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The HIV Netherlands Australia Thailand Research Collaboration 001.4 Study

Highly Active Antiretroviral Therapy (HAART) Retreatment in Patients on CD4-Guided Therapy Achieved Similar Virologic Suppression Compared With Patients on Continuous HAART

The HIV Netherlands Australia Thailand Research Collaboration 001.4 Study

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Objective: To assess the safety of 2 intermittent treatment strategies compared with continuous therapy for patients with virologic suppression on highly active antiretroviral therapy (HAART) at baseline.

Design: Seventy-four nucleoside reverse transcriptase inhibitor (NRTI) and protease inhibitor (PI) pretreated patients with an HIV RNA level <50 copies at screening were randomized to continuous treatment, CD4-guided treatment, or week-on-week-off treatment with 2 NNRTIs plus 1600 mg/100 mg of saquinavir/ritonavir once daily. At week 96 (end of the randomized phase of the study), all patients were given continuous HAART for 12 weeks to week 108. Primary outcomes were the proportion of patients with a CD4 count >350 cells/μL and HIV RNA level <400 copies/mL at week 108.

Methods: Patients were followed up every 12 weeks for CD4 count, HIV RNA level, and clinical and laboratory toxicities. In the CD4-guided arm, treatment was stopped and restarted using a CD4 count threshold (above or below 350 cells/μL or reduction of 30%).

Results: Seventy-four patients were enrolled with a median CD4 count of 644 cells/μL before the structured treatment interruption (STI). The week-on-week-off arm (n = 26) was discontinued at week 72 because of high rates (46%) of HIV RNA rebound above 50 copies/mL. In the continuous arm, 25 (100%) of 25 patients and 24 (96%) of 25 patients had an HIV RNA level <400 copies/mL and <50 copies/mL, respectively, at week 108, and 96% had a CD4 count above 350 cells/μL, with a median CD4 count of 661 cells/μL.

Patients in the CD4-guided arm had a significantly lower median CD4 count (489 cells/μL) than the patients in the continuous arm (P = 0.03), but all had a CD4 count above 350 cells/μL and 1 had a new HIV-related illness. At week 108, 21 (91%) of 23 patients and 13 (57%) of 23 patients had an HIV RNA level <400 copies/mL and <50 copies/mL, respectively. Those who did not achieve an HIV RNA level <50 copies/mL had a higher HIV RNA load before retreatment, and 4 of 5 patients subsequently achieved viral suppression after an additional 12 weeks of HAART (week 120). Therefore, 17 (94%) of 18 evaluable CD4-guided arm patients achieved viral suppression after retreatment. Antiretroviral (ARV) side effects were similar in all arms. CD4-guided treatment had a 54% ARV cost savings.

Conclusions: This pilot study suggests that CD4-guided HAART is a well-tolerated and cost-saving treatment strategy for patients with high pre-ARV and pre-STI CD4 counts. Week-on-week-off treatment had a high virologic failure rate and was discontinued. The HIV RNA suppression rate was similar in patients treated with continuous HAART and in those retreated with 12 to 24 weeks of HAART after CD4-guided therapy.

Key Words: HIV, HAART, intermittent therapy, structured treatment interruption, CD4-guided

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Whereas the introduction of highly active antiretroviral therapy (HAART) has significantly improved AIDS-free survival, lifelong treatment may lead to acute and progressive drug toxicities, and treatment costs may limit the long-term affordability of HAART. By decreasing the time patients receive medications, intermittent HAART could reduce the toxicity and cost of long-term treatment. Stopping HAART increases the risk of clinical disease progression if CD4 counts fall below 200 cells/μL, however, and there is the potential for the emergence of drug resistance from residual drug levels persisting after drug discontinuation.
Treatment interruptions are likely to be more beneficial for patients with little or no prior HIV drug resistance than in the salvage setting, where clinical trials of treatment interruptions have led to mixed results.\(^6\)\(^,\)\(^11\)

Intermittent treatment of patients with virologic suppression on HAART has been studied in prospective trials with 2 approaches. With CD4-guided treatment, HAART is stopped for those with high CD4 counts and restarted if CD4 counts fall below preset limits (eg, 350 cells/μL); these limits are set to ensure a continued low risk of HIV disease progression during CD4-guided treatment.\(^6\)\(^,\)\(^11\) With short-cycle treatment, HAART is stopped and restarted at regular intervals. A pilot study of week-on–week-off HAART with stavudine (d4T)/lamivudine (3TC) plus indinavir/ritonavir in 10 patients led to sustained viral suppression for 32 to 68 weeks.\(^12\) The Staccato study showed high rates of virologic failure using this same approach, however, leading to the premature discontinuation of the week-on–week-off arm.\(^13\) Regular cycles of treatment with longer treatment interruption intervals have led to viral rebound during the treatment discontinuation phase.\(^14\)\(^,\)\(^15\)

