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Prolonged viral suppression without therapy in an HIV-1 seroconverter following early antiretroviral therapy and daily interleukin-2

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Interleukin (IL)-2 has been studied as a treatment for HIV infection because it stimulates the proliferation of T cells and augments antiviral immune functions [1,2]. Two regimens have been used: intermittent IL-2 (5 days every 8 weeks, usually 4.5–9 million international units (mIU)/day) and ultra-low-dose (ULD) IL-2 (1.2 mIU/m²/day), which can be given daily for weeks or months [1]. In patients with chronic and early/acute HIV infection, neither regimen has conferred any health benefit when given with concurrent antiretroviral therapy (ART) [3–7], and in patients with chronic HIV infection, ULD IL-2 did not improve viral control after stopping ART [8]. However, treatment of acute/early HIV infection with daily ULD IL-2 and interruption of ART has not been studied. We treated one patient who had taken ART since 1 month after HIV seroconversion with daily ULD IL-2.

After receiving IL-2, this patient's viral load set point off highly active antiretroviral therapy (HAART) was less than 50 copies/ml as compared with 39 000 copies/ml when ART was stopped without IL-2. Further, after IL-2 was stopped, viral load did not rebound for 14 months without ART.

A 29-year-old man tested HIV-positive by ELISA and western blot 1.5 months after a negative ELISA, and was treated 30 days later with zidovudine, lamivudine, and efavirenz.

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Viral load was undetectable for 4 years on ART (with minor changes in regimen), except for occasional blips (all <900 copies/ml) (Fig. 1a).

He then entered a study to determine whether treatment with ULD IL-2 could lower the viral load set point in patients who began ART during very early HIV infection. As per protocol, he underwent two ART interruptions: the first prior to the use of IL-2 and the second 4.5 months after daily IL-2 (Chiron, Inc., Charlotte, North Carolina, USA; 1.2mIU/M²/day subcutaneously, self-administered) was added to ART. After the second ART interruption, IL-2 monotherapy was continued for 1.5 months, and then all therapy was stopped. He was the only patient to complete this protocol. The study was approved by the local institutional review board, and informed consent was obtained.

After the first ART interruption, viral load became detectable within 2 weeks to a set point of 39 000 ($4.6 \pm 0.3 \log_{10}$) copies/ml (Fig. 1a). After the second ART interruption, viral load set point was below 50 ($1.7 \log_{10}$) copies/ml. Viral load remained undetectable for 14 months after all therapy was stopped (with one blip), then rebounded to approximately 5.0 $\log_{10}$ copies/ml; ART was restarted with resuppression of viral load to below 50 copies/ml.

Five months after the second interruption of ART (3.5 months off IL-2), viral load was 4 ($0.6 \log_{10}$) copies/ml by a specialized assay [9], and replication-competent HIV was present at 2.5 infectious units per million resting CD4 T cells using established procedures [10]. CD8 suppressor function against autologous HIV (assayed as described [11]) was weaker than that of an elite HIV controller studied simultaneously (data not shown).

During IL-2 administration, serum IL-2 concentrations ranged from 15 to 18 pmol/l by ELISA (Quest Diagnostics, Madison, New Jersey, USA), concentrations which affect primarily high-affinity IL-2 receptors [1]; biologic effects included increases of five- to seven-fold in circulating eosinophils and natural killer cells and of five- to 20-fold in serum levels of several cytokines and chemokines [assessed by multiplex electrochemiluminescence (MSD, Gaithersburg, Maryland, USA; now Novartis International AG, Basel, Switzerland) on stored serum], including interferon- γ , IL-5, IL-10, IL-13, thymus and activation-regulated chemokine [chemokine (C-C motif) ligand (CCL)17], monocyte chemoattractant protein (MCP)-1 (CCL2), MCP-4 (CCL13), IP10 (chemokine (C-X-C motif) ligand 10), and eotaxin-3 (CCL26) (data not shown). The CD4/CD8 ratio, which had almost always been less than 1, became consistently more than 1 (Fig. 1b). Thus, the cytokine milieu *in vivo* leading up to and following the second ART interruption was quite different from that surrounding the first ART interruption.

After IL-2 was stopped, serum levels of cytokines and chemokines returned to pre-IL-2 levels. However, the CD4/CD8 ratio remained more than 1 until the second viral rebound 14 months later (Fig. 1b), and median absolute eosinophil and B-cell counts were significantly higher in the year following IL-2 administration than the year preceding it (for eosinophils, 80/ μ l vs. 50/ μ l, respectively, $P = 0.003$ by rank sum test; for B cells, 452/ μ l vs. 247/ μ l, respectively, $P = 0.01$). Tests for antiretroviral drug levels while viral load was undetectable following the second ART discontinuation were negative. The patient was human leukocyte

antigen (HLA)-A*11, HLA-A*24, HLA-B*3503, HLA-B*400102 (TriCore Laboratories, Albuquerque, New Mexico, USA).

To our knowledge, this is the only patient who has been treated with ULD IL-2 following years of viral suppression by ART initiated during very early HIV infection, and also the first reported case of spontaneous suppression of viral load to below 50 copies/ml for more than 2 months after a second ART interruption, in a patient whose viral load rebounded after the first interruption. In the study by Kaufman *et al.* [12], for example, all 11 such patients had detectable viral loads within 5 weeks of stopping HAART. It is striking that this unique response should be achieved in the only patient who has been treated with both early ART and subsequent daily ULD IL-2. Suppression of viral load to undetectable levels can occur in people who discontinue ART after starting it during early HIV infection [13], but this outcome is rare and may be unrelated to ART. This patient's two viral load rebounds when HAART was interrupted demonstrate that he was not simply destined to maintain an undetectable viral load. Taken together, the data argue that ULD IL-2 enhanced anti-HIV immunity and viral suppression in this patient until the effects of IL-2 eventually abated. This interpretation is supported by the persistence of some of the effects of IL-2 in this patient, such as elevation in circulating eosinophils, circulating B cells, and the CD4/ CD8 ratio after IL-2 was stopped, and by findings in the mouse lymphocytic choriomeningitis virus model, in which administration of daily low-dose IL-2 for 1 week stimulated antiviral immunity for several months [2]. The possibility that this patient's prolonged virological control after the second ART interruption was unrelated to ULD IL-2 therapy cannot be completely excluded [14]; nevertheless, it will be important to test the reproducibility of this putative effect of daily ULD IL-2, along with early initiation of ART, in additional patients. Moreover, understanding the mechanism of this patient's prolonged viral suppression could be important in identifying targets for candidate vaccines and surrogate markers for vaccine efficacy. That the patient's viral suppression was not permanent does not diminish the importance of these studies.

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Fig. 1. Antiretroviral treatment, viral load, and immunological parameters in the patient
 Treatment is indicated by the bar at the top of the graph, along with the two periods of no treatment (No Tx #1 and #2). (a) Viral load and CD4 T-cell count. (b) CD4/CD8 ratio. Vertical lines indicate times of changes in treatment.