A Prospective Trial of Structured Treatment Interruptions in Human Immunodeficiency Virus Infection

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Background: According to the “autovaccination hypothesis,” reexposure to human immunodeficiency virus (HIV) during treatment interruptions may stimulate the HIV-specific immune response and lead to low viremia after withdrawal of highly active antiretroviral treatment (HAART). Many patients who started HAART earlier in their disease course than is currently recommended would like to discontinue, but it is unknown whether it is safe to do so.

Objectives: To determine whether repeated treatment interruptions of HAART (1) stimulated the cytotoxic HIV-specific immune response and whether such stimulation correlated with low viremia off treatment, and (2) were safe with respect to clinical complications, development of viral resistance, and decline in CD4 cell counts.

Design: Interventional study with before-after comparison.

Setting: Outpatient clinics of university hospitals in Switzerland and Spain.

Patients: A total of 133 patients receiving HAART, with a median CD4 cell count of 740/µL, and whose viral load had been undetectable for a median of 21 months.

Interventions: HAART was interrupted for 2 weeks, restarted, and continued for 8 weeks. After 4 such cycles, treatment was indefinitely suspended 40 weeks after study entry.

Main Outcome Measures: HIV-specific cytotoxic T-cell responses were evaluated by interferon γ enzyme-linked immunospot analysis. The proportion of “responders” (viral load <5000 copies/mL) was measured at weeks 52 and 96. HIV-related diseases and CD4 cell counts were recorded.

Results: Seventeen percent of patients (95% confidence interval, 11%-25%) were responders at week 52, and 8% at week 96. Low pre-HAART viral load and lack of rebound during weeks 0 to 40 predicted response. HIV-specific CD8+ T cells increased between week 0 (median, 343 spot-forming cells per million peripheral blood lymphocytes [SFC/10^6 PBL]) and week 52 (median, 1930 SFC/10^6 PBL), but there was an inverse correlation between response and the number of spot-forming cells. Eighty-five (64%) of 133 patients stopped therapy for at least 12 weeks, and 55 (41%) for at least 56 weeks. The median CD4 cell count decreased from 792/µL to 615/µL during the first 12 weeks without treatment, but stabilized thereafter. One patient (0.75%) developed drug resistance necessitating salvage treatment. There were no AIDS-related clinical complications.

Conclusions: Results of this study do not favor the autovaccination hypothesis. Treatment interruptions did not provoke clinical complications, and there was little drug resistance. Comparative trials will have to show what benefit, if any, is associated with intermittent, as opposed to continuous treatment.

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After introduction of highly active antiretroviral treatment (HAART), morbidity and mortality of human immunodeficiency virus (HIV) infection have declined. However, many patients find it difficult to comply with long-term HAART, especially if they experience adverse effects. Treatment interruptions in patients with HIV infections are being studied for 3 main reasons. (1) An increase in time off drug treatment may improve quality of life and diminish adverse effects and costs. (2) After HIV has become resistant to antiretroviral drugs, treatment interruptions may allow repopulation of plasma with drug-susceptible virus and therefore improve the chances of success of subsequent salvage therapy. (3) Reexposure to viral antigens during treatment interruption may stimulate anti-HIV im-
The treatment schedule is shown in Figure 1. HAART was interrupted for 2 weeks, restarted, and continued for 8 weeks, and after 4 such cycles, treatment was indefinitely suspended at week 40 after study entry. If viral load remained above 50 copies/mL after 8 weeks’ retreatment, patients did not undergo further treatment interruptions. At week 40, treatment was also restarted if CD4 cell counts were below 400/µL. Otherwise, at week 40, treatment was stopped. From week 40 to week 52, restarting treatment was recommended if symptoms of acute HIV infection occurred or if viral load exceeded 50,000 copies/mL 3 times, 100,000 copies/mL twice, or 500,000 copies/mL once. The drugs used for each individual patient remained identical between weeks 0 and 52, unless a change was indicated because of viral escape (n=1, see below) or drug intolerance.

At week 52, patients who had undergone four 2-week and one 12-week treatment interruption were classified as “responders” if their viral load was below 5000 copies/mL. If their viral load was higher, or if they had stopped treatment interruptions for any reason before week 52 they were considered “nonresponders.” The protocol recommended HAART for nonresponders, and for responders whose viral load rebounded above 5000 copies/mL after week 52. From week 52 to week 64, viral load and CD4 cell counts were measured every 4 weeks, and every 8 weeks from week 64 to week 96.

