Outcomes by Sex Following Treatment Initiation With Atazanavir Plus Ritonavir or Efavirenz With Abacavir/Lamivudine or Tenofovir/Entecavir

Kimberly Y. Smith,1 Camlin Tierney,2 Katie Mollan,2,3 Charles S. Venuto,4 Chakra Budhathoki,2 Qing Ma,5 Gene D. Morse,6 Paul Sax,7 David Katzenstein,9 Catherine Godfrey,10 Margaret Fischl,11 Eric S. Daar,12 Ann C. Collier,13 and AIDS Clinical Trials Group 5202 Study Team

1Department of Medicine Division of Infectious Diseases, Rush University Medical Center, Chicago, Illinois; 2Statistical Data Analysis Center, Harvard School of Public Health, Boston, Massachusetts; 3Center for AIDS Research, University of North Carolina at Chapel Hill; 4Center for Human Experimental Therapeutics, University of Rochester, New York; 5Department of Pharmacy Practice and 6School of Pharmacy and Pharmaceutical Sciences, University of Buffalo, State University of New York; 7Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts; 8Department of Medicine, Division of Infectious Diseases, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts; 9School of Medicine, Division of Infectious Diseases, Stanford University, California; 10Division of AIDS, National Institutes of Health, Bethesda, Maryland; 11Department of Internal Medicine, University of Miami, Florida; 12Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, California; 13Department of Medicine, Division of Infectious Diseases, University of Washington Medical Center, Seattle

Background. We aimed to evaluate treatment responses to atazanavir plus ritonavir (ATV/r) or efavirenz (EFV) in initial antiretroviral regimens among women and men, and determine if treatment outcomes differ by sex.

Methods. We performed a randomized trial of open-label ATV/r or EFV combined with abacavir/lamivudine (ABC/3TC) or tenofovir/emtricitabine (TDF/FTC) in 1857 human immunodeficiency virus type 1–infected, treatment-naive persons enrolled between September 2005 and November 2007 at 59 sites in the United States and Puerto Rico. Associations of sex with 3 primary study endpoints of time to virologic failure, safety, and tolerability events were analyzed using Cox proportional hazards models. Model-based population pharmacokinetic analysis was performed using nonlinear mixed effects modeling (NONMEM version VII).

Results. Of 1857 participants, 322 were women. Women assigned to ATV/r had a higher risk of virologic failure with either nucleoside reverse transcriptase inhibitor backbone than women assigned to EFV, or men assigned to ATV/r. The effects of ATV/r and EFV upon safety and tolerability risk did not differ significantly by sex. With ABC/3TC, women had a significantly higher (32%) safety risk compared to men; with TDF/FTC, the safety risk was 20% larger for women compared to men, but not statistically significant. Women had slower ATV clearance and higher predose levels of ATV compared to men. Self-reported adherence did not differ significantly by sex.

Conclusions. This is the first randomized clinical trial to identify a significantly earlier time to virologic failure in women randomized to ATV/r compared to women randomized to EFV. This finding has important clinical implications given that boosted protease inhibitors are often favored over EFV in women of childbearing potential.

Clinical Trials Registration. NCT00118898.

Keywords. sex; atazanavir; efavirenz; abacavir; tenofovir.

The Department of Health and Human Services and the International Antiviral Society–USA treatment guidelines for human immunodeficiency virus type 1 (HIV-1) indicate that the best choices for first-line therapy include either efavirenz (EFV), raltegravir, or the ritonavir-boosted protease inhibitors (PIs) atazanavir (ATV/r) or darunavir combined with fixed-dose...
combination tenofovir (TDF) plus emtricitabine (FTC) [1, 2]. Women account for 27% of new HIV-1 infections in the United States [3]. With the exception of treatment during pregnancy, there is little in the published literature to suggest that the treatment of choice for treatment-naive patients should be determined by the patient’s sex [4]. A few adequately powered studies have examined association of sex with treatment outcome, with mixed results [5–7]. With women comprising a substantial proportion of HIV-1–infected persons in the United States and globally and given the importance of treatment efficacy for optimal long-term outcomes, improved understanding of responses to recommended regimens by sex is needed. This report summarizes preplanned analyses of AIDS Clinical Trials Group (ACTG) study A5202 to evaluate treatment effects on virologic failure, safety, and tolerability by sex.

METHODS

Study Design
A5202 was a phase IIIb, randomized, equivalence study of 4 regimens for initial treatment of HIV-1 conducted at 59 US and Puerto Rican ACTG sites. Eligible participants were enrolled from September 2005 to November 2007, had documented HIV-1, had undergone <8 days of previous antiretroviral therapy (ART), and were aged 16 years or older. Additional entry criteria have been published [8, 9]. The human subjects committees of all sites approved the A5202 protocol, and written informed consent was obtained from all participants in compliance with human experimentation guidelines of the US Department of Health and Human Services.

