Long-Term Follow-Up of Asymptomatic HIV-Infected Patients Who Discontinued Antiretroviral Therapy

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Background. Whether asymptomatic human immunodeficiency virus (HIV)–infected patients can interrupt treatment remains unknown.

Methods. We performed a prospective, observational study of 46 patients who started therapy with >300 CD4+ cells/mm³ and/or <70,000 HIV-1 RNA copies/mL. Patients had been receiving highly active antiretroviral therapy (HAART) for at least 6 months. HAART was discontinued, and plasma HIV-1 RNA loads and CD4+ cell counts were determined at 4-month intervals.

Results. At the time of HAART discontinuation, the median CD4+ cell count was 793 cells/mm³, and all patients had undetectable viral loads. A rapid decrease of 173 cells/mm³ in the median CD4+ cell count was observed during the first 4 months after HAART was stopped, followed by a slower decrease of 234 cells/mm³ between months 5 and 20. The decrease in the median CD4+ cell count early after HAART discontinuation was inversely correlated with the increase that occurred during receipt of therapy (r = -0.653) and with the count at the time of HAART discontinuation (r = -0.589). The decrease in the median CD4+ cell count after the fourth month without HAART was correlated with the nadir count before HAART initiation (r = -0.349) and the increase during treatment (r = -0.322). The median follow-up duration was 20 months. After 12, 24, and 36 months of observation, 33 patients (71.7%), 22 patients (47.8%), and 16 patients (34.7%), respectively, remained free of therapy. Adverse clinical events were not seen, and all patients who reinitiated HAART responded rapidly.

Conclusion. Selected asymptomatic HIV-infected patients can safely discontinue therapy for prolonged periods of time.

In the early days of the AIDS epidemic, decisions about starting treatment were fairly straightforward, and most experts agreed that therapy should be initiated as early as possible during the infection course [1]. With the advent of methodology to assess plasma HIV RNA load, a threshold of 10,000 copies/mL was proposed as a strong indication for treatment [2–4]. This threshold was later increased to 30,000 copies/mL and then to 55,000 copies/mL in subsequent revised recommendations by experts of the International AIDS Society–USA [5, 6]. Recommendations have become more flexible than ever before, and although the most recent guidelines for the use of antiretroviral therapy in asymptomatic HIV-infected adults indicate the need for starting therapy when the CD4+ cell count reaches 200 cells/mm³, treatment decisions must be individualized for patients with CD4+ cell counts between 200 and 350 cells/mm³ [7]. For the latter group, plasma HIV RNA levels >100,000 copies/mL may be a reason to initiate therapy [7]. The need for flexibility has been imposed by the knowledge of the risk of progression to AIDS, by our present inability to eradicate the latent reservoir of HIV, and by concerns about the long-term safety of therapy, its toxic effects, potential cardiovascular consequences, and the negative impact of fat redistribution on quality of life [7–9].

As recommendations have evolved, patients who initiated HAART with CD4+ cell counts >300 cells/mm³ might wish to discontinue treatment. Literature about the discontinuation of antiretroviral therapy for people with 300–500 CD4+ cells/mm³ is limited [10–13], and
the safety and efficacy of treatment interruption has not been clearly established. The aim of this study was to evaluate the long-term effect of discontinuation of therapy and to assess how asymptomatic HIV-infected patients could safely remain free of therapy.

PATIENTS AND METHODS

Study design and enrollment. The study began in December 1999. Two authors (M.F.G. and M.G.) identified asymptomatic individuals with CD4+ cell counts >300 cell/mm³ and HIV RNA levels <70,000 copies/mL who began therapy when they had CD4+ cell counts <500 cell/mm³ and/or HIV RNA loads >10,000 copies/mL [2, 4]. Patients had been receiving HAART for at least 6 months and had had undetectable viral loads for ≥4 months at the time of interruption. The purpose of the study and its possible risks and benefits were explained to the patients, and individuals who decided to discontinue therapy provided informed consent to participate. Patients were advised of a possible higher risk of HIV transmission to sexual partners during treatment interruption and were encouraged to follow strict preventive measures during sexual intercourse.

