Commentary

Structured intermittent treatment for HIV disease: Necessary concession or premature compromise?

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The entree of potent antiretroviral therapy into the therapeutic armamentarium of HIV disease was an extraordinary moment in the history of the AIDS epidemic. Mortality declined, morbidity diminished, hospitalizations decreased, and the transition of HIV from a hospital-based to an outpatient disease commenced (1). The guiding principles of antiretroviral therapy were grounded on landmark studies of HIV viral dynamics and our understanding of drug resistance (2, 3). The production of 10 million particles of HIV daily combined with the knowledge that viral load predicted HIV disease progression provided the rationale to treat HIV with multidrug regimens that maximally suppressed viral replication (4, 5). Selection of HIV drug resistance and viral rebound were reduced by using therapies that initially suppressed HIV RNA levels in the plasma below 20 copies/ml (6). On the contrary, any reduction in regimen potency—either through simplification of therapy or through suboptimal patient adherence—led to rapid virologic failure and eventual drug resistance (7–10). Continuous lifelong therapy was thus adapted as the optimal treatment approach for HIV disease.

The clinical paradigm of treating HIV disease from the onset of infection, for life, is now under intense scrutiny. HIV therapy unequivocally reduces the risk for HIV-related complications. Yet HIV, despite early optimistic projections to the contrary, is unlikely to be eradicated even with decades of therapy (11–14). HIV therapy itself has produced an entirely new set of serious complications for HIV-infected patients including body deformities, insulin resistance, lactic acidosis, osteoporosis, neuropathy, osteonecrosis, lipid abnormalities, and cardiovascular disease (15). Most disconcerting is the fact that both the mechanisms of these toxicities as well as the long-term consequences are unknown. Several strategies are under investigation to address the conundrum that interventions may harm the host more than the virus before progression to AIDS. These strategies include the development of less toxic drugs and regimens and immune-based therapies. In practice, the nihilist approach of simply delaying therapy until absolutely necessary has generated the most enthusiasm, and is now endorsed in official treatment guidelines (U.S. Department of Health and Human Services and the Henry J. Kaiser Family Foundation, available at http://www.hivatis.org/trtgdlns.html). There is some uneasiness within the field about the wisdom in this rather extreme shift in thinking, which has been generated by studies of relatively short duration.

Structured treatment interruption (STI) represents a less extreme strategy aimed at reducing dependence on antiretroviral drugs. The original interest in this approach was based on the concept of ''auto-vaccination.'' In theory, increased exposure to autologous virus through treatment interruptions in patients with viral suppression could stimulate HIV-specific immune responses and attenuate viral rebound. This approach may be most effective in patients treated immediately after HIV infection where HIV-specific immune responses are preserved and viral escape mutants have not been selected (16). Indeed, in macaque monkeys treated immediately after acute simian immunodeficiency virus infection, subsequent repeated treatment interruptions lead to enhanced cytotoxic T lymphocytes (CTL) responses and diminished viral rebound compared with animals receiving continuous therapy (17). Results from human studies are enticing, but inconsistent and inconclusive, and use of a therapeutic vaccine as opposed to treatment interruptions as a vehicle to stimulate CTL responses may be more fruitful (18).

Interventions may harm the host more than the virus before progression to AIDS.

Even if STI proves useful in patients with acute HIV infection, among the millions of individuals with HIV disease only a tiny proportion accesses care during primary infection. Small and nonrandomized studies of STI in patients with chronic infection suggest that HIV-specific immune responses are boosted in some patients with STIs (19, 20). The clinical significance of these *in vitro* responses have yet to be proven. In one study, where therapy was discontinued in patients after five cycles of STIs of 2- to 12-week duration, HIV RNA levels rebounded to a steady-state level below the pretreatment level in only 10% of patients.[†] After the STIs, HIV RNA levels in the rest of this cohort rose to a magnitude greater than or equal to initial levels. Although these results are not encouraging from a clinical standpoint, identification of the host factors or virus characteristics that distinguish patients who exhibit attenuated viral rebound in this setting could provide important insights into HIV protective immunity.

Another strategy aimed at reducing drug exposure is flexible STI schedules where reinstitution of therapy is dictated only by CD4 cell count, without regard to HIV RNA levels. Here, a patient who has achieved a CD4 cell count above a certain threshold, such as 500 cells/ml with therapy, would interrupt therapy until CD4 cell counts declined to a threshold such as 250 cells/ml. The purpose of this approach is to maintain immune function at a level that does not put the patient at risk for HIV-related complications with the least amount of therapy necessary. Studies are underway to address the risks and benefits of this approach.

There are both hypothetical and documented negative consequences for patients attempting treatment interruptions. Considering the potential detrimental outcomes of the currently outlined STI approaches, interrupting

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[†]Fagard, C., Lebraz, M., Gunthard, H., Tortajada, C., Garcia, F., Battegay, Furrer, H. J., Vernazza, P., Bernasconi, E., Ruiz, L., *et al.*, 8th Conference on Retrovirus and Opportunistic Infections, Feb. 4–8, 2001, Chicago, abstr. 357.

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therapy in patients with chronic HIV disease remains confined to the research setting. Selection of drug-resistant virus, failure to resuppress virus upon therapy re-initiation, reseeding of cellular reservoirs, diminished adherence, and increases in central nervous system viral load all have been reported with STIs (19, 21, 22).[†‡] Interestingly, a small proportion of patients develop a clinical syndrome mimicking the acute HIV primary infection syndrome, suggesting a replay of viral dynamics and host response (23, 24). Theoretically, patients with viral rebound will have an increased risk to transmit HIV compared with patients receiving continuous therapy who have suppressed viral load (25). This increased risk would apply both for horizontal transmission among adults and for vertical transmission to infants among pregnant women (26).