MEASUREMENT OF HIV-SPECIFIC CD8 T-LYMPHOCYTE RESPONSE, HLA TYPING, AND LYMPHOCYTE TYPING

The HIV-specific CD8 T-cell frequencies were determined on frozen peripheral blood mononuclear cells, by direct ex vivo interferon γ enzyme-linked immunospot assay.11,12 Synthetic peptides corresponding to previously described optimal HLA class I–restricted cytotoxic T-lymphocyte epitopes were used at a concentration of 2mM. According to the HLA genotype, each patient was screened at each time point for responses to a median of 16 (range, 2–32) different cytotoxic T-lymphocyte epitopes (the list of peptide epitopes is available from the authors). Results were expressed as spot-forming cells per million peripheral blood lymphocytes (5FC/10⁶ PBL). A positive response to a given peptide epitope was defined as 5FC/10⁶ PBL greater than 3 SEs above background and equal to or above 50 5FC/10⁶ PBL. HLA type was determined by gene amplification.13 CD3, CD4, and CD8 lymphocyte counts were determined by flow cytometry (Coulter EPICS IV, Basel, Switzerland) using fluoresecinated DAKO-T3, DAKO-T8, and R-Phycerythrin DAKO-CD4 (Dako Corp, Glostrup, Denmark).

RESISTANCE TESTING

Resistance was defined as the occurrence of mutations associated with resistance in the reverse transcriptase or protease genes, whereas “virologic escape” was defined as a viral load
above 500 copies/mL in patients who were compliant with HAART, after at least 4 months of continuous treatment. Compliance was assessed by the number of prescriptions filled and by patient interview.

STATISTICAL ANALYSIS

Participants were described using simple statistics (proportions with 95% confidence intervals, means, medians, and ranges). Viral loads and CD4 cell counts were compared using nonparametric tests for matched data (Friedman test to compare 4 cycles, Wilcoxon test for paired comparisons); proportions of participants with a viral load greater than 200 copies/mL were compared using the Cochran Q test (to compare 4 cycles) and McNemar tests (paired comparisons). Baseline characteristics of responders were compared with those of nonresponders using Mann-Whitney tests (for continuous variables) and χ² tests (for discrete variables). We also compared the HIV-specific cytotoxic response (ie, the number of HIV-specific interferon γ–producing CD8⁺ T lymphocytes) in responders and nonresponders at week 52, and examined the Spearman correlation between cytotoxic response and the cumulative exposure to the HIV antigen (estimated by the sum of the heights of rebounds in viral load at weeks 2 to 42). All calculations were done with SPSS version 9.0 statistical software (SPSS Inc, Chicago, Ill).

RESULTS

PATIENT CHARACTERISTICS

Ninety-two men and 41 women were recruited. Thirty-six (27%) were from several hospitals in Spain, mostly in Barcelona, and 97 (73%) were from Switzerland (Zurich, 29; Geneva, 26; Bern, 11; Basel, 11; St Gall, 8; Lugano, 7; and Lausanne, 5). Ninety-two (69%) were men. The probable route of acquisition of HIV was homosexual intercourse in 38%, heterosexual intercourse in 45%, and intravenous drug abuse in 17%. Most (83%) had always been asymptomatic, with pretreatment CD4 cell counts ranging from 1/µL to 1892/µL (median, 398/µL), and the log₁₀ of the pretreatment viral load ranging from 60% to 66%; Cochran test, P=.7) or in the height of the median rebound (2.7 to 3 log₁₀; Friedman test, P=.25).

After 4 cycles of stopping and starting therapy again, HAART was definitively suspended at week 40. The percentage of patients who experienced viral load rebound (>200 copies/mL) was 86% at week 44, and 97% at week 46. In 65% of patients, viral load peaked and then fell spontaneously by greater than 0.5 logs before week 52; in the other patients viral load rose and then remained stable (variation of <0.5 logs between peak measured viral load, and viral load at week 52).

ANALYSIS OF RESPONDERS VS NONRESPONDERS

Results were analyzed at the protocol-defined time point, ie, week 52 (after 12 weeks off treatment). Twenty-three (17%) of the 133 patients (95% confidence interval, 11%-25%) were responders at week 52. Among the 115 patients with a pretreatment viral load of greater than 5000 copies/mL, the response rate was 14% (95% confidence interval, 8%-22%).

Among the 110 nonresponders, 43 did not continue the study protocol before week 40. An additional 11 restarted treatment between weeks 40 and 52, 9 because of an excessive rebound of viremia and 2 for other reasons. Fifty-six additional patients were nonresponders because their viral load at week 52 exceeded 5000 copies/mL.

