A prospective, randomized trial of structured treatment interruption for patients with chronic HIV type 1 infection


Published in:
Clinical infectious diseases

DOI:
10.1086/427695

Citation for published version (APA):
A Prospective, Randomized Trial of Structured Treatment Interruption for Patients with Chronic HIV Type 1 Infection

Peter G. Cardiello,1,2 Elly Hassink,1,3 Jintanat Ananworanich,1 Preeyaporn Srasuebkul,1 Tarika Samor,3 Apicha Mahanontharat,1 Kiat Ruxrunghdam,1,2 Bernard Hirschel,4 Joep Lange,3 Praphan Phanuphak,1,2 and David A. Cooper5

1The HIV Netherlands Australia Thailand Research Collaborative, The Thai Red Cross AIDS Research Center, and 2Faculty of Medicine, Division of Infectious Diseases, Chulalongkorn University, Bangkok, Thailand; 3International Antiviral Therapy Evaluation Center, Academic Medical Center, University of Amsterdam, The Netherlands; 4University Hospital of Geneva, Switzerland; and 5National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney, Australia

(See the editorial commentary by Montaner et al. on pages 601–3)

Background. Structured treatment interruption was evaluated in 74 patients who had been pretreated with antiretrovirals, consisting of 2 nucleoside reverse-transcriptase inhibitors (NRTIs) for 1 year followed by 3 years of highly active antiretroviral therapy containing a protease inhibitor.

Methods. Patients with a CD4 cell count of ≥350 cells/μL and a plasma viral load of <50 copies/mL were randomized to 3 therapy arms: (1) continuous therapy, (2) CD4 cell count–guided therapy, and (3) week-on/week-off (WOWO) therapy. The efficacy and safety of structured treatment interruption and antiretroviral use were evaluated in human immunodeficiency type 1 (HIV-1)–infected patients. The study end points were percentage of patients who developed AIDS or who died and a CD4 cell count of ≥350 cells/μL. Intergroup differences were analyzed using analysis of variance and Kruskal-Wallis tests.

Results. Baseline characteristics at the start of the structured treatment interruption were similar. At week 48, no patient had died, and 1 patient in the WOWO group had an AIDS-defining condition. The proportions of patients with a CD4 cell count of ≥350 cells/μL were 100%, 87%, and 96% in treatment arms 1, 2, and 3, respectively. The percentages of weeks of antiretroviral use were 100%, 41.1%, and 69.8% in arms 1, 2, and 3, respectively. The adverse events were not significantly different among arms (P = .27). Thirty-one percent of patients in the WOWO group experienced virological failure.

Conclusion. WOWO therapy maintained a CD4 cell count of ≥350 cells/μL in almost all patients but was associated with high virological failures rates (possibly resulting from previous dual-NRTI therapy), indicating that this strategy is less useful. Receipt of CD4 cell count–guided therapy resulted in comparable clinical outcomes to continuous therapy and may save antiretroviral-associated costs, but this needs to be confirmed by a larger trial.

Although combination therapy that involves ≥3 antiretroviral drugs remains the current standard of care for maintenance of undetectable plasma HIV-1 RNA levels in HIV-1–infected patients, maintenance of an adequate CD4 cell count (greater than a level that is protective against most opportunistic infections) may provide significant benefits, even if the plasma viral load is not suppressed at all times [1]. The use of structured treatment interruptions may be a viable alternative to continuous suppression of the plasma viral load by maintaining an adequate CD4 cell count, saving some of the costs of antiretroviral therapy, and decreasing a patient’s overall exposure to antiretrovirals, which can result in multiple toxicities [2]. Decreases in costs and in the number of toxicities would be beneficial. This is a pilot study to evaluate the safety of structured treatment interruptions, because there were little data regarding the safety of structured treatment interruptions when this trial was initiated in 2001. We report data on the safety of therapy, antiretroviral use, and adverse events associated with structured treatment interrup-
tions in HIV-1–infected Thai patients after up to 48 weeks of study of CD4 cell count–guided and week-on/week-off (WOWO) therapy approaches, compared with continuous receipt of antiretroviral treatment.

