Decay of the HIV Reservoir in Patients Receiving Antiretroviral Therapy for Extended Periods: Implications for Eradication of Virus

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(See the editorial commentary by Margolis and Archin, on pages 1734–6.)

The persistence of latently infected resting CD4+ T cells has been clearly demonstrated in human immunodeficiency virus (HIV)–infected individuals receiving effective antiretroviral therapy. However, estimates of the half-life of this viral reservoir have been quite divergent. We demonstrate clear evidence for decay of this HIV reservoir in patients who initiated antiretroviral therapy early in infection. The half-life of this latent viral reservoir was estimated to be 4.6 months. It is projected that it will take up to 7.7 years of continuous therapy to completely eliminate latently infected resting CD4+ T cells in infected individuals who initiate antiretroviral therapy early in HIV infection.

Despite the development of successful therapeutic strategies, it has not been possible to eradicate HIV in infected individuals, mainly because of the persistence of various viral reservoirs [1–5]. Among these reservoirs, a pool of latently infected cells in the resting CD4+ T cell compartment has been one of the most extensively studied to date and is considered to be a major impediment to HIV eradication [1–3]. Given that eradication of HIV is not possible as long as such infected cells persist, precise measurements of the half-life of this viral reservoir could shed light on the feasibility of completely eliminating HIV in patients receiving antiretroviral therapy, particularly as more potent therapeutic regimens become available, such as those that might contain an entry or integrase inhibitor; integration of provirus is critical for the establishment and replenishment of latently infected CD4+ T cells. However, previous studies addressing this subject have generated conflicting data (half-life ranging from 6.4 to 44.2 months) [6, 7]. To further delineate the decay rate of HIV and the possibility of the eradication of virus in a subset of patients who initiated antiretroviral therapy early in infection, we conducted longitudinal measurements of the frequency of resting CD4+ T cells carrying replication-competent virus from a previously identified cohort of patients in whom antiretroviral therapy was initiated soon after primary infection and in whom viral replication was extremely well controlled by therapy [8].

Patients, materials, and methods. Seven HIV-infected individuals who had received antiretroviral therapy for an average of 40.4 months (range, 31.1–54 months) (table 1) were studied. These individuals were participants in an earlier study [8]. The average time between the onset of symptoms of primary HIV infection and initiation of antiretroviral therapy was 2.7 months (range, 0.3–4.4 months). All patients received various antiretroviral regimens containing at least 1 protease inhibitor in addition to 2 reverse-transcriptase inhibitors and achieved maximal suppression of plasma viremia. Leukapheresis was conducted in accordance with protocols approved by the institutional review boards of the University of Washington, Seattle, and the National Institute of Allergy and Infectious Diseases, National Institutes of Health. Multiple leukapheresis procedures followed by isolation of resting CD4+ T cells were conducted on each of the patients studied. Purified resting CD4+ T cells (up to 350 million cells) were subjected to a high-input coculture assay, and the frequency of cells carrying replication-competent HIV was calculated as described elsewhere [9].

Results. As shown in figure 1, decay of the latent viral reservoir was evident in all 7 individuals studied. Linear regression using censored intervals for infectious units per million resting CD4+ T cells below the level of detection with first-order kinetics was applied [10, 11]. On the basis of this analysis, the half-life of the latent reservoir was estimated to be 4.6 months (range, 1.9–8.7 months). With an assumption that
1 × 10^6 latently infected resting CD4+ T cells are present in an infected person, the projected time for complete elimination of HIV in the above cellular compartment would be 7.7 years (range, 3.1–14.5 years).

**Discussion.** The persistence of HIV in the resting CD4+ T cell compartment has long been recognized as one of the major obstacles to achieving eradication of virus in infected individuals receiving effective antiviral therapy [1–3]. Previous studies have demonstrated that a long intrinsic half-life of the latent viral reservoir [7], along with low levels of residual viral replication in the periphery [5] and in lymphoid tissue [12], make eradication of virus all but impossible in infected individuals in whom antiviral therapy was initiated during the chronic phase of infection. However, the present study demonstrates that decay of the latent viral reservoir does occur in resting CD4+ T cells in patients in whom antiviral therapy was initiated during the early phase of HIV infection. The present study has potentially significant clinical implications, especially regarding the design of future therapeutic strategies aimed at eradicating HIV in infected individuals. Although ongoing HIV replication cannot be ruled out in infected individuals who began antiviral therapy early in HIV infection, it would be of considerable interest to begin to pursue evidence for the possibility of eradicating HIV in such individuals whose duration of therapy has reached the above figure. In this regard, recent studies have suggested that initiation of treatment shortly after seroconversion may facilitate decay of HIV in the CD4+ T cell compartment both in blood [13] and in gut-associated lymphoid tissues [14] in infected individuals receiving relatively short-term antiviral therapy. It is conceivable, if not likely, that eradication is not possible, at least with the currently available antiretroviral drug regimens; however, we are approaching the opportunity to address adequately this question based on projected half-lives of viral reservoirs in certain patients whose plasma viremia has been suppressed over extended periods of time. Of note, we have previously demonstrated that HIV rebounded on discontinuation of antiviral therapy in 2 of 2 chronically infected patients who were aviremic for 2–3 years and in whom no detectable virus could be demonstrated in CD4+ T cells in peripheral blood or lymph nodes [15]. However, these patients initiated antiviral therapy during the chronic phase of viral infection, and the duration of antiviral therapy was considerably less than 7.7 years, the projected time to eliminate HIV in the latent viral reservoir as demonstrated in the present study.

![Image](image-url)

**Figure 1.** Decay of latently infected resting CD4+ T cells in patients receiving effective antiviral therapy. The data points for each individual are shown. The open symbols indicate values below the limit of detection. The solid line indicates the mean rate of decay.
Given that it has already been 10 years since antiviral therapy became available on a widespread basis, there are a number of patients who are or will soon fall into this category. A close monitoring of the size of viral reservoirs in patients who initiated antiviral therapy early in infection after successful control of HIV for longer than 8 years and who elect to discontinue therapy will be of considerable value in assessing the feasibility of eradication of HIV.

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References