Responders differed from nonresponders with regard to viral load before HAART (median, 4.09 logs vs 4.57 logs in nonresponders; Mann-Whitney test, P=.001). None of the 44 patients with a pre-HAART viral load of more than 60,000 copies/mL was a responder (Figure 2).

The proportion of patients experiencing rebounds during weeks 0 to 42 also differed between responders and nonresponders (Table).

There was a tendency for responders to have started HAART earlier than nonresponders, with 10 of (44%) 23 responders starting within 2 years of the probable date of infection, compared with 24 (23%) of 103 nonre-
sponders (P = .10). Six patients (2 responders and 4 non-
sponders) had started HAART within 3 months of sero-
conversion. No correlation could be established between
response and pre-HAART CD4 cell counts (responders:
median, 441/µL; range, 131-745/µL; nonresponders: me-
dian, 392/µL; range, 1-1892/µL [P = .7]), and CD4 cell
counts at start of SSITT (responders: median, 752/µL; non-
responders: median, 744/µL [P = .8]).

We compared viral loads after 12 weeks’ treatment
interruption (at week 52) with the last viral load before
starting HAART. Eighteen (13.5%) of 133 had a viral load
less than 5000 copies/mL before HAART, and 25 (19%)
at week 52 (McNemar test, P = .2).

LONG-TERM FOLLOW-UP

All 23 responders continued to be followed up without
HAART. At the second protocol-specified time point
(week 96), 10 (8%) of the original collective of 133 pa-
tients still had a viral load below 5000 copies/mL, with-
out antiretroviral treatment. For nonresponders, the protocol (written in 1999)
specified reintroduction of HAART at week 52. How-
ever, because official guidelines for antiviral therapy had
changed in the meantime,14 many nonresponders elected
not to start treatment again. Among all 133 patients start-
ing SSITT, the percentage of those without treatment was
64% at week 52 and 41% at week 96.

SAFETY OF TREATMENT INTERRUPTION

No major (Centers for Disease Control and Prevention
[CDC] class C17) or minor (CDC class B17) HIV-related
opportunistic diseases were observed during SSITT.

CD4 Cell Counts in the Absence of HAART

There was a slight rise of CD4 cell counts after the 4 cycles
of short treatment interruptions (medians, 759/µL at week
0 and 792/µL at week 40; paired Wilcoxon test, P = .02).
After suspension of HAART at week 40, median CD4 cell
counts decreased from 792/µL to 615/µL at week 52
(P < .001). The decrease was observed in both respond-
ers (from 699 to 549/µL; P = .002) and nonresponders
(from 860 to 618/µL; P < .001), and was greater in non-
responders (P = .01, Mann-Whitney test).

After week 52, the fall in median CD4 cell counts was slower: from 625/µL at week 52 to 569/µL at last follow-
up after a median of 56 weeks without treatment
(P = .01, paired Wilcoxon test). Nonresponders went from
a median of 643/µL at week 52 to 564/µL (P < .005),
whereas responders showed a nonsignificant increase from
549/µL to 574/µL. The difference in CD4 cell count
changes between responders and nonresponders did not
reach statistical significance (P = .13, Mann-Whitney test).

Viral Escape and Resistance

One (0.7%) of 133 patients developed virologic escape.
He had a viral load of 141 copies/mL at week 9 and had
no further treatment interruptions. He continued his
initial treatment (a combination of lamivudine, zidovu-
dine, and nelfinavir); his viral load rose to 2730
copies/mL after a further 23 weeks. His treatment was
changed to a regimen of stavudine, efavirenz, abacavir,
and saquinavir boosted with ritonavir, with a decrease
of the viral load to less than 10 copies/mL after a further
6 weeks.

The protocol specified viral genotyping for all pa-
tients with virologic escape, and for all patients from
Geneva. The 1 patient with virologic escape had the 184V
mutation in the reverse transcriptase (RT) gene, and mul-
tiple mutations in the protease gene before he was
switched to salvage treatment. Of the 24 Geneva pa-
tients, 8 did not continue treatment interruptions be-
tween weeks 0 and 40 because viral load remained above
50 copies/mL after retreatment. In these patients, we
analyzed the viral genotype during the last viral rebound
before discontinuing treatment interruptions. Regarding the
RT gene, viruses from 3 patients were wild type, and 5
had the 184 mutation. When the earliest available sample
(week 2) was analyzed in these 5 patients, the 184 mu-
tation was already present in 3. There were no relevant
mutations in the protease gene.