METHODS

Patients and Study Design
Patients were recruited from the Thai Red Cross Society’s Anonymous STD/HIV screening clinic and the HIV outpatient immune clinic of King Chulalongkorn Memorial Hospital (Bangkok, Thailand). After 226 weeks, a group of 74 patients who were enrolled in the HIV Netherlands Australia Thailand Research Collaborative (HIVNAT) 001 trial series (which involved 1 year of dual–nucleoside reverse-transcriptase inhibitor [NRTI] therapy, followed by 3 years of protease inhibitor–based HAART) were randomized for this study if their most recent CD4 cell count was ≥350 cells/µL and their plasma viral load had been <50 copies/mL for ≥6 months [3, 4]. This open-label, prospective study examined 3 antiretroviral regimen arms to evaluate 2 structured treatment interruption strategies: continuous treatment, CD4 cell count–guided treatment, and WOWO treatment (figure 1). This small sample size limited our ability to obtain sufficient power to detect a difference between study arms. The study was approved by the Ethics Committee of the Faculty of Medicine, Chulalongkorn University (Bangkok). Written informed consent was obtained from all patients.

Antiretroviral Therapy Regimens for All Treatment Arms
Antiretroviral therapy consisted of saquinavir soft-gel caps (1600 mg q.d.) boosted with ritonavir (100 mg q.d.) plus 2 NRTIs (standard doses of either zidovudine and lamivudine or didanosine and stavudine). The NRTI regimen was determined in the randomization process at the start of the HIVNAT 001 series several years before this structured treatment interruption trial (table 1).

Management of Antiretroviral Therapy
Continuous and WOWO treatment arms. Patients in the continuous treatment arm took their antiretrovirals every day. In the WOWO therapy arm, patients alternated between 1 week with therapy and 1 week without therapy, and the viral load was determined at the end of the week that included therapy to assess whether the patient’s plasma viral load was suppressed.

Commencement of antiretroviral therapy in the CD4 cell count–guided arm and immunological failure criteria for the continuous and WOWO arms. The patients in the CD4 cell count–guided treatment arm began the study while not receiving therapy and only started antiretroviral therapy if the CD4 cell count had decreased in accordance with the criteria noted in table 2. The criteria for commencement or recommencement of antiretroviral therapy in the CD4 cell count–guided arm are the same as the criteria as for immunological failure in the continuous and WOWO treatment arms. In the continuous therapy arm and the WOWO treatment arm, treatment failure was defined as virological failure (i.e., the plasma viral load was >1000 copies/mL). The criterion of immunological failure was a decrease in the CD4 cell count to <350 cells/µL or by 30%. Patients in the continuous therapy arm and the WOWO treatment arm who met these treatment failure criteria discontinued therapy with once-daily saquinavir soft-gel caps and switched to continuous therapy with saquinavir soft-gel caps (1000 mg b.i.d.) and ritonavir (100 mg b.i.d.), in addition to the same 2 NRTIs. There were no treatment failure criteria for the CD4 cell count–guided treatment arm.

Cessation of antiretroviral therapy in the CD4 cell count–guided treatment arm. After receipt of ≥12 weeks of daily doses of HAART, patients in the CD4 cell count–guided treatment arm would stop therapy ≥1 time if the following conditions were met: the CD4 cell count increased to a level that is greater than the threshold of 50 cells/µL less than the baseline level (defined as the CD4 cell count at the start of structured treatment interruption) when the baseline CD4 cell count was 350–399 cells/µL, if the CD4 cell count recovered to ≥350 cells/µL when the baseline CD4 cell count was 400–500 cells/µL, or if the CD4 cell count increased to >70% of the baseline level when the baseline CD4 cell count was >500 cells/µL.

Patient Monitoring
At each study visit, clinical findings, adverse events, and hematological, biochemical, and immunological parameters were evaluated. Follow-up visits occurred every 12 weeks in the continuous treatment arm and at weeks 0, 4, and 8 and every 8 weeks thereafter in the CD4 cell count–guided and WOWO treatment arms. The study period was a maximum of 48 weeks.

