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Sustained HIV Viral Suppression following Treatment Interruption: An Observational Study

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ABSTRACT

Treatment of HIV-infected patients with HAART can result in long-term suppression of viral loads to undetectable levels. Rapid virologic rebound typically follows treatment interruption (TI), with a potential for significant loss of $CD4^+$ cells. Patients who maintain virologic suppression despite interrupting treatment have not been well described. All patients with a pretreatment viral load (VL) ≥5000 copies/ml, who had been on therapy for ≥2 weeks, and who underwent a TI lasting ≥180 days were analyzed. Patients whose maximum VL did not exceed 5000 copies/ml ≥6 months after starting TI ("nonrebounders") were compared with those whose VL exceeded 5000 copies/ml (rebounders). Seventy-one patients were included in the analysis. Nineteen (27%) were nonrebounders. Ninety-four percent of patients in each group interrupted treatment for reasons unrelated to virologic response. Median change in CD4 count during TI was not significantly different between the nonrebounder and rebounder groups ($-20.5/\mu$l vs. $-64.0/\mu$l; $p < 0.086$). In a multivariate logistic regression analysis, the following factors predicted nonrebounder status: peak VL before TI ($\log_{10}$ copies/ml) (OR = 0.14, 95% CI = 0.04–0.48, $p = 0.0016$); having received HAART (vs. mono/dual therapy) as initial regimen (OR: 11.0, 95% CI: 2.04–59.8, $p = 0.0054$); and female gender (OR = 4.8, 95% CI = 1.09–21.5, $p = 0.0384$). The large majority of chronically infected HIV patients with a TI ≥180 days interrupted treatment for reasons unrelated to virologic response. Almost 30% did not have a significant virologic rebound. Those patients were more likely to be female, had a lower peak VL prior to treatment, and their initial regimen was more likely to be HAART. Examining the immune responses of nonrebounders may contribute to the understanding of protective immunity to HIV.

INTRODUCTION

Treatment of HIV-infected patients with highly active antiretroviral therapy (HAART) can result in long-term suppression of viral loads to undetectable levels. However, patients often discontinue antiretroviral therapy for various reasons and for durations ranging from a few days to several months. Reasons for treatment interruption (supervised or, most often, unsupervised) could be broadly divided into three categories: (1) minimization of drug exposure, toxicity, and cost in patients who either have achieved complete or near-complete viral control under treatment, or would not meet today's DHHS criteria for treatment,[1–3] (2) removal of selection pressure in patients with multidrug-resistant HIV, failing to respond to therapy,[4,5] and (3) reasons unrelated to treatment response, including poor adherence to therapy, loss to follow-up, adverse events, intercurrent illness, and financial reasons.

Viral and CD4 count dynamics following treatment interruption have been extensively studied. It has been established that virologic relapse occurs rapidly in chronically HIV-1-infected patients who discontinue drug therapy after sustained viral suppression. This rebound is thought not to be associated with a significant decline in CD4 cells, clinical complications, or selection of resistant mutants.[1,6–8] Viremia can be effectively controlled by reintroduction of HAART.[2,9] However, among patients with multidrug-resistant HIV, concerns have recently been raised over the structured interruption of treatment. In one study, it was associated with greater risk of disease progression and did not confer immunologic or virologic benefits or improve the overall quality of life.[4]

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Patients who maintain virologic suppression despite interrupting treatment have not been well described. Also, for patients interrupting treatment after neither sustained viral suppression nor complete virologic failure, viral load and CD4 dynamics, as well as disease progression upon reintroduction of HAART, have not been studied. We analyzed data on all patients followed in our clinic who interrupted therapy for at least 6 months to determine factors correlated with prolonged virologic suppression.

MATERIALS AND METHODS

Patient population

A prospective, computerized database of adult HIV-infected patients, known as the Studies of HIV/AIDS Longitudinal Outcome Metrics (SHALOM) cohort, followed at the University of Alabama at Birmingham HIV Clinic in Birmingham, Alabama was utilized to identify patients with treatment interruptions (TI). Patients were included in the analysis if (1) they had a documented pretreatment viral load (VL) of at least 5000 copies/ml, (2) had been on HAART for at least 14 consecutive days, and (3) underwent a TI between 1996 and 2001 lasting 180 days or more. The patients were then classified as "nonrebounders" (NR) if their maximum VL did not exceed 5000 copies/ml for 180 days or more after starting TI. Those who had a VL exceeding 5000 copies/ml within 180 days of TI constituted the rebounder group.

