AIDS RESEARCH AND HUMAN RETROVIRUSES
Volume 18, Number 13, 2002, pp. 909–916

Immunologic and Virologic Consequences of Temporary Antiretroviral Treatment Interruption in Clinical Practice

RAY Y. CHEN,[1] ANDREW O. WESTFALL,[1] JAMES L. RAPER,[1] GRETCHEN A. CLOUD,[1] ASHLEE K. CHATHAM,[1] EDWARD P. ACOSTA,[1] SISSI V. PHAM,[2] JERRY M. TOLSON,[2] GUSTAVO R. HEUDEBERT,[1] and MICHAEL S. SAAG[1]

ABSTRACT

To determine the long-term immunologic and virologic effects of antiretroviral treatment interruptions, a retrospective analysis of an ongoing observational database was performed at a university HIV clinic. All patients who began highly active antiretroviral therapy (HAART) after January 1, 1996 and (1) were HAART experienced for ≥90 days, (2) had a treatment interruption (TI) for ≥30 days, (3) resumed HAART for ≥30 days, and (4) had CD4$^+$ cell counts performed pre- and post-TI were included. Main outcome measures included the following: Immunologic success was defined as a post-TI CD4$^+$ cell count >90% of the pre-TI CD4$^+$ cell count (post-TI/pre-TI, >90%). Virologic success was defined as a post-TI viral load (VL) less or equal to twice the pre-TI VL (post-TI/pre-TI, ≤2) or a post-TI VL of <1000 copies/ml. The pre-TI (baseline) value was the value at the start of the TI (range, −20 to +7 days); the post-TI value was the highest CD4$^+$ cell count and lowest VL copy achieved during the follow-up window (270 days). One thousand and eight patients were included in the analysis and 75 met the inclusion criteria. Forty-four of 75 patients (58.6%) achieved a successful immunologic outcome and 52 of 68 patients (76.5%; 7 patients did not have a VL determined within the specified periods) achieved a successful virologic outcome. No factors predicting success were identified. The median CD4$^+$ cell counts pre- and post-TI were 233 and 231 cells/μl, respectively; the median VLs pre- and post-TI were 11,456 and 404 copies/ml, respectively. We conclude that the majority of our patients in virologic failure who underwent a temporary TI recovered 90% of their baseline CD4$^+$ cell counts and returned to within 2-fold of their baseline VL when HAART was resumed.

INTRODUCTION

CONTINUOUS, LONG-TERM, highly active antiretroviral therapy (HAART) was once thought to be a potential cure for human immunodeficiency virus (HIV) infection. On the basis of initial estimates of the life span of latently infected lymphocytes, complete eradication was believed to be possible after 3 to 4 years of continuous therapy.[1–4] More recent estimates, however, show that the life span of these chronically infected cells is substantially longer than the original predictions.[5,6] When combined with evidence of ongoing replication of HIV even when viremia is below the level of detection,[7–9] the concept of achieving eradication with antiretroviral therapy alone has been deemphasized. In addition to adopting a model of lifelong treatment, unanticipated drug toxicities are being encountered with increased frequency throughout the course of treatment. On occasion, treatment-related toxicities are managed with treatment interruptions (TIs), although the clinical consequences of such interruptions are not fully understood.

Interruptions of HAART have been examined in acutely and chronically infected patients for a variety of reasons. "Structured" or "scheduled" treatment interruptions have been evaluated as an immunologic tool to prime the immune system with the intent of boosting a cytotoxic T lymphocyte response sufficient to control HIV infection.[10–12] In chronically infected patients, especially among those with advanced disease, the immunologic benefits of this strategy have not been clearly demonstrated.[13–17] It is clear, however, that implementing TIs increases the risk of potentially irreversible CD4$^+$ cell loss and increased plasma HIV RNA.[18–25] Owing to the relative lack of data and the uncertainty of the clinical consequences, TIs are still considered experimental and currently are not recom-

[1]Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama 35294.
[2]GlaxoSmithKline, Research Triangle Park, North Carolina 27709.

mended for patients outside of clinical research studies. Still, patients in clinical practice today commonly undergo "supervised" TIs of different durations, mostly due to toxicities. While providing a short-term reprieve from many of the adverse effects of HAART, the long-term immunologic and virologic consequences of supervised TIs are unknown. The underlying clinical question is whether the short-term benefits of supervised TIs to avoid toxicity outweigh the long-term consequences of potentially irreversible immunologic decline. We report immunologic and virologic outcomes of supervised TIs in a cohort of chronically HIV-infected outpatients at the University of Alabama at Birmingham (UAB).

