HAART Interruption Strategies: How, When, and Why?

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ALTHOUGH STRUCTURED TREATMENT interruptions (STIs) are no longer the most pressing topic among the many researchers who were initially charmed by their multifaceted potential, STIs very much remain in the hearts and minds of clinicians and people living with HIV. And why shouldn't they? The reasons for wanting to halt therapy, even temporarily, are just as valid today as they once were. Even in this day and age, in which once-daily drug regimens with low pill burdens are plausible, there are countless patients who continue to grapple with adherence issues and treatment "burnout." There is also the issue of long-term side effects, whether it's preventing, delaying, or reversing their onset. Immune augmentation still remains a worthwhile goal, although its potential seems limited to those fortunate few diagnosed during the primary stages of infection. Finally, there is the possibility of using STIs to overcome drug-resistant virus in patients running low on fresh treatment options.

It is encouraging to know that numerous researchers, Dr. Mark Dybul being one of them, still see hope in treatment interruption strategies. "It's important to remember that treatment interruptions have implications on a global scale," Dr. Dybul said during his opening remarks. "Both in resource-rich and resource-poor areas of the world, toxicities and quality-of-life issues are important factors to consider when discussing long-term treatment. In resource-poor settings, there is also the cost issue to consider. The costs of antiretroviral medication are prohibitive if our goal is to make these therapies more widely available. Reducing the length of time a patient needs to be treated is certainly one way to deal with this issue."

But Dr. Dybul is by no means a Pollyanna when it comes to discussing global clinical treatment interruption strategies. "It is important that we consider what is ideal and what is realistic," he said. "The efficacy and potential benefits of treatment interruptions are vital in framing this discussion. However, there are also risks and the need for risk/benefit analyses, which will vary considerably, depending on the global region being discussed."

STIs in Review: Hoping for Wild-Type in Times of Virologic Failure

AS REVIEWED IN AN EXTENSIVE STI-FOCUSED article published in the September 2001 issue of *The PRN Notebook*—and summarized again by Dr. Dybul—the rationale for STIs among patients experiencing virologic failure is quite different from the autoimmunization and drug-sparing interruption strategies discussed below. In brief, patients with underlying HIV drug-resistance mutations who initiate an STI while experiencing virologic failure on a HAART regimen essentially remove the selective pressure being exerted on the virus. This, in theory, should permit the "optimally fit" wild-type virus to outgrow drug-resistant variants, thus having a dominant drug-sensitive phenotypic population. And once therapy is reinitiated, a profound and perhaps durable response to therapy would ensue.

Unfortunately, the results of two clinical trials published to date proved STIs to be of limited value in the setting of salvage therapy. In one study reported by Dr. Stephen Deeks and his colleagues in the *New England Journal of Medicine*, 16 patients who had HIV-RNA levels above 2,500 copies/mL during HAART were randomly assigned, in a 2:1 ratio, to discontinue or continue therapy (Deeks, 2001). Discontinuation of therapy for 12 weeks was associated with a median decrease of 128 CD4+ cells/mm^3 and an increase in viral load of 0.84 log. Virus from all patients with detectable resistance at entry became susceptible to protease inhibitors within 16 weeks after the discontinuation of therapy, with susceptibility emerging approximately six weeks into the STI. Yet, despite the loss of detectable resistance by the end of the STI, resistant virus was cultured from PBMCs in 5/9 evaluable patients.

As for the subsequent response to treatment, the median decrease in HIV-RNA levels between the time treatment was resumed and 12 and 24 weeks later were 2.3 and 1.6 log copies/mL, respectively, and the median increases in CD4+ counts were 102 and 77 cells/mm^3, respectively. After 24 weeks of therapy, approximately 40% of the patients had viral loads below 200 copies/mL, which was more likely to occur in patients naive to one of three antiretroviral drug classes—many patients were naive to the non-nucleoside reverse transcriptase inhibitors in this study—prior to initiating the STI. In contrast, undetectable viral loads in patients who did not have at least one new potent drug to choose from were either not achieved or short-lived.

