Clinical Challenge

Patients Who Want to Stop Their Medications: Treatment Interruption in HIV Infection

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Introduction

Typically referred to as structured treatment interruption (STI), the concept of discontinuing HIV medication, even for a brief period, is being assessed for several reasons, not the least of which is patient convenience. The cases presented here represent 3 situations in which patients and their providers need to discuss the risks and benefits of stopping antiretroviral therapy.

Case 1

AM is a 48-year-old woman with a lifelong history of polysubstance abuse and anxiety. She was clean for 8 years in the 1990s, briefly relapsed in 2000, and has again been receiving methadone since November 2001. Her HIV infection was diagnosed in 1994, and she began receiving zidovudine and didanosine sequentially. Her nadir CD4+ cell count was 60/µL. She had no opportunistic infections but complained intermittently of peripheral neuropathy. Her anxiety limited her ability to drive and interact with others. She was tortured by being infected with HIV and worried that any sneeze or bruise was "the beginning of the end." She took lorazepam 3 times a day and struggled not to take twice as much. In 1996, AM began a HAART regimen with indinavir, stavudine, and lamivudine; her viral load became undetectable, and her CD4+ cell count rose to 310/µL. She was thrilled with these results and never missed a dose. Her peripheral neuropathy remained fairly stable.

By 2000, she was noting clear evidence of lipoatrophy. The veins in her arms and legs were very prominent, her extremities were increasingly thin, and worsening facial wasting developed. These
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physical changes upset her, but she was adamantly opposed to changing her regimen. When a regimen without protease inhibitors was suggested, she flatly refused. She wanted no medication that would interact in any way with her methadone. She was thin to begin with, and her weight slowly declined to under 50 kg (111 lb), with her facial features becoming still more gaunt. Her boyfriend was also HIV-positive and was receiving care at another facility. In 2001, she asked that her indinavir be changed to a boosted dose. She was cautioned that this might affect her methadone treatment, but she insisted, stating that her boyfriend was receiving boosted indinavir and doing well. Ritonavir was added to her regimen, and indinavir dosing was reduced to twice a day. She claimed to have no difficulty with this adjustment; yet her weight declined further, and she frequently vomited after taking her medications. In 2002, AM reported that her boyfriend’s antiretroviral medications had been discontinued and she wanted the same.

Case 2

EG is a Spanish-speaking man from Puerto Rico in whom HIV infection was diagnosed in 1995. He came to the clinic for the first time in June 2001, after having received care at an outside facility. He was not entirely clear about what antiretroviral medications he had previously received but said there had been many and they had not worked. His CD4⁺ cell count and viral load on that first visit were 75/µL and 117,000 copies/mL, respectively. He claimed to be on a regimen of abacavir and lamivudine. Genotype testing revealed resistance to 10 medications, including the ones he was taking. Lopinavir and stavudine were added; later, the regimen was changed to include amprenavir, tenofovir, and didanosine. However, it became apparent that his adherence was never consistent. He said he always took his medications, but questioning revealed missed doses on nearly a daily basis.

In 2002, fevers and wasting developed. Disseminated *Mycobacterium avium-intracellulare* was eventually identified on blood cultures, and EG began receiving a combination of ethambutol, clarithromycin, and a quinolone. At this point, he revealed that he had stopped all of his medications a few weeks earlier. A repeated genotype test revealed panresistance. Do you discontinue all of his medications or press on with treatment that clearly is not going to reduce his viral burden?

Case 3

LS is a 54-year-old man with a long history of heroin use, which he stopped when his HIV infection was diagnosed in 1993. In 1998, when his CD4⁺ cell count was 380/µL and his viral load was 30,000 copies/mL, he agreed to begin receiving HAART. He was given nelfinavir and lamivudine/zidovudine and tolerated them well. His viral load quickly became undetectable, and his CD4⁺ cell count rose to 650/µL within 2 years. LS is adherent to his medication regimen. Although he frequently complains of nonspecific aches and pains, he has been happy with his CD4⁺ cell counts and has not sought to alter or stop his antiretroviral medication regimen.

Structured Treatment Interruption

The limitations of the drugs used against HIV include their toxicity, their tolerability, their propensity to induce resistance when not taken with absolute consistency, and their cost. Some drugs are more
potent than others; some require lifestyle adjustments such as taking medication several times a day or on an empty stomach. The long-term side effects of these drugs are still not well understood. Issues of lipid and glucose metabolism, bone density, mitochondrial toxicity, lipoatrophy, and lactic acidosis are all recognized problems associated with treatment of HIV infection. Reducing one’s exposure to the medications through treatment interruption may delay or prevent some of these associated toxicities. In addition, treatment interruption may induce improved immune function through the stimulation of host immune factors and through the shift of multiply resistant viruses to wild-type viruses, which results in improved drug susceptibility.

