Perspective

Where Do Strategic Treatment Interruptions Fit in the Management of HIV Infection?

At the International AIDS Society–USA course in Chicago in April 2002, W. Keith Henry, MD, reviewed recent findings in studies of strategic treatment interruptions in the settings of acute HIV infection, chronic infection, and the management of virologic failure. He discussed the implications of these findings for clinical practice and the need for further research in this area.

From the beginning of the AIDS epidemic until 1996, the major focus of HIV clinical research was the development of effective antiretroviral therapy. The introduction of potent antiretroviral therapy regimens and the availability of quantitative plasma HIV-1 RNA measurements revolutionized the treatment of HIV infection in resource-rich countries (Palella et al, *N Engl J Med*, 1998; Mellors et al, *Ann Intern Med*, 1997). Until that time, the concept of stopping effective therapy understandably received little attention.

Studies of the immunology of HIV infection led to new understanding about the typical consequences of the use of potent antiretroviral therapy in the setting of established HIV infection. In most instances, potent antiretroviral therapy results in reconstitution of much of the immune system except for HIV-specific immunity (Pitcher et al, *Nat Med*, 1999). Additional research revealed that a reservoir of HIV persists in patients treated with potent antiretroviral therapy, and projections for the time needed before a theoretical cure could be achieved ranged from 10 years to infinity (Finzi et al, *Science*, 1997). Coupled with new concerns about the long-term toxicity of antiretroviral therapy (Carr et al, *Lancet*, 2000), these insights provided incentive to explore alternatives to the use of early, continuous potent antiretroviral therapy for the long-term management of HIV infection.

The description of the "Berlin patient" (Lisziewicz et al, *N Engl J Med*, 1999), in whom interruption of antiretroviral therapy was followed by spontaneous control of HIV infection, introduced the concept of treatment interruption following use of potent antiretroviral therapy soon after HIV infection. Since then, there have been several other reports involving discontinuation of potent therapy either in the setting of chronic HIV infection (Ortiz et al, *J Clin Invest*, 1999) or with a focus on immunologic factors associated with control of HIV viremia (Papasavvas et al, *J Infect Dis*, 2000). The concept of strategic treatment interruptions (STIs) as a strategy to be studied prospectively was introduced in the clinical setting of acute human HIV infection (Rosenberg et al, *Nature*, 2000) and in the laboratory setting of acute simian immunodeficiency virus infection (Lori et al, *Science*, 2000). Soon thereafter, STIs were studied in patients receiving successful treatment for chronic HIV infection (Dybul et al, *Proc Natl Acad Sci USA*, 2001; Hirschel et al, 9th CROI, 2002, Abstract 528-M) and in patients with highly resistant HIV in whom potent therapy was failing (Miller et al, *AIDS*, 2000; Deeks et al, *N Engl J Med*, 2001). Finally, the use of intermittent therapy was proposed as a way to reduce drug exposure, thus possibly reducing toxicity and costs, but without the intention of stimulating enhanced anti-HIV immunity.

Terminology

An increasing number of terms are being used to refer to different aspects of stopping and starting potent antiretroviral therapy. There is no consensus as to precise definitions to describe different scenarios. "Strategic treatment interruption" is often used as an all-encompassing term to describe situations in which potent antiretroviral therapy is stopped in a planned manner for a specific purpose. Some have proposed that "STI" be used only in situations in which the objective of the treatment interruption is to boost anti-HIV immunity. The terms "intermittent therapy" and "pulse therapy" have been used to refer to treatment interruption with the aim of decreasing drug exposure to minimize cost and toxicity. Use of treatment interruption in the management of virologic failure, also termed "salvage therapy," has a more virologic or clinical focus; the goal in this setting is to induce reversion of the principal HIV quasi species to the drug-sensitive wild-type, thus increasing the chances for successful viral suppression with the use of recycled drugs. For the purposes of this discussion, the topic of treatment interruptions is organized according to immunologic focus (boosting HIV-specific immunity), virologic focus (managing treatment failure), and the focus of decreasing drug exposure to reduce cost and toxicity.