In another study conducted by Dr. Veronica Miller and her colleagues, drug susceptibility was assessed using phenotypic and genotypic assays in 48 patients who had interrupted treatment for two months or longer (Miller, 2000). Prior to initiating their STIs, all of the patients had

been receiving HAART but had a median viral load of 5.07 log and were resistant to an average of eight antiretrovirals. Similar to the observations made by Dr. Deeks and his colleagues, Dr. Miller's team observed an average viral load increase of 0.7 log during the patients' STIs. The median CD4+ count was 49 cells/mm^3 by the end of the treatment interruption, reflecting a rather profound median drop of 89 cells/mm^3.

A complete shift to wild-type virus at the phenotypic, genotypic and clonal level was observed in 28/45 evaluable patients. Of the patients with virus resistant (>tenfold increase in IC_{50}) to at least one drug from each class, 68% experienced a shift to wild-type virus, whereas 32% did not. At the end of the treatment interruption period, the median CD4+ counts were 58 cells/mm^3 and 34 cells/mm^3 for those who either did or did not experience a wild-type shift, respectively. Looking at these data another way, patients who saw their drug-resistant virus shift to wild type experienced a median CD4+ decrease of 122 cells/mm,^{3} compared to a median 25 CD4+ cell/mm^3 decrease among patients who did not experience a full drug-resistant to wild-type shift during the interruption.

"In essence," Dr. Dybul said during his summarization of the data, "a shift to drug-sensitive virus does occur, but drug-resistant virus still remains. We see an increase in viral load and a decrease in CD4+ cell counts, which mean significant clinical risks in patients with advanced HIV disease." Still, the possibility of using STIs safely in patients with dwindling treatment options is not without hope—there are still studies under way to shed additional light on STIs in this population of patients and to determine in whom, and under what circumstances, they are possible.

STIs in Review: Autoimmunization Efforts

PERHAPS THE GREATEST AMOUNT OF STI DATA come from clinical trials in which therapy is temporarily halted for the sake of augmenting HIV-specific CD4+ and CD8+ cells to gain better control of viral replication (*The PRN Notebook* has reviewed the principles of STI-induced immune response augmentation in several past issues, most recently in the September 2001 publication). And what we now know is that STIs to achieve this goal are a mixed bag of tricks.

One of the best known—and most successful—efforts to augment HIV-specific immune responses with the use of STIs comes from Massachusetts General Hospital, where Dr. Eric Rosenberg and his colleagues have had great fortune with a group of patients who entered the MGH clinic with primary HIV infection. One highly publicized cohort involved 14 patients who began treatment prior to, or at the time of, HIV seroconversion. After maintaining an undetectable viral load for at least one year, these 14 patients initiated their first STI, with the plan being to restart treatment if their viral load exceeded 5,000 copies/mL for three consecutive weeks or if viral load exceeded 50,000 copies/mL at any one time.

During the first STI, HIV-RNA levels increased in all patients within 17 days, but levels in four patients soon dropped below 5,000 copies/mL. Three of these patients have remained off therapy for more than three years. Among the remaining 11 patients, four have maintained viral loads below 5,000 copies/mL as a result of subsequent STIs, some for longer than three years. STI cycles are still being conducted in six of the remaining patients. One patient who saw his viral load rebound to 7,500 copies/mL opted not to restart therapy but is still being followed by Dr. Rosenberg's team.

Dr. Dybul also noted that, compared to the first STI, the majority of patients experienced a much slower rebound in HIV-RNA levels during the second STI that would require them to restart therapy (36 days vs. 184 days, respectively). "This was a fairly impressive finding," Dr. Dybul commented, "and Dr. Rosenberg's group has done a lot of elegant work demonstrating that, in fact, the immune response is broadening and is becoming stronger during treatment interruptions, which may well indicate why the patients are able to control their virus."

While the role of STIs in the setting of primary HIV infection appears promising, their potential in chronically infected patients—loosely defined as patients infected with HIV for more than six months—is not at all clear. Now, with 52-week follow-up data available from the Swiss-Spanish Intermittent Treatment Trial (SSITT), a more complete picture is coming into focus (Fagard, 2001).