MATERIALS AND METHODS

Patients

The UAB Outpatient HIV Clinic began prospectively collecting information on all patients into an ongoing observational database in January 1994. Trained medical records personnel use standardized procedures to collect clinical and treatment data from medical records daily. Laboratory data are downloaded from the hospital laboratory system directly into the database. All outside laboratory values are entered into the database manually. The UAB Institutional Review Board has approved the protocol. Because the data evaluated in this study were reviewed retrospectively, no informed consent was obtained from the subjects.

The inclusion criteria for this study were as follows: (1) HAART experienced for $\geq$90 days, (2) TI for $\geq$30 days, (3) resumption of any HAART regimen for $\geq$30 days, and (4) measured $CD4^+$ cell count values pre- and post-TI. HAART was defined as therapy with three or more drugs, at least one of which was a protease inhibitor or nonnucleoside reverse transcriptase inhibitor. For patients with more than one TI, the most recently completed TI was used.

Definitions of success

Successful immunologic outcome was defined as a post-TI $CD4^+$ cell count that returned to greater than 90% of the pre-TI $CD4^+$ cell count (post-TI/pre-TI, $>$90%). Virologic success was defined as a post-TI viral load (VL) that returned to less than or equal to two times the pre-TI VL (post-TI/pre-TI, $\leq$2) or a post-TI VL $<$1000 copies/ml. The pre-TI (baseline) value was defined as the value at the start of the TI, ranging from 20 days before the TI to 7 days after the TI began. The post-TI value was the best value achieved during the follow-up window (270 days), that is, the highest $CD4^+$ cell count and lowest VL copy, beginning at least 30 days after the TI.

Statistical analysis

We examined outcomes based on immunologic and virologic responses to HAART after the TI. All calculations were performed with SAS software, version 6.12 (SAS Institute, Cary, NC). Demographics are presented using descriptive statistics. Comparison between patients included in the study versus not included utilized χ^2 statistics for categorical variables and the Kruskal–Wallis test for continuous factors. Similarly, comparisons between immunologic success and failure groups also utilized the χ^2 test for categorical data and the Kruskal–Wallis test for continuous data. The covariates examined included minimum $CD4^+$ cell count and maximum VL ever, $CD4^+$ cell count and VL at TI start, $CD4^+$ cell count and VL at TI end, duration of TI, number of previous TIs, number of previous regimens, and duration of follow-up.

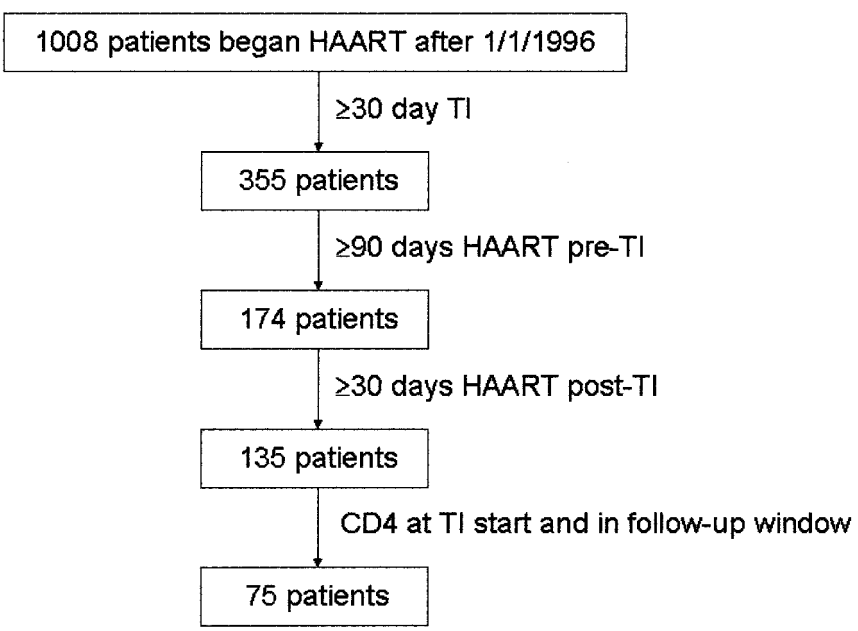

FIG. 1. Patient selection process. HAART, Highly active antiretroviral therapy; TI, treatment interruption.

TABLE 1. COMPARISON OF THE 75 PATIENTS INCLUDED IN THE STUDY WITH THE 933 PATIENTS EXCLUDED FROM THE STUDY

Characteristic	*Included*	*Excluded*	p *Value*
White	71%	57%	0.02
Male	83%	81%	0.68
Age[a]	36 years	37 years	0.54
$CD4^+$ cell count at TI[a]	156 cells/μl	192 cells/μl	0.41
Follow-up duration[a]	1142 days	649 days	0.0001

Abbreviations: TI, Treatment interruption.
[a]Median values.