Immunologic Focus

Acute Infection

A number of small studies of treatment interruption in patients with acute HIV infection have been reported. Walker and colleagues, for example, found that plasma viremia rebounds tended to become smaller with successive interruptions, with 5 of 8 patients initially studied maintaining a plasma HIV-1 RNA level of less than 5000 copies/mL after 5 to 9 months off therapy (Rosenberg et al, *Nature*, 2000). Patients showed evidence of stimulation of HIV-specific CD4+ helper T cell and CD8+ cytotoxic T lymphocyte (CTL) response. Similar findings have been reported elsewhere (Yu et al, 9th CROI, 2002; Hoen et al, 9th CROI, 2002).

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Chronic Infection

The relative success observed with STIs in acute HIV infection led to interest in applying a similar strategy to patients with chronic HIV infection with long-term, high-level viral suppression on potent antiretroviral therapy. The Swiss-Spanish Intermittent Therapy Trial (Hirschel et al, 9th CROI, 2002, Abstract 528-M; Hirschel, 9th CROI, 2002, Abstract S18) may be the best study of treatment interruption in chronic infection to date. This study examined the effect of 4 off/on cycles (2 weeks off then 8 weeks back on potent antiretroviral therapy) in 133 patients with initial plasma HIV-1 RNA levels below 50 copies/mL and CD4+ counts above 300 cells/µL. At the end of the 4 cycles (40 weeks), treatment was stopped until viral rebound occurred (>5000 copies/mL). A primary study measure was the proportion of patients maintaining plasma HIV-1 RNA levels of less than 5000 copies/mL at week 52.

Patients had received no antiretroviral treatment before initiating potent therapy, and in order to prevent the promotion of high-level resistance with treatment interruption, they did not receive nonnucleoside reverse transcriptase inhibitors (NNRTIs). Prior to beginning potent antiretroviral therapy, patients had a median CD4+ cell count of 398/µL and a median plasma HIV-1 RNA level of 4.5 $\log_{10}$ copies/mL. They had been receiving therapy for a median of 26 months and had maintained plasma HIV-1 RNA levels below 50 copies/mL for a median of 21.5 months. At the start of the study, median CD4+ cell count was 740/µL.

Of the 133 patients, 43 dropped out of the study during the initial 40-week period of STIs and another 23 withdrew during the 12-week period after stopping therapy. Of the 67 remaining patients, 23 were considered responders for maintaining plasma HIV-1 RNA levels of less than 5000 copies/mL at week 52. Responders had a significantly lower median plasma HIV-1 RNA level prior to treatment than did nonresponders (4.09 $\log_{10}$ vs 4.57 $\log_{10}$, P=.002), as well as a nonsignificantly greater median CD4+ count (441 vs 392 cells/µL). Absence of viral rebound during the first 2-week treatment interruption significantly predicted response at week 52 (odds ratio, 5; P<.001). At week 2, 15 (65%) of 23 responders had no viral rebound, compared with 30 (27%) of 110 nonresponders.

Among 61 patients with week-52 data, there was a significant increase in levels of HIV-specific CTLs from the start of the study, suggesting induction of HIV-specific immune response. However, responders had significantly lower HIV-specific CTL levels than did nonresponders. This finding indicates that increased CTL response is associated with exposure to the HIV antigen during viremia, but is not predictive of low viremia after treatment interruption.

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The overall conclusion of the Swiss-Spanish Intermittent Therapy Trial was that use of STIs to stimulate HIV immunity (ie, "autovaccination") in the setting of chronic HIV infection cannot be recommended. Other small trials have also found little evidence of virologic or immunologic benefit with STIs in chronic infection (Carcelain et al, *J Virol*, 2001; Ruiz et al, AIDS, 2001). However, reports of the concept's demise might be premature. It could be that the criterion of plasma HIV-1 RNA level less than 5000 copies/mL was too stringent a standard for response and that longer follow-up would have revealed reductions in plasma HIV-1 RNA level in additional patients over time. It would also have been of interest to investigate the effects of interruptions on CD4+ cell counts over time in these patients to determine whether there were potential immunologic benefits to the approach.