SSITTI enrolled 133 patients being treated with HAART and having had a viral load less than 50 copies/mL for at least months. All patients underwent four STI cycles, composed of eight weeks on treatment followed by two weeks off. At 40 weeks, treatment would be discontinued through week 52, at which time it would be determined how many patients maintained a viral load below 5,000 copies/mL and, as a result, would be permitted to delay the reinitiation of treatment. At the 52-week mark, 24/133 (17%) patients had HIV-RNA levels below 5,000 copies/mL. After 96 weeks—56 weeks after the long break in treatment was initiated—only 6% had viral loads below this point.

"What we had here were less than desirable responses," Dr. Dybul said. "Some studies do suggest that autoimmunization can occur in a very small percentage of effectively treated chronically infected patients, but the benefit of autoimmunization in these patients out to a year off treatment is practically zero. At this point, what we need are clear insights into virologic and immunologic differences between acute and chronic autoimmunization strategies."

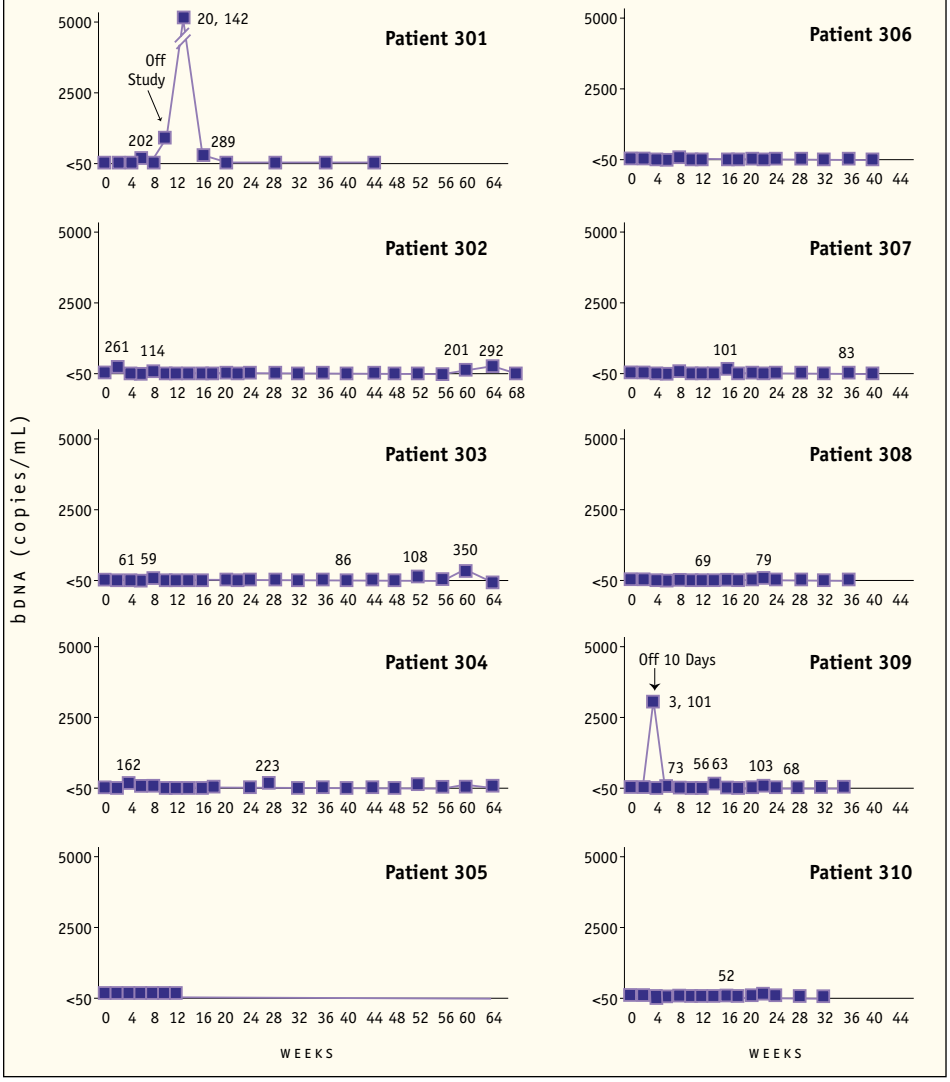
Less Time on Therapy: Is It Still a Reasonable Goal?

