

Acute HIV Syndrome after Discontinuation of Antiretroviral Therapy in a Patient Treated before Seroconversion

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Primary HIV infection is associated with high levels of viral replication and the development of HIV-specific immune responses (1-5). Treating patients during primary HIV infection is recommended (6), but little is known about the effects of such therapy (7-9). We report the results of virologic and immunologic studies in a patient who began receiving antiretroviral therapy during primary HIV infection and chose to discontinue therapy after 6 months.

Case Report

A 38-year-old homosexual man presented on day 5 of an acute retroviral syndrome characterized by fever, pharyngitis, myalgia, headache, lymphadenopathy, and rash. The patient's leukocyte count was $2.6 \times 10^9/L$, his platelet count was $85.0 \times 10^9/L$, and his plasma HIV RNA level was 1 800 000 copies/mL. No HIV antibodies were detectable. Primary HIV infection was diagnosed. Infection was probably a result of a receptive orogenital sexual encounter that took place 13 days before presentation, when the patient had a hard-palate ulcer. Two days after presentation, HIV antibodies remained undetectable; the plasma HIV RNA level was 5 600 000 copies/mL; and therapy with standard doses of zidovudine, lamivudine, and zalcitabine was started.

Because of toxicity, therapy was altered several times over the next 6 months. At 6 months, the patient chose to stop antiretroviral treatment despite being counseled about the possible outcomes of doing so. Thirty-five days later, he developed

an acute illness that was indistinguishable from the acute retroviral syndrome. Results of serologic evaluation for Epstein-Barr virus, cytomegalovirus, rubella, roseola, parvovirus B19, and human herpesvirus-6 were inconsistent with acute disease. The patient chose not to reinstate treatment, and his acute symptoms resolved during the following 10 to 14 days.

Methods

Antibodies to HIV were measured by enzyme immunoassay (Abbott Laboratories, North Chicago, Illinois) and Western blot (Genetic Systems, Seattle, Washington). Plasma HIV RNA was quantified by a branched-DNA assay (version 2.0, Chiron Diagnostics, Emeryville, California), which measured as few as 500 copies/mL. Quantitative cultures of plasma and peripheral blood mononuclear cells (1, 10) and memory cytotoxic T-lymphocyte assays (11) were performed as described elsewhere.

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Results

Our patient began receiving antiretroviral therapy before a humoral immune response was detected. Virologic and immunologic measurements were made during the treatment and post-treatment phases (Figure 1). As seen in other patients treated during primary HIV infection (7, 8), our patient's plasma HIV RNA declined to undetectable levels. In addition, plasma titers of infectious virus declined to less than 1 tissue-culture infectious dose per mL; cellular titers of infectious virus decreased to less than 0.1 infectious units per million peripheral blood mononuclear cells. Although not tested earlier, cytotoxic T-lymphocyte memory-cell activity was undetectable after 5 months of treatment (Figure 2). Also at this time, minimal CD8⁺ cell activation was detected by using previously described methods (11, 12).

Viremia rebounded after therapy was discontinued (Figure 1). In addition, memory cytotoxic T-lymphocyte activity (Figure 2) and high levels of CD8⁺ T-lymphocyte activation (data not shown),

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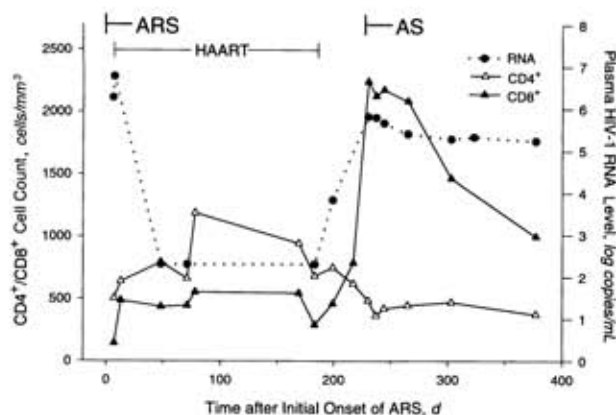


Figure 1. Temporal relation among clinical symptoms, antiretroviral therapy, plasma HIV RNA levels, and CD4⁺ and CD8⁺ T-lymphocyte counts in a patient treated during primary HIV infection before HIV-specific antibodies were detectable. ARS = acute retroviral syndrome; AS = acute syndrome; HAART = highly active antiretroviral therapy; RNA = plasma HIV RNA.

which correlate with the presence of cytotoxic T lymphocytes (13), were detected. The presence of memory cytotoxic T-cell activity against HIV Gag and Pol (but not against control cells, which do not express HIV proteins) indicates that the donor had CD8⁺ T cells primed against HIV antigens. These memory cells provide rapid secondary responses to antigens to which the host has been sensitized.

Discussion

Although declining cytotoxic T-lymphocyte activity has been described in patients treated during primary HIV infection (7, 14), we are not aware of such observations in treated patients with chronic HIV infection. Whether absence of memory cytotoxic T-lymphocyte activity is a frequent outcome of treatment during seronegative primary HIV infection needs to be confirmed in larger studies. Nevertheless, our results suggest that HIV replication

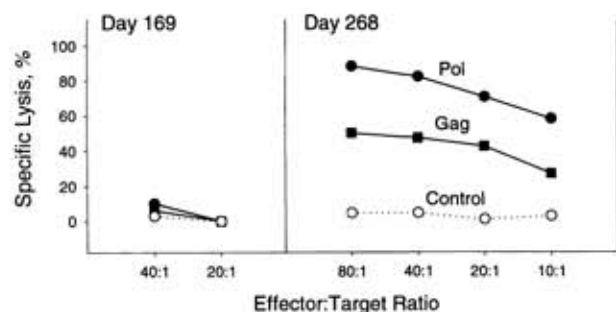


Figure 2. Memory cytotoxic T-lymphocyte activity in blood, measured as the percentage of specific lysis at different effector-to-target ratios. Left. Results while the patient was receiving antiretroviral therapy, 169 days after the onset of the acute retroviral syndrome. Right. Results 2.5 months after therapy was stopped, 268 days after the onset of the acute retroviral syndrome. Gag = targets expressing Gag proteins; Pol = targets expressing Pol proteins; control = targets infected with wild-type vaccinia.

sustained for some minimal period may be needed to establish a durable CD8⁺ cell-mediated response. This observation has implications for HIV vaccination protocols because brief exposures to viral antigens may not result in the sustained immune response needed for HIV immunity. This is in contrast to observations in other viral systems (15–17).

The rebound in viremia after our patient stopped therapy was anticipated because of the cellular reservoirs of infectious HIV (18–20). In contrast, the associated clinical syndrome was unexpected and may be explained by the emergence, at that time, of a CD8⁺ cell-mediated immune response similar to the response in newly infected persons. Further investigation is required to determine the clinical significance of this second acute syndrome and the effect of early therapy on HIV-specific immune responses.

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