**Acute HIV Infection**

There are 4 situations in which STI is being evaluated. The first involves patients who are being treated at the time of acute HIV infection. STI in these patients seeks to improve cellular immunity through the stimulation of specific immune mechanisms. The "Berlin patient" described by Lisziewicz and colleagues[1] in 1999 was perhaps the first recognized example of this concept. The Berlin patient was a man who began receiving antiretroviral therapy at the time of HIV seroconversion. The patient stopped his medications 2 weeks after starting them and then resumed therapy a week later, only to stop again after 3 months. Although his viral load rose from less than 500 copies/mL to about 8000 copies/mL during the first drug hiatus, when he restarted medications after a week, his viral load went back to less than 500 copies/mL and remained undetectable for more than 2 years after he discontinued medication the second time. The presence of increased levels of certain HIV-specific CD4+ cellular responses in this patient led researchers to conclude that the interrupted treatment cycles had induced a higher level of immunity through "autovaccination." That is, reexposure to viral antigen had stimulated an improved, HIV-specific cellular immune response.

In 1998, Kahn and Walker[2] noted that patients who began treatment at the time of seroconversion had levels of HIV-1 Gag-specific helper-T-cell stimulation similar to those of untreated long-term nonprogressing patients with HIV infection. This is in contrast to untreated patients with acute infection and to patients whose medications were started later in their illness. The second 2 groups had little or no HIV-1 Gag-specific helper-T-cell responses.[2]

A subsequent study by Rosenberg and colleagues[3] identified 8 patients who began receiving HAART at the time of seroconversion (within 2 to 34 days) and later underwent 1 or more STIs. In this group, all patients had viral rebound after a median of 17 days (range, 7 to 38 days) following the first discontinuation. Three patients' viremia levels stabilized below 5000 copies/mL. Two of these remained free of therapy for an average of 8 months. The third restarted medications after 3 months despite the fact that his viral load did not exceed 5000 copies/mL. Four of the remaining 5 patients restarted therapy when their viral loads exceeded 50,000 copies/mL. The fifth patient had 3 successive weeks of viral loads above 5000 copies/mL and then restarted treatment.

All 5 patients underwent a second treatment interruption. Their viral rebound was significantly lower after the second interruption than after the first, with viral loads below 5000 copies/mL for all 5. Two patients remained free of treatment for 5 to 6 months after the second interruption. Three restarted treatment, 1 with a viral load of 4600 copies/mL after 4 months without treatment and 1 with a viral load of 11,000 copies/mL after 5 months without treatment. The third patient restarted treatment with
a viral load of 17,000 copies/mL after 5.5 months without therapy. In all 5 patients, levels of cytotoxic T lymphocytes and Gag-specific helper-T-cell responses rose during the second treatment interruption. This study supports the concept of STI in patients who begin antiretroviral therapy during or very shortly after HIV seroconversion. The most difficult aspect of STI in these patients is identifying the acute HIV infection in the first place.

**Chronic HIV Infection With Controlled Viremia**

The second situation in which STI is being evaluated is in patients receiving treatment of chronic HIV infection who have an undetectable viral load. In the largest study of this to date, the Swiss-Spanish Intermittent Treatment Trial (SSITT) followed 133 patients through a series of treatment interruptions. Viral load, T-cell responses, and various host immune responses were measured. Patients in this study interrupted therapy for 2 weeks and restarted for 8 weeks in 4 successive cycles. They then stopped medication indefinitely. At enrollment, these patients had CD4+ cell counts above 300/µL, had had undetectable viral loads for 6 months (below 50 or 400 copies/mL), and had never had a treatment regimen failure or received a nonnucleoside reverse transcriptase inhibitor (NNRTI).

Of the initial 133 patients, 23 (17%) had a viral load below 5000 copies/mL at 52 weeks (responders). Eight percent maintained this response at 96 weeks. Patients who had viral loads above 5000 copies/mL at week 52 or who had stopped the treatment interruptions for any reason before week 52 were considered nonresponders. The protocol, from 1999, recommended restarting HAART for any nonresponders or for those with a viral load above 5000 copies/mL at 52 weeks. Because the guidelines for treatment changed in this period, many nonresponders chose not to restart therapy. As a result, at week 52, 64% of the original 133 patients remained without therapy, and 41% remained free of therapy at week 96.[4]