BEYOND THE POTENTIAL IMPACT OF STIS ON autoimmunization and the "conversion" of drug-resistant quasispecies to wild-type virus, lingering questions remain regarding the overall safety and effectiveness of continuous drug treatment in light of short- and long-term side effects, adherence issues, and the inevitable "burnout" faced by many patients after several years of complex drug therapy.

As discussed by Dr. Dybul in the September 2001 issue of *The PRN Notebook*, "It seems like every day a new toxicity is being promulgated from one or more of the agents we're using, not in everyone, but certainly in a significant number of patients. We have toxicities that can be quickly fatal, such as pancreatitis, and life-threatening toxicities that develop more slowly, such as liver damage and an array of metabolic complications." Dr. Dybul also pointed to a number of side effects that, while not life threatening, remain a major source of angst among HIV-positive patients. "Lipodystrophy and lipoatrophy are the modern-day equivalents of Kaposi's sarcoma," he added. "They are stigmatizing and remind patients every day that they are living with HIV and that it shows."

Dr. Dybul also commented that side ef-

FIGURE 1. Effect of Short-Cycle Intermittent Therapy on HIV-RNA



Ten patients receiving cycles of 7 days on HAART followed by 7 days off of HAART had measurements of plasma HIV-RNA after every other off-HAART period. The results are shown as HIV-RNA copies per ml of plasma as determined by branched-chain DNA assays (bDNA); all values >50 copies per ml of plasma are indicated at the designated time points. Patient 301 was removed from the study (arrow) after a 21-day interruption. Patient 309 had a 10-day interruption during the second off-drug cycle (week 4). Patient 305 withdrew from the study at week 12 for personal reasons.

Source: Dybul, 2001. Reprinted with permission of the *Proceedings of the National Academy of Sciences* and the National Academy of Sciences.

fects, along with the near-religious fervor with which these medications need to be taken, create adherence problems. "We need to have greater than 95% adherence, but in some patients adherence doesn't exceed 50%," he commented. "We, as physicians, are supposed to set our patients right about this. Yet, if you give physicians a 14-day course of antibiotics to take, only 40% of them will complete the full two weeks of therapy. And we're asking these patients to stick to their multiple daily regimens for the rest of their lives?"

There is also the fact that access to antiretroviral therapy, let alone its side effects and immune-boosting capabilities, is limited to approximately 5% of the HIV-infected world. "For patients in the developing world, side effects might be considered a luxury," Dr. Dybul wryly commented. "We clearly need treatment strategies that are both affordable and effective for people living with HIV in resource-poor areas. If we can find a way to reduce the total amount of drug needed by 30% or 50%, we may be talking about a much more affordable option."

Certainly, STIs with their stop-restart criteria dictated by predetermined CD4+ cell count and viral load margins are one approach to reduce the length of time a patient receives drug treatment. But such protocols are complex and probably best conducted in the setting of clinical research, given the explicit need—and exorbitant costs—of frequent laboratory monitoring. "STIs of this nature may not be applicable in many clinical settings, especially in resource-poor areas," Dr. Dybul commented. A philosophically different approach is that of structured intermittent therapy (SIT), generally defined as regular scheduled periods off treatment, regardless of steady-state HIV-RNA levels or CTL responses. "SIT is intended to spare patients from having to take medication on a continual basis, while at the same time maintaining clinical efficacy. Perhaps we can use SIT to reduce the costs of therapy and either slow, prevent, or reverse some of the side effects of HAART."

Structured Intermittent Therapy

SIT IS A LOWER-MAINTENANCE, LESS STYLIZED adaptation of the STI. It is, in essence, a pulsed-therapy approach to HAART—a relatively structured protocol to reduce overall drug exposure, regardless of immunologic outcome, without (hypothetically) compromising the long-term health of the patient. "It's about the benefits and drawbacks that come with being on and off treatment," Dr. Dybul said. "The key to SIT approaches is finding the balance."

