Retroviral Rebound Syndrome with Fatal Outcome after Discontinuation of Antiretroviral Therapy

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We report the case of a patient with AIDS who developed retroviral rebound syndrome that led to death after antiretroviral therapy was stopped because of toxicity. Cases of retroviral rebound syndrome reported in the literature are briefly reviewed.

Antiretroviral therapy may be discontinued in patients who have virologic suppression for several reasons, including drug toxicity, patient preference, or as part of an investigational strategy of periodic treatment interruptions. Although such treatment interruptions are usually clinically benign, a minority of individuals will experience symptoms similar to those of acute HIV infection [1]. Rarely, this “retroviral rebound syndrome” may be severe enough to require hospitalization [2]; however, no significant long-term morbidity or mortality has been reported. We describe a patient in whom severe retroviral rebound syndrome led to hospitalization and death.

Case report. A 44-year-old man had been diagnosed with HIV infection in 1998, when he had presented with weight loss. His initial CD4 cell count was 20 cells/mL. He began treatment with zidovudine, lamivudine, and indinavir in 1998. Poor adherence to antiretroviral therapy due to alcoholism initially limited the treatment response, and the patient was hospitalized in 1999 with severe Pneumocystis jiroveci pneumonia. At that time, his CD4 cell count was 95 cells/mL and his HIV RNA level was >100,000 copies/mL. After discharge from the hospital, he continued to receive the same antiretrovirals until he developed severe anemia, which resolved after zidovudine was replaced with didanosine and stavudine. The patient had no other AIDS-related complications, his CD4 cell count rebounded to >300 cells/mL, and, after ritonavir was added to his regimen in August 2003, his HIV RNA level was <75 copies/mL.

In September 2004, the patient was referred for evaluation because of severe fatigue, myalgia, diarrhea, dry mouth, and a weight loss of 23 kg. The findings of his physical examination were notable for cachexia. The patient’s CD4 cell count was 318 cells/mL (CD4 cell percentage, 10%), and his HIV RNA level had been stably suppressed below the level of detection (<75 copies/mL) for >1 year with a regimen of stavudine, didanosine, lamivudine, indinavir, and ritonavir. Because there was concern about antiretroviral drug toxicity, the patient was instructed to stop all medications and return in 2 weeks. Initial laboratory evaluation showed mild hyperbilirubinemia and elevated transaminase levels with normal pancreatic enzyme levels, a mildly elevated total WBC count with a normal hematocrit and platelet count, a lactate level of 2.8 mmol/L, and a lactate dehydrogenase level of 299 U/L.

One week later, the patient’s fatigue and myalgia were worse, and he had developed a new fever with a temperature of up to 39.8°C and dermatomal zoster. He was admitted to the hospital and treated with broad-spectrum antibiotics and valacyclovir. His CD4 cell count on admission was 26 cells/mL (CD4 cell percentage, 9%), and his HIV RNA level was >500,000 copies/mL. Antiretroviral therapy was resumed with tenofovir, lamivudine, atazanavir, and ritonavir. The patient’s hospital course was notable for development of respiratory distress, with bilateral alveolar and interstitial infiltrates visible on a chest radiograph, and negative results of microbiologic studies, including varicella-zoster virus culture and PCR of a bronchoalveolar lavage fluid sample. In addition, he sustained embolic events to the CNS and right foot. The patient had no prior history of thrombotic events, but he was a heavy smoker and had diabetes mellitus and was infected with hepatitis C. Diagnostic workup for a hypercoagulable state showed presence of antiphospholipid antibody and a low protein S level (56%; range, 70%–134%). The patient eventually underwent amputation below the right knee; the procedure was complicated by an asymptomatic cardiac arrest, and he died on hospital day 25. Pathologic examination of vessels in the amputated leg showed no signs of vasculitis. Results from tests performed 2 weeks after the patient had resumed antiretroviral therapy showed that the HIV RNA level had returned to <75 copies/mL and the CD4 cell count had returned to 294 cells/mL. The patient’s family declined postmortem examination of the patient.

Discussion. When antiretroviral therapy is discontinued for a patient with virologic suppression, a clinical syndrome with...
Retroviral rebound syndrome has been described in several case reports, cohort studies, and trials of treatment interruption (table 1). In the majority of reported cases for which virologic data is available, a high plasma or CSF viral load is noted. Because of limited information, it is not clear whether there are other common factors among patients who experience clinically significant retroviral rebound syndrome. Symptoms are reported to have begun from 1 to 6 weeks after the discontinuation of therapy, and all cases in the literature resolved either spontaneously or soon after antiretroviral therapy was resumed.