RESULTS

Patient characteristics

A total of 1008 patients began HAART after January 1, 1996 (prior ART allowed). Of these, 75 met the inclusion criteria (Fig. 1). Compared with the 933 excluded patients, the 75 included patients had significantly more white than nonwhite patients (Table 1). All other demographic characteristics were similar between the two groups. The 75 included patients had a median minimum $CD4^+$ cell count (ever) of 85 cells/μl and a median maximum VL (ever) of 145,760 copies/ml (5.16 $\log_{10}$) during their treatment history before the TI, indicating that they were relatively advanced in their disease before the initiation of HAART.

The patients had a median 573 days of HAART experience, with a median of three different HAART regimens (range, 1–17) before their TI (Fig. 2). A new HAART regimen was defined as any change in medications, including TIs, other than dosage changes. The median $CD4^+$ cell count and VL pre-TI was 233 cells/μl and 11,456 copies/ml (4.06 $\log_{10}$), respectively. Of note, the majority of these patients were experiencing virologic rebound (VL $>$ 500) at the time of TI. Among the 68 patients who had recorded VL values pre-TI, only 9 patients had a VL $<$ 50 copies/ml and 11 had a VL between 50 and 500 copies/ml. Toxicity, mostly gastrointestinal, was the primary reason for the TI (Table 2). The median duration of the TI was 67 days (range, 31–1018 days); after the TI, HAART was resumed for a median of 171 days (range, 35–266 days; Fig. 2). Sixty-six of 75 patients reinitiated treatment with a different HAART regimen. The majority of these patients did not have resistance testing data available.

Immunologic and virologic responses

$CD4^+$ cell count and VL data were analyzed beginning 30 days after the resumption of therapy until the end of the follow-up window (270 days). The median value of the best $CD4^+$ cell count achieved for all patients during this follow-up period was 231 cells/μl (Fig. 2), with 44 of 75 patients (58.6%) achieving a post-TI/pre-TI $CD4^+$ cell count ratio $>$ 90% (Fig. 3A). On the basis of the $CD4^+$ cell count measurements obtained, a median of 92 days (range, 32–261 days) was required to achieve this best $CD4^+$ cell count. Seven patients (9.3%) were unable to attain a post-TI $CD4^+$ cell count greater than 50% of their pre-TI $CD4^+$ cell count. Virologically, the median of the lowest VL attained in the follow-up period was 404 (Fig. 2), with 56 of 68 patients (82.4%) achieving successful VL outcome (Fig. 3B). Fifty-four patients had a post-TI VL within 2-fold of their pre-TI VL and 2 patients had a follow-up VL less than 1000 copies/ml (114 and 523 copies/ml). On the basis of the VL measurements obtained, a median of 83 days (range, 32–259 days) was required to achieve this best VL. Forty-eight of these 56 patients (70.6% of total) attained a post-TI VL less than or

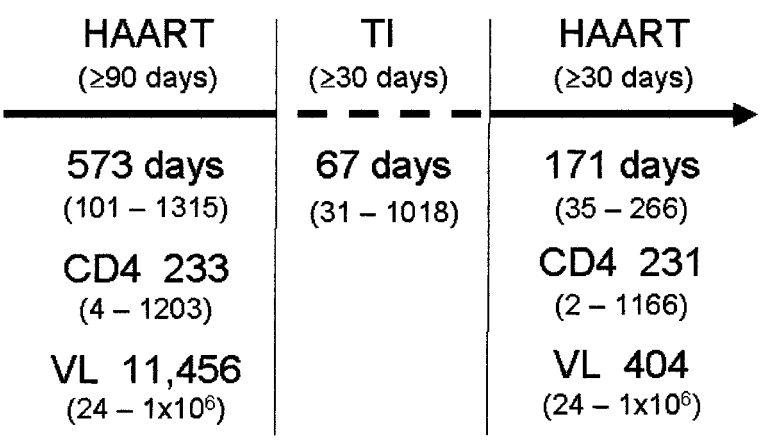

FIG. 2. Median and range of days, $CD4^+$ cell count, and viral load (VL) during each segment of therapy. HAART, Highly active antiretroviral therapy; TI, treatment interruption.

TABLE 2. REASONS FOR TREATMENT INTERRUPTION[a]

Reason for treatment interruption	*No. of patients*
Toxicities	
GI symptoms (nausea, vomiting, diarrhea, abdominal pain)	35
Metabolic abnormalities (hyperlipidemia, diabetes mellitus, lactic acidosis)	13
Neuropathy	6
CNS symptoms (fatigue, depression, nightmares)	6
New opportunistic infection (PCP)	1
Virologic failure[b]	9
Nonadherence	5
Financial	11

Abbreviations: GI, Gastrointestinal; PCP, *Pneumocystis carinii* pneumonia.

[a]Some patients had more than one reason for their treatment interruption.