The study was conducted in accordance with the principles of good clinical practice under the guidance of a written protocol. Medical history, physical examination, blood tests, CD4 cell counts, and HIV RNA levels were determined or performed when antiretroviral therapy was started (baseline), when treatment was discontinued, and every 4 months thereafter. The end points were the slope of the CD4 cell count decrease in the absence of treatment and the need for reintiation of treatment. We also tried to assess the factors associated with a better outcome in the absence of treatment. Criteria for reintiation of HAART were CD4+ cell count <300 cells/mm³, HIV-1 RNA load >100,000 copies/mL during 2 consecutive visits, onset of systemic symptoms or opportunistic infections, and patient withdrawal of consent. Patients who missed 2 consecutive visits were considered to have reinitiated HAART.

Plasma viral load assay and CD4+ cell count. Plasma HIV RNA levels were determined using the Amplicor HIV-1 Monitor Ultrasensitive Specimen Preparation Protocol Ultra Direct Assay (Roche Molecular Systems), with a limit of quantification of 20 copies/mL. Determinations of plasma HIV RNA load were performed in duplicate [14]. Subpopulations of CD3+, CD4+, and CD8+ T cells were determined by means of 3-color flow cytometry using a Facs-Calibur cytometer (Becton-Dickinson) and direct staining with appropriate monoclonal antibodies (Becton-Dickinson).

Genotypic analysis for drug resistance. Genotypic detection of reverse-transcriptase mutations and mutations conferring resistance to protease inhibitors was performed by means of the LIPA assay (Innogenetics) using HIV-1 RNA specimens obtained with the Amplicor method mentioned above.

Statistical methods. The categorical variables considered were sex, exposure group, and presence of chronic hepatitis B or C. Continuous variables included age, duration of antiretroviral therapy, duration that the virus load was undetectable, magnitude of CD4+ cell count increase while receiving therapy, and CD4+ cell count and viral load before starting therapy, at the time of treatment discontinuation, and every 4 months thereafter. Univariate summary statistics are presented as means ± SD, medians (interquartile range), and proportions, as appropriate. To compare CD4+ cell counts between each time point, we used repeated-measures analysis of variance and the Bonferroni method to adjust for the problem of multiple comparisons.

Relationships between the slope of CD4+ cell count decrease and quantitative variables were determined by means of Spearman’s rank-order correlation coefficient. Relationships between mean values of qualitative variables were evaluated using parametric and nonparametric tests, as appropriate. Variables with a high to moderate correlation (r > 0.2 or r < −0.2) and simple statistical association (P < .2) were introduced in a linear regression analysis.

Cox proportional hazards models were used to determine which factors were independently related to a longer time to reinitiation of HAART. In these models, univariate analysis was first used to examine the association between these factors and the time to reinitiation of HAART, and factors with a statistically significant (P < .05) association were entered into multivariate analyses to analyze their relationship with the study end points. SPSS software, version 11.0 (SPSS), was used.

RESULTS

Demographic characteristics and risk factors. A total 46 of 75 potential candidates agreed to participate; 35 (76%) were male. The age was 41 ± 10.2 years. A total of 65% of the participants were men who had sex with men, 22% had acquired HIV infection through heterosexual practices, and 13% had abused drugs. Forty-six percent of patients had Centers for Disease Control and Prevention HIV disease category A1 events, and 54% had category A2 events [15]. Eleven patients were coincfected with hepatitis C virus.

Pretreatment CD4+ cell counts and viral loads. The nadir CD4+ cell count was 488 cells/mm³ (400–631 cells/mm³), with minimum and maximum values of 304 and 1260 cells/mm³, respectively. The baseline HIV-1 RNA load was 34,480 copies/mL (22,700–46,000 copies/mL), with minimum and maximum values of 1100 and 67,900 copies/mL, respectively.