Virologic Focus

A substantial number of patients experience failure of successive antiretroviral regimens. For many of these patients, resistance studies indicate that their predominant HIV strain is resistant to most or all of the available drugs and their treatment options are very limited. The concept of interrupting antiretroviral therapy in the setting of persistent or increasing viremia as a means to reestablish a dominant population of drug-sensitive virus is attributed to Miller and colleagues (AIDS, 2000). They reported data from a cohort of 48 patients with treatment failure and multidrug-resistant virus who underwent a treatment interruption of at least 2 months. During the treatment interruption, plasma HIV-1 RNA level increased by a mean of 0.7 $\log_{10}$ and CD4+ count decreased by a mean of 89 cells/µL. A complete shift to wild-type virus was observed in 28 of the 45 subjects with phenotypic data at baseline and follow-up and was associated with a higher baseline CD4+ count (mean of 192 vs 59 cells/µL, P=.007). Better response to reinitiation of therapy was related to lower baseline plasma HIV-1 RNA levels prior to treatment interruption, number of active drugs used, and shift to wild-type virus.

In a subsequent study, Miller and colleagues (Sabin et al, 8th CROI, 2001) assessed the effect of treatment interruption and reinitiation of therapy in 252 patients in whom prior treatment had failed. At baseline, prior to the treatment interruption, patients had a median CD4+ cell count of 207/µL and a median plasma HIV-1 RNA level of 4.84 $\log_{10}$ copies/mL. The pretreatment nadir CD4+ cell count was 70/µL with a median peak plasma HIV-1 RNA level of 5.9 $\log_{10}$. The median length of the treatment interruption was 4.3 months. A median of 3 drugs were restarted. The median CD4+ cell count at the end of the treatment interruption was 93/µL with a median increase in plasma HIV-1 RNA level of 0.45 $\log_{10}$. Multivariate analysis of the data from 182 subjects reinitiating treatment identified CD4+ count and plasma

HIV-1 RNA level at the start of the treatment interruption and the number of drugs started as independent predictors of treatment response.

Observations from the original cohort indicate, however, that there is significant risk associated with treatment interruption. While virus is recovering drug susceptibility, plasma HIV-1 RNA levels increase and CD4+ cell counts fall, with the decrease in the original cohort being from 155/µL to 49/µL over 12 weeks. Such decreases pose considerable risk for opportunistic disease.

Deeks and colleagues reported on the use of STI in the setting of chronic failure of a protease inhibitor-based regimen (*N Engl J Med*, 2001). For 22 subjects studied, the baseline median CD4+ cell count was 217/µL and plasma HIV-1 RNA level was 4.6 $\log_{10}$ copies/mL (minimum of 2500 copies/mL). The patients had been on protease inhibitor-based therapy for 36 months and virologic failure had been present for 31 months. During STI of a median duration of 20 weeks, there was a median increase in plasma HIV-1 RNA level of 0.74 $\log_{10}$ copies/mL and a median decrease in CD4+ cell count of 88/µL. A complete shift to drug-sensitive virus at around week 6 to week 8 was seen for protease inhibitors in 18 subjects and nucleoside reverse transcriptase inhibitors in 16 subjects. However, resistant virus was still detectable in the circulating lymphocytes of most patients. Forty-eight weeks of salvage therapy in 23 patients resulted in a 2.9-$\log_{10}$ median decrease in plasma HIV-1 RNA level and a median increase in CD4+ cell count of 121/µL. The overall change in plasma HIV-1 RNA level from baseline (before STI) was a 2.1-$\log_{10}$ decrease. However, the increase in CD4+ cell count during salvage therapy produced no net change in count from the pre-STI baseline. Clinical events did occur during the CD4+ cell nadir period of the STI, including *Pneumocystis carinii* pneumonia, non-Hodgkin's lymphoma, progressive Kaposi's sarcoma and death, and advanced AIDS and death.

> Use of treatment interruptions in failing therapy to induce a shift in predominant HIV species from drug-resistant to drug-susceptible has some merit but considerable clinical risk

The conclusions of the study by Deeks and colleagues were that antiretroviral treatment produces immunologic and virologic benefit despite persistent viremia and reduced drug susceptibility of virus during chronic antiretroviral failure. The benefit reflects continued antiretroviral activity and the maintenance under antiretroviral pressure of resistant strains. These resistant strains have reduced replicative capacity compared with the drug-susceptible strains that are present before therapy and that reemerge upon treatment interruption. Durable resuppression was achieved if the new regimen after STI contained at least 1 drug active against pre-STI isolates.