[b]Although these patients began their treatment interruption primarily for virologic failure, the majority of the other patients were in virologic failure (VL > 500 copies/ml) as well.

equal to their pre-TI VL. Of the TI failure patients, most failed because of either immunologic or virologic relapse (31 or 12 patients, respectively). Only six patients failed both.

χ^2 and Kruskal–Wallis tests were used to compare factors between the immunologic success and failure groups (Table 3). Although no significant differences were found, a trend toward immunologic success was seen with a shorter duration of TI and a longer duration of follow-up. In a subgroup analysis of the patients in virologic failure (VL $\geq$ 500 copies/ml) at the TI, 31 of 49 patients (63.2%) had successful $CD4^+$ cell count outcomes and 40 of 48 patients (83.3%; 1 patient did not have a follow-up VL value in the specified window) had successful VL outcomes (post-TI/pre-TI, $\geq$2; or a post-TI VL of $<$1000 copies/ml). A subgroup analysis of all patients at 24 weeks ($\pm$4 weeks) post-TI showed 20 of 35 patients (57.1%) with successful $CD4^+$ cell count outcomes and 24 of 33 patients (72.7%) with successful VL outcomes. To help determine whether patients who initially achieved successful outcomes subsequently experienced relapse and clinical progression, a time trend analysis was performed in which the follow-up window was divided in half and $CD4^+$ cell count outcomes were analyzed for each half. Thirty-nine of 72 patients (54.2%) and 27 of 43 patients (62.8%) had successful $CD4^+$ cell count outcomes during the first and second halves, respectively. Forty-nine of 64 patients (76.6%) and 32 of 39 patients (82.1%) had successful VL outcomes during the first and second halves, respectively. Although the total number of patients in the second half declined significantly, the proportion of patients with successful outcomes tended to improve over time. This is consistent with the trend noted earlier of immunologic success with a longer duration of follow-up. There were no deaths during the follow-up period and only one opportunistic infection (progressive multifocal leukoencephalopathy), which occurred 3 months after the TI.

DISCUSSION

Owing to the chronic nature of HAART and the increasing incidence of treatment-limiting toxicities, temporary TIs are being used more frequently to manage drug-related toxicities. Yet, to date, there is little information about whether virologic and immunologic ($CD4^+$ cell count) responses can be regained once therapy is resumed. Our retrospective analysis of 75 chronically HIV-infected patients suggests that TIs, employed mainly for toxicity to an ongoing treatment regimen, are relatively safe. As shown in Fig. 3, the majority of our patients subsequently experienced a successful recovery of $CD4^+$ cell counts and suppression of VL back to their baseline (TI start) levels after the resumption of HAART.

Treatment interruptions have been used in HIV therapeutics for many reasons. So-called strategic or structured TIs have been used as a means to stimulate the immune system response to HIV. With the exception of their use in acutely infected individuals,[11] studies of structured TIs have yielded disappointing degrees of immune system control of viral replication and have defined many risks to interrupting therapy.[18,23,26,27] Among chronically infected patients on receiving HAART with high $CD4^+$ cell counts and undetectable VL, several studies[18,23] have shown prompt viral rebound back to pretreatment levels, usually within 2 to 4 weeks, when HAART was discontinued. There have been case reports of such patients developing symptoms of acute HIV infection.[26,27] In patients with advanced disease who have experienced multiple treatment failures and high-level viral resistance. TIs have been proposed as a potential strategy to improve virologic responsiveness to antiretroviral therapy. Studies of the rebounding virus following TIs in this setting have shown a shift from multidrug-resistant virus back to wild-type virus within 8 to 12 weeks, often associated with increased viral fitness and replicative capacity.[25,28,29] The immunologic consequences associated with these shifts in viral fitness appear ominous, with dramatic declines in $CD4^+$ cell counts observed at the time of conversion to wild-type virus. Anecdotal reports suggest that several of these patients never recover their $CD4^+$ cell counts to pre-TI levels, causing significant concern.[20,23,25] The true incidence of this worrisome response and whether these patients subsequently will recover immunologic and virologic control remain unknown.

The most common use of TIs in clinical practice is to manage toxicities and "treatment fatigue." Despite the potential long-term consequences suggested by studies of "structured" TIs, patients undergoing continuous HAART often undergo a "supervised" TI by their physicians for treatment toxicities. An increasing number of patients today develop treatment-associated adverse effects, such as nausea, vomiting, lipodystrophy, diabetes mellitus, or hyperlipidemia. Continuing therapy in these patients increases the likelihood of poor adherence along with the potential development of viral resistance, or other complications of therapy, such as pancreatitis, coronary artery disease, or lactic acidosis. Other patients simply develop treatment fatigue and request a TI for a period of time.

The use of TIs in these settings leads to several critical questions: Do the immunologic and virologic risks of a TI to allow the acute issue to improve or resolve, followed by restarting therapy, outweigh the risks of continued therapy? Do TIs have any role in the management of long-term treatment toxicities?

