time, but it is also associated with low replicative capacity, which may or may not increase.”

**Partial Treatment Interruptions**

Dr. Deeks is one of several investigators currently looking into novel methods of using antiretroviral therapy in HIV-positive individuals who have limited options, most notably those who may not yet require an aggressive mega-HAART regimen. “We’re talking about patients who have used up two or three regimens, are relatively healthy and have stable CD4+ cell counts, and also have a stable detectable viral load while on therapy.” Dr. Deeks argues that one of the primary benefits of treatment is simply to prevent the rebound of wild-type virus. “In other words,” Dr. Deeks said, “drugs are primarily treating the virus that you do not see with a genotypic assay, namely wild-type and partially resistant variants. The second benefit of therapy is to maintain the less fit aspects of the virus, in order to limit HIV’s virulence and pathogenicity. The chief drawback of this approach, aside for the various toxicities of the drugs being used, is ongoing evolution of drug resistance and the loss of future drug options.

“We’ve looked at these observations and have come up with a conceptual framework and hypothesis,” Dr. Deeks said. “Can we use fewer drugs, not more, with the goal of preventing wild-type HIV from rebounding?” This, he suggested, may not only help keep HIV’s rc low and the CD4+ cell count stable, it may also reduce the pill burden for treatment-fatigued patients and help to limit the evolution of drug resistance, thereby retaining drug options for an eventual switch when necessary.

In putting together a study, Dr. Deeks turned to a cohort of HIV-positive individuals who had a history of excellent treatment adherence, had drug-resistant viremia (greater than 400 copies/mL), and were experiencing a documented treatment-mediated benefit (e.g., a viral load below and CD4+ cell count above pretreatment levels). Patients entered into a prospective study in which they stopped their protease inhibitor(s) or their reverse transcriptase inhibitors. The therapeutic class that was discontinued was based on patient- and provider-perceived toxicities.

One patient discovered by Dr. Deeks was initially switched to a regimen consisting of stavudine (Zerit), abacavir (Ziagen), efavirenz (Sustiva), and nelfinavir (Viracept). After 150 weeks of treatment, his viral load hovered between 500 and 1,000 copies/mL. Genotypic testing yielded the following mutations: D67N, K70R, K103E, and G190A in the reverse transcriptase gene, and L101I, G58V, I54V, L63P, V77I, and V82A in the protease gene. He opted to stop his nelfinavir because of extreme pill fatigue and persistent diarrhea. Seventy-two weeks after stopping the nelfinavir, his viral load remained relatively stable, barely grazing the 1,000 copies/mL mark. Similar outcomes were observed in most—but not all—patients who interrupted their protease inhibitors. CD4+ cell counts generally remained stable, as did the level of both phenotypic and genotypic resistance.

The finding that resistance to protease inhibitors remained detectable, despite the fact that protease inhibitor therapy had been terminated, was intriguing. “This obviously contrasts the observation that many groups have had, including ours, in terms of what happens when patients stop all drugs,” Dr. Deeks explained. “After six weeks, we tend to see a resurgence of wild-type virus with complete susceptibility to the drug. We have not observed, in any of our patients in a partial treatment interruption mode, the emergence of a wild-type virus. Drug resistance has persisted for the most part, not only to the drugs that were continued, but also to the therapeutic class that was discontinued.”

Dr. Deeks and his colleagues have also evaluated several patients who underwent nucleoside reverse transcriptase inhibitor (NRTI) partial treatment interruptions—patients who dropped all of their NRTIs and continued on protease inhibitor therapy only. Interestingly, all experienced an immediate and rapid increase in viral load within a week, suggesting that NRTIs had persistent and noteworthy activity, despite documented viral resistance to them.
Viral dynamics data aside, protease inhibitor partial treatment interruptions may be associated with a number of substantial advantages. First, there is the possibility of fewer toxicities and side effects. “In our cohort,” Dr. Deeks said, “we’ve seen a rapid and dramatic decrease in lipids in our patients stopping protease inhibitor therapy. It goes without saying that this is a significant plus.” He also noted that numerous patients partaking in a partial treatment interruption reported notable improvements in quality of life and appreciated the reduced pill burden. “Reducing treatment exposure also theoretically reduces the cost of therapy, which could be a significant advantage in resource-poor areas.”

A primary reason to consider this approach in the clinic is the preservation of future treatment options. Tipranavir, for example, is a leading protease inhibitor candidate for HIV-positive individuals who have developed resistance to currently available protease inhibitor options. It is on the verge of becoming much more widely available — through clinical trials, expanded access programs, and pending approval — and has been shown to be effective against HIV harboring a variety of primary and secondary protease mutations. However, tipranavir may have limited effectiveness for individuals with HIV containing a high number of protease mutations. For example, in a study reported at the 9th Conference on Retroviruses and Opportunistic Infections, held in 2002 in Seattle, decreased tipranavir susceptibility was found to be associated with a mean of 16 mutations including three or more of the following family of mutations: L33I/V/F, V82F/L/T, I84V, and L90M (Schwartz, 2002). The longer an individual remains on a failing protease inhibitor, the greater the possibility that multiple mutations will arise and reduce the effectiveness of tipranavir. “In theory,” Dr. Deeks said, “if you’re in the mindset of preserving options to combine with Fuzeon or other drugs, which might mean waiting for tipranavir to become more widely available, continuing someone in the presence of partial viral load suppression and protease inhibitor therapy does have some risk.”

Conclusion

THE TREATMENT OF HIV IS AN EVOLVING ART. AS RESEARCH CONTINUES TO settle a score of existing questions, it ends up yielding a batch of new questions in return. Determining the best possible treatment decisions for individuals with multiple-drug-resistant virus is very much a part of this research process in which unique and incredibly resourceful options are being discovered.

In concluding his lecture, Dr. Deeks made it clear that individuals with a long history of drug failure are not without options. If an aggressive switch to a new antiretroviral regimen is necessary, he stressed that patients really need to be provided with two or more fully “effective” agents to achieve the degree of viral suppression necessary to prevent ongoing viral replication and the accelerated loss of therapeutic options. In deciding which antiretroviral agents to use as part of an aggressive switch, Dr. Deeks stressed the importance of drug-resistance testing. “I use resistance testing much more now than I have in the past,” he confessed. “I know many of my patients very well and I know which drugs they’ve been on, and generally did not find resistance testing able to provide any information that I could not have gleaned from their medical histories. But I’ve been thinking about this issue, regarding whether or not to switch patients, and have found resistance testing to be very helpful in this regard. These tests have allowed me to determine whether or not I have enough agents to pursue a successful switch or modification.”

With respect to structured treatment interruptions, Dr. Deeks believes that temporary cessation of all therapies may still have its time and place. “We’re no longer talking about stopping all therapies to bring back wild-type virus to get a better response to a salvage regimen,” he said. “We’re talking about using structured treatment interruptions to stop the virus from evolving as we wait for new drugs to become available. I might consider full stav in some patients with long-term treatment failure. But this all depends on their CD4+ cell count nadir. If their nadir was above 200 cells/mm³ I’d seriously consider stopping all drugs until better options came along.”

Finally, regarding maintaining an individual on a failing drug regimen versus initiating a partial treatment interruption, Dr. Deeks warned that additional information is very much needed. “The frustrating thing about this approach,” he said, “is that we don’t have the necessary measurements — the assays — to provide the necessary prognostic information in this particular setting. Theoretical markers included replication capacity, immune activation markers, and proviral DNA, which may provide information well beyond viral load in these patients. The bottom line is that this potential option requires further explanation and refinement.”

References