At the heart of Dr. Dybul's discussion of SIT are two studies conducted at the National Institutes of Health. Dubbed the long-cycle and short-cycle SIT studies, significant amounts of data are now available to better understand this unique—and altogether unorthodox—treatment approach.

In the long-cycle study, which will ultimately enroll a total of 70 HIV-infected individuals, patients have been randomly assigned to receive either continuous HAART, or repeated cycles of eight weeks on HAART followed by four weeks off HAART. As this study is still ongoing, preliminary data continue to be reported at various congresses. Finalized data will be published once the study has been fully en-

rolled and sufficient follow-up data have been collected.

In the short-cycle study, 10 patients who had undetectable HIV-RNA levels while receiving a HAART regimen were switched to a predetermined four-drug regimen. This regimen was taken for seven days and then stopped for seven days, a cycle that was repeated for at least a year. Rigorous analyses of data from this study were published in the December 18, 2001, issue of the *Proceedings of the National Academy of Sciences* and orally reviewed, most recently, at the XIV International AIDS Conference in Barcelona (Dybul, 2001; 2002).

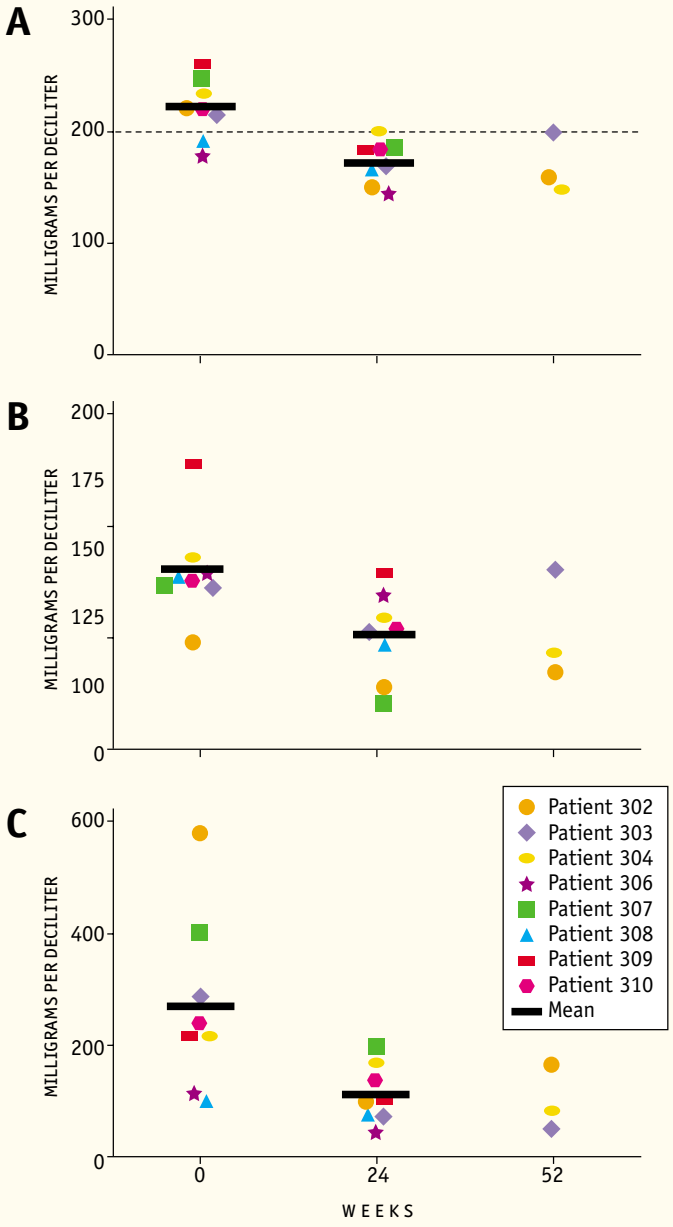
Long-Cycle SIT: Preliminary Data

HIV-POSITIVE PATIENTS WERE permitted to participate in the long-cycle SIT study provided that they had been successfully treated with HAART—defined as an undetectable viral load (below 500 copies/mL for at least six months—usually under the care of their own doctors. Patients also had to have a CD4+ cell count above 300 cells/mm;[3] the mean CD4+ count among patients entering this study was 740 cells/mm[3].

