Plasma HIV-1 RNA Dynamics in Antiretroviral-Naive Subjects Receiving either Triple-Nucleoside or Efavirenz-Containing Regimens: ACTG A5166s

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(See the editorial commentary by Markowitz and Perelson, on pages 1087–8.)

Objective. We sought to compare clearance rates of plasma human immunodeficiency virus type 1 (HIV-1) RNA in men and women starting triple-nucleoside–based versus efavirenz (EFV)–based regimens.

Methods. First- and second-phase decay rates of plasma HIV-1 were compared in men and women initiating a triple nucleoside reverse-transcriptase inhibitor (NRTI) regimen versus regimens that included EFV plus an NRTI. Subjects (n = 64) were randomized to receive zidovudine/lamivudine/abacavir (triple-nucleoside regimen), zidovudine/lamivudine plus EFV (3-drug EFV regimen) or zidovudine/lamivudine/abacavir plus EFV (4-drug EFV regimen). Plasma HIV-1 RNA levels were fitted to a biexponential viral-dynamics model using a nonlinear mixed-effects model. Nonparametric Wilcoxon tests compared empirical Bayes estimates of first- and second-phase viral decay rates between treatment arms and sex.

Results. Median first-phase viral decay rates were significantly faster in subjects receiving the 3-drug EFV regimen (0.67/day), compared with those receiving the triple-nucleoside regimen (0.56/day; P = .02). The second-phase viral decay rate was also faster in the 3-drug EFV group than in the triple-nucleoside group (P = .09). Decay rates in the 4-drug EFV group were intermediate. Viral decay rates were not significantly different in men and women.

Conclusions. Faster initial viral decay in subjects randomized to a 3-drug EFV-based regimen corresponded to the overall superior efficacy of that regimen. Viral decay rates did not differ by sex.

The chronic phase of HIV-1 infection is characterized by persistent high levels of viral replication that result from a dynamic equilibrium between virus production and clearance. This quasi steady state results in continuous turnover of the virus population, with approximately one-half of the circulating virus being replaced with newly produced virus each day [1, 2]. Viral-dynamic studies have estimated the half-life of HIV-1 particles in plasma to be 0.24 days [3]; the half-life of infectious virus is on the order of minutes [4].


Financial support: National Institute of Allergy and Infectious Diseases (grant AI038858 to AIDS Clinical Trials Groups; grant AI038858 to the Statistics and Data Analysis Center; grants AI025869, AI025888, AI025915, AI025924, AI027658, AI027659, AI027761, AI027663, AI027668, AI027669, AI027673, AI027675, AI032770, AI033273, AI034832, AI036339, AI036340, and AI036348 to AIDS Clinical Trials Units; and grant AI45808 to the University of Pennsylvania Center for AIDS Research); National Center for Research Resources (grants RR00044, RR00046, RR00047, RR00051, and RR00052 to the General Clinical Research Centers and grant K24 AI051666 to R.M.G.). Bristol-Myers Squibb and GlaxoSmithKline provided drug for the study, as well as financial support for plasma HIV-1 RNA determinations.

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The introduction of potent antiretroviral therapy perturbs the quasi steady state by preventing the infection of uninfected lymphocytes and monocytes. The resultant decrease in plasma viremia proceeds through several phases. The rapid first phase of decay, which lasts for 7–10 days, represents the death of short-lived, productively infected cells, such as activated CD4+ T lymphocytes [5]. With the elimination of the productively infected lymphocytes, a slower second phase of decay becomes evident. This second-phase decay is believed to represent the more gradual loss of long-lived productively infected cells, such as macrophages, as well as of latently infected lymphocytes that might become activated to produce virus [5]. Results of mathematical modeling have suggested that the decay of long-lived infected cells, with an average half-life of 14 days, is the major determinant of the second-phase decay. The pool of resting, latently infected cells decays even more slowly; estimates for the half-life of these cells vary widely, from 6 to 43 months [6, 7].