The incidence of retroviral rebound syndrome is unknown for a variety of reasons. Mild cases may not be reported, or, given the nonspecificity of symptoms, may be attributed to an alternative diagnosis. In addition, not all studies of treatment interruption report the rates of this complication. From the studies that did report retroviral rebound syndrome, the rates range from 0% (0 cases reported) [9, 10] to 17% [3]. There are no reports of deaths or significant permanent morbidity associated with retroviral rebound syndrome. A full description of the incidence, predictors, and clinical manifestations of retroviral rebound syndrome awaits the results of larger studies of treatment interruption, such as the ongoing Strategies for the Management of Anti-Retroviral Therapy (SMART) Study [11].

Table 1. A summary of cases of retroviral rebound syndrome (RRS) that have been reported in literature.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of study</th>
<th>No. of cases of RRS</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daar et al. [1]</td>
<td>Case report</td>
<td>1</td>
<td>Patient treated during acute HIV infection; lost cytotoxic T lymphocyte memory cell activity and CD8 cell activation during treatment, which returned after treatment interruption.</td>
</tr>
<tr>
<td>Colven et al. [2]</td>
<td>Case series</td>
<td>3</td>
<td>No patients treated during acute infection; all had been receiving ART for 2 years, and developed symptoms 10 days–6 weeks after stopping. One patient had a high CSF VL and meningitis, and 2 patients had plasma VLs of &gt;100,000 copies/mL.</td>
</tr>
<tr>
<td>Kilby et al. [4]</td>
<td>Case report</td>
<td>1</td>
<td>Patient experienced symptoms “identical” to seroconversion 3 weeks after stopping ART, with a VL of 1,000,000 copies/mL.</td>
</tr>
<tr>
<td>Breton et al. [5]</td>
<td>Case report</td>
<td>1</td>
<td>Patient developed febrile meningoencephalitis after stopping ART because of lactic acidosis and had a high CSF VL.</td>
</tr>
<tr>
<td>Skeist et al. [6]</td>
<td>Prospective trial of treatment interruption (n = 107)</td>
<td>2</td>
<td>Limited information provided. Symptoms of patients improved after resumption of ART.</td>
</tr>
<tr>
<td>Ortiz et al. [3]</td>
<td>Prospective trial of treatment interruption (n = 12)</td>
<td>2</td>
<td>Two subjects were symptomatic after onset of STI, with VL rebound of &gt;80,000 copies/mL.</td>
</tr>
<tr>
<td>Tarwater et al. [7]</td>
<td>Retrospective review of patients who interrupted therapy (n = 105)</td>
<td>3</td>
<td>Three subjects became symptomatic after onset of STI, with VLs of &gt;750,000 copies/mL; 2 resumed ART; for 1, symptoms resolved within weeks after discontinuing ART.</td>
</tr>
<tr>
<td>Fagard et al. [8]</td>
<td>Prospective study of treatment interruption (n = 133)</td>
<td>2</td>
<td>Patients developed symptoms and VLs of &gt;500,000 copies/mL after onset of STI, which resolved when ART was resumed.</td>
</tr>
<tr>
<td>Tebas et al. [9]</td>
<td>Retrospective cohort (n = 72)</td>
<td>0</td>
<td>Patients who resumed ART within 3 months after stopping were excluded.</td>
</tr>
<tr>
<td>Papasavvas et al. [10]</td>
<td>Prospective trial (n = 42)</td>
<td>0</td>
<td>Three-armed STI trial; all participants had a CD4 cell count nadir of &gt;100 cells/mL.</td>
</tr>
</tbody>
</table>

**NOTE.** ART, antiretroviral therapy; STI, sexually transmitted infection; VL, viral load.

**Conclusion.** In the case presented here, a patient discontinuing antiretroviral therapy experienced dermatomal zoster, high fever, acute respiratory distress syndrome–like respiratory failure, and elicitation of a hypercoagulable state with multiple arterial thromboses. Marked HIV RNA level rebound from undetectable to high levels (>500,000 copies/mL) and substantial CD4 cell depletion occurred within 2 weeks after antiretroviral therapy was stopped. Although the patient’s fever and respiratory symptoms resolved when antiretroviral therapy was resumed, complications that occurred after the amputation of his nonviable infarcted foot led to his death. Our patient’s multiple major clinical events corresponded temporally with the increase in viral load after antiretroviral therapy was discontinued, and no other etiology was apparent despite extensive investigations. Thrombotic events with detection of anticirodilipin antibodies have been reported in association with acute HIV infection [12], and a similar process may have occurred in our patient in association with high-level virologic rebound.

This case illustrates an extreme example of the potential serious sequelae of severe retroviral rebound syndrome in a patient with multiple comorbidities and low pretreatment CD4 cell count. Although retroviral rebound syndrome is rare, its consequences may be severe enough that the patient requires hospitalization. Because of this, health care providers should inform patients about the signs and symptoms of retroviral
rebound syndrome and should have a low threshold for resumption antiretroviral therapy when it occurs.

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References