Study End Points
The primary end points were progression to AIDS or death. The secondary end points were proportion of patients with a CD4 cell count of ≥350 cells/µL, antiretroviral use, occurrence of adverse events, and the plasma viral load at the end of the study period. This study was underpowered as a result of the limited number of study subjects.

Analysis of Plasma Samples
Plasma HIV-1 RNA levels were assessed with the Roche Amplicor HIV-1 Monitor assay, version 1.5, which has a lower limit of detection of 50 HIV-1 RNA copies/mL. CD4 lymphocyte counts were determined by flow cytometry. Resistance sequences were analyzed on proviral DNA at the time of treatment failure in WOWO arm.
Figure 1. Flow chart showing the patients from the time of the start of the The HIV Netherlands Australia Thailand Research Collaborative (HIVNAT) 001 trial to the start of this structured treatment interruption trial. AZT, zidovudine; ddc, zalcitabine; ddl, didanosine; d4T, stavudine; RTV, ritonavir; SQV-SGC, saquinavir soft-gel caps; STI, structured treatment interruption; 3TC, lamivudine.

Statistical Analysis

Analysis was scheduled when all patients had reached up to week 48 of follow-up after inclusion in the study. Statistical calculations were performed using either SAS statistical software, version 8.02 (SAS Institute), or SPSS software for Windows, version 9.0 (SPSS). Because this study was developed as a pilot study, the sample size was not enough to detect a difference with an $\alpha$ of 0.05 and a power of 0.80 for the primary end point. The primary analysis involved the percentage of patients who developed AIDS or died. Secondary analyses involved the percentage of patients with a CD4 cell count of $\geq 350$ cells/$\mu$L, a change in the CD4 cell count over time, the percentage of days receiving antiretrovirals, the occurrence of adverse events, and the plasma viral load. Changes in the CD4 cell count were analyzed by a repeated-measurements procedure that used a generalized linear model (PROC MIXED) from
### Table 1. Baseline demographic, treatment, and clinical data for patients before commencement in a structured treatment interruption (STI) trial.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Continuous treatment group</th>
<th>CD4 cell count–guided treatment group</th>
<th>WOWO treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients at randomization&lt;sup&gt;a&lt;/sup&gt;</td>
<td>25</td>
<td>23</td>
<td>26</td>
</tr>
<tr>
<td>Week of randomization&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>226</td>
<td>17</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>230</td>
<td>4</td>
<td>...</td>
<td>4</td>
</tr>
<tr>
<td>242</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>254</td>
<td>...</td>
<td>...</td>
<td>1</td>
</tr>
<tr>
<td>262</td>
<td>1</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>266</td>
<td>1</td>
<td>...</td>
<td>1</td>
</tr>
<tr>
<td>Duration of follow-up, median weeks (IQR)</td>
<td>48 (48–48)</td>
<td>48 (48–48)</td>
<td>49 (48–49)</td>
</tr>
<tr>
<td>Sex, no. of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>12</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Female</td>
<td>13</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Age, mean years ± SD</td>
<td>34.4 ± 5.7</td>
<td>33.9 ± 6.0</td>
<td>35.5 ± 7.5</td>
</tr>
<tr>
<td>Weight, mean kg ± SD</td>
<td>55.0 ± 8.7</td>
<td>59.0 ± 11.9</td>
<td>51.5 ± 8.1</td>
</tr>
<tr>
<td>HIV-1 RNA level, mean log&lt;sub&gt;10&lt;/sub&gt; copies/mL ± SD</td>
<td>1.70 ± 0.03</td>
<td>1.71 ± 0.04</td>
<td>1.73 ± 0.18</td>
</tr>
<tr>
<td>CD4 cell count, median cells/µL (range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before commencement of antiretroviral therapy</td>
<td>359 (313–451)</td>
<td>379 (309–428)</td>
<td>328 (281–422)</td>
</tr>
<tr>
<td>Before STI trial</td>
<td>653 (595–803)</td>
<td>766 (550–872)</td>
<td>555 (468–779)</td>
</tr>
<tr>
<td>NRTIs received, no. of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine and lamivudine</td>
<td>12</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Didanosine and stavudine</td>
<td>13</td>
<td>9</td>
<td>11</td>
</tr>
</tbody>
</table>

**NOTE.** The week of randomization indicates when a patient met the eligibility criteria for randomization into this study. HIVNAT, HIV Netherlands Australia Thailand Research Collaborative; IQR, interquartile range; NRTI, nucleoside reverse-transcriptase inhibitor; WOWO, week-on/week-off.