Early viral-dynamics models assumed that antiretroviral therapy was perfectly effective and resulted in complete inhibition of virus replication. As more potent combination regimens became available, subsequent studies noted faster apparent clearance rates, leading to revised (shorter) estimates of the viral half-life [8]. Under the assumption that treatment has no direct effect on the death rate of productively infected cells or on the rate at which virus particles are removed from plasma, then differences in first-phase decay rates must reflect differences in the extent to which treatment deviates from ideal (perfect) efficacy. This realization led to refinements in viral-dynamics models and provided a theoretical rationale for comparing the short-term activity of regimens on the basis of first-phase decay rates [9]. Differences in HIV-1 RNA decay have been linked to treatment responses with some regimens [10–12], but, to our knowledge, clearance rates for triple-nucleoside– and efavirenz (EFV)–based regimens have not been compared directly.

If steady-state levels of plasma viremia represent a balance between virus production and clearance, then differences in plasma HIV-1 RNA levels between groups might reflect differences in these parameters [3]. Several studies have shown lower levels of steady-state plasma viremia in HIV-1–infected women than in men, particularly in persons with earlier stages of disease [10–14]; men and women with advanced HIV-1 disease, however, have comparable plasma HIV-1 RNA levels [15]. Despite these differences in plasma viremia, rates of disease progression are similar in men and women, which suggests that women experience disease progression at lower plasma HIV-1 RNA levels than do men [16]. The biological basis for the difference in steady-state viremia is unclear. To date, no studies have compared HIV-1 clearance rates in men and women.

AIDS Clinical Trials Group (ACTG) study A5095 was a phase 3, randomized, placebo-controlled clinical trial that compared the efficacy of a triple-nucleoside regimen (a fixed-dose combination of zidovudine [ZDV], lamivudine [3TC], and abacavir [ABC]) with 2 regimens containing EFV—a standard 3-drug regimen (fixed-dose ZDV/3TC plus EFV) or a 4-drug regimen (ZDV/3TC/ABC plus EFV)—in treatment-naive HIV-1–infected men and women. That study found the triple-nucleoside regimen to be virologically inferior to the EFV-based regimens but found no difference between the 3- and 4-drug EFV regimens [17, 18]. We conducted a prospectively designed viral-dynamics substudy to compare the first- and second-phase viral decay rates in subjects initiating antiretroviral treatment with these regimens and to compare viral dynamics in HIV-1–infected men and women.

MATERIALS AND METHODS

Study design. The viral-dynamics substudy (A5166s) was designed to enroll 66 treatment-naive subjects (11 men and 11 women from each of the 3 treatment groups) who were registered to ACTG A5095; enrollment was offered to all subjects at sites participating in the substudy. Enrollment in ACTG A5095 was stratified by baseline HIV-1 RNA level (≤ 100,000 copies/mL). Study subjects self-reported race as non-Hispanic white, non-Hispanic black, or Hispanic. All subjects provided signed informed consent to participate in the substudy in addition to consent to participate in the parent study. Samples for plasma HIV-1 RNA determination were obtained at preentry; entry; days 2, 7, and 10; and weeks 2, 4, and 8 and were assayed using the HIV-1 Monitor Assay (version 1.0; Roche Molecular Systems).

For the accurate estimation of viral decay rates, it was important that the subjects ingested their medications as prescribed during the intensive sampling phase (entry to day 14). Therefore, subjects were asked to record the times when they ingested their medication in a diary that was reviewed by site personnel at each substudy visit for the first 14 days after the initiation of therapy. Subjects who discontinued or interrupted study treatment during this period were replaced if possible. For every subject with measurements excluded before day 7, an additional subject was to be randomized. In addition, for every 3 subjects with measurements excluded after day 7, an additional subject was to be randomized.

