A Multicenter Observational Study of the Potential Benefits of Initiating Combination Antiretroviral Therapy during Acute HIV Infection

Frederick M. Hecht, Lei Wang, Ann Collier, Susan Little, Martin Markowitz, Joseph Margolick, J. Michael Kilby, Eric Daar, Brian Conway, and Sarah Holte, for the AIEDRP Network

1University of California, San Francisco, San Francisco; 2University of California, San Diego, San Diego; 3University of California, Los Angeles, Los Angeles; 4Fred Hutchinson Cancer Research Center and 5University of Washington, Seattle, Washington; 6Aaron Diamond AIDS Research Center, New York, New York; 7Johns Hopkins University School of Public Health, Baltimore, Maryland; 8University of Alabama at Birmingham, Birmingham; 9University of British Columbia, Vancouver, Canada

(See the brief report by Streeck et al., on pages 734–9, and the editorial commentary by Kinloch–de Loes, on pages 721–4.)

Objective. Uncontrolled studies have suggested a benefit, after treatment discontinuation, of initiating highly active antiretroviral therapy (HAART) during primary human immunodeficiency virus (HIV) infection. We assessed whether initiation of HAART within 2 weeks of (acute treatment) or between 2 weeks and 6 months after (early treatment) HIV seroconversion was associated with improvements in the viral load and the CD4+ T cell count after discontinuation of treatment in an observational cohort.

Methods. Subjects from the multicenter Acute Infection and Early Disease Research Program cohort were enrolled in the present study within 6 months of HIV seroconversion and self-selected whether to initiate HAART. Subjects who received acute (n = 13) or early (n = 45) treatment received HAART for at least 12 weeks and then subsequently stopped treatment, whereas untreated subjects (n = 337) declined treatment. HIV RNA levels and CD4+ T cell counts at 24, 48, and 72 weeks after treatment cessation in the 2 treatment groups were compared with those noted in the untreated group during the same periods of observation after enrollment.

Results. The acute treatment group had lower mean HIV RNA levels at 24 weeks without therapy (-0.48 log_{10} copies/mL [95% confidence interval (CI), -0.82 to -0.13 log_{10} copies/mL]) and higher mean CD4+ T cell counts (112 cells/μL [95% CI, 20–205 cells/μL]), compared with the untreated group at 24 weeks. The differences in the laboratory values for the acute treatment group versus the untreated group at 72 weeks without therapy were as follows: for the HIV RNA level, -0.35 log_{10} copies/mL (95% CI, -0.91 to 0.21 log_{10} copies/mL) and, for the CD4 T+ cell count, 112 cells/μL (95% CI, -15 to 213 cells/μL). The early treatment group had lower HIV RNA levels at 24 weeks than did the untreated group, but differences were no longer apparent by week 48; CD4+ T cell counts were higher in the early treatment group at week 24 (116 cells/μL [95% CI, 75–157 cells/μL]) and week 72 (70 cells/μL [95% CI, 2–138 cells/μL]).

Conclusions. Initiation of HAART within 2 weeks of antibody seroconversion was associated with viral load and CD4+ T cell count benefits for 24 weeks after termination of HAART, with there being trends toward a longer-term benefit. Later initiation of HAART was associated with a persistent but decreasing CD4+ T cell count benefit and a loss of the viral load benefit by week 72 after discontinuation of treatment.

The long-term course of HIV infection can be accurately predicted based on the HIV RNA level that is established soon after infection occurs [1, 2]. The viral load typically becomes high during primary HIV infection and then decreases under the pressure of immune responses [3–5]. Individuals with plasma viral loads that remain elevated during the first year of HIV infection have a high risk of disease progression, whereas those with low viral loads have a more favorable course of disease [1]. This finding implies that there are key early events in the pathogenesis of HIV infection that determine the long-term pace of disease progression.
One randomized, controlled trial of zidovudine monotherapy found that, compared with the placebo group, the treatment group maintained higher CD4+ T cell counts for 12 months after cessation of treatment [7]. However, HIV RNA levels did not appear to be altered by zidovudine monotherapy once treatment was stopped. A pilot study of 8 persons who had HAART initiated during primary HIV infection and then stopped receiving HAART according to a structured treatment interruption protocol found that 5 of 8 persons maintained an HIV RNA level of <500 copies/mL at a median of 6.5 months after cessation of HAART [8]. In contrast, only 4 of 109 persons in a historical comparison group achieved such low viral loads. At longer-term follow-up, however, this level of control of viremia was not maintained in most persons [9]. Despite the provocative findings of these studies, it remains unclear whether the long-term findings regarding viral loads and CD4+ T cell counts achieved with this treatment approach are better than the findings that would have been achieved had the treatment not been given.

