Highly active antiretroviral therapy (HAART) often leads to increases in a patient’s CD4+ T-cell count of 100–200 cells/µl or more, even though individual responses in cases of HIV-1 infection are quite variable [1, 2, 3]. The CD4+ T-cell responses are generally related to the degree of viral load suppression [1, 2]. However, a substantial proportion of patients undergoing HAART have had persistently detectable viremia despite their strict adherence to treatment [4, 5]. What happens to those patients who remain highly viremic while undergoing HAART is not fully understood, though a sustained CD4+ T-cell response in patients taking protease inhibitor (PI)-based regimens has been reported [3, 4]. Diminished fitness of heavily mutated viruses (that is, reduced ability of resistant virus to replicate and deplete CD4+ T cells) could partly explain these observations [6].

The durability of these immunologic responses that occur despite failure of virological suppression is still unknown, though a 24-month benefit has been reported in patients continuing on PI-containing regimens [4]. We report the results of a 36-month observational study performed on 16 patients who had a sustained CD4+ T-cell response despite high-level viremia and extensive drug resistance while continuing combination antiretroviral therapy.

The study population was selected from outpatients at the Infectious Diseases Unit of the Pistoia Hospital, Pistoia, Italy. The study design was single center, open-label, and observational. On the basis of available records from a 3-year period, 16 (14 male and 2 female) patients (10% of all HIV patients regularly followed) between the ages of 29 and 52 years (mean, 37 years) met the study purpose. At baseline, the mean±SD viral load was 4.36±1.05 log RNA copies/ml, and the mean CD4+ T-cell count was 400±353 cells/mm³. Seven patients were in CDC stage A (A2=4; A3=3); two in stage B (B1=1; B2=1); and seven in stage C (C2=1; C3=6) [7].

The plasma HIV-1 load was quantitated using the Roche Amplicor method (Roche Laboratories, Switzerland). The detection limit of the assay was 400 copies/ml. For genotypic antiretroviral resistance testing, RNA was extracted from plasma stored at −7°C using the QIAmp Viral RNA kit (Qiagen, Germany). The HIV-1 pol regions coding for RT amino acids 1–230 and for the whole protease were generated by reverse transcription-nested polymerase chain reaction amplification and directly sequenced as described elsewhere [8]. Mutations conferring resistance to the different reverse transcriptase inhibitors and PIs were retrieved from available databases, and drug susceptibility was inferred with use of a comprehensive set of rules [9].
Values of normally and not normally distributed variables are presented as mean±SD and median with range, respectively. Correlation and paired differences between normally distributed variables were analyzed by the Pearson correlation and paired t tests, respectively. All tests were performed with SPSS 8.0 and all P values are two-tailed.

After the 36-month follow-up period, there was a significant change in CD4+ T-cell counts but not in HIV RNA levels, with respect to baseline (mean±SD 583±480 vs. 400±353 cells/mm³, P=0.012, and 4.11±0.99 vs. 4.36±1.05 log copies/ml, P=0.318, respectively: Fig. 1). When all the available measurements were taken into account, there was a mean HIV RNA increase of 0.04 log copies/ml per year and a mean CD4+ increase of 27 cells/mm³ per year. There was no significant correlation between CD4+ T-cell and HIV RNA slope (r=−0.326, P=0.218). Adherence was good to excellent in all patients. All patients were found to harbor virus with some extent of drug resistance during the follow-up period. The median number of NRTI, non-nucleoside reverse transcriptase inhibitor, and PI key resis-

Fig. 1 HIV-1 RNA (full circles) and CD4+ (open squares) time course for the 16 subjects studied. The left and right y axes indicate CD4+ cell counts per microliter and log HIV-1 RNA copies per milliliter, respectively. The x axis indicates the follow-up time in months.