Statistical analysis. For comparison of viral decay rates, the first 8 weeks of HIV-1 RNA data were used. Data points collected for subjects after the discontinuation of treatment, drug interruption, or nonadherence (as determined from the diary summaries) were excluded from the primary analysis. A total of 11 subjects had data points excluded; 2 in the triple-nucleoside group, 3 in the 3-drug EFV group, and 4 in the 4-drug EFV group. In addition, to facilitate estimation of the
RESULTS

Baseline characteristics. A total of 64 subjects enrolled: 21 (14 men and 7 women) from the 4-drug EFV group, 25 (13 men and 12 women) from the triple-nucleoside group, and 18 (11 men and 7 women) from the 3-drug EFV group (table 1). Subjects were 59% male and 25% non-Hispanic white, 42% non-Hispanic black, and 30% Hispanic. The distribution of race and/or ethnicity was not significantly different by sex ($P = .74$). The median baseline plasma HIV-1 RNA level was 4.7 log$_{10}$ copies/mL, and the median baseline CD4 cell count was 261 cells/mm$^3$. Baseline characteristics of subjects enrolled in A5166s did not differ significantly from those of subjects in A5095 who did not participate in the substudy, except for the distribution of race/ethnicity ($P = .042$) (there was a greater proportion of Hispanic subjects in the substudy than in the main study [30% vs. 21%] because the University of Puerto Rico AIDS Clinical Trials Unit contributed a large number of subjects to the substudy).

Plasma HIV-1 RNA decay rates. Plasma HIV-1 RNA decay profiles were generated for each subject. Most profiles showed a steep decrease in HIV-1 RNA levels during the first 7–10 days, followed by a less steep but still decreasing phase through day 56; in some cases, this decline was observed despite an interruption in therapy (data not shown). Figure 1 shows the geometric mean plasma HIV-1 RNA level of the 3 treatment groups at each time point and suggests a faster rate of decrease in plasma HIV-1 RNA level in the 3-drug EFV group, compared with the triple-nucleoside group.

Table 2 summarizes the distributions of the estimated first-phase decay by treatment group. The median first-phase decay rate for subjects in the 3-drug EFV group was significantly greater than that for subjects in the triple-nucleoside group.
Table 2. Estimated first- and second-phase decay parameters, by treatment group.

<table>
<thead>
<tr>
<th>Phase, regimen (no.)</th>
<th>Median decay rate/day (Q1, Q3)</th>
<th>Median half-life, days</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>A vs. B</td>
</tr>
<tr>
<td>Phase 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm A (18)</td>
<td>0.59 (0.60, 0.71)</td>
<td>1.17</td>
<td>.19</td>
</tr>
<tr>
<td>Arm B (22)</td>
<td>0.56 (0.50, 0.66)</td>
<td>1.25</td>
<td></td>
</tr>
<tr>
<td>Arm C (16)</td>
<td>0.67 (0.60, 0.73)</td>
<td>1.03</td>
<td></td>
</tr>
<tr>
<td>Phase 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm A (18)</td>
<td>0.047 (0.040, 0.063)</td>
<td>14.9</td>
<td>.30</td>
</tr>
<tr>
<td>Arm B (22)</td>
<td>0.040 (0.027, 0.065)</td>
<td>17.2</td>
<td></td>
</tr>
<tr>
<td>Arm C (16)</td>
<td>0.055 (0.046, 0.070)</td>
<td>12.6</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. Arm A, zidovudine/lamivudine/abacavir plus efavirenz; arm B, zidovudine/lamivudine/abacavir; arm C, zidovudine/lamivudine plus efavirenz; Q1, first quartile; Q3, third quartile.
Figure 2. Predicted population average plasma HIV-1 RNA levels over time by treatment group. Predicted profiles were obtained on the population estimates of biexponential viral-dynamics models fitted for each treatment group separately. Because a single model could not be obtained for the 4-drug efavirenz group, the curve plotted represents the realized curve based on a simple average of each of the model parameters over the 6 convergent subsets (see text). Triple-nucleoside, zidovudine/lamivudine/abacavir; 3-drug efavirenz, zidovudine/lamivudine plus efavirenz; 4-drug efavirenz, zidovudine/lamivudine/abacavir plus efavirenz.

