

Recurrence of the Acute HIV Syndrome after Interruption of Antiretroviral Therapy in a Patient with Chronic HIV Infection: A Case Report

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Background: Clinical and virologic consequences of temporary interruption of HIV therapy are incompletely understood.

Objective: To describe a febrile illness that was consistent with the acute HIV syndrome and occurred after interruption of antiretroviral therapy.

Design: Case report.

Setting: University clinic.

Patient: HIV-infected man.

Measurements: Plasma viral load, lymphocyte subsets, diagnostic evaluation (including cultures and serologic tests), and analysis of lymph node tissue.

Results: The patient began antiretroviral therapy 3 months after

initial HIV exposure and had sustained viral suppression, except during a brief scheduled treatment interruption. One hundred sixty-nine days after resuming therapy, the patient discontinued it again immediately following an influenza vaccination. Eleven days later, he presented with a febrile mononucleosis-like syndrome associated with dramatic shifts in plasma HIV RNA level (<50 to $>1\,000\,000$ copies/mL) and CD4 cell count (0.743×10^9 cells/L to 0.086×10^9 cells/L). Evaluation for alternative causes of fever was unrevealing. Symptoms resolved rapidly with resumption of HIV therapy.

Conclusion: Therapeutic interruption may be associated with profound viral rebound and recurrence of the acute HIV syndrome.

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Acute HIV infection frequently results in a syndrome characterized by high fevers, headache, erythematous rash, myalgia, and adenopathy concurrent with extremely high plasma HIV RNA levels, often more than 1 000 000 copies/mL (1, 2). Anecdotal experience suggests that acute HIV symptoms improve with potent antiviral therapy but may recur if therapy is not sustained over several weeks (3). Little is known about the potential consequences of temporary interruptions in therapy, either in cases of acute seroconversion illness or in the more common clinical setting of established HIV infection.

Scheduled treatment interruption is being explored as a component of immune-based therapeutic strategies for HIV infection (4), but the long-term risks and benefits of this approach are uncertain. We recently completed a pilot study to evaluate the effects and safety of a single 8-day interruption of highly active antiretroviral therapy in chronically infected, successfully treated patients. Since the conception of this study, other reports have suggested that incomplete or intermittent viral load suppression in selected patients with primary HIV infection may stimulate effective HIV-specific cellular immune responses and allow persistent immune control after therapy is stopped (5-7).

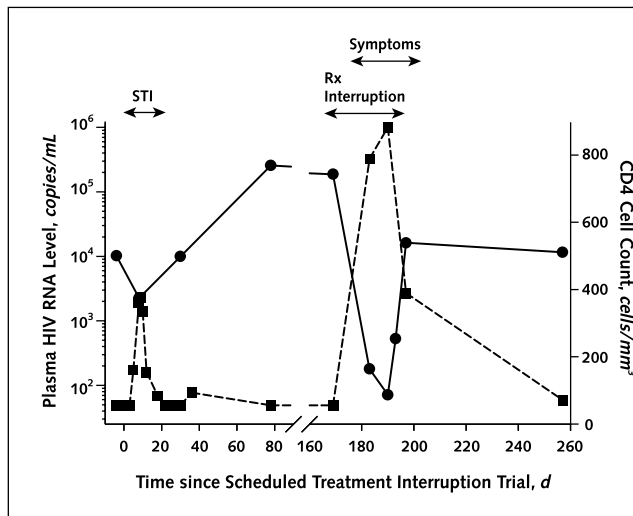
It is not clear whether similar results will be seen in patients initiating therapy long after primary HIV infection. The risks and benefits of this approach are likely to be different in later stages of HIV infection than in acute HIV infection.

We describe the evaluation of a febrile syndrome that developed when one of the previous participants in our pilot study again self-discontinued therapy. Plasma viral load assays were performed by using standard methods (Amplicor, Roche, Somerville, New Jersey). Flow cytometry for T-cell subset analysis was performed by using standard methods certified by the AIDS Clinical Trials Group. The funding sources had no role in gathering, analyzing, or interpreting the data or in the decision to submit the paper for publication.

Case Report

The patient, a 30-year-old man, began taking antiretroviral therapy (zidovudine, 300 mg twice daily; lamivudine, 150 mg twice daily; and indinavir sulfate, 800 mg three times daily) approximately 3 months after a high-risk HIV exposure event that was followed by a self-limited

Figure. Changes in plasma viral load (squares) and absolute CD4 cell count (circles) over time in a patient with chronic HIV infection.



Viral loads less than 50 copies/mL are depicted as $1.7 \log_{10}$ copies/mL. Broken lines indicate the period in which viral load and CD4 cell count remained stable. To convert CD4 cell counts to $\times 10^9$ cells/L, divide by 1000. STI = standard treatment interruption.

mononucleosis-like illness. His pretherapy plasma HIV RNA level was 880 000 copies/mL. While he maintained this antiretroviral regimen (>2 years), his viral load remained less than 50 copies/mL and his absolute CD4 cell count increased from a nadir of 0.085×10^9 cells/L to sustained levels of more than 0.500×10^9 cells/L.

The patient temporarily interrupted antiretroviral therapy more than 2 years later as part of an investigational pilot study described elsewhere (Kilby and colleagues. In preparation). Over the 8-day scheduled treatment interruption, his viral load increased from less than 50 copies/mL to 1921 copies/mL and his absolute CD4 count decreased from 0.501×10^9 cells/L to 0.375×10^9 cells/L. After the patient resumed the same antiretroviral regimen, his viral load was again repeatedly less than 50 copies/mL, except for two isolated minimal elevations (77 copies/mL and 737 copies/mL). His CD4 count consistently remained above 0.500×10^9 cells/L (Figure).