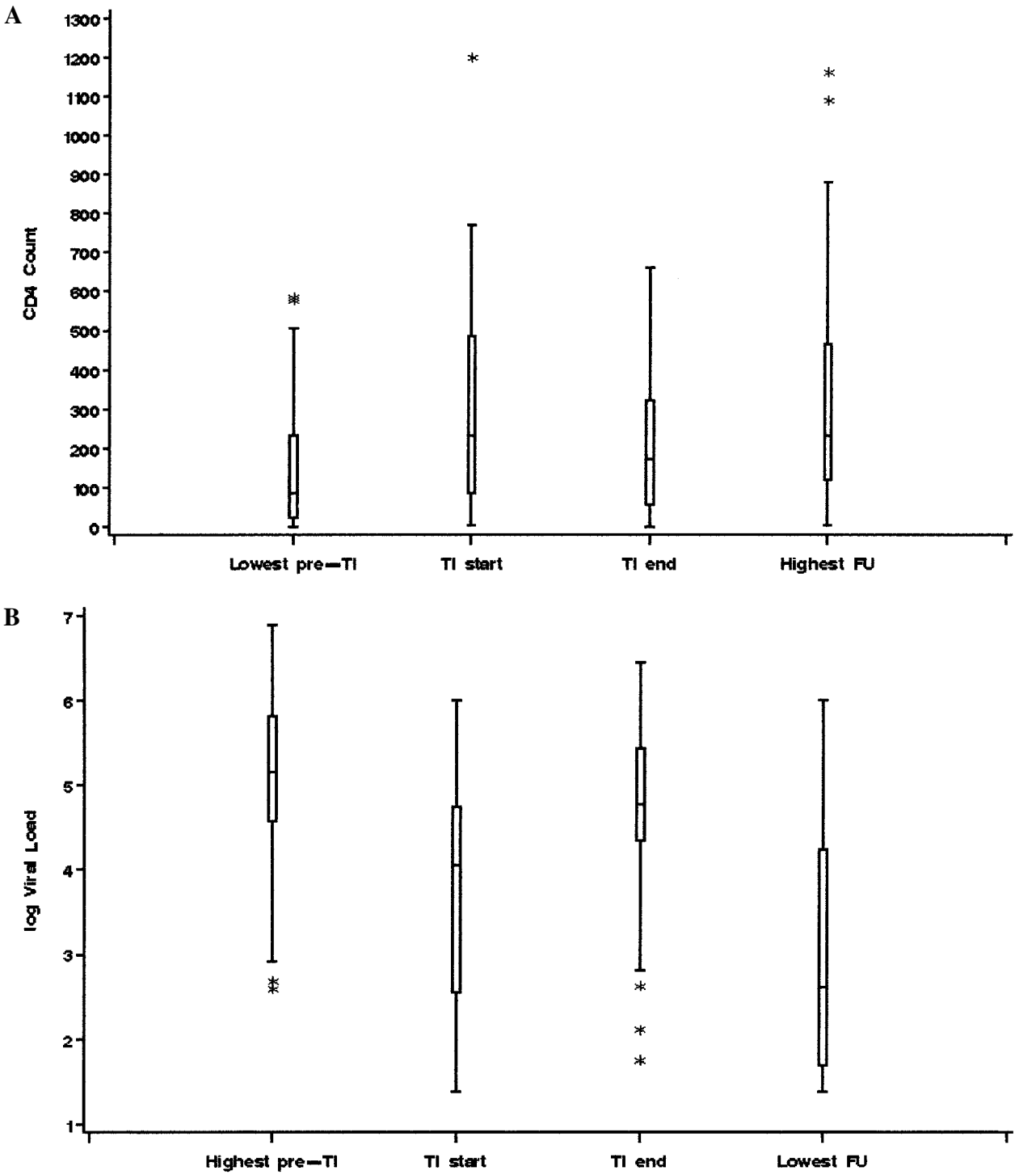

FIG. 3. (**A**) Box plots of $CD4^+$ cell count nadir before the treatment interruption (TI), at the start of the TI, at the end of the TI, and the highest value during follow-up (FU). (**B**) Box plots of VL copy peak before the TI, at the start of the TI, at the end of the TI, and the lowest value during follow-up. *, outliers.