In the remaining 16 patients from Geneva, who sus-
pended treatment at week 40, the HIV genotype was de-
termined when the viremia first exceeded 10000 copies/mL
(weeks 42 to 46). Regarding the protease gene, viruses from 16 patients had wild-type sequences, or mi-
nor variants corresponding to polymorphism. Regarding the
RT gene, in 1 patient the virus had multiple RT
mutations (41L, 67N, 210W, 215Y). He had been treated
with the

<table>
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<th>Rebound Status</th>
<th>Total No.</th>
<th>Responders, No. (%)</th>
<th>Nonresponders, No. (%)</th>
<th>P Value</th>
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<td>88</td>
<td>8 (9)</td>
<td>80 (91)</td>
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<tr>
<td>With no rebound at week 2</td>
<td>45</td>
<td>15 (33)</td>
<td>30 (67)</td>
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<tr>
<td>With at least 1 rebound at</td>
<td>71</td>
<td>12 (17)</td>
<td>59 (83)</td>
<td>&lt;.001</td>
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<tr>
<td>week 2, 12, 22, 32, or 42</td>
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<td></td>
<td></td>
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<tr>
<td>With no rebound at week 2</td>
<td>15</td>
<td>10 (67)</td>
<td>5 (33)</td>
<td></td>
</tr>
<tr>
<td>2, 12, 22, 32, and 42</td>
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Occurrence of the Acute Retroviral Syndrome

Symptoms resembling those of the acute retroviral syn-
drome may occur during treatment interruptions.18 Two
patients developed fever, skin lesions, and pharyngitis
in association with viremia above 500000 copies/mL.
Symptoms resolved promptly upon retreatment, and these
2 patients did not continue the protocol.
Although patients were warned about the importance of using condoms, there was one instance of probable transmission of HIV.19

Results of Retreatment After SSITT

Eighty-two patients restarted treatment after SSITT. When last checked 3 to 6 months after starting treatment again, 68 had an “undetectable” viral load less than 200 copies/mL, 12 had a detectable viral load above 200 copies/mL but were either off drugs or noncompliant, 1 patient (mentioned above) was receiving salvage therapy after viral escape, and 1 was lost to follow-up.

HIV-SPECIFIC CYTOTOXIC T-CELL RESPONSES

The HIV-specific CD8+ T-cell responses are shown in Figure 3. Results of enzyme-linked immunospot analysis in all 71 patients for whom results from weeks 0 and 52 were available. A, Numbers of human immunodeficiency virus–specific, interferon γ-producing, CD8+ spot-forming cells per million peripheral blood lymphocytes (HIV-IFN-CD8+ SFC/10^6 PBL) from weeks 0 to 52. B, Numbers of SFC/10^6 PBL (and median) at week 52 in responders and nonresponders. All patients stayed off therapy between weeks 40 and 52. Responders have statistically lower number of SFC than nonresponders (P=.01, Mann-Whitney test).

At week 52, responders had a median of 813 SFC/10^6 PBL, whereas nonresponders had a median of 2999 (Mann-Whitney test, P=.01; Figure 3B). The number of SFC at week 52 correlated with the degree of antigen exposure, as measured by the mean of the rebounds in viral load at weeks 2 to 42 (Spearman coefficient r=0.38, P=.002).

Results of the SSITT do not favor the autovaccination hypothesis. Viral loads after SSITT were similar to those before HAART. Response was more frequent in patients who showed few, or no rebounds during on-off cycling (Table 1). Increases in HIV-specific CD8+ T-cell frequencies did not correlate with control of viral replication (low viral load) at week 52. Indeed, there was a statistically significant trend in the other direction: nonresponders tended to have more SFCs at week 52 than responders. Direct correlation of CD8+ HIV-specific T-cell response and viral load has also been shown in untreated chronic HIV infection and most probably reflect the extent of antigen exposure.20 Our findings do not exclude the possibility that changes in other components of the immune response, not measured here, might predict viremia during treatment interruptions.

The patients who were eligible for SSITT are representative of a population commonly found in clinical practice. Ninety-five percent had started HAART after the acute retroviral syndrome had passed, usually years after infection. Half had been immunosuppressed (<400 CD4 cells/µL) before HAART. Treatment before SSITT had been effective, as evidenced by a viral load that had remained undetectable for a median of 21 months, and a CD4 cell count that had risen from a median of 398/µL to a median of 740/µL. Among 5248 patients receiving HAART in the Swiss HIV Cohort Study in August 2001, 1405 (27%) had been antiretroviral-naive before HAART, had had a viral load below the limits of detection for at least 6 months, and had never changed therapy because of a rise in viral load. It is to these patients that the results of SSITT are potentially applicable.