Antiretroviral therapy, CD4+ cell count, and viral load at the time therapy was stopped. Thirty-five (76%) patients were receiving a triple combination of drugs that included 2 nucleoside reverse-transcriptase inhibitors (NRTIs) and 1 non-nucleoside reverse-transcriptase inhibitor. Twenty-nine (82.8%)
of these patients had previously received a regimen that included protease inhibitors. Eleven (24%) patients were receiving 2 NRTIs plus 1 protease inhibitor at the time of discontinuation. The duration of antiretroviral therapy before discontinuation was 34 months (19–41 months), with a minimum and maximum duration of 6 and 48 months, respectively.

The CD4+ cell count at the time of interruption was 793 cells/mm³ (633–1036 cells/mm³). The increase in CD4+ cell count during HAART was 305 cells/mm³ (112–476 cells/mm³). Overall, patients had had undetectable viral loads for 19 months (12–36 months).

**Evolution of HIV RNA levels and CD4+ T cell counts.** Figure 1 shows the median CD4 cell count and HIV RNA level at baseline, at treatment discontinuation, and at follow-up visits 4–36 months after treatment was stopped. The number of patients at each interval is also shown.

A rapid rebound of the viral load to baseline levels occurred after 4 months without therapy, followed by a relatively stable plateau during the rest of the follow-up period. The decrease in the CD4+ cell count occurred in 2 phases after treatment was stopped: an initial, rapid decrease of 173 cells/mm³ (88–345 cells/mm³; rate, 43 cells/mm³ per month) occurred during the first 4 months, followed by a significantly smaller relative decrease of 234 cells/mm³ (161–345 cells/mm³; rate, 14 cells/mm³ per month) during months 5–20 (P = .018). Median CD4+ cell counts during months 4–20 after HAART discontinuation were not statistically significantly different from CD4+ cell counts at baseline.

The slope of the CD4+ cell decrease during the first 4 months without therapy was inversely correlated to the increase in CD4+ cells during receipt of therapy (r = −0.653) and to the CD4+ cell count at the time of interruption (r = −0.589). In other words, patients who experienced greater increases in the CD4+ cell count while receiving therapy had steeper slopes associated with decreases in the CD4+ cell count after interruption. The slower rate of CD4+ cell loss that occurred after the fourth month without therapy was correlated to the nadir CD4+ cell count before HAART was initiated (r = −0.349), the increase in the CD4+ cell count during treatment (r = −0.322), and the CD4+ cell count at the time of treatment interruption (r = −0.497). In the multivariate analysis, only the increase in the CD4+ cell count (R² = 0.496; P = .001) and the CD4+ cell count at the time of treatment interruption (R² = 0.216; P = .002) were associated with the slope of the CD4+ cell decrease during months 0–4 and 5–36 after interruption, respectively.

**Outcome, reinitiation of HAART, and cost savings.** Figure 2 shows the proportion of patients who reinitiated therapy during a follow-up period of 60 months. The observation time was 20 months (8–32 months), with a minimum and a maximum duration of 4 and 60 months, respectively. After follow-up periods of 12, 24, and 36 months, 33 patients (71.7%), 22 patients (47.8%), and 16 patients (34.7%), respectively, remained without therapy. At the time of censoring, 2 patients had been without therapy for 40 months, and 1 each had been without therapy for 44, 48, and 60 months. Patients did not develop adverse clinical events, and progression to AIDS was not observed.
FTM. Kaplan-Meier survival function showing the time to reinitiation of therapy for 30 HIV-infected patients during a 60-month follow-up period.

Thirty patients (65%) reinitiated HAART because of a CD4+ cell count <300 cells/mm3 (7 patients), a viral load >100,000 copies/mL during 2 consecutive follow-up visits (11 patients), or both (5 patients); 4 patients were lost to follow-up, and 3 withdrew consent.