<sup>a</sup> Seventy-four of the 87 patients at start of the HIVNAT 001.4 trial were randomized.

<sup>b</sup> Study weeks refer to the week of HIVNAT trial 001 and correspond to weeks 0, 4, 16, 28, 36, and 40, respectively, of the present study.

SAS software. All Centers for Disease Control and Prevention (CDC) clinical events and grade 3 and 4 adverse events, including the serious adverse events, were evaluated for safety.

### RESULTS

A total of 74 HIV-1–infected Thai patients (36 male and 38 female patients) were randomized to this structured treatment interruption study. Baseline characteristics, including the CD4 cell count at the start of antiretroviral therapy, are noted in table 1. The number of patients, age, sex, plasma viral load, and median CD4 cell count before randomization were well matched for all treatment arms.

Patients were randomized to a treatment arm as soon as they were eligible, after finishing the previous once-daily therapy trial. One can see in table 1 that, although most patients were randomized 226 weeks after the start of the HIVNAT 001 trial or at the start of this structured treatment interruption trial, 17 patients did not meet the eligibility criteria until some weeks later, thus delaying their dates of randomization to this study.

The median duration of patient follow-up after randomization was 48 weeks for the continuous and CD4 cell count-guided treatment arms and 49 weeks for the WOWO treatment arm (table 1).

The proportion of weeks of antiretroviral use over 48 weeks was 100% (interquartile range [IQR], 100%–100%) in the continuous treatment arm, 41.1% (IQR, 10.2%–60.7%) in the CD4 cell count–guided treatment arm, and 69.8% (IQR, 50.0%–98.0%) in the WOWO treatment arm (P < .001 for comparison of all 3 groups and for the CD4 cell count–guided treatment arm vs. the WOWO treatment arm). The proportion of patients with a CD4 cell count of ≥350 cells/µL at the end of follow-up was 100% in the continuous treatment arm, 87% in the CD4 cell count–guided arm, and 96% in the WOWO treatment arm. Only 3 patients in the CD4 cell count–guided treatment arm had a CD4 cell count of <350 cells/µL at the end of the study (P = .03 for comparison of all 3 treatment arms, by Fisher exact test).

In the CD4 cell count–guided treatment arm, 5 patients...
3 patients were counts before the structured treatment interruption for these all of whom were in the WOWO treatment arm. The CD4 cell in 1 patient, and esophageal candidiasis occurred in 1 patient, papular pruritic eruptions in 1 patient, oral hairy leukoplakia A to class C disease. CDC-classified clinical events included the WOWO treatment arm had progression from CDC class .87, respectively. Only 1 patient, who was randomized to the continuous treatment arm resulted in the largest decrease in the CD4 cell count occurred in the CD4 cell count–guided treatment arm. The median CD4 cell count decreased from the baseline level in all treatment arms, although increased from the baseline level in all treatment arms, although the largest decrease in the CD4 cell count occurred in the CD4 cell count–guided treatment arm. The CD4 cell count decreased from 550 to 370 cells/μL (IQR, 1.69–1.69 copies/mL) in the WOWO treatment arm. The CD4 cell count decreased from 450 to 340 cells/μL (IQR, 1.69–4.12 copies/mL) in the CD4 cell count–guided treatment arm, and 1.70 copies/mL (IQR, 1.69–1.77 copies/mL) in the WOWO treatment arm. The percentages of patients in each arm who were randomized immediately and who had undetectable plasma viral loads (i.e., <50 copies/mL) after 48 weeks in this structured treatment interruption study were 100% in the continuous treatment arm, 45% in the CD4 cell count–guided treatment arm, and 72% in the WOWO treatment arm. The median CD4 cell count for patients with 48 weeks of follow-up data was 637 cells/μL (IQR, 484–794 cells/μL) in the continuous treatment arm, but it was 547 cells/μL (IQR, 373–596 cells/μL) in the CD4 cell count–guided treatment arm and 582 cells/μL (IQR, 468–787 cells/μL) in the WOWO treatment arm. The CD4 cell count decreased from the baseline level in all treatment arms, although the largest decrease in the CD4 cell count occurred in the CD4 cell count–guided treatment arm.