Will chronically infected patients who undergo a supervised TI recover the same degree of immunologic and virologic control on resumption of therapy? Our data suggest that most patients experiencing virologic failure who have a TI will recover at least 90% of their baseline $CD4^+$ cell counts and return to within 2-fold of their baseline VL or less than 1000 copies/ml when HAART is resumed. Acute treatment toxicities generally resolve with the TI and with most patients resuming a different HAART regimen. The effect on chronic toxicities, however, could not be assessed with a follow-up window of only 270

Table 3. Kruskal–Wallis Analyses Based on $CD4^+$ Cell Counts Comparing Immunologic Success and Failure Groups

Factor	*Median success (range)*	*Medial failure (range)*	*Kruskal–Wallis (p value)*
Duration of TI	58 days (32–395)	89 days (31–1018)	0.10
Duration of follow-up	194 days (35–266)	147 days (35–265)	0.09
Number of prior regimens	3 (1–12)	4 (1–17)	0.42
≥1 prior TI	40.9%	38.7%	0.85[a]
Total duration of prior TI	0 days[b] (0–267)	0 days[b] (0–243)	0.83
Duration of TI/duration of HAART before TI	0.15 (0.03–1.55)	0.17 (0.03–3.47)	0.53
$CD4^+$ cell count, min (ever)	92 cells/μl (1–580)	85 cells/μl (5–587)	0.37
VL, max (ever)	134,567 copies/ml (2,837–7,721,715)	176,940 copies/ml (399–4,546,496)	0.83
$CD4^+$ cell count at TI	180 cells/μl (4–770)	254 cells/μl (19–1203)	0.11
VL at TI	14,485 copies/ml (49–614,370)	1,575 copies/ml (49–1,000,000)	0.49
End of TI $CD4^+$ cell count	207 cells/μl (1–662)	96 cells/μl (17–469)	0.32
End of TI VL	54,731 copies/ml (57–1,000,000)	103,335 copies/ml (131–2,824,714)	0.27

Abbreviations: HAART, Highly active antiretroviral therapy; TI, treatment interruption; VL, viral load.
[a]χ^2 value.
[b]The majority of patients had no previous TI.

days. Whether the benefits of a temporary TI for "treatment fatigue" outweigh the risks can be answered only by a randomized clinical trial.

Although the majority of our patients had successful outcomes by our definitions, the successful virologic response seemed to outpace the successful immunologic response, with the median viral loads improving from 11,456 to 404 copies/ml and median $CD4^+$ cell counts staying about the same, from 233 to 231 cells/μl (Fig. 2). The good virologic response was likely because most of our patients were in virologic relapse (VL > 500) at the time of the TI and subsequently restarted a new regimen to which they responded well. The immunologic response was not as dramatic possibly because the modest VL decrease from 11,456 to 404 copies/ml did not allow for a substantial rise in $CD4^+$ cell counts but did allow the $CD4^+$ cell count to rise back to its baseline value. The more substantial $CD4^+$ cell response most likely had already occurred with the original initiation of HAART, demonstrated by the difference between the patients' median nadir $CD4^+$ cell count (92 cells/μl; Table 3) and the median $CD4^+$ cell count at the TI (233 cells/μl; Fig. 3a).

Despite the successful outcomes of most of the patients, a minority of patients failed to regain virologic or immunologic control. We could identify no significant predictors of failure within our cohort (Table 3). A trend toward failure, however, was seen with a shorter duration of follow-up and a longer duration of TI. The shorter duration of follow-up likely reflects the importance of allowing patients enough time to recover. Failure among patients with a longer duration of TI may be related to drug-resistant virus reverting back to wild-type virus, with concomitant increased viral fitness and loss of $CD4^+$ cells. This has been shown to occur at about 8–12 weeks,[25–27] which is precisely the time difference between the median duration of TI in the success and failure groups (58 and 89 days, respectively). If reversion to wild type is the reason for this trend, the duration of the TI will be important in predicting failure. Seven of the 31 patients who failed immunologically were unable to return to >50% of their baseline $CD4^+$ cell counts. One cannot draw significant conclusions from such few numbers but these patients tended to be highly HAART experienced with a median of 10 different HAART regimens (range, 3–14) and a median of 435 days of HAART (range, 225–969 days) before the TI. Almost all used antiretroviral medications to which they were previously exposed. The duration of the TI ranged from 52 to 213 days with a median of 67 days. Baseline $CD4^+$ cell counts and VL copies varied widely. Of note, three patients had only one $CD4^+$ cell count measurement performed during the follow-up period (on days 63, 70, and 70), as their TIs were recent. These patients may do better with continued follow-up. Among the 31 patients who failed immunologically and the 12 patients who failed virologically, only 6 patients failed both. The reason for this discordance is unclear and, again, meaningful conclusions are difficult. These patients also tended to be HAART experienced (median of 4.5 prior HAART regimens and 592 prior days of HAART), with a median TI duration of 103 days. Again, almost all used recycled medicines. One patient had only one set of laboratory values during the follow-up period (day 98). One possible explanation for this discordance likely relates to each patient's original virologic set point. Under this scenario, a patient who failed by $CD4^+$ cell count but was successful by VL likely ended with a VL that, although successful by our definition, was still too high for that patient's immune status and the patient therefore suffered immunologic decline. Likewise, a patient who failed by VL but was successful by $CD4^+$ cell count likely ended with a VL that, although a failure by our definition, was

still low enough to allow the patient immunologic success. The level that defines true virologic failure is, as yet, undefined and is under investigation.