Dr. Dybul reported follow-up data involving 22 patients in the intermittent therapy arm followed for at least 52 weeks. Among these individuals, HIV levels rebounded to varying degrees when HAART was discontinued. Upon resuming therapy, Dr. Dybul was pleased to report that viral load consistently dropped to undetectable levels in most of the patients. "But we weren't able to do this in all of our patients," he said. "The reason appears to be resistance, which makes us a little concerned."

"We've all been a little weary of two-months-on, one-month-off study approach," Dr. Dybul admitted. "We knew that we would see rebounds in viral load during the one month off treatment and we speculated that we'd end up seeing results similar to those of the SSITT study, in that some patients wouldn't be able to bring their viral load back down to undetectable levels. Another concern is the fact that patients are highly infectious during a viral load rebound, which definitely increases the risk of transmission of HIV to a partner." These concerns gave way to a second SIT study idea: "We noticed that our patients rarely experienced a rebound in viral load during the first seven days off treatment. Therefore, we wanted to find out what would happen if we interrupted therapy every other week."

FIGURE 2. Effect of Short-Cycle Intermittent Therapy on Serum Cholesterol and Triglyceride Levels



Serum total cholesterol (A), low density lipoprotein cholesterol (B), and serum triglyceride levels (C) were determined before enrollment (week 0) and at 24 and 52 weeks of intermittent therapy. The mean levels are shown as indicated.

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Short-Cycle SIT: Published Results

AS DISCUSSED ABOVE, THE SHORT-cycle SIT study consisted of ten patients who had HIV-RNA levels below 500 copies/mL for at least six months as a result of a potent HAART regimen. After enrollment, all patients received ritonavir, indinavir, stavudine, and lamivudine in an intermittent schedule of seven days on therapy followed by seven days off therapy. The last dose of ritonavir was held at the end of each on-drug period to ensure more rapid clearance of the last dose of indinavir. Failure criteria were a 30% decline in CD4+ cell counts compared with baseline or an HIV-RNA level greater than 500 copies/mL on two consecutive determinations. The patients had laboratory and clinical evaluations at least every other off-treatment period.

Eight of eight patients who remained on the study regimen maintained viral load suppression for up to 68 weeks (see Figure 1). Two patients left the study, one for personal reasons at week 12 and one for protocol violations.

To evaluate the effect of short-cycle SIT on the frequency of replication-competent HIV in CD4+ cells, Dr. Dybul's team analyzed cell-associated RNA and proviral DNA. There was no difference in the mean HIV-RNA of 30.38 and 21.44 copies per million PBMCs at enrollment and after 24 weeks of SIT, respectively. In addition, there was no difference in the mean proviral DNA of 474 and 404 copies per million CD4+ cells at en-

rollment and after 24 weeks of SIT, respectively. "What's more, three patients maintained suppression of cellular HIV RNA and proviral DNA during 52 weeks of short-cycle SIT," Dr. Dybul added.

As for HIV-RNA in reservoir sites, inguinal lymph nodes were obtained from four patients after six months of SIT and from one of these patients at 52 weeks. There was no HIV-RNA detected by *in situ* hybridization and low levels of HIV-RNA per million PBMCs obtained at 24 weeks. "These observations were commensurate with those reported for individuals receiving continuous HAART," Dr. Dybul said.

As for CD4+ cells, there was no change in mean counts at enrollment compared to 24 weeks of SIT (921 cells/mm^3 vs. 900 cells/mm,^{3} respectively). In addition, there was no change in the mean CD4+ cell percentage at enrollment compared to 24 weeks of SIT (40% vs. 41%, respectively).