Reasons for TI among nonrebounders and rebounders were classified as follows: (1) patients with complete viral suppression, or who did not meet DHHS criteria for treatment initiation, (2) patients who have failed multiple antiretroviral therapies, and (3) patients interrupting treatment for reasons unrelated to treatment response.

Demographic characteristics, antiretroviral therapy history, and virologic and immunologic characteristics of nonrebounders and rebounders were compared to determine factors associated with virologic control following treatment interruption. To assess the outcomes of treatment interruption, virologic and immunological data were collected for each patient at 180 days ($\pm$30 days) following the start of treatment interruption (T + 180). Upon reintroduction of HAART, subsequent control of viremia and disease progression (assessed by frequency of opportunistic infections and deaths) were also evaluated.

Statistical methods

Demographics and other potential confounders are presented as either categorical or continuous variables. Demographics are presented using descriptive statistics. For categorical variables Fisher's exact tests were used to test for differences between nonrebounders and rebounders. For continuous variables nonparametric Wilcoxon rank sum tests were used. Univariate logistic regression models were fit to identify factors associated with virologic control following treatment interruption. Factors that were univariately significant ($p < 0.05$) were then considered in a multivariable model. Nonsignificant variables ($p > 0.05$) were removed, beginning with the least significant variables first, until the final full model was determined. For the purpose of this analysis, an undetectable viral load was counted as 50 copies/ml, or 1.7 logs. Statistical analyses were performed using SAS software, version 8.2, SAS Institute Inc., Cary, NC.

RESULTS

Patient characteristics

Seventy-one patients met the selection criteria and were included in the analysis. They had a median age of 37 years. Fifty-four (76%) were male and 17 (24%) were female. Sixty-eight percent were white, 72% were homosexuals, and 14% were intravenous drug users (Table 1). Nineteen patients (27%) were nonrebounders. Table 1 presents the demographics, treatment, and virologic and immunologic characteristics of nonrebounders and rebounders.

Reasons for treatment interruption

The large majority of patients in both the nonrebounder (93.7%) and the rebounder (93.6%) groups interrupted treatment for reasons unrelated to virologic response to HAART: nonadherence and lost to follow-up (56.3% in the NR group and 55.1% in the rebounder group), adverse events or intercurrent illnesses (31.3% and 34.7%, respectively), or financial reasons (6.3% and 4.1%, respectively). Only one patient in the nonrebounder group (6.3%) interrupted treatment after complete virologic response, and three patients in the rebounder group (6.1%) interrupted treatment after virologic failure.

Factors associated with virologic control following treatment interruption

The nonrebounder and rebounder groups did not significantly differ in age (median 36.1 years and 37.1 years, respectively, $p = 0.31$), ethnicity (57.9% and 71.2%, respectively, $p = 0.13$), or percent IV drug use (10.5% and 15.7%; $p = 0.27$). Nonrebounders were less likely than rebounders to be male (47.4% vs. 86.5%; $p = 0.0014$) and MSM (50.0% vs. 79.6%; $p = 0.0500$). The two groups did not significantly differ in the proportion of patients with a history of opportunistic infections prior to treatment interruption (10.5% of NR patients and 25.0% of rebounders; $p = 0.119$).

Antiretroviral therapy was instituted after a mean of 237 and 335 days following HIV diagnosis among nonrebounders and rebounders, respectively ($p = 0.6629$). No patient was treated during acute HIV infection and none received experimental vaccine or immunotherapy. HAART (vs. mono/dual therapy) was the initial antiretroviral regimen in 47.4% of nonrebounders and 15.4% of rebounders ($p = 0.0067$). At the time of treatment interruption, nonrebounders had been on antiretroviral therapy for a mean of 743 days (range: 50–2978), vs. 1298 days (range: 142–3401) for the rebounders ($p = 0.0033$). They had also experienced an average of 5.2 different antiretroviral regimens (vs. 2.2 different regimens for the rebounders; $p < 0.0001$).