The patient returned for a regular clinic visit 169 days after the scheduled treatment interruption. At this visit, he was asymptomatic, the CD4 count was 0.743×10^9 cells/L, the leukocyte count was 9.1×10^9 cells/L, the hematocrit was 0.49, the platelet count was 195×10^9 cells/L, and the viral load was less than 50 copies/mL. The patient received a routine influenza vaccination. On the

same day, without informing caregivers, he chose to interrupt his antiretroviral regimen because of concerns about impending insurance problems. He returned 11 days later with fever (body temperature, 39.4°C) and reported malaise, tender adenopathy, myalgia, emesis, and loose stools. He stated that his symptoms were identical to but more severe than those experienced during his episode of presumed acute HIV syndrome 4 years previously. He initially said that he had not discontinued therapy and was treated symptomatically with antipyretics and analgesics.

The patient returned for follow-up after 14 days without therapy and showed no improvement. Laboratory analysis revealed a CD4 count of 0.164×10^9 cells/L, a leukocyte count of 3.2×10^9 cells/L, a platelet count of 68×10^9 cells/L, and a viral load of 327 874 copies/mL. He was admitted to the hospital because he had had a fever (body temperature $> 39^\circ\text{C}$) for more than 10 days and had additional symptoms of pharyngitis and a transient erythematous truncal rash. On the 21st day after interruption of therapy, the patient informed physicians that he had stopped therapy immediately after receiving the influenza vaccination. At this time, his viral load was more than 1 000 000 copies/mL and his CD4 count was 0.086×10^9 cells/L.

Physical examination was notable only for a transient erythematous rash on the torso and tender cervical and inguinal adenopathy. Routine and lysis centrifugation blood cultures for mycobacteria and fungi were negative. Acute and convalescent serologic tests showed no evidence of acute infection with cytomegalovirus, Epstein-Barr virus, human herpesvirus 6, parvovirus, rubeola, or rubella. A tuberculin skin test was nonreactive. Antigen assays and serologic tests for cryptococcosis, histoplasmosis, and coccidioidomycosis were also negative. Routine throat culture was negative. An excisional cervical lymph node biopsy revealed preserved architecture but marked depletion of paracortical T cells. Flow cytometry showed no evidence of a clonal lymphoproliferative process. Special stains for mycobacterial and fungal pathogens were negative. Immunoperoxidase reactions for cytomegalovirus and Epstein-Barr virus were negative, and HIV p24 antigen staining was positive.

When the same antiretroviral regimen was reinstated on the 21st day, the patient's fever and other symptoms rapidly resolved. In less than 2 weeks, his viral load decreased to 2743 copies/mL and his absolute CD4 count increased to more than 0.500×10^9 cells/L. Two months

later, his viral load was 59 copies/mL and his absolute CD4 count was 0.511×10^9 cells/L.

Discussion

Our report describes recapitulation of the acute retroviral syndrome in a patient with chronic HIV infection. This syndrome was associated with profound viral rebound that followed simultaneous administration of influenza vaccination and interruption of HIV therapy. The dynamic increase in plasma HIV RNA level after discontinuation of therapy coincided with a prolonged febrile illness indistinguishable from the patient's primary seroconversion symptoms. This case suggests that relapses of the acute retroviral syndrome, described in a recent report involving therapeutic interruption during acute HIV seroconversion (3), may also occur in persons who have undergone successful virologic suppression for years after primary HIV infection.

It is not clear whether the patient's history of a brief scheduled treatment interruption had any effect on the results of the second interruption. Although nonspecific immune activation resulting from a brief increase in viremia could provoke the acute HIV syndrome during subsequent interruptions, this would seem to be an unlikely explanation for events occurring after 6 more months of potent viral suppression. The temporal relationship between these acute symptoms and influenza vaccination may be merely coincidental. However, it is conceivable that vaccination within hours of treatment interruption could have escalated the viral rebound syndrome. In the absence of potent combination therapy, influenza vaccinations (8) as well as other routine immunizations (9, 10) have been shown to transiently activate HIV replication; however, this phenomenon is generally attenuated and is not associated with symptoms in patients receiving potent antiretroviral regimens (11, 12).

In our patient, the dramatic rate of change in plasma viral load suggests that the extraordinarily high level of HIV replication, *de novo* infection, and cellular activation probably played a role in the development of symptoms. It is notable that the patient had not been symptomatic when he presented with a similarly high viral load before initiation of treatment 4 years previously. The brisk, dramatic shifts in absolute CD4 count on and off therapy in this case may reflect redistribution of cells from inflamed tissues to blood rather than production of new T cells, as previ-

ously described (13, 14). Carefully designed investigations involving immune-based strategies, including scheduled treatment interruption and therapeutic immunization, seem warranted. However, our report reinforces the importance of diligent, frequent monitoring of patients with chronic HIV infection whenever effective antiretroviral therapy is abruptly discontinued.

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Some discouragement, some faintness of heart at the new real future which replaces the imaginary, is not unusual, and we do not expect people to be deeply moved by what is not unusual. That element of tragedy which lies in the very fact of frequency, has not yet wrought itself into the coarse emotion of mankind; and perhaps our frames could hardly bear much of it. If we had a keen vision and feeling of all ordinary human life, it would be like hearing the grass grow and the squirrel's heart beat, and we should die of that roar which lies on the other side of silence. As it is, the quickest of us walk about well wadded with stupidity.

George Eliot
Middlemarch
New York: Random House; 1994:185

Submitted by:
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