About 1 in 6 participants was a “responder,” with a viral load less than 5000 copies/mL at week 52, after 12 weeks off treatment. Viremia was significantly lower before initiation of HAART in responders than in nonresponders (P=.001). Contrary to expectations, the presence or absence of immunodeficiency before HAART did not seem to make a difference, as the pre-HAART CD4 cell counts were similar among responders and nonresponders.

Many additional nonresponding patients stayed off therapy for varying periods, up to more than 1 year. In the absence of HAART, CD4 cell counts fell rapidly during the first 12 weeks, then stabilized. Patients in SSITT stopped therapy when the CD4 cell count was relatively high (median of 740/µL), so that the fall during the first 12 weeks did not have clinical consequences. These results suggest that a substantial minority of patients who are presently treated with HAART can safely discontinue the drugs for several months without undue rise in viremia or a dangerous fall in CD4 cell counts. How-

Figure 3. Results of enzyme-linked immunospot analysis in all 71 patients for whom results from weeks 0 and 52 were available. A, Numbers of human immunodeficiency virus–specific, interferon γ-producing, CD8+ spot-forming cells per million peripheral blood lymphocytes (HIV-IFN-CD8+ SFC/10^6 PBL) from weeks 0 to 52. B, Numbers of SFC/10^6 PBL (and median) at week 52 in responders and nonresponders. All patients stayed off therapy between weeks 40 and 52. Responders have statistically lower number of SFC than nonresponders (P=.01, Mann-Whitney test).
ever, whether such discontinuation is beneficial or harmful can only be determined in future studies, with randomized comparison of continuous with intermittent treatment.

Indeed, one important question may arise regarding the study design: Why did the SSITT not include control groups? Two types of controls were considered: (1) A “simple-stop” control group would have stopped treatment without on-off cycling. Preliminary inquiries indicated that a simple-stop group would not be approved by institutional review boards in 1999, because of then current guidelines that mandated continued treatment for almost all HIV-infected patients.21

(2) Another possible control group would have received continuous therapy, the current standard. With a total of 133 patients, such a comparison between continuous and intermittent therapy would have lacked power and could only have detected improbable large differences between groups. It would have halved the number of patients in the intermittent treatment group and would have endangered attainment of our primary goal, which was to explore the correlation between HIV-specific immune response and control of viremia without therapy. We therefore believe that the study design was well adapted to the goals of the study.

Were the 2-week interruptions optimal to stimulate HIV-specific immunity, or would longer interruptions have been more productive? We decided on 2 weeks because previous experience indicated that most patients would show a rebound22-25; and because longer interruptions might be associated with an increased risk of the acute retroviral syndrome26 and might depress, rather than enhance, HIV-specific immune responses.27 Rebounds after 2 weeks were measurable in 86 of our patients (66%), and 2 instances of the acute retroviral syndrome occurred. The HIV-specific CD8+ T-cell frequencies, as measured by interferon γ enzyme-linked immunospot analysis, were enhanced. It seems therefore unlikely that changing the duration of interruptions would have produced substantially different results.

Treatment interruption was quite safe in this population in that no opportunistic events and little viral resistance were observed. It should be noted, however, that SSITT did not enroll patients who had been exposed to partial effective treatment before HAART, thus eliminating a group at high risk for development of resistance.28

The SSITT lends perspective to some previously reported studies with smaller numbers of patients. In comparison to patients who started their treatment during acute HIV infection,10 the frequency of response appears lower in the SSITT patients. In contrast to the study by Lori et al,23 we found no evidence that the time until detection of rebound increased. Lori et al observed an increase in time to rebound, during successive treatment interruptions in 3 patients, to above 20 days. In our study, such an increase would have produced an increasing proportion of patients without rebound during the four 2-week treatment interruptions from week 0 to week 40. However, the proportion of patients with rebound remained similar.

Results of SSITT show that iterative treatment interruptions by themselves are rarely sufficient to attain the goal of low, or even undetectable, viremia without antiretroviral therapy. Additional measures such as non-specific immune stimulation using cytokines (in analogy to cancer vaccinology)29 or specific immune stimulation through therapeutic vaccination30,31 should be explored.

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