As mentioned above, all patients had a peak viremia of more than 5000 copies/ml (3.70 $\log_{10}$ copies/ml) prior to treatment. The median peak viral loads of the nonrebounder and rebounder groups were 4.39 (range: 3.72–6.62) and 5.22 (range: 3.95–6.62), respectively ($p < 0.001$). The nonrebounder group had a higher median pretreatment nadir CD4 count (330 vs. 122;

Table 1. Characteristics of Patients Undergonig Treatment Interruption

	Nonrebounders (n = *19*)	*Rebounders* (n = *52*)	p *value*
White (%)	57.9	71.2	0.1278
Male (%)	47.4	86.5	0.0014
MSM[a] (%)	50.0	79.6	0.0500
IV drug users (%)	10.5	15.7	0.2745
Median age (years)	36.1	37.1	0.4244
Received HAART[b] As first regimen (%)	47.4	15.4	0.0067
Time from diagnosis to TI[c] (days)	237	335	0.6690
Median pretreatment max $\log_{10}$VL (range)	4.39 (3.72–6.62)	5.22 (3.95–6.62)	<0.001
Median pretreatment nadir CD4 (range)	330 (31–821)	122 (2–587)	0.0023
Mean ART[d] duration prior to TI in days (range)	743 (50–2978)	1298 (142–3401)	0.0033
Mean number of ART regimens prior to TI	2.2	5.2	<0.0001
An h/o OI[e] (%)	10.5	25.0	0.119
Reasons for TI			
Complete viral suppression	6.3%	0%	
Treatment failure	0%	6.1%	
Nonadherence, AE,[f] other	93.7%	93.9%	NS

[a]Men who have sex with men.
[b]Highly active antiretroviral therapy.
[c]Treatment interruption.
[d]Antiretroviral therapy.
[e]Opportunistic infections.
[f]Adverse events.

$p = 0.0023$) and a higher median CD4 count at the start of treatment interruption (441 vs. 224; $p = 0.014$).

In a multivariate logistic regression analysis, the following factors predicted nonrebounder status: peak VL before TI ($\log_{10}$ copies/ml) (OR = 0.14, 95% CI = 0.04–0.48, $p = 0.0016$); having received HAART as initial regimen (OR: 11.0, 95% CI: 2.04–59.8, $p = 0.0054$), and female gender (OR = 4.8, 95% CI = 1.09–21.5, $p = 0.0384$).

Outcomes of treatment interruption

By definition, all patients in the nonrebounder group had a viremia of less than 3.70 $\log_{10}$ copies/ml at T + 180, whereas all patients in the rebounder group exceeded that value at the same time point. The median change in viremia during treatment interruption was +3.38 $\log_{10}$ copies/ml for the nonrebounder group and 5.02 $\log_{10}$ copies/ml for the rebounder group (Table 2). The median CD4 count at T + 180 was 383 and 182 for the nonrebounder and rebounder groups, respectively ($p = 0.019$). The median change in CD4 count during TI was $-20.5/\mu$l for nonrebounders and $-64.0/\mu$l in rebounders.

Upon resumption of HAART, nonrebounders were not more likely to have achieved complete virologic response than rebounders at the end of the follow-up period (47% vs. 29%; $p = 0.144$). They were, however, less likely to develop opportunistic infections (0% vs. 21%; $p = 0.029$) or die (0% vs. 21%; $p = 0.029$) during follow-up than rebounders.

DISCUSSION

Our results show that the large majority (94%) of patients followed at our clinic who interrupt antiretroviral therapy for at least 180 days do so for reasons unrelated to virologic response. Unlike patients who have previously achieved sustained viral suppression or patients with multidrug-resistant HIV, viral load and CD4 dynamics, as well as disease progression upon reintroduction of HAART have not been studied among this group of patients.

At 180 days following treatment interruption, almost 30% of the patients in our cohort did not have a subsequent rebound of viremia to more than 5000 copies/ml. A combination of the following factors is likely to determine sustained virologic control following antiretroviral treatment interruption: viral fitness, patient's demographics and immune response to the virus, and the effect of the antiviral therapy.

Nonrebounders were less likely than rebounders to be male (47.4% vs. 86.5%) and MSM (50.5% vs. 79.6%); the two factors are likely related, as the large majority of our male patient

Table 2. Virologic and Immunologic Impact of Treatment Interruption

	Nonrebounders (n = *19*)	*Rebounders* (n = *52*)	p *value*
Median CD4 at end of TI[a]	383.0	182.0	0.0019
Median change in CD4 during TI (range)	−20.5 (−196 to +179)	−64.0 (−680 to +97)	0.086
CD4 >350 at end of TI (%)	55.6	16.7	0.0024
Median change in VL during TI (log_{10} copies/ml)	3.38	5.02	<0.001

[a]Treatment interruption.

population is homosexual. Female gender remained an independent predictor of the nonrebounder status after multivariate analysis (OR = 4.8, 95% CI = 1.09–21.5, $p = 0.0384$) (Table 3). Our small sample size did not allow a closer analysis of this apparent gender disparity. However, it appears consistent with previous observations that plasma viremia is lower in women than in men at similar CD4 lymphocyte counts.[10–12] Also, the higher likelihood of women to maintain virologic suppression following treatment interruption may not translate into lower risk of disease progression, since studies have shown that compared to men, lower HIV RNA levels have been associated with disease progression in women.[11,13] Should these gender differences in virologic control following TI be confirmed, they might need to be taken into account when considering treatment interruption.