A critical question is whether it is possible to intervene early in the course of HIV infection to improve the subsequent course of disease. One reason why more-effective immune responses do not develop may be that HIV targets CD4+ T lymphocytes and preferentially infects activated CD4+ T cells [6]. To the extent that CD4+ T cells are important in immune responses to HIV, the virus may disrupt the early development of these responses by directly or indirectly triggering the death of the CD4+ T cells that most effectively respond to the virus. If antiretroviral therapy (ART) is initiated during early infection, the disruption caused by HIV may be minimized, allowing better development of these early CD4+ T cell anti-HIV responses.

Subjects and Methods

Subjects. The AIEDRP cohort study is a multicenter, observational cohort study of persons enrolled within 1 year of having HIV antibody seroconversion. Participants in the cohort self-selected whether or not to start receiving HAART. For this analysis, we recruited persons enrolled at 10 of the original study sites located in the United States and Canada. Participants in the cohort had to meet one of the following criteria for acute or early HIV infection at enrollment: (1) a negative or indeterminate result of an antibody test and an HIV RNA load of <5000 copies/mL, (2) a documented negative result of an HIV antibody test performed within 12 months of enrollment of a participant in whom the current HIV antibody test result is positive, or (3) a history consistent with recent HIV infection and an optical density of <1.0, as determined by a less-sensitive EIA antibody test [10, 11]. A history consistent with recent HIV infection meant that a subject had no prior positive result of HIV antibody tests or had not previously received treatment for HIV infection, had a CD4+ T cell percentage of >14%, and had self-reported a recent negative HIV antibody test result or a recent illness consistent with an acute retroviral syndrome.

For this analysis, participants had to meet additional criteria specific to inclusion in either the treated or untreated groups. The treated subjects had to initiate HAART either within 6 months of receiving a negative or indeterminate result of an HIV antibody test or while a less-sensitive EIA antibody test revealed a standardized optical density of <0.75 (a finding consistent with a duration of <6 months from antibody seroconversion). The untreated subjects met the same study-entry criteria as did the treated subjects, but the untreated subjects did not receive HAART and had to be monitored for at least 6 months after enrollment. HAART was defined as treatment with ≥3 antiretroviral agents. The treated subjects had to maintain treatment for at least 12 weeks but then stop treatment for at least 4 weeks. Subjects elected whether or not to start HAART and typically had knowledge of at least one viral load measurement and CD4+ T cell count when making that decision. HAART regimens were either site-specific protocols or regimens chosen by a subject’s physician. The subjects in the study were enrolled in protocols approved by the institutional review boards of each of the participating study centers.