The current pilot study, the HIV Netherlands Australia Thailand Research Collaboration (HIV-NAT) 001.4, was conducted to assess CD4-guided and week-on–week-off strategies in comparison to continuous HAART for patients who had been exposed to dual nucleoside reverse transcriptase inhibitors (NRTIs) before HAART. This report shows the results at the end of the study (week 108), which includes a HAART retreatment period between weeks 96 and 108 in all arms. To our knowledge, this is the first study to compare virologic suppression rates directly in patients treated with continuous HAART and those retreated with HAART after CD4-guided therapy.

METHODS

Clinical Assessment

This 3-arm, open-label, prospective 108-week trial was conducted at a single center in Thailand (HIV-NAT, Bangkok). The trial was approved by the Chulalongkorn University Institutional Review Board, and all patients signed a written informed consent form at screening.

The trial enrolled 74 HIV-1–infected adults with CD4 counts above 350 cells/μL and HIV RNA levels <50 copies/mL for at least 6 months before screening. The patients were randomized at a 1:1:1 ratio to receive continuous (n = 25), CD4-guided (n = 23), and week-on–week-off (n = 26) HAART. The primary end points were proportions of patients with CD4 counts >350 cells/μL and with HIV RNA levels <400 copies/mL at week 108.

All patients had received 66 weeks of dual NRTI treatment during which only 20% had HIV RNA levels below 400 copies/mL,\(^16\) followed by 160 weeks of HAART with saquinavir (SQV) in combination with 2 NRTIs (Fig. 1).\(^17\) The HAART regimen used for all patients during this structured treatment interruption (STI) study was 2 nucleoside analogues (NRTIs) plus 1600 mg/100 mg of SQV/ritonavir administered once daily. The study was conducted in 2 consecutive periods: weeks 0 through 48 and weeks 48 through 108. The results of the initial 48-week period have been reported.\(^18\) During the first 48 weeks, half of the patients received azidothymidine (AZT)/3TC and half received d4T/didanosine (ddI), whereas after week 48, all patients received d4T/ddI and the SQV-soft gel capsule (SGC) was switched to an SQV-hard gel capsule (HGC).

Patients attended study visits at screening; baseline; weeks 4, 8, and 12; and every 8 weeks for the first 48 weeks and every 12 weeks thereafter to week 108. Patients were assessed for CD4 count, HIV RNA level (Roche Amplicor Ultra-sensitive assay, Palo Alto, CA), fasting lipids, hematology, clinical chemistry, adverse events, and HIV disease progression. Clinical and laboratory adverse events were graded by severity.

For the CD4-guided arm, all patients started the trial by discontinuing HAART. They restarted at least 12 weeks of HAART if their CD4 count was below 350 cells/μL or dropped more than 30% from baseline according to patient preference. They stopped again if their CD4 count rose above 350 cells/μL or increased at least 70% from baseline. Virologic failure was classified as HIV RNA levels above 400 copies/mL on 2 consecutive visits or above 1000 copies/mL at a single visit in any patient in the continuous and week-on–week-off arms and in patients in the CD4-guided arm who had received at least 12 weeks of HAART. In the CD4-guided arm, all

FIGURE 1. Diagram shows treatments received by the 74 patients who participated in this STI study.
patients received continuous HAART from weeks 96 to 108. Those who did not achieve an HIV RNA level <50 copies/mL were treated for an additional 12 weeks (week 120).

**Statistical Analysis**

An intention-to-treat (ITT) approach was used. In addition, an on-treatment (OT) approach was used to compare HIV RNA outcome at weeks 108 and 120 between the CD4-guided and continuous arms. Data were analyzed using SPSS for Windows, version 9.0, software (SPSS, Chicago, IL). Tests were matched to data type and distribution. Statistical analyses included the Kruskal-Wallis test, Mann-Whitney U test, Wilcoxon signed-rank test, x² test, Fisher exact test, McNemar test, and general descriptive statistics. Probability values less than 0.05 were considered statistically significant. Given the small sample size of this pilot study, there is no statistical power to detect differences in HIV RNA response or CD4 counts between treatment arms.