Treatment failure, which is defined in Methods and in table 2 as virological or immunological failure during treatment in the continuous and WOWO treatment arms, occurred in 8 (31%) of 26 patients in the WOWO treatment arm (7 patients had a plasma viral load of >1000 copies/mL, and 1 had a CD4 cell count of <350 cells/μL). Of the 7 patients with viremia, no drug resistance was found in 2 patients; for 4 patients, samples were not able to be amplified; and virus from 1 patient was found to have zidovudine resistance (codons 41, 210, and 215) [5]. None of the patients in the continuous treatment arm experienced treatment failure. The median time to treatment failure was 16 weeks after randomization (IQR, 8–32 weeks). Two patients were lost to follow-up. All patients with treatment failure had plasma viral loads of <50 copies/mL after a median time of 12 weeks of continuous twice-daily administration of antiretrovirals.
DISCUSSION

This structured treatment interruption trial demonstrates that adequate immunological function (i.e., a CD4 cell count of $\geq 350$ cells/$\mu$L) may be preserved by use of a CD4 cell count–guided or WOWO approach to therapy withdrawal and reintroduction, compared with continuous antiretroviral therapy. However, the high rate of virological failure in the WOWO treatment arm indicates that this strategy may not be useful for patients who are receiving long-term antiretroviral treatment that includes dual-agent therapy. The rates of adverse events do not differ among the study arms, although 3 patients in the WOWO treatment arm had 3 new CDC-defined clinical events during this period. Significantly fewer antiretrovirals were used in the CD4 cell count–guided and WOWO treatment arms, which makes use of this structured treatment interruption approach worthy of additional study as a cost-saving strategy. In addition, the small sample size increases the likelihood of $\beta$ error, because interarm differences may not be apparent, even if they exist. The short follow-up period could exacerbate this error. Results of a longer trial that is sufficiently powered to answer questions about the risks and benefits of structured treatment interruption are required to confirm our findings before conclusions can be drawn.

In patients who had 48 weeks of follow-up data, the plasma viral load was obviously not suppressed in the CD4 cell count–guided treatment arm, but it was suppressed in 72% of patients in the WOWO treatment arm. Immunological function was not preserved as well in the CD4 cell count–guided treatment arm as in the continuous and WOWO treatment arms. However, immune system preservation, as indicated by a CD4 cell count of $\geq 350$ cells/$\mu$L, was found in all patients in the continuous treatment arm, in 87% of patients in the CD4 cell count–guided treatment arm, and in 96% of patients in the WOWO treatment arm. The differences in the pre–structured treatment interruption CD4 cell counts among treatment arms and the small cohort size may have been responsible for some differences between arms in the immunological and virological comparisons.

The high rate of treatment failures in the WOWO treatment arm may have been due to the occurrence of undetected mutations during previous suboptimal dual-NRTI antiretroviral therapy (for first year of antiretroviral treatment) or long-term HAART exposure (for the 3 years immediately preceding this structured treatment interruption study), even though only 1 patient was found to have resistance mutations. The WOWO approach was also problematic for the Staccato international structured treatment interruption trial [6], which measured the plasma viral load after the week without therapy, whereas our study checked the plasma viral load after the week with therapy. The 31% rate of failure in the WOWO treatment arm in our study may have been higher if the plasma viral load had been measured after the week without therapy. A small sample size and the lower median CD4 cell count in this treatment arm may have also affected the percentage of patients who met the failure criteria in the WOWO treatment arm. Adhering to a complicated regimen may have been more difficult, leading to antiretroviral failure due to poor adherence. Another study that used the weekly structured treatment interruption strategy had more success, but the cohort possibly had a shorter duration of antiretroviral exposure [2]. The use of a triple-drug antiretroviral regimen containing efavirenz in a WOWO approach was successful in a proof-of-concept trial, perhaps indicating that the longer half-life of non-NRTI may be important for prevention of intermittent viremia and subsequent development of a drug-resistant virus [7]. Finally, the greater number of visits to the clinic in the WOWO and the CD4 cell count–guided treatment arms may have had an impact on adherence and on some outcomes, but this is difficult to conclude with a small cohort and short study period.