Participants were randomly assigned to 1 of 4 partially blinded once-daily regimens: open-label ATV (300 mg, Bristol-Myers Squibb, Plainsboro, New Jersey) plus ritonavir (100 mg, Abbott Laboratories, Abbott Park, Illinois) or EFV (600 mg, Bristol-Myers Squibb) with either placebo-controlled abacavir (ABC) 600 mg/lamivudine (3TC) 300 mg (GlaxoSmithKline, Research Triangle Park, North Carolina) or TDF 300 mg/FTC 200 mg (Gilead Sciences, Gilead Sciences, Foster City, California). Randomization was stratified by screening HIV-1 RNA level (<100 000 or ≥100 000 copies/mL). Further study details have been published previously [8–10].

Primary efficacy, safety, and tolerability endpoints were time to (1) virologic failure (VF; confirmed HIV-1 RNA ≥100 copies/mL at or after 16 weeks and before 24 weeks or ≥200 copies/mL at or after 24 weeks); (2) first grade 3 or 4 sign, symptom, or laboratory abnormality that was at least 1 grade higher than baseline, excluding unconjugated hyperbilirubinemia and creatine kinase; and (3) for the current analyses, change in assigned antiretroviral third agent, ignoring changes to nucleoside reverse transcriptase inhibitors (NRTIs).

ATV Pharmacokinetic Substudy
A sparse sampling strategy approach was designed for measuring steady-state plasma drug levels with an observed dose at 1 or 2 clinic visits during week 4, 8, 16, or 24. Samples were collected before the observed dose and 3–4 hours after the dose. A third blood sample was collected 5–15 hours after a dose. Atazanavir concentrations were measured using a previously reported and validated reverse-phase high-performance liquid chromatography method at the University at Buffalo, ACTG Pharmacology Specialty Laboratory [11].

Statistical Analysis
ACTG A5202 included a preplanned secondary objective to evaluate VF, safety, and tolerability by sex; however, the study was not specifically powered for this objective. A detailed description of the statistical analysis performed to assess the primary efficacy, safety, and tolerability endpoints has been published [8–10]. In brief, overall, ATV/r and EFV demonstrated similar antiviral activity when used with ABC/3TC or with TDF/FTC [9]. After interim review by an independent data safety and monitoring board showed a higher VF rate in subjects with screening HIV-1 RNA ≥100 000 copies/mL assigned to ABC/3TC compared to TDF/FTC (hazard ratio [HR] overall, 2.33 [95% confidence interval [CI], 1.46–3.72]), these groups were unblinded to their NRTIs [8]. Secondary analyses found that this effect differed by sex, and was larger among men (HR, 3.00 [95% CI, 1.74–5.17]) than women (HR, 0.85 [95% CI, 0.30–2.39]) with treatment × sex interaction P = .04 [8]. Subjects with screening HIV-1 RNA <100 000 copies/mL continued to be followed on blinded treatment through study’s end and had similar rates of VF in the NRTI groups [10]. Given these results, current analyses focus on the third drug (non-NRTI) comparison of ATV/r vs EFV, and these were carried out within each NRTI arm.

Analyses of VF were intent-to-treat, including all study HIV-1 RNA values starting at randomization; safety data were analyzed as-treated while on initially assigned third drug. Statistical significance level for treatment effect modification/interaction test was a priori set at 0.10. Time-to-event survival distributions were estimated by Kaplan-Meier method, and HRs were estimated with Cox proportional hazards models stratified by screening HIV-1 RNA level. Multivariable analyses were adjusted for baseline age, race/ethnicity (white, black, Hispanic; other racial groups were excluded due to small sample sizes), CD4+ lymphocyte count, plasma HIV-1 RNA, history of AIDS, chronic hepatitis B infection and hepatitis C, injection drug use history, and whether screening HIV-1 genotype was performed. Sensitivity analyses for VF included as-treated analyses. Adherence was categorized as 100% vs <100% based upon self-report over the preceding 7 days from each visit at weeks 8 and 24 and every 24 weeks thereafter. In post hoc analysis, association between sex and repeated
measurements of 100% vs <100% adherence at weeks 8, 24, 48, 72, and 96 was evaluated with a generalized estimating equation model with a logit link and compound symmetry covariance structure, adjusted for third drug.