**RESULTS**

Seventy-four patients were enrolled into the trial. Baseline characteristics were well balanced across the treatment arms (Table 1). Overall, there were 36 men and 38 women, with a median age of 35 years and median body weight of 55 kg. Most patients were in Centers for Disease Control and Prevention (CDC) stage A (51%) or B (43%) at baseline. Patients had an overall duration of prior treatment of almost 5 years, with dual NRTIs and then HAART, including SQV. Before starting antiretrovirals (ARVs), the overall median CD4 count had been 358 cells/µL, which had improved to 644 cells/µL by the baseline visit for this trial. CD4 counts at baseline were above 500 cells/µL in 81% of patients overall; HIV RNA levels were below 400 copies/mL for all 74 patients at baseline, and below 50 copies/mL for 71 (96%) of 74 patients. The 3 patients who had HIV RNA levels above 50 copies/mL had HIV RNA levels below 50 copies/mL at the time of randomization.

All 25 patients in the continuous treatment arm completed the 108-week trial. In the CD4-guided arm, all 23 completed the trial but 1 had to stop ARVs because of severe mitochondrial toxicity (edema, weight loss, muscle weakness, and high lactate). In the week-on–week-off arm, 23 of 26 patients completed the trial and 1 interrupted ARV because of severe hepatotoxicity. The discontinuations were attributed to patient request (n = 1), lost to follow-up (n = 1), and death as the result of a brain tumor (n = 1).

Patients in the continuous arm maintained CD4 counts at baseline levels throughout the 108 weeks of the trial (Fig. 2), with HIV RNA levels remaining below 400 copies/mL for all patients and below 50 copies/mL for 24 (96%) of 25 patients by week 108 (Fig. 3).

The week-on–week-off arm was stopped after a median 15 months of follow-up after excessive virologic failure rates (46%) were observed. By week 24, 11 (42%) of 26 of these patients had a rebound in HIV RNA to above 500 copies/mL, but RNA levels were still below 400 copies/mL in 81% of patients overall (see Fig. 3). Interestingly, the CD4 counts remained close to baseline levels in this treatment arm, despite the rebound in viremia (see Fig. 2A). All 26 patients in this arm converted to continuous HAART with the same regimen (2 NRTIs with boosted SQV) by week 72 of the trial. At week 108, 21 (81%) of 26 patients had HIV RNA levels below 50 copies/mL. Of the 22 patients who were on treatment, 21 (95%) had HIV RNA levels <50 copies/mL.

For the CD4-guided arm, stopping HAART at baseline led to a wide range of outcomes during the 96-week randomized phase of the trial. Overall, patients in this arm were taking HAART for a median of 44 weeks (46% of the 96-week trial duration).

**TABLE 1. Baseline Characteristics and Patient Disposition (n = 74)**

<table>
<thead>
<tr>
<th></th>
<th>Continuous (n = 25)</th>
<th>CD4-Guided (n = 23)</th>
<th>Week-On-Week-Off (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline HIV RNA (copies/mL)</td>
<td>Median: 4.3</td>
<td>Median: 4.8</td>
<td>Median: 4.9</td>
</tr>
<tr>
<td></td>
<td>95% CI: 3.8-4.7</td>
<td>95% CI: 4.1-5.4</td>
<td>95% CI: 4.7-5.2</td>
</tr>
<tr>
<td>Pre-ARV CD4 count (cells/µL)</td>
<td>Median: 653</td>
<td>Median: 766</td>
<td>Median: 555</td>
</tr>
<tr>
<td></td>
<td>95% CI: 594-866</td>
<td>95% CI: 550-872</td>
<td>95% CI: 465-780</td>
</tr>
<tr>
<td>Discontinued study (n)</td>
<td>0</td>
<td>0</td>
<td>3* (12%)</td>
</tr>
</tbody>
</table>

Baseline is defined as the start date of STI study. *Lost to follow-up (n = 1), severe hepatotoxicity from ARV (n = 1), death from brain tumor (n = 1). One patient in the CD4-guided arm stopped HAART at week 96 due to severe mitochondrial toxicity.
Chapter 8: Structured treatment interruption pilot study  67

FIGURE 2. Median CD4 count (A) and median change for individual patient in CD4 count (B) versus time (weeks) by treatment arm (ITT analysis). Probability value represents the difference between the continuous arm versus the CD4-guided arm in both graphs by the Mann-Whitney U test. The lines and symbols are as follows: continuous line, square symbols represent the continuous arm; dotted line, circle symbols represent the CD4-guided arm; and dashed line, triangle symbols represent the week-on-week-off arm. The vertical line at week 96 represents the end of randomized treatment and retreatment of all patients with continuous HAART.