In this study, half of the patients had a pre-HAART CD4+ cell count nadir below 400/µL. CD4+ cell count did not predict who would be a responder at week 52. On the other hand, none of the 44 patients who had a pre-HAART viral load greater than 60,000 copies/mL were responders. Interestingly, nonresponders had a statistically higher number of spot-forming cells (SFCs) (2999 vs 813 SFCs/million peripheral blood lymphocytes) after week 52, a reflection of higher numbers of HIV-specific CD8+ T cells. This result is in contrast to Rosenberg's finding in patients treated for acute HIV infection. The lack of correlation between low viral load in responders and number of HIV-specific CD8+ T cells in the SSITT may reflect antigen exposure (more virus, better immune response) in addition to factors unmeasured or unknown.[4]

A second study of STI in patients treated for chronic infection was published in 2001 by Dybul and colleagues.[5] In this study, 10 patients with stable, undetectable viral loads and CD4+ cell counts above 300/µL (range, 548 to 1375/µL) underwent repeated cycles of 7 days with and 7 days without medication. Patients maintained viral suppression for 32 to 68 weeks without a change in CD4+ cell counts and without development of resistance or significant increase in HIV-specific CD4+ or CD8+ T-cell immune responses. Patients' lipid levels improved over the course of the study. The authors concluded that this approach could reduce toxicity and cost -- but they also noted that patients with lower CD4+ cell counts, more baseline antiretroviral experience, and shorter treatment histories
would need to be studied before recommendations for STI can be made for them.

For AM, the patient in Case 1, whose virus is well-controlled but who had a low nadir T-cell count, the idea of STI and reduction of toxicity sounds appealing. STI might halt her lipodystrophy, but it would not reverse it. Her low CD4+ cell count would need close monitoring. As in the SSITT, treatment interruption might not result in an intolerable rise in her viral load. The majority of patients in the SSITT remained without medications after 52 weeks because their viral loads had not risen nor had their CD4+ cell counts fallen significantly based on the 2001 guidelines. AM's T-cell count, however, is less than half the median CD4+ cell count of the 133 patients who participated in the SSITT. With a median CD4+ cell count of 740/µL in that study, a drop of 30%, for example, after treatment interruption would have had little, if any, clinical effect. For AM, however, a 30% drop in her CD4+ cell count of 301/µL could have real clinical sequelae. If her medications were discontinued indefinitely, it is likely that her CD4+ cell count would fall to her pretreatment levels, putting her at clear risk for clinical progression. STI cannot be recommended for AM at this time based on the information available.

**Chronic Infection With Uncontrolled Viremia**

The third instance of STI is in treatment of patients with chronic infection and poorly controlled viremia. These patients are candidates for salvage therapy. This group comprises a large and growing number of patients; it is estimated that therapy fails to suppress viral load in 40% to 70% of treated patients.[6] EG, in Case 2, is an example of someone who has taken most of the antiretroviral medications offered and according to genotype testing is resistant to all of them. For such patients, stopping treatment leads to reemergence of a wild-type strain of virus, one that is pansensitive.

Miller and colleagues[7] and Deeks and colleagues[6] have published studies that describe a shift to wild-type virus in treatment-experienced patients with treatment failure who had multiply resistant virus and interrupted their therapy. In Deeks' study, 17 patients whose treatment was failing discontinued medications. In the 12 weeks that followed, these patients had a greater rise in viral loads and fall in CD4+ cell counts than had 5 patients who had not stopped treatment. By week 16, the virus in all of the patients who discontinued treatment had undergone a shift to wild-type virus (median, 6 weeks), although persistence of resistant virus was documented in peripheral blood mononucleocytes. The shift to wild-type virus was accompanied by an acceleration of both the rise in viral load and the fall in CD4+ cell count. The shift to wild-type virus was also accompanied by a rise in replicative capacity, from 20% in the multiply resistant viruses to 50% in the wild-type viruses.

When these patients were re-treated with antiretroviral medication, 40% of them maintained a viral load of less than 200 copies/mL after 24 weeks of treatment. Patients who started a new class of drugs (for example, an NNRTI) were more likely to be in this group. The conclusion of Deeks' study was that the reemergence of wild-type virus could mean an escalation in the clinical deterioration of the patient through a rise in the viral load and a fall in the CD4+ cell count. Deeks argues that despite a detectable viral load, a resistant virus lacks "fitness" to replicate and the drugs, while not completely suppressive, still limit the progression of disease to some degree.
Miller's group identified 48 patients who had stopped their antiretroviral regimens for at least 2 months despite having detectable viral loads. Most of the patients had resistance testing done; the median number of resistant drugs was 8. Patients' viral loads increased during the interruption by a mean of 0.7 log, from a preinterruption mean of 5.07 logs (approximately 120,000 copies/mL) to 5.87 logs (approximately 740,000 copies/mL). The mean CD4+ cell count, which had been 155/µL (range, 2/µL to 777/µL), fell to 49/µL (range, 1/µL to 439/µL). Twenty-eight of 45 patients experienced a shift to wild-type virus during treatment interruption, a change associated with shorter duration of previous antiretroviral treatment and higher pretreatment CD4+ cell count. Seventeen patients' virus remained drug-resistant. When medication was restarted, a shift to wild-type virus was associated with a significantly improved viral response. At 24 weeks after restarting medications, 18 (72%) of 25 patients in the wild-type-virus group had viral loads of less than 500 copies/mL, in contrast to 2 (17%) of 12 in the resistant-virus group. However, during the STI, 17 AIDS-defining events were noted in 15 patients.