Analysis. The key end points of the study were defined as the HIV RNA levels and the CD4+ T cell counts determined at 24, 48, and 72 weeks of untreated observation. For the untreated subjects, this was the time since enrollment in the study, with censoring done at the time that HAART was initiated, if this occurred. For the treated subjects, the observation period started 4 weeks after treatment was stopped, to allow return of viremia after treatment discontinuation. The time receiving treatment or any time occurring before treatment was not
Table 1. Characteristics of the study subjects.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Untreated group (n = 337)</th>
<th>Acute treatment group(^a) (n = 13)</th>
<th>Early treatment group(^b) (n = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory value at baseline, median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA level, (\log_{10}) copies/mL</td>
<td>4.9 (4.3–5.7)</td>
<td>5.8 (5.3–6.2)</td>
<td>4.9 (4.2–5.5)</td>
</tr>
<tr>
<td>CD4(^+) T cell count, cells/μL</td>
<td>483 (324–638)</td>
<td>452 (255–519)</td>
<td>499 (376–593)</td>
</tr>
<tr>
<td>Sex, male, % of subjects</td>
<td>91</td>
<td>100</td>
<td>87</td>
</tr>
<tr>
<td>Race/ethnicity, % of subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td>11</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>White</td>
<td>75</td>
<td>77</td>
<td>87</td>
</tr>
<tr>
<td>Hispanic</td>
<td>8</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Age, years, median (range)</td>
<td>33 (15–61)</td>
<td>34 (18–56)</td>
<td>34 (20–60)</td>
</tr>
<tr>
<td>Estimated time from infection to treatment, weeks, median</td>
<td>NA</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Longest duration of follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;24 weeks</td>
<td>218</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>24 to &lt;48 weeks</td>
<td>48</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>48 to &lt;72 weeks</td>
<td>21</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>≥72 weeks</td>
<td>50</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Duration of HAART, weeks, median (range)</td>
<td>NA</td>
<td>81 (13–173)</td>
<td>70 (13–260)</td>
</tr>
<tr>
<td>Received a HAART regimen containing PI, % of subjects</td>
<td>NA</td>
<td>92</td>
<td>80</td>
</tr>
</tbody>
</table>

**NOTE.** For comparisons across groups and for pairwise comparisons between treated and untreated groups, \(P > .1\), except for the comparison of the HIV-1 RNA level in the untreated and acute treatment groups, for which \(P = .07\), and the estimated no. of weeks from infection to treatment between the acute and early treatment groups, for which \(P < .001\). HAART, highly active antiretroviral therapy; IQR, interquartile range; NA, not applicable; PI, protease inhibitor.

\(^a\) Subjects who started receiving HAART within 2 weeks of antibody seroconversion.

\(^b\) Subjects who started receiving HAART between 2 weeks and 6 months after antibody seroconversion.
in the acute treatment group and 45 of whom were considered to be in the early treatment group). There were no significant demographic differences between these groups (table 1). The subjects in the acute treatment group had a higher mean viral load and tended to have a lower mean CD4$^+$ T cell count at study entry than did the subjects in either the untreated or early treatment groups, but the differences were not statistically significant.

On the basis of our selection criteria, all treated subjects received $\geq 3$ antiretroviral agents. For 12 (92%) of the 13 participants in the acute treatment group and for 35 (80%) of the 45 participants in the early treatment group, treatment was initiated with regimens containing a protease inhibitor. One of the subjects in the acute treatment group and 4 of the subjects in the early treatment group who were receiving a protease inhibitor also received a nonnucleoside reverse-transcriptase inhibitor as part of their regimen. Of the remaining subjects, 4 (9%) of those in the early treatment group received a nonnucleoside reverse-transcriptase–based regimen, and 1 participant (8%) in the acute treatment group and 5 participants (11%) in the early treatment group received an abacavir-based regimen. All of the participants in the early treatment group...
had HIV-1 RNA levels of <500 copies/mL, as did 11 of 13 participants in the acute treatment group. The median duration of ART in both treatment groups was ~1.5 years (table 1).

In the untreated group, viral loads initially decreased (figure 1A) and then slowly increased over time. The initial decrease is consistent with the viral load decrease that is expected very early in untreated HIV infection, which presumably occurs as developing immune responses control viremia. In both treatment groups, the viral load initially increased rapidly after ART was stopped, and it then increased slowly over time (figures 1B and 1C). At 24 weeks of posttreatment observation, both treatment groups had HIV-1 RNA levels that were ~0.5 log10 copies/mL lower in unadjusted analyses than those in the untreated group (table 2). After adjustment for the viral loads and CD4+ T cell counts at baseline, the difference in the viral load, when compared with that in the untreated group, remained similar in the early treatment group but was 0.69 log10 copies/mL lower in the acute treatment group. In the acute treatment group, the viral load remained 0.35 log10 copies/mL lower than that in the untreated group, in unadjusted analysis after 72 weeks of untreated observation; however, this difference was no longer statistically significant. In adjusted analysis, however, the viral load advantage for the acute treatment group at 72 weeks (0.68 log10 copies/mL) was similar to that noted at 24 weeks (0.69 log10 copies/mL), and the difference continued to be statistically significant. In contrast, the mean viral load in the early treatment group became similar to that in the untreated group after 24 weeks (figure 1D), and there was no statistically significant difference in the viral load between the 2 groups at 48 and 72 weeks, in either the unadjusted or adjusted analysis (table 2).