The median HIV RNA level had risen from <50 copies/mL at baseline to 63,095 copies/mL at week 4, with the CD4 count falling from 766 cells/μL at baseline to 598 cells/μL during the same interval.

Four patients (17%) stopped HAART for the entire 96-week duration of the randomized trial without restarting. For the 19 patients who restarted HAART, 5 restarted within 12 weeks of baseline, 4 restarted from 12 to 24 weeks after baseline, and 10 restarted HAART from 24 to 96 weeks after baseline. Eight of the 19 patients who restarted HAART remained on treatment to week 96 because they chose to, whereas 11 subsequently stopped HAART again before week 96. The median CD4 count at the time of first restarting HAART was 442 cells/μL (interquartile [IQ] range: 340–498 cells/μL); at this time, the CD4 count had fallen by a median 41% from its baseline level. During the 96-week randomized phase, more than 70% of patients maintained CD4 counts above the threshold of 350 cells/μL on or off HAART.

After the 96-week randomized phase, all patients in the CD4-guided arm restarted HAART for 12 weeks. The proportion of patients with HIV RNA levels less than 400 copies/mL (A) and HIV RNA levels less than 50 copies/mL (B) versus time (weeks) by treatment arm (ITT analysis). Probability value represents the difference between the continuous arm versus the CD4-guided arm in both graphs by the χ² test. The lines and symbols are as follows: continuous line, square symbols represent the continuous arm; dotted line, circle symbols represent the CD4-guided arm; and dashed line, triangle symbols represent the week-on-week-off arm. The vertical line at week 96 represents the end of randomized treatment and retreatment of all patients with continuous HAART.

FIGURE 3. Proportion of patients with HIV RNA levels less than 400 copies/mL (A) and HIV RNA levels less than 50 copies/mL (B) versus time (weeks) by treatment arm (ITT analysis). Probability value represents the difference between the continuous arm versus the CD4-guided arm in both graphs by the χ² test. The lines and symbols are as follows: continuous line, square symbols represent the continuous arm; dotted line, circle symbols represent the CD4-guided arm; and dashed line, triangle symbols represent the week-on-week-off arm. The vertical line at week 96 represents the end of randomized treatment and retreatment of all patients with continuous HAART.
was 53%, with no significant differences between treatment groups. Liver enzyme levels showed no significant changes within or between groups during the trial. Surprisingly, there was a 25% rise in median high-density lipoprotein (HDL) cholesterol and a 10% reduction in low-density lipoprotein (LDL) cholesterol in all 3 treatment arms, which improved the overall ratio of total cholesterol to HDL cholesterol ($P < 0.001$). Triglyceride levels showed small rises in the 3 treatment groups of no statistical significance. Glucose levels rose by 7% overall, with statistically significant rises in all 3 treatment groups but no overall difference between the treatment groups. There were no differences in lipodystrophy and quality of life between the treatment arms.

**DISCUSSION**

This was a randomized, 108-week, pilot STI study of patients with full viral suppression and high CD4 counts before ARVs and before STI who were randomized to continuous, CD4-guided, or week-on-week-off treatment. The week-on-week-off arm had a 46% virologic failure rate, and all patients resumed continuous HAART with the same regimen by week 72. Patients in the continuous and week-on-week-off arms had CD4 counts $>350$ cells/μL, but the patients in the CD4-guided arm did not recover their CD4 count up to what it was before STI. Between weeks 96 and 108, all patients in the CD4-guided arm were retreated with HAART to assess whether viral suppression after STI was possible. At week 108, the HIV RNA suppression rate below 400 copies/mL was similar between the 3 arms. Fewer patients in the CD4-guided arm had HIV RNA levels $<50$ copies/mL compared with the other 2 arms, however. We found that the patients in the CD4-guided arm who were able to achieve viral suppression after 12 weeks of HAART retreatment had a lower HIV RNA level before retreatment. After knowing these results, we tried to assess whether the unsuppressed patients would also be able to achieve HIV RNA levels $<50$ copies/mL if they were treated for an additional 12 weeks after the study ended. At the follow-up 12 weeks later (week 120), however, half of the patients were already off ARVs and were not able to be evaluated. Of the 18 evaluable patients, 94% had HIV RNA levels less than 50 copies/mL. Therefore, the rate of HIV RNA suppression for patients who received adequate retreatment time was similar to that of patients receiving continuous HAART. There was no progression to CDC stage C during the trial.