Nonrebounders had been on antiretroviral therapy for a shorter duration than rebounders (743 days vs. 1298 days) and had experienced fewer different antiretroviral regimens (2.2 vs. 5.2). However, the only treatment factor associated with the nonrebounder status after multivariate analysis was the nature of the initial antiretroviral regimen. Nonrebounders were more likely to have received HAART (vs. mono/dual antiretroviral regimens) as their initial regimen (47.4% vs. 15.4%; OR: 11.0, 95% CI: 2.04–59.8, $p = 0.0054$).

The initial antiretroviral regimen might have a significant impact on the patient's ability to subsequently control the viremia following treatment interruption by modulating either the patient's HIV-specific immune response or the viral phenotype. Examining the immune responses of nonrebounders may yield a better understanding of protective immunity to HIV.

It has been reported that treatment during acute HIV infection might induce a strong neutralizing antibody response against autologous virus[14] leading to a condition whereby the host is better able to control viremia in the absence of therapy.[15,16] Some of these patients have been able to achieve significant and sustained control of viral replication off treatment.[15] While the mechanisms of this phenomenon are incompletely understood, treatment during chronic HIV infection may induce significant immune modulation, potentially altering the subsequent course of the disease even after the treatment is interrupted.[2,6,17]

Examining the immune responses of nonrebounders may yield a better understanding of protective immunity to HIV. Ruiz *et al.*[2] showed a substantial increase in HIV-specific CD8 T cell frequencies in patients interrupting treatment three consecutive times following complete virologic response. Some patients also experienced a weak and transient p24-specific T helper response. These and similar observations argue for a potential benefit for strategic treatment interruptions (STI) and the development of HIV-specific immune-based therapeutic strategies. There is, however, a potential risk for a significant CD4 depreciation if therapy was interrupted, and HIV-specific $CD4^+$ cells might be destroyed in patients who fail to control viremia during STI.[18] Our results show that the CD4 decay is moderate after treatment interruption and even minimal in patients who maintain virologic control. There remains the possibility that despite normal or subnormal lymphocyte counts, HIV patients might have significant dysfunction of the cellular immunity, such as lack of CD45 RO^+ memory cells, lack of CD38 activation markers, and coreceptor CD28-expressing CD4 cells.[19] However, measuring the specific immune response to HIV is not well established, and the clinical correlates of these markers of HIV immunity are unclear.

Table 3. Factors Predicting Nonrebounder Status: Multivariable Analysis

	Odds ratio	*95% confidence interval*	p *value*
Peak viral load before TI[a] (log_{10} copies/ml)	0.14	0.04–0.48	0.0016
Initial regimen was HAART[b]	11.0	2.04–59.8	0.0054
Female gender	4.8	1.09–21.5	0.0384

[a]Treatment Interruption.
[b]Highly active antiretroviral therapy.

Nonrebounders were not significantly more likely to achieve complete virologic suppression following reinstitution of HAART than rebounders. Their greater ability to control viremia following treatment interruption might therefore be transient. Deeks *et al.*[5] showed that viral replicative capacity increased after therapy was discontinued in patients who were multidrug resistant. Studying the replication capacity of viral isolates of patients who maintain virologic control after treatment interruption might help improve our understanding of the potential modulations of the treatment and HIV-specific immunity on the viral phenotype. Our limitations include the relatively small size of our cohort and the fact that it was drawn from a single site, which might have specific demographics limiting the generalizability of our results. Also, DHHS antiretroviral treatment indications are frequently updated, and this is reflected in trends in providers' decisions. However, the advantages include a uniformity in clinical practices in antiretroviral treatment initiation and discontinuation in a single clinic setting, as well as uniformity in data collection.

In conclusion, our study shows that the majority of patients interrupting treatment during routine HIV care do so for reasons unrelated to treatment interruption. A large proportion of those patients do not experience a significant virologic rebound. A better understanding of the factors related to sustained virologic control following treatment interruption, such as gender and antiretroviral treatment experience, will likely yield insight regarding the mechanism of patients' responses to both HIV infection and antiretroviral therapy.

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