There are several limitations to our study. First, this is a retrospective analysis of an ongoing observational database. The follow-up laboratory values were not always done at set intervals and thus vary somewhat for each patient. Most patients had $CD4^+$ cell count and VL values through the 9-month follow-up window, but some patients had their TI more recently and did not have a full 9 months of follow-up. These patients may have actually done better or worse than our data indicate. Second, we did not assess for mortality during the TI, as all patients included were required to resume HAART. However, there were no deaths during the follow-up period among the patients who resumed HAART. The only opportunistic infection during the TI or follow-up period was one episode of progressive multifocal leukoencephalopathy, which occurred 3 months after the start of the TI. The low incidence of opportunistic infections suggests that morbidity and mortality were not major contributors of bias in this study. Third, our numbers were small. Our study did not have enough power to adequately determine the potential factors that affected the immunologic or virologic outcomes of patients who underwent a TI. In a power analysis based on our data for $CD4^+$ cell counts, a Wilcoxon rank sum test showed that 99 patients in each group (success/failure) would have been required to have 80% power in identifying a difference between the two groups. Fourth, we were not able to assess for the potential development of viral resistance during the TI as only a few of the patients had resistance genotype or phenotype data available. The lack of resistance data could potentially bias the results of this study compared with patients who do have these data. This bias, however, would be a bias towards the null, as our results would be a minimal estimate of the true effect had the resistance data been available. The successful outcomes achieved by the majority of patients despite this, however, argue even more strongly for the safety of temporary TIs, especially if resistance information were available.

It is still too soon to recommend temporary TIs in routine clinical practice. If used, however, they should be conducted in a closely supervised setting. Owing to the nature of long-term adverse effects of antiretroviral therapy, many clinicians are choosing this option more frequently, despite the lack of clinical study data. Further study of TIs needs to be done, especially in the area of duration of TIs. If our results are supported by other studies, clinicians who put their patients on a temporary TI should be reassured that they are not likely to cause long-term harm to their patients, especially when viewed in the context of harm reduction from chronic exposure to drug-related adverse events. In addition, if temporary TIs are shown to be safe, they may significantly reduce adverse effects and provide substantial cost savings in the long-term treatment of chronically HIV-infected individuals.

ACKNOWLEDGMENTS

This work was supported in part by a grant from GlaxoSmithKline, Inc., the UAB Center for AIDS Research, and NIAID P30-AI27767.

REFERENCES

1. Wei X, Ghosh SK, Taylor ME, *et al.*: Viral dynamics in human immunodeficiency virus type 1 infection. Nature 1995;373:117–122.
2. Ho DD, Neumann AU, Perelson AS, Chen W, Leonard JM, and Markowitz M: Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. Nature 1995;373:123–126.
3. Perelson AS, Neumann AU, Markowitz M, Leonard JM, and Ho DD: HIV-1 dynamics in vivo: Virion clearance rate, infected cell life-span, and viral generation time. Science 1996;271:1582–1586.
4. Perelson AS, Essunger P, and Cao Y: Decay characteristics of HIV-1-infected compartments during combination therapy. Nature 1997;387:188–191.
5. Finzi D, Blankson J, Siliciano JD, *et al.*: Latent infection of $CD4^+$ T cells provides a mechanism for lifelong persistence of HIV-1, even in patients on effective combination therapy. Nat Med 1999;5:512–517.
6. Zhang L, Ramratnam B, Tenner-Racz K, *et al.*: Quantifying residual HIV-1 replication in patients receiving combination antiretroviral therapy. N Engl J Med 1999;340:1605–1613.
7. Wong JK, Hezareh M, Günthard HF, *et al.*: Recovery on replication-competent HIV despite prolonged suppression of plasma viremia. Science 1997;278:1291–1295.
8. Finzi D, Hermankova M, Pierson T, *et al.*: Identification of a reservoir for HIV-1 in patients on highly active antiretroviral therapy. Science 1997;278:1295–1300.
9. Saag MS and Kilby JM: HIV-1 and HAART: A time to cure, a time to kill. Nat Med 1999;5:609–611.
10. Haslett PA, Nixon DF, Shen Z, *et al.*: Strong human immunodeficiency virus (HIV)-specific $CD4^+$ T cell responses in a cohort of chronically infected patients are associated with interruptions in anti-HIV chemotherapy. J Infect Dis 2000;181:1264–1272.
11. Rosenberg ES, Altfeld M, Poon SH, *et al.*: Immune control of HIV-1 after early treatment of acute infection. Nature 2000;407: 523–526.
12. Miro JM, Tortajada C, Plana M, *et al.*: HIV-1 specific T-cell responses and spontaneous control of viremia can be detected after the first cycle of structured treatment interruptions (STI) in patients receiving HAART since primary HIV-1 infection. Abstract 359. In: *VIIIth Conference on Retroviruses and Opportunistic Infections.* Chicago, Illinois, February 4–8, 2001.
13. Ruiz L, Martinez-Picado J, Romeu J, *et al.*: Structured treatment interruption in chronically HIV-1 infected patients after long-term viral suppression. AIDS 2000;14:397-403.
14. Carcelain G, Tubiana R, Mollet L, *et al.*: Intermittent interruptions of antiretroviral therapy in chronically HIV-infected patients do not induce immune control of HIV. Abstract 346. In: *VIIth Conference on Retroviruses and Opportunistic Infections.* San Francisco, California, January 30–February 2, 2000.
15. Lori F, Foli A, Maserati R, *et al.*: Control of viremia after treatment interruption. Abstract 352. In: *VIIth Conference on Retroviruses and Opportunistic Infections*, San Francisco, California, January 30–February 2, 2000.
16. Lori F, Maserati R, Foli A, Seminari E, Timpone J, and Lisziewicz J: Structured treatment interruptions to control HIV-1 infection. Lancet 2000;355:287–288.
17. Fagard C, Lebraz M, Gunthard H, *et al.*: A prospective trial of strategic treatment interruptions in 128 patients. Abstract 357. In: *VIIIth Conference on Retroviruses and Opportunistic Infections*, Chicago, Illinois, February 4–8, 2001.
18. Hatano H, Vogel S, Yoder C, *et al.*: Pre-HAART HIV burden approximates post-HAART viral levels following interruption of therapy in patients with sustained viral suppression. AIDS 2000;14:1357–1363.
19. Zhang L, Chung C, Hu BS, *et al.*: Genetic characterization of re-