Results from this small randomized trial are consistent with those of cohort studies of CD4-guided treatment. For those with high CD4 counts at discontinuation of HAART and no prior failure on ARVs, a range of slopes of CD4 decline have been seen in other studies, with high interpatient variability, allowing some patients to remain off treatment for long periods. Considering that 80% of our patients had virologic failure on dual NRTI before they were treated with HAART, the potential risk of drug resistance emerging after discontinuation does not seem to have affected the response to
reinitiation of boosted SQV-based HAART in this trial. A similar conclusion emerged from the Staccato trial, where 8 patients with rebounding HIV RNA levels during week-on–
week-off treatment with boosted SQV-based HAART had no
evidence of PI resistance and could be resuppressed on the
same treatment.13 Similar observations have been made for patients stopping treatment with other ritonavir-boosted PIs, where no evidence of PI resistance is found.12 This may be different for PI-resistant patients, where resistance
generated from single amino-acid substitutions has been
detected in a significant proportion of patients discon-
suming NRTI-based HAART.2,8

There were no rises in CD4 count in the continuous treat-
ment arm. The baseline CD4 count in this arm (653 cells/µL)
was close to the lower limits of the normal range of CD4
counts in healthy volunteers, however. An apparent plateau in
CD4 count increases has also been seen in analysis of long-
term HAART treatment of patients with high pre-HAART
CD4 counts.22 It is unclear whether the results of this trial
could be extrapolated to other populations with lower prether-
apy CD4 counts, for whom the risk of opportunistic infections
may be higher during treatment interruptions; however, regular
monitoring for CD4 counts in this situation should minimize
this risk.

Failure of the week-on–week-off treatment is consistent
with the results of the Staccato trial,1,3 which also evaluated
mainly boosted SQV-based HAART in a randomized com-
parison with continuous HAART. A single-arm pilot study
using 2 NRTIs plus boosted indinavir did show continued suppression of HIV RNA for more than 1 year in 10 patients,12
however, with undetectable HIV RNA at baseline. In addition,
a recent study of 20 patients with HIV RNA suppression at
baseline given NNRTI-based HAART for 5 days with an
interruption of 2 days per week also showed durable suppres-
sion of HIV RNA levels.23 In a large treatment interruption
study of a variety of HAART regimens with intensive sam-
ppling, HIV RNA levels started to rebound within 4 days in
some patients.24 The reasons for these apparent mismatches in
results are unclear.

The main limitations of this trial are its small sample size
and the selection of the patients; the eligible patients were
those who had successfully responded to HAART for several
years and had high CD4 counts before ARVs and before STI
and may not be representative of the wider population. It is
also uncertain whether similar results would be seen for ARV
combinations with different pharmacokinetics or safety pro-
files. The potential saving in treatment cost for CD4-guided
treatment could be partially offset by a need for more intensive
monitoring for CD4 counts. Using new technologies, there is
the potential for low-cost CD4 testing, however, on the order
of S5 US per test.27 The interval of retreatment at week 96 may
have been too short to ensure HIV RNA suppression to less
than 50 copies/mL for all patients in the CD4-guided arm, and
the OT analysis of data to week 108 is to some extent ex-
ploratory; longer treatment durations were necessary in an-
other study of HAART based on SQV-ritonavir in naive
patients.28 The lack of difference in adverse events between
the continuous and CD4-guided arms may be a function of the
small sample size in this pilot study as well as the selection of
this patient population with a history of long prior exposure to
NRTI/PI-based HAART before the trial.

The median pre-ARV CD4 count in this trial was
358 cells/µL (IQR range: 309–436 cells/µL); this is relatively
high for initiation of treatment in many countries. In other
cohort studies, patients with lower pre-HAART CD4 counts
had a higher risk of the CD4 count falling to low levels during
treatment interruptions.11 This may provide support in the
future for earlier initiation of HAART: starting HAART earlier,
when the CD4 count is above 350 cells/µL, could offer the
potential for extended treatment interruptions, which may not
be feasible for those starting treatment later but with lower
CD4 counts.

In summary, in this small randomized study of patients
pretreated with dual NRTI who had high CD4 counts and
undetectable HIV RNA levels before STI, CD4-guided treat-
ment had a virologic outcome comparable to continuous
HAART with a 54% ARV cost savings. The week-on–week-off
strategy had a high rate of virologic failure and was pre-
maturely stopped. CD4-guided treatment can be recommended
for use in clinical practice only if the benefits are confirmed by
larger trials (eg, SMART, Windows, ISS-Part, Staccato,
DART) that are also evaluating these strategies in larger sam-
ple sizes and with longer follow-up time.

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