The triple-nucleoside group, compared with either the 3-drug EFV group \((P = .009)\) or the 4-drug EFV group \((P = .05)\). There was no evidence of a difference in the change from baseline HIV-1 RNA level to day 10 \((P = .57)\) between the 3-drug and 4-drug EFV groups. There was evidence of an interaction between baseline viral level and treatment group when we examined the change from baseline to day 10 \((P = .05)\).

### Table 3. Censored regression analyses of change in HIV-1 RNA from baseline to day 10 and 56 by treatment arm and baseline virus level.

<table>
<thead>
<tr>
<th>Analysis, covariate</th>
<th>Parameter estimate, mean ± SE (95% CI)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change from baseline to day 10, (\log_{10}) copies/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triple nucleoside (reference)</td>
<td>1.60 ± 0.09 (1.43–1.76)</td>
<td></td>
</tr>
<tr>
<td>Difference from reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-drug efavirenz</td>
<td>0.27 ± 0.13 (0.00–0.53)</td>
<td>.05</td>
</tr>
<tr>
<td>3-drug efavirenz</td>
<td>0.34 ± 0.13 (0.09–0.60)</td>
<td>.009</td>
</tr>
<tr>
<td>Baseline HIV-1 RNA level</td>
<td>0.24 ± 0.08 (0.08–0.40)</td>
<td>.003</td>
</tr>
<tr>
<td>Change from baseline to day 56, (\log_{10}) copies/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triple nucleoside (reference)</td>
<td>2.82 ± 0.13 (2.56–3.07)</td>
<td></td>
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<tr>
<td>Difference from reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-drug efavirenz</td>
<td>0.14 ± 0.22 (–0.29 to 0.57)</td>
<td>.53</td>
</tr>
<tr>
<td>3-drug efavirenz</td>
<td>0.58 ± 0.21 (0.17–0.98)</td>
<td>.005</td>
</tr>
<tr>
<td>Baseline HIV-1 RNA level</td>
<td>0.38 ± 0.15 (0.08–0.67)</td>
<td>.013</td>
</tr>
</tbody>
</table>

**NOTE.** The parameter estimates of the reference case provide the modeled reduction in plasma HIV-1 RNA at day 10 or 56, respectively, for an individual subject entering the study with baseline virus level of 50,000 copies/mL and assigned to the triple-nucleoside arm. Parameter estimates for the 4- and 3-drug efavirenz arms show the difference in virus level reduction (i.e., additional reduction), compared with the reference group, and the additional reduction observed for each \(1–\log_{10}\) increment in baseline HIV-1 RNA level (independent of treatment arm). Triple-nucleoside, zidovudine/lamivudine/abacavir; 3-drug efavirenz, zidovudine/lamivudine plus efavirenz; 4-drug efavirenz, zidovudine/lamivudine/abacavir plus efavirenz. CI, confidence interval.
Table 4. Estimated decay parameters by sex.

<table>
<thead>
<tr>
<th>Phase, sex</th>
<th>No.</th>
<th>Median decay rate/day (Q1, Q3)</th>
<th>Median half-life, days</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>24</td>
<td>0.60 (0.52, 0.68)</td>
<td>1.16</td>
<td>.52</td>
</tr>
<tr>
<td>Male</td>
<td>32</td>
<td>0.61 (0.55, 0.72)</td>
<td>1.14</td>
<td></td>
</tr>
<tr>
<td>Phase 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>24</td>
<td>0.045 (0.033, 0.067)</td>
<td>15.5</td>
<td>.52</td>
</tr>
<tr>
<td>Male</td>
<td>32</td>
<td>0.049 (0.037, 0.064)</td>
<td>14.3</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** Q1, first quartile; Q3, third quartile.

compared with the 3-drug EFV group ($P = .005$), but not with the 4-drug EFV group ($P = .53$). There was no evidence of an interaction between baseline viral level and treatment group when we examined the change from baseline to day 56 ($P = .64$). Univariate Cox proportional hazards models did not show a significant association between the half-life of productively infected cells and time to virologic failure (data not shown).