bounding HIV-1 after cessation of highly active antiretroviral therapy. J Clin Invest 2000;106:839–845.
20. Youle M, Janossy G, Turnbull W, *et al.*: Changes in CD4 lymphocyte counts after interruption of therapy in patients with viral failure on protease inhibitor-containing regimens. AIDS 2000;14: 1717–1720.
21. Ioannidis JP, Havlir DV, Tebas P, Hirsch MS, Collier AC, and Richman DD: Dynamics of HIV-1 viral load rebound among patients with previous suppression of viral replication. AIDS 2000;14:1481–1488.
22. Chun TW, Davey RT, Ostroski M, *et al.*: Relationship between pre-existing viral reservoirs and the re-emergence of plasma viremia after discontinuation of highly active anti-retroviral therapy. Nat Med 2000;6:757–761.
23. Davey RT, Bhat N, Yoder C, *et al.*: HIV-1 and T cell dynamics after interruption of highly active antiretroviral therapy (HAART) in patients with a history of sustained viral suppression. Proc Natl Acad Sci USA 1999;96:15109–15114.
24. Tebas P, Henry K, Mondy K, *et al.*: Effects of prolonged discontinuation of successful antiretroviral therapy. Abstract 31. In: *1st IAS Conference on HIV Pathogenesis and Treatment*, Buenos Aires, Argentina, July 8–11, 2001.
25. Sabin C, Phillips A, Fusco J, *et al.*: The effect of treatment interruption in patients with virologic failure: Results from a multi-cohort collaborative study. Abstract 365. In: *VIIIth Conference on Retroviruses and Opportunistic Infections*, Chicago, Illinois, February 4–8, 2001.
26. Colven R, Harrington RD, Spach DH, Cohen CJ, and Hooten TM: Retroviral rebound syndrome after cessation of suppressive antiretroviral therapy in three patients with chronic HIV infection. Ann Intern Med 2000;133:430–434.
27. Kilby JM, Goepfert PA, Miller AP, *et al.*: Recurrence of the acute HIV syndrome after interruption of antiretroviral therapy in a patient with chronic HIV infection: A Case Report. Ann Intern Med 2000;133:435–438.
28. Devereux HL, Youle M, Johnson MA, and Loveday C: Rapid decline in detectability of HIV-1 drug resistance mutations after stopping therapy. AIDS 1999;13:F123–F127.
29. Deeks SG, Wrin T, Liegler T, *et al.*: Virologic and immunologic consequences of discontinuing combination antiretroviral-drug therapy in HIV-infected patients with detectable viremia. N Engl J Med 2001;344:472–480.

Address reprint requests to:
Michael S. Saag
UAB 1917 Clinic
908 20th Street South, Room 142
Birmingham, Alabama 35294-2050

E-mail: msaag@uab.edu