Factors associated with a higher probability of reinitiating therapy were long duration of undetectable viral load during treatment (hazard ratio [HR], 1.065; 95% CI, 1.022–1.109; \( P = .003 \)) and low CD4+ cell count at the time of therapy interruption (HR, 0.998; 95% CI, 0.997–1.000; \( P = .048 \)). Only duration of undetectable viral load remained significant in the multivariate analysis (HR, 1.065; 95% CI, 1.022–1.109; \( P = .003 \)).

Genotypic analysis of HIV strains was done for the 30 patients who reinitiated HAART. All of these patients had wild-type strains, and resistance to antiretroviral drugs was not observed. Patients restarted the same HAART regimen, and after 4 months, the CD4+ cell count increase was 161 cells/mm3 (85–244 cells/mm3). Twenty-seven patients (90%) had undetectable viral loads after 4 months of HAART. Three patients had viral loads of 66–529 copies/mL, which became undetectable after 8 months of treatment. At the time of writing, the virus loads for all 30 patients remained undetectable.

Patients were without therapy for 992 months, for a mean treatment-free period of 21 months. Because the monthly cost of antiretroviral regimens given to these patients was, on average, €633 (US $791), it was estimated that the hospital pharmacy saved €627,936 (€13,293/patient) because of the reduced number of drugs that were administered.

DISCUSSION

Several studies have documented the present impossibility of eradicating the cellular reservoir of HIV and the considerable viral burden that remains, even during effective antiretroviral therapy [8, 16, 17]. After stopping treatment, a rapid viral load rebound is observed, with increases in the plasma HIV RNA load of \( \sim 0.2 \log_{10} \) copies/day, reaching detectable levels within 1–2 weeks after discontinuation of therapy [17, 18]. Most patients experience a rapid decrease in CD4+ cell count after therapy is stopped, which has been ascribed to the redistribution of lymphocytes back into tissues, followed by a slower but progressive decrease [19–21].

Our findings are in agreement with the most recent observations in which both viral load and CD4+ cell count returned to baseline levels after 4 months without treatment [10]. The loss of CD4 cells occurred in 2 phases: an initial, rapid decay during the first 4 months after treatment was discontinued, followed by a slower decrease during the following months [12]. As shown by others, the main predictor of the slope of the decrease in CD4+ cell count early after stopping treatment was the increase in the CD4+ cell count during receipt of therapy; therefore, patients with larger CD4+ cell count increases during HAART had larger decreases after discontinuation of therapy [10, 12]. On the other hand, during the second phase (i.e., >4 months after treatment discontinuation), the nadir CD4+ cell count was the main predictor of the CD4+ cell count decrease [12]. These findings agreed with previous observations showing that patients with lower nadir CD4+ cell counts had to resume therapy in a significantly higher proportion and within a shorter period after treatment discontinuation, compared with patients with a higher nadir CD4+ cell count [11, 13].

Nowadays, the risk of progression to AIDS among patients starting antiretroviral therapy with CD4+ cell counts of at least 200 cells/mm3 is low, and even advanced immunosuppression can be overcome with HAART [22–24]. Although the optimal time to start treatment has not yet been determined, it is conceivable that deferral of treatment may be considered for patients with a low risk of progression to AIDS.

This study suggests that asymptomatic HIV-infected patients with a low risk of progression to AIDS who started antiretroviral therapy with a CD4+ cell count of 300–500 cells/mm3 and/or an HIV-1 RNA load <70,000 copies/mL can safely discontinue therapy for prolonged periods. Patients with higher CD4+ cell counts and greater increases in the CD4+ cell count during treatment are the best candidates. Patients with lower CD4+ cell counts when treatment was started were more likely to resume therapy. Fortunately, the latter patients responded to
reinitiated therapy before irreversible immunologic damage occurred.

Potential benefits of discontinuation of treatment include reduced toxicities, drug-drug interactions, and selection of resistant variants. Because of the unknown durability of the effects of the currently available therapies, it seems reasonable to stop unnecessary treatment. Improvement in the quality of life and significant decreases in pharmacy expenses are other expected benefits. Because of the risk of immunologic deterioration during the period without therapy, patients who have discontinued treatment should be closely monitored.

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References