This structured treatment interruption study demonstrates that all 3 study arms resulted in similar clinical function over this short follow-up period of up to 48 weeks, with the CD4 cell count–guided and WOWO treatment arms being the most cost-effective with regard to antiretroviral costs. The immune function was adequate in all arms if considering the percentage of patients with a CD4 cell count of $\geq 350$ cells/$\mu$L, whereas the continuous and WOWO treatment arms were more successful than the CD4 cell count–guided treatment arm in maintaining the CD4 cell count at the baseline level. Calculations regarding the savings in antiretroviral costs must take into consideration the time that an antiretroviral-naive patient must take continuous therapy to achieve a plasma viral load of $<50$ copies/mL. Most patients (78%) in the CD4 cell count–guided treatment arm had received $\geq 12$ weeks of re-treatment with antiretrovirals, thereby reducing some of the expected savings in antiretroviral–associated costs. Because this study was conducted before current antiretroviral initiation criteria were in place, these patients started receiving antiretroviral therapy while they had relatively high CD4 cell counts (100–500 cells/$\mu$L). Because current criteria for initiation of antiretroviral therapy indicate that a patient should begin therapy at relatively lower CD4 cell counts, this treatment cohort may not be reflective of the HIV-infected population in the developing world who are eligible for treatment. Because most patients in the CD4 cell count–guided treatment arm required re-treatment, use of this strategy may be less useful in areas in the developing world with resource limitations. Additionally, the high CD4 cell counts before the structured treatment interruption may have positively influenced the results in the CD4 cell count–guided treatment arm, which may not occur if a patient began to...
receive treatment with a lower CD4 cell count. The high treatment failure rate in the WOWO arm makes this strategy less useful in terms of virological control. The use of structured treatment interruption—in particular, the CD4 cell count–guided strategy—for virologically well-controlled patients with shorter (and more optimal) antiretroviral exposure and lower pre–antiretroviral therapy/pre–structured treatment interruption CD4 cell counts may prove to be an appropriate HAART administration strategy that can save costs associated with antiretroviral use, preserve adequate immune function, and provide comparable safety profiles to continuous HAART therapy.

Acknowledgments

We would like to thank all the patients in the trial, the staff of the HIV Netherlands Australia Thailand Research Collaborative, Chulalongkorn University Immune Clinic, and the Thai Red Cross AIDS Research Centre.

Financial support. Roche (Thailand).

Potential conflicts of interest. J.A. has received travel grants and honoraria from Hoffmann-LaRoche. K.R. has received travel grants, research grants, consultancy fees, and/or honoraria from Hoffmann-LaRoche; Merck, Sharp and Dohme; Bristol-Myers Squibb; Gilead; and Abbott. B.H. has received consultancy fees and honoraria from GlaxoSmithKline; Hoffmann-LaRoche; Merck, Sharp and Dohme; and Virco/Tibotec. J.L. has received consultancy fees and honoraria from GlaxoSmithKline; Boehringer-Ingelheim; Bristol-Myers Squibb; Hoffmann-LaRoche; Merck, Sharp and Dohme; Schering-Plough; Bayer; Shire Pharmaceuticals; Agouron/Pfizer; and Virco/Tibotec. P.P. has received honoraria from Bristol-Myers Squibb and has been a scientific consultant for and received research grants from Bristol-Myers Squibb, Hoffmann-LaRoche, GlaxoSmithKline, and Merck, Sharp and Dohme. D.A.C. has received research grants/funding, honoraria, and/or lecture sponsorships from and has been a consultant or advisor to Abbott; Boehringer-Ingelheim; Bristol-Myers Squibb; Chiron; Gilead; GlaxoSmithKline; Merck, Sharp and Dohme; Pfizer; and Roche. All other authors: no conflicts.

References