CD4+ T cell counts decreased gradually in the untreated and treated groups (figure 2). CD4+ T cell counts remained >100 cells/µL higher in the acute treatment group than in the untreated group throughout the period of observation (table 3), in both unadjusted and adjusted analyses. The acute treatment group had a statistically significant difference in the CD4+ T cell count in both unadjusted and adjusted analyses at 24 weeks. The difference remained statistically significant only in the adjusted analyses at weeks 48 and 72, because there were fewer observations; however, the magnitude of difference remained similar in both adjusted and unadjusted analyses (table 2).

The early treatment group had a mean CD4+ T cell count that was ≥100 cells/µL higher than that noted in the untreated group at 24 and 48 weeks (figure 2 and table 3). There was a statistically significant CD4+ T cell count advantage in the early treatment group, compared with the untreated group, in both unadjusted and adjusted analyses at 24, 48, and 72 weeks. However, the magnitude of the CD4+ T cell count advantage decreased in both adjusted and unadjusted analyses after week 48 (table 1 and figure 2).

We also performed analyses of the viral load and CD4+ T cell count trajectories, dividing the treatment group into subjects receiving treatment for more or for less time than the median duration of ART. We found no differences associated with treatment duration (data not shown), but our power to detect differences is limited because of the small sample sizes resulting from subdividing the treatment group.

**DISCUSSION**

We found that initiation of HAART within 2 weeks of HIV antibody seroconversion was associated with sustained viral load and CD4+ T cell count benefits for up to 72 weeks after termination of therapy. The differences between the acute treatment group and the untreated group, however, were statistically significant only in analyses that adjusted for the CD4+ T cell count and viral load at baseline. Because study subjects typically decided whether to start receiving ART after they knew their viral load and CD4+ T cell count, the untreated group is likely to be enriched for persons who rapidly achieved low viral loads and maintained good CD4+ T cell counts. Although our statistical adjustment will account for this selection bias, it is likely to overcorrect for higher viral loads that are associated with earlier stages of acute HIV infection. Thus, the unadjusted analy-
Figure 2. CD4⁺ T cell counts, by study group. A, Points in time when CD4⁺ T cell counts were determined for the untreated subjects, starting at study enrollment during early HIV infection. The line denotes the mean CD4⁺ T cell count for the study group. B and C, Points in time when the CD4⁺ T cell counts were determined for subjects receiving treatment within 2 weeks of antibody seroconversion (the acute treatment group) and for subjects receiving treatment between 2 weeks and 6 months after antibody seroconversion (the early treatment group), respectively, after discontinuation of antiretroviral therapy. Note that the earliest time points in panels B and C do not denote the baseline CD4⁺ T cell counts before treatment but, rather, the first measurements obtained after treatment discontinuation. D, Mean CD4⁺ T cell counts in the untreated subjects (solid line) and in the subjects receiving acute treatment (dotted line) and early treatment (dashed line). Time in the untreated group began at study enrollment, whereas time in the treatment groups began at treatment discontinuation. The nos. of persons with observations for specified periods of time are provided in Table 1.

Our results suggest that treatment given during acute HIV infection may modify the long-term course of disease; however, the results must be viewed cautiously because of the lack of statistical significance of the CD4⁺ T cell count and viral load benefits at 72 weeks, the small sample size, and the need for longer follow-up to assess the durability of benefit. The 0.48-log₁₀ reduction in viral load observed at 72 weeks in unadjusted analyses would be clinically significant. In previous treatment studies, a >0.4-log reduction in viral load was biologically significant [13], and a two-thirds-log reduction in viral load, which was the magnitude of viral load reduction that we observed in adjusted analysis at 72 weeks, corresponded to an ~50% reduction in the risk of disease progression over 6 years [2].