Of particular interest to Dr. Dybul's team were lipid-related side effects in the study (see Figure 2). Impressively, there was a significant decrease in mean serum cholesterol of 22% during the first 24 weeks of SIT. In addition, although 6/8 patients had total serum cholesterol above 200 mg/dL before SIT, none had levels greater than 200 mg/dL after 24 weeks in the study. These lower cholesterol levels were maintained up to 52 weeks in three individuals. Although one patient began receiving pravachol at week 20, he had already experienced a reduction in total cholesterol from 222 mg/dL at enrollment to 140 mg/dL at week 16 of SIT. What's more, there was a significant decrease in the mean level of LDL cholesterol, from a mean of 142 mg/dL at enrollment to a mean of 118 mg/dL after 24 weeks of SIT. There was also a significant decrease of 51% in triglycerides after 24 weeks of intermittent treatment.

As for lipid levels in the long-cycle SIT study, Dr. Dybul mentioned that significant decreases—at least in triglyceride levels—were, for the most part, not seen in patients undergoing intermittent treatment for 52 weeks. "The good thing here is that we didn't see any increases in triglyceride levels, which is usually the case in patients receiving continuous therapy."

SIT: The Potential Downsides

IF THERE IS ONE CENTRAL CONCERN MANY clinicians have regarding treatment interruptions, it is the potential for drug resistance. This has, in fact, been an issue in numerous treatment interruption studies conducted to date, the long-cycle SIT trial notwithstanding. As is discussed above, not all patients in the long-cycle SIT study were able to bring their viral loads back down to undetectable levels after each treatment interruption. "We had four patients receiving efavirenz who developed the K103N mutation during the fourth, fifth, or sixth interruption," pointed out Dr. Dybul. "We also had several patients who developed the M184V mutation while taking a protease inhibitor-based regimen, resulting in lamivudine resistance. While we did learn that four of these patients had lamivudine resistance before starting SIT, two additional patients developed lamivudine resistance while in the study."

As a rule of thumb, Dr. Dybul pointed out that patients who experienced a high rebound in HIV-RNA during their treatment interruptions were the most likely to develop mutations down the line. "Among patients who developed resistance, the mean viral load rebound while off therapy was 30,000 copies/mL, compared to a mean increase of 1,500 copies/mL among patients who maintained wild-type virus. "The bottom line is that there's a possibility of resistance in patients taking either protease inhibitors on NNRTIs."

In the short-cycle SIT study, no patients developed new resistance-conferring genetic mutations during the course of the trial, nor did any patient develop phenotypic evidence of decreased susceptibility to the available antiretroviral drugs during up to 52 weeks of SIT.

Concluding Remarks

GENERALLY SPEAKING, TREATMENT INTERruptions are not yet being recommended by experts for use in the clinical setting, except in patients who have high CD4+ cell counts and low viral loads at the time therapy was initially started; that is, if patients want to stop therapy because of side effects or the fear of developing toxicities. "This is a clinically relevant group of patients who I think a lot of clinicians are now comfortable saying, 'yes, it's okay to stop treatment.' Obviously, these patients need to be followed carefully, just as clinicians would follow untreated patients."

For everyone else, which includes patients in the "salvage" stage of treatment and patients who want to base treatment interruptions on predetermined times or laboratory changes, STIs are not recommended outside of clinical studies. As clearly illustrated by Dr. Dybul, long-cycle intermittent therapy carries substantial risks of drug resistance and, quite possibly, an increased risk of transmission because of the increase in viral load.

As for the potential benefits, "decreases in toxicities and costs are important and need to be weighed carefully against the potential drawbacks of treatment interruptions," Dr. Dybul said. "For example, if you get a 10% increase in resistance and a 70% decrease in toxicities over time, is that enough of a justification in this country to do the treatment interruptions or intermittent therapy? For some patients you might think that that is a good idea. On the other hand, if you get a 10% increase in resistance and no decrease in toxicities, that probably is not a very beneficial clinical approach. On the other hand, if you are talking about Africa, where you might have an increase in resistance of 10% but a decrease in cost of 50%, that might be a reason in and of itself regardless of what happens in toxicities to pursue these approaches." prn

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