**Effect of sex on viral decay rates.** There was no evidence of differences in the first- or second-phase decay rates by sex (table 4). Likewise, analyses of change in plasma HIV-1 RNA level from baseline by sex showed no apparent difference in response between men and women (at day 10, $P = .91$; at day 56, $P = .78$) (table 5).

**DISCUSSION**

The present viral-dynamics substudy of a randomized clinical trial allowed us to compare clearance rates for plasma HIV-1 RNA level in treatment-naïve subjects initiating triple-nucleoside or EFV-based antiretroviral regimens. First-phase decay rates were significantly greater in subjects randomized to receive a 3-drug regimen containing EFV (ZDV/3TC plus EFV), compared with a triple-nucleoside regimen (ZDV/3TC/ABC).

The finding of a slower decay rate for plasma HIV-1 RNA level among recipients of the triple-nucleoside regimen suggests that this regimen resulted in less complete inhibition of HIV-1 replication, compared with an EFV-based regimen. A comparison of the median decay rates for these 2 regimens provides an estimate of the relative efficacies of different regimens [23] and suggests that the triple-nucleoside regimen was $\sim$83% as effective as the 3-drug EFV regimen at interrupting the production of infectious virions. One explanation for this observation is the need for all 3 drugs in the triple-nucleoside regimen to undergo activation through phosphorylation, resulting in a pharmacological delay before the onset of drug activity. By contrast, nonnucleoside reverse-transcriptase (RT) inhibitors can diffuse unchanged into viral particles in the plasma and bind to RT, so that the enzyme is inactivated before viral entry into target CD4$^+$ cells [24]. An alternative explanation is that inhibition of RT by 2 distinct mechanisms is more effective than inhibition by a single mechanism.

Another possible explanation is that CD4$^+$ cells in different anatomical or pharmacological compartments phosphorylate the nucleoside analogs to different degrees because of differ-

Table 5. Censored regression analyses of change in HIV-1 RNA level from baseline to day 10 and 56 by sex and baseline virus level.

<table>
<thead>
<tr>
<th>Analysis, covariate</th>
<th>Parameter estimate ± SE (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change from baseline to day 10, log$_{10}$ copies/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (reference)</td>
<td>1.78 ± 0.08 (1.63–1.93)</td>
<td></td>
</tr>
<tr>
<td>Difference from reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>-0.01 ± 0.12 (-0.25 to 0.22)</td>
<td>.913</td>
</tr>
<tr>
<td>Baseline HIV-1 RNA level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (reference)</td>
<td>0.27 ± 0.09 (0.10–0.44)</td>
<td>.002</td>
</tr>
<tr>
<td>Change from baseline to day 56, log$_{10}$ copies/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (reference)</td>
<td>3.07 ± 0.14 (2.80–3.34)</td>
<td></td>
</tr>
<tr>
<td>Difference from reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>-0.06 ± 0.20 (-0.44 to 0.33)</td>
<td>.78</td>
</tr>
<tr>
<td>Baseline HIV-1 RNA level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (reference)</td>
<td>0.39 ± 0.16 (0.06–0.71)</td>
<td>.019</td>
</tr>
</tbody>
</table>

**NOTE.** The parameter estimates of the reference case provide the modeled reduction in plasma HIV-1 RNA level at day 10 or 56, respectively, for a male subject entering the study with baseline virus level of 50,000 copies/mL. The parameter estimates for females shows the difference in virus level reduction compared with the reference group, and the additional reduction observed for each 1-log$_{10}$ increment in baseline HIV-1 RNA level (independent of sex). CI, confidence interval.
ences in expression of the nucleoside kinases [25]. Such differences in kinase activity could lead to heterogeneity in the extent of viral inhibition, resulting ultimately in less than complete inhibition of viral replication. Although differences in treatment adherence could potentially produce similar results, adherence rates were high and similar for subjects in all 3 blinded treatment groups [17]. Moreover, we controlled for this possibility by excluding from the analysis subjects who interrupted dosing of the study drug or who showed a non-monotonic decrease in plasma HIV-1 RNA levels.