In contrast to subjects in the acute treatment group, subjects who initiated HAART later but within 6 months of seroconversion appeared to receive more temporary benefits. After stopping therapy for 24 weeks, the early treatment group had a viral load that was lower than that in untreated subjects, but this advantage was lost by 48 weeks. There was a more sustained CD4⁺ T cell count advantage in the early treatment group, when compared with the untreated group. The magnitude of the CD4⁺ T cell count benefit, however, appeared to decrease 72 weeks after stopping treatment; this finding is potentially consistent with a delayed effect of the viral load rebound on CD4⁺
of HIV infection [9, 15], they have not had significant power to shows dramatic, sustained virological benefits of early treatment. Although earlier studies of acute treatment of HIV infection have suggested that there are significant improvement in viral load. Although earlier studies of benefit resulting from early treatment, despite a lack of significant improvement in viral load between the early treatment and untreated groups.

There are both parallels and differences between our findings and those of Desquilbet et al. [14], who recently reported an observational comparison of persons who did and did not receive ART for acute or early HIV infection. Similar to the early treatment group in our study, the treatment group in the study of Desquilbet et al. [14] also had HIV-1 RNA levels that were initially lower than those in the untreated group; however, by 12 months after treatment, the HIV-1 RNA levels in the groups were similar. When Desquilbet and colleagues analyzed participants who met our criteria for acute infection separately, they did not note a difference in the HIV-1 RNA levels of these subjects, compared with the levels noted in the untreated subjects. However, their study included only 7 subjects with acute HIV infection and a smaller overall study population. The small sample size means that there is higher risk of a type II error of concluding that there is no benefit resulting from treatment initiated during acute infection, when, in fact, there is a benefit.

It is also possible that subtle differences in the duration of infection before initiation of HAART in the 2 studies may influence results.

The CD4+ T cell count benefit that we noted is consistent with that found by Kinloch–de Loes et al. [7] in an earlier trial of zidovudine in subjects with early HIV infection, although the magnitude of benefit that we noted was larger, possibly because of the greater potency of the regimens used in our study. Of note, the earlier study also found a CD4+ T cell count benefit resulting from early treatment, despite a lack of significant improvement in viral load. Although earlier studies of acute treatment of HIV infection have suggested that there are no dramatic, sustained virological benefits of early treatment of HIV infection [9, 15], they have not had significant power or an adequate comparison group to determine whether there is a virological benefit of the magnitude that we observed.

The exact mechanism of the sustained viral load and CD4+ T cell count benefit noted after initiation of HAART for acute HIV infection cannot be answered by the present study. The results, however, are consistent with the hypothesis that early initiation of ART improves immune responses to HIV infection, because HIV-1 RNA levels were persistently lower in the acute treatment group. Treatment also decreases T cell activation, which is high during acute HIV infection [16] and has been shown to be a strong predictor of CD4+ T cell depletion [16, 17]. It is possible that early treatment leads to a shorter period of high activation of T cells, potentially reducing damage to the immune system. Recent data from rhesus macaques with acute simian immunodeficiency virus infection indicate that there is far more widespread infection of memory CD4+ T cells than previously was appreciated, with 30%–60% of such cells infected and killed within weeks of infection [18] and with massive depletion of the memory CD4+ T cells in gut-associated lymphatic tissue [19], which may result in long-term damage to the immune system that influences disease progression. Early treatment may reduce initial depletion of CD4+ T cells and might be responsible for the sustained CD4+ T cell count benefit that we found.