Experience with "drug holiday" treatment interruptions comes from the EuroSIDA study population (Lundgren et al, 9th CROI, 2002). Among 3610 patients starting potent antiretroviral therapy, 565 (10%) stopped therapy, with 49% restarting treatment. After adjustment for demographic variables, the relative risk for an AIDS-defining event or death was 6 for 3 months off treatment. After adjustment for the most recent CD4+ cell count and plasma HIV-1 RNA level, the relative risk was 2.4 for 6 months off treatment. Overall, risk was closely linked to CD4+ cell count, and was highest for CD4+ cell count less than 200/µL.

These studies suggest that the use of treatment interruptions in the setting of failing antiretroviral therapy as a strategy to induce a shift in predominant HIV species from drug-resistant to drug-susceptible has some merit but considerable clinical risk. More studies are needed to further evaluate which patient populations might benefit from such a strategy and to determine the long-term risks and benefits.

Focus on Reducing Drug Exposure in Chronic Infection

For the large number of patients with chronic HIV infection who are doing well on antiretroviral therapy, there is interest in developing strategies to decrease drug costs and toxicities by decreasing the time on treatment. One such approach was used in a pilot study of 10 subjects utilizing short on-and-off cycles of therapy (1 week on and 1 week off) (Dybul et al, *Proc Natl Acad Sci USA*, 2001). That approach was selected based on observations from other STI studies indicating that the time to detectable viremia when fully suppressive therapy was stopped usually exceeded 1 week. The results of that study demonstrated the feasibility of reducing the amount of antiretroviral therapy by 50% over a 1-year period while maintaining suppression of HIV, preserving CD4+ cell counts, and reducing markers of toxicity. Four subjects in that study utilized an NNRTI-based regimen and 6 subjects used a protease inhibitor-based regimen. No resistance was observed, although there is concern about using NNRTI-based regimens in situations in which longer on-and-off cycles are employed. Some benefit in terms of reduction in metabolic toxicity was also observed in the form of significant reductions in serum triglyceride and low-density lipoprotein cholesterol levels.

Another approach to decreasing drug exposure is to focus on the CD4+ cell count as the key marker for starting and stopping therapy. In order to consider such an approach, data are needed regarding the effect on CD4+ cell counts of stopping suppressive therapy. One study (Tebas et al, 1st IAS Conf, 2001) examined CD4+ cell count changes in 72 patients who interrupted suppressive therapy. These patients had a median baseline plasma HIV-1 RNA level of 108,146 copies/mL and maintained levels below the limit of assay detection for 36 weeks. The median CD4+ cell count at the time of stopping therapy was 571/µL

and the prior nadir count was 272/µL.

During a mean follow-up of 45 weeks after stopping therapy, the average drop in CD4+ count was 16 cells/µL per month (interquartile range, -6 to -34 cells/µL per month). The CD4+ cell decay was more rapid during the first several months off therapy, as was observed in the Swiss-Spanish Intermittent Therapy Trial. The plasma HIV-1 RNA level almost always rebounded to the pretreatment level. On multivariate analysis, only the CD4+ cell count gain on therapy significantly predicted the rate of decay—that is, the patients who gained more cells on therapy lost more cells after stopping therapy. Eleven patients restarted therapy and viral suppression was initially achieved in each, although viral rebound subsequently occurred in two. Four patients whose CD4+ cell counts dropped below 200/µL while off therapy developed an AIDS-defining event or serious infection (sepsis in one, wasting in one, and *Pneumocystis carinii* pneumonia in two). None of the patients developed acute retroviral syndrome.

A recent observational study examined outcomes when treatment was discontinued in patients with marginal indications for starting treatment (Parish et al, 41st ICAAC, 2001). All patients had CD4+ cell counts that never fell below 200/µL and no history of AIDS-defining events, and all had the intention to resume therapy based on plasma HIV-1 RNA or CD4+ cell count criteria or clinical criteria. Among the 62 patients studied, the major reasons for stopping therapy were lack of indication for treatment (44%), nonadherence (18%), and toxicity (18%). After stopping therapy, plasma HIV-1 RNA level returned to pretreatment levels.