The slower rate of viral decay in the triple-nucleoside group could contribute to a greater risk of virological failure if ongoing viral replication during the initial decay phase leads to selection of drug-resistant variants that might contribute to subsequent treatment failure. The finding that differences between treatment groups in the magnitude of the decrease in HIV-1 RNA levels during the first 7-10 days were more pronounced in subjects with higher virus levels suggests the possibility that slower viral decay allowed for the emergence of drug-resistant viruses during the first few weeks of treatment. It would be interesting to apply sensitive techniques for detecting the presence of minor drug-resistant variants to samples obtained during the decay phase to test this hypothesis.

Mean ± SD population estimates of initial viral decay rates in all 3 groups in our study (0.58 ± 0.06 to 0.70 ± 0.18/day) compare favorably with rates observed in other studies. First-phase decay rates of 0.47 ± 0.02 to 0.49 ± 0.04/day were reported in subjects beginning ritonavir monotherapy [19] or ABC plus a protease inhibitor [26]. The decay rates in our study were similar to those observed in subjects initiating lopinavir/ritonavir, EFV, 3TC, and tenofovir (0.62 ± 0.18/day) but were slower than in subjects in whom enfuvirtide was added as a fifth drug (0.80 ± 0.13/day) [27]. It has been suggested that differences in decay rates may predict subsequent longer term virologic responses and that adding additional antiretroviral drugs could improve viral decay rates [28]. However, adding drugs to a regimen may adversely affect adherence and increase toxicity, which may compromise longer term virologic responses. We did not find a significant evidence of an association between initial viral decay rate and treatment outcome in the present study, nor did the addition of a fourth drug (ABC) improve the efficacy of the 3-drug EFV regimen [18].

The results of the present study are similar to those reported in Pediatric ACTG (PACTG) trial 381, which compared the efficacy of ZDV/3TC plus EFV with that of ZDV/3TC plus nelfinavir in HIV-1–infected adolescents. In that study, first-phase decay rates of 0.62 ± 0.09 and 0.56 ± 0.10/day were reported for the EFV and nelfinavir groups, respectively [29]. As in the present study, PACTG 381 found that the treatment arm with the best virologic responses had the fastest first-phase decay. That study also noted a correlation between baseline plasma HIV-1 RNA levels and the first-phase decay rate. Although initial viral decay rates were not associated with baseline plasma HIV-1 RNA levels in the present study, we did find an interaction between baseline virus level and treatment group with respect to viral level reductions at day 10, which suggests that the difference in initial viral level reduction between the 3-drug EFV group and triple-nucleoside group was accentuated among individuals with higher virus levels.

No difference in first- or second-phase decay rates was observed between men and women receiving these regimens. A limitation of this finding is that baseline virus levels were comparable in male and female patients participating in the study. Therefore, our results do not preclude differences in viral dynamics at earlier times after initial infection, when sex-based differences in steady-state viremia are more pronounced [15].

In conclusion, faster initial viral decay in subjects randomized to a 3-drug EFV-based regimen corresponded to the overall superior efficacy of that regimen, compared with a triple-nucleoside regimen. Similarly, a lack of difference in viral decay between 3- and 4-drug EFV-based regimens also paralleled the lack of difference over the course of 3 years of follow-up. Although it is reasonable, from a pathogenesis point of view, to expect that differences in short-term viral decay rates among antiretroviral regimens would predict differences in long-term virologic responses, practical clinical issues (e.g., convenience and toxicity) complicate this assessment.

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Acknowledgments

We thank Bristol-Myers Squibb and GlaxoSmithKline for donating drugs for the study.

References