The present study has several limitations. Treatment was not assigned randomly, and unmeasured differences in the study groups may account for our results. Treatment regimens were heterogeneous, the duration of treatment varied between participants, and the data on treated persons did not include assessment of the reasons for stopping therapy. Results from the present study characterize the impact of treatment initiated during acute HIV infection for only 72 weeks after discontinuation of therapy, and the benefits may wane, similar to our findings for the early treatment group. The acute treatment group was small, and the viral load and CD4+ T cell count differences remained significant at 72 weeks only in adjusted analyses. As noted, it is possible that the statistical adjustments overcorrected for differences at baseline. The results at 72 weeks

<table>
<thead>
<tr>
<th>Follow-up time point</th>
<th>Acute treatment group minus untreated group</th>
<th>Early treatment group minus untreated group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
<td>Adjusted</td>
</tr>
<tr>
<td>24 weeks</td>
<td>112± (20–205)</td>
<td>132± (51–213)</td>
</tr>
<tr>
<td>48 weeks</td>
<td>103 (–2 to 207)</td>
<td>120± (24–217)</td>
</tr>
<tr>
<td>72 weeks</td>
<td>112 (–15 to 213)</td>
<td>125± (3–247)</td>
</tr>
</tbody>
</table>

NOTE: Data in parentheses are 95% confidence intervals.

a Subjects who started receiving HAART within 2 weeks of antibody seroconversion.
b Subjects who started receiving HAART between 2 weeks and 6 months after antibody seroconversion.
c P<.05.
depend, to some extent, on the nonparametric spline model and earlier data, rather than complete data for all study subjects at week 72 after discontinuation of treatment. Our definition of 2 weeks after seroconversion as the end of the period of acute HIV infection was arbitrary, and a more sustained treatment benefit may occur after this time point; however, we did not have adequate numbers of subjects to effectively compare smaller differences in the timing of HAART initiation.

Although the results of the present study support initiation of HAART during acute HIV infection, we believe that caution is indicated in making this recommendation on a clinical basis, because of both the limitations of observational studies and the lack of randomized, controlled studies; the lack of statistical significance of our unadjusted analyses after 24 weeks; and the need for longer-term assessment to further evaluate the durability of potential benefits. We believe that, on the basis of current evidence, patients need to be informed of the possible benefits of treatment, especially when HIV infection is diagnosed during the acute stage; they also need to be informed of the remaining uncertainties about the reliability of current data and the durability of benefit. Balanced against the possible benefits of treatment are the financial costs, the potential toxicities of treatment, and the risk of developing drug resistance.

The possible benefits of treatment during acute HIV infection may add to the rationale for diagnosis of acute HIV infection, on the basis of the public health benefits of early diagnosis in potentially preventing HIV transmission [20]. The typical symptoms of primary HIV infection and the role of HIV RNA testing in diagnosis have been well described elsewhere [21–25].

Our results suggest more limited benefit from treatment initiated longer than a few weeks after seroconversion. A randomized, controlled trial of treatment during this stage would be useful to better define the potential benefits of treatment during this period. Additional studies are also needed to determine whether the benefit that we observed in association with treatment initiated during acute HIV infection can be corroborated and to assess the optimal duration of HAART for persons with acute HIV infection.

Acknowledgments

We thank the patients who participated in this study and the study staffs at each study site who collected the data at enrollment and follow-up that made this study possible.

Financial support. National Institute of Allergy and Infectious Diseases of the National Institutes of Health (NIH) Acute Infection Early Disease Research Program (grants AI041531, AI 041533, AI 041536, AI041534, and AI043638). Additional support was provided by the NIH Center for AIDS Research (grants AI027763 and AI27767), the NIH General Clinical Research Center (grants SM01 RR00032-38 and M01-RR00102), and the NIH (grant R01 AI05343), and the State of California’s University-wide AIDS Research Program (grant IS02-SD-701).

Potential conflicts of interest. E.M.H. has received honoraria from Abbott and GenProbe and research support from GlaxoSmithKline (GSK), Bayer Diagnostics, and Monogram Biosciences. A.C. has received research support from Boehringer-Ingelheim, Johnson and Johnson (Tibotec-Virco), and Hoffmann-La Roche and is a consultant to GSK and Tibotec-Virco. M.M. has received research support from Merck, Gilead, Tibotec, and GSK; has received honoraria from Merck, Gilead, GSK, and Vertex; and serves on advisory boards for Abbott and Roche. E.D. has served as a consultant for and/or received honoraria from Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead, GSK, Merck, Schering-Plough, and Pfizer. All other authors: no conflicts.

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