If rebound of HIV is the major risk both for the individual and from a public health standpoint for STI strategies, then the following question is begged. What if therapy could be interrupted for a time period that was insufficient for viral rebound to occur? In a recent issue of PNAS, Dybul *et al.* (27) present their observations from a study designed to address that specific question. Abandoning the rationale that stimulation of HIV-specific immunity was necessary for the success of STI, this group instead aimed at reducing drug exposure in a manner that minimized risks associated with viral rebound, yet maintained the immunologic benefits of therapy. They selected the duration of treatment interruption by examining the dynamics of viral rebound in a small, intensely studied cohort of patients with chronic infection who interrupted therapy (28). Up to 7 days after treatment interruption, HIV RNA levels in the plasma among this cohort remained below 50/copies, a threshold that is a harbinger of virologic failure. In Dybul *et al*.'s pilot study of structured intermittent therapy (SIT), 10 patients with chronic HIV disease achieving virologic suppression on a potent antiretroviral regimen for at least 6 months initiated a treatment schedule 7 days of treatment interruption followed by 7 days of treatment.

Observations from this cohort treated with 7-day SIT are preliminary, but nevertheless are both fascinating and important. In eight of the subjects, neither viral rebound nor new drug resistance mutations have been detected for up to a year. Limiting the treatment interruption period to 7 days proved essential. The two patients with virologic rebound above 400 copies both discontinued therapy for 10 and 21 days. CD4 cell counts remained stable during follow-up. There was a significant decrease in serum triglyceride and cholesterol levels. Although temporary success of the 7-day SIT strategy was perhaps predicted by prior data, the durability of the success is quite remarkable. We know that even patients with low viral loads receiving therapy have evidence of productive viral infection and the capacity to select for drug resistant populations. The relatively high viral load set points, the repeated treatment interruptions, the sequential therapy, and documented drug-resistant mutants identified at baseline all increase risk for virologic rebound in this cohort. One factor that may have contributed to the virologic success in these patients is that the treatment regimen used during the SIT was probably more potent than the therapy the patients had been receiving continuously during prior chronic therapy. Thus both a short period of interruption and an augmented potent treatment regimen may be key elements to this strategy.

Reduction in lipids has been previously reported in patients discontinuing antiretroviral therapy (29), but this is the first longitudinal study where continued treatment in the form of SIT was associated with a reduction in lipids (27). This observation must be considered preliminary. It is entirely possible that the co-incident increased awareness among the HIV community that a low-cholesterol diet was the explanation for diminished lipid levels. Nonetheless, the plausibility that lipids were reduced because of SIT is increased by observations among other cohorts and the fact that the drug regimen used during the SIT is associated with a greater risk for lipid disturbances than the regimens some of the patients were receiving before study initiation (30).

Are we outsmarting the virus, or once again, will the follies of our thinking be exposed?

There are many caveats to Dybul *et al*.'s study (27). The patient cohort is a small, highly select group of individuals that may not represent the HIV population under treatment. Differing half-lives among antiretroviral agents and the potential to expose HIV to monotherapy using other drugs combinations is another issue. If the success of SIT depends on the single regimen used in the Dybul *et al*. study, the ultimate applicability would diminish. Larger randomized trials and trials using alternate drug regimens need to be conducted. The ability for patients to adhere to SIT also would play a major role in the success of this approach. Although lowered lipids might motivate some patients, the prospect that SIT would reduce the severity of body habitus changes might provide a greater impetus for adherence to SIT regimens. These data also open the door for studies of other brief periods of treatment interruption.

From a global health perspective, one of the greatest challenges today is availing life-saving antiretroviral therapies to the millions of patients dying from HIV disease in resource-poor settings (31). Drug costs are one of many major obstacles to global access to HIV therapy. In fact, in Africa, interrupted therapy caused by lack of funds is more the norm than continuous therapy. These treatment interruptions at present are unplanned and chaotic. Determining the most efficacious way to administer intermittent therapy in countries with constrained resources would provide key information for health policy makers. Two appealing features of 7-day SIT for the developing world is that drug costs would be reduced and the public health benefits of reducing risk of HIV transmission by continuous therapy probably would not be lost. Not withstanding, it is both naïve and simplistic to bank on SIT as the solution. Instead, exploration of SIT strategies in both the developed and developing world should occur and will likely be catalyzed by self- interests of both constituencies.

Over the last two decades, it is evident that HIV is a formidable opponent, adapting to humans in a remarkably effective way and decimating populations on a trajectory unsurpassed in history. At the end of the day, one is left wondering whether advocating less therapy for this virus represents a cutting-edge strategy, a necessary concession, or a shortsighted, premature compromise. Are we outsmarting the virus, or once again, will the follies of our thinking be exposed? In view of the enormity of the HIV epidemic, I think we are obligated to urgently pursue the evaluation of novel therapeutic strategies with available drugs such as that presented by Dybul *et al*. (27). The priorities of HIV prevention efforts and drug and vaccine development will take time to realize, and in the meantime, we must pursue opportunities that offer a chance to improve quality of life for chronically infected patients and to increase global access to therapy.

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