Both Miller and Deeks recognized that in the short term, reinitiation of treatment in patients with wild-type virus was often successful. Resistant virus reemerges, but the exact time frame in which reemergence occurs is unknown. Because of the increase in replication capacity that occurs with the shift to wild-type, clinical deterioration may be precipitous. Both authors felt that STIs could not be recommended at this point for this group of patients.

At the 10th Retrovirus Conference, held this year in Boston, Katlama and colleagues[8] presented data on 70 patients who were very treatment-experienced. The patients were randomized either to switch immediately to a GIGHAART regimen or to interrupt therapy for 8 weeks before switching. Treatment interruption was associated with significantly more patients achieving a greater than 1 log reduction in viral load for 24 weeks. More patients in the treatment-interruption group maintained viral loads below 400 copies/mL at weeks 12 and 24 than in the immediate-switch group. These differences did not quite achieve significance. The authors concluded that there was a benefit to treatment interruption.

In Case 2, EG could not afford to increase the replicative capacity of his virus, although a drop in his CD4+ cell count would make little real difference. Because of his long treatment history, shift to wild-type might take some time. A shift to wild-type virus would give him some treatment options but leave him very vulnerable to clinical deterioration in the interim. His panresistant virus is very "unfit," and he is getting some benefit from continued treatment. The studies to date do not support a treatment interruption for patients with poor viral control and multiply resistant viruses.

### Change in Guidelines

Case 3 represents the fourth situation in which treatment interruption is being considered. In 2001, guidelines for starting treatment in patients with HIV infection shifted from the "hit early, hit hard" philosophy to one of waiting until the patient's immune status shows significant signs of failing. Suddenly, a viral load of 10,000, 15,000, or even 50,000 copies/mL in a patient with 500 CD4+ cells/µL did not make a huge difference in prognosis.
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The change in the guidelines is largely about T cells. Patients with 200 CD4+ cells/µL or fewer are advised to begin a medication regimen, whereas those with more than 200 cells/µL are advised to wait unless there are other clinical factors or they have a viral load greater than 55,000 copies/mL. As a result, there are many patients who are receiving medications now in whom treatment would not have been started when it was had the current guidelines been in place at the time. For those whose regimens have repeatedly failed, this may be a moot point and is unfortunate. But for patients such as LS in Case 3, with a high CD4+ cell count, an undetectable viral load, and pretreatment values such that he would not have been given medications in the first place, a treatment interruption might mean that his viral load would rise and his CD4+ cell count would fall only to a level as high as 350/µL. This may have no clinical impact. The AIDS Clinical Trials Group is currently undertaking an observational study of patients in this category.

Today, LS, with his viral load of 30,000 copies/mL and his CD4+ cell count of 380/µL, would not be starting to receive medication. There is a clear benefit in terms of cost and toxicity to discontinuing his antiretroviral drugs until his laboratory values reflect a need for treatment based on current guidelines. Given the dramatic changes in the modes of and indications for treatment of HIV disease in the last 10 years, it is hard to say with certainty that stopping treatment in LS is absolutely the right thing to do. In all likelihood, however, he will do just fine.

Gallant and colleagues[9] recently presented data on 75 patients who had median pre-HAART CD4+ cell counts of 426/µL and viral loads of 27,000 copies/mL. Sixty-nine percent remained without treatment 69 weeks after treatment interruption. Higher CD4+ cell counts and lower viral loads pre-HAART indicated those patients who were likely to remain free of therapy following interruption. "Thus the best candidates for prolonged treatment interruption are those with higher baseline CD4+ cell counts and lower viral loads, patients who are less likely to be treated based on current guidelines," the investigators concluded.

In summary, STI attempts to reduce toxicity and cost, improve immune function through induction of HIV-specific T-cell stimulation, and enhance medication effectiveness through reversion of multiply resistant virus to wild-type. The risks of treatment interruption include worsening of clinical status, virologic rebound, emergence of new resistance patterns, and improved viral replication capacity. In both Case 1 (chronic infection, controlled viremia) and Case 2 (chronic infection, uncontrolled viremia), treatment interruption is not supported by the studies to date. In Case 3 (treatment pre-2001 guidelines), an interruption of treatment is unlikely to lead to clinical sequelae and will diminish and delay the long-term toxicities of the antiretroviral medication.

References


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