Sixteen (26%) of the patients resumed therapy after a mean of 36 weeks, and 46 patients (74%) were still off therapy after a mean of 64 weeks. The major reasons for resuming therapy were increased plasma HIV-1 RNA level alone (37%) and increased plasma HIV-1 RNA level with decreased CD4+ cell count (31%). The pretreatment CD4+ cell count nadir for the patients resuming therapy was 389/µL versus 442/µL for the patients not resuming therapy. The estimated time to CD4+ cell count of less than 200/µL after stopping therapy, based on the observed rate of decay, was a median of 0.8 years in those resuming treatment and a median of 2.7 years in those not resuming treatment. With multivariate analysis, pretreatment plasma HIV-1 RNA levels were associated with resumption of therapy and pretreatment CD4+ cell count nadir was associated with the rate of CD4+ decline during treatment interruption. Viral suppression to pre-interruption levels occurred in most of the patients resuming treatment, although not all patients had sufficient follow-up to determine whether maximal reductions had occurred. Among patients in whom plasma HIV-1 RNA level was reduced to less than 50 copies/mL, reduction to this level occurred at an average of 20.1 weeks after resuming treatment. Among patients with suppression to 50 to 400 copies/mL, reduction to this level occurred at an average of 12.3 weeks.

Findings in these studies suggest that the best candidate patients for pulse therapy or treatment interruption are those with lower plasma HIV-1 RNA levels and higher CD4+ cell counts at baseline prior to starting therapy. However, these approaches require examination in randomized controlled trials.

Conclusions

Large randomized trials are needed to further evaluate the potential roles of STI. A number of studies are already in progress. The Strategies for Management of Antiretroviral Therapy (SMART) Study is a randomized trial examining long-term (7- to 9-year) clinical outcomes in 6000 patients assigned to a viral-suppression arm or a drug-conservation arm. The viral-suppression strategy is continuous use of potent antiretroviral therapy to achieve the lowest plasma HIV-1 RNA levels possible. The drug-conservation strategy consists of using potent antiretroviral therapy when the CD4+ count falls to less than 250 cells/µL and stopping therapy when the CD4+ count is greater than 350 cells/µL.

In the STACCATO trial, 600 patients with viral suppression on antiretroviral therapy are being randomized to 1 of 3 treatment arms: continuous therapy; 1 week on therapy, 1 week off therapy; and pulse therapy based on CD4+ cell counts (treatment only if CD4+ cell count is <350/µL). All patients will receive potent antiretroviral therapy from month 24 to month 27. The primary study outcome measures are the proportion of subjects with plasma HIV-1 RNA level below 400 copies/mL and the proportion of subjects with CD4+ counts above 350 cells/µL at month 27. In addition, the AIDS Clinical Trials Group Study A5102 is examining whether increases in CD4+ cell count induced by interleukin-2 can prolong treatment pauses. The purpose of this study is to assess the rate of CD4+ cell count decline after stopping treatment in 80 patients receiving 24 weeks of potent antiretroviral therapy with or without 3 1-week cycles of moderate-dose interleukin-2. Treatment is to be resumed when CD4+ cell counts fall to below 350/µL.

> The best candidate patients for "pulse therapy" may be those with lower HIV RNA levels and higher CD4+ counts at baseline prior to starting therapy

The relative dearth of controlled study data on STIs makes it difficult to answer the question of whether treatment interruption has a role in current clinical management. STI can be used in the setting of primary HIV infection, but use in a research setting is recommended until any utility of the approach is proved. The strategy should not be used in the setting of chronic infection as a way of stimulating HIV-specific immunity. It may be used to minimize drug exposure in the setting of chronic infection in patients with high nadir pretreatment CD4+ cell counts (eg, >350/µL) and lower pretreatment HIV-1 RNA levels (eg, <100,000 copies/mL); however, it is prudent to use the approach only in the research setting since its long-term

safety is unproven. Recent data (Douek et al, *Nature*, 2002) has demonstrated that HIV-specific CD4+ T cells are preferentially infected by HIV in vivo, suggesting that viremia during treatment interruptions results in further impairment of HIV-specific immunity. Use of this approach only in the research setting is especially recommended for patients with lower pretreatment CD4+ cell counts and higher plasma HIV-1 RNA levels. Extreme caution is warranted in the use of STI in treatment-experienced patients, particularly in patients with low CD4+ cell counts. In this setting, the virologic benefit achieved may come at a high immunologic and clinical cost. If use of the strategy in this setting is contemplated, enrollment in a research study would be the best option.

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