Model-based population pharmacokinetic analysis was performed using nonlinear mixed effects modeling (NONMEM version VII). Individual ATV apparent oral clearance (CL/F) values were derived using Bayesian estimation from a 1-compartment population pharmacokinetic structural model. A separate model-independent analysis included ATV concentration data from subjects with assay results between 22 and 25 hours postdose (C_{24h}). Each subject’s ATV plasma concentration vs postdose time profile was reviewed for inconsistencies. Excluded were those without an ATV concentration between 22 and 25 hours postdose, those with only 1 evaluable ATV concentration, or those with obvious inconsistencies between concentration time points based on the known pharmacokinetic profile of ATV/r. If a subject had >1 evaluable trough concentration, results were averaged. The pharmacokinetic concentration data were natural log-transformed before statistical analysis.

RESULTS

Participant Characteristics

Table 1 compares baseline characteristics of male and female participants. Women were more likely to have reported black race, lower creatinine clearance (CrCl), and lower baseline HIV RNA, and less likely to have undergone genotyping at screening.

Primary Endpoint Analyses

In Figure 1, time-to-event distributions are illustrated for men and women for efficacy (Figure 1A), safety (Figure 1B), and tolerability (Figure 1C) endpoints. Figure 2 shows the results for efficacy, safety, and tolerability from Cox proportional hazards models by assigned treatment arm and sex. As-treated analyses showed similar results (data not shown).

Efficacy

With ABC/3TC

As shown in Figure 2A, overall ATV/r and EFV had similar virologic efficacy (HR, 1.13 [95% CI, .82–1.56]), [9] but there was a significant treatment effect interaction by sex ($P$ = .017). VF risk was higher among women randomized to ATV/r than to EFV, with incidence rates (IRs) per 100 person-years of 12.42 vs 4.86, respectively, and an HR of 2.55 (95% CI, 1.20–5.41). There was no significant difference in VF risk for men assigned to ATV/r vs EFV, with IRs of 7.41 and 7.77 per 100 person-years, respectively, and an HR of 0.94 (95% CI, .66–1.34); adjusted model showed similar results (interaction $P$ = .006; Figure 2A).

Comparing women to men, women randomized to ATV/r had higher VF hazard in multivariable models, with an HR of 1.72 (95% CI, .99–2.99; Figure 2B). Among those randomized to EFV, there was no significant evidence of increased VF risk in women vs men (Figure 2B).

Table 1. Baseline Characteristics by Sex

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men (n = 1535)</th>
<th>Women (n = 322)</th>
<th>Total (n = 1857)</th>
<th>$P$ Value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>38.1 (10.0)</td>
<td>39.5 (10.2)</td>
<td>38.4 (10.1)</td>
<td>.043</td>
</tr>
<tr>
<td>&gt;40 y, No. (%)</td>
<td>673 (44)</td>
<td>155 (48)</td>
<td>828 (45)</td>
<td>. . .</td>
</tr>
<tr>
<td>Race/ethnicity, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>689 (45)</td>
<td>57 (18)</td>
<td>746 (40)</td>
<td></td>
</tr>
<tr>
<td>Black, non-Hispanic</td>
<td>443 (29)</td>
<td>172 (53)</td>
<td>615 (33)</td>
<td></td>
</tr>
<tr>
<td>Hispanica</td>
<td>347 (23)</td>
<td>82 (25)</td>
<td>429 (23)</td>
<td></td>
</tr>
<tr>
<td>Otherb</td>
<td>51 (3)</td>
<td>11 (3)</td>
<td>62 (3)</td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA log_{10} copies/mL, mean (SD)</td>
<td>4.7 (0.7)</td>
<td>4.6 (0.7)</td>
<td>4.7 (0.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Screening HIV-1 RNA ≥100 000 copies/mL, No. (%)</td>
<td>676 (44)</td>
<td>121 (38)</td>
<td>797 (43)</td>
<td>.033</td>
</tr>
<tr>
<td>CD4+ cells/µL, mean (SD)</td>
<td>236 (170)</td>
<td>219 (148)</td>
<td>233 (167)</td>
<td>.256</td>
</tr>
<tr>
<td>CD4+ &lt;50 cells/µL, No. (%)</td>
<td>278 (18)</td>
<td>61 (19)</td>
<td>339 (18)</td>
<td>.104</td>
</tr>
<tr>
<td>Genotype results available at entry, No. (%)c</td>
<td>706 (46)</td>
<td>124 (39)</td>
<td>830 (45)</td>
<td>.009</td>
</tr>
<tr>
<td>History of AIDS, No. (%)</td>
<td>250 (16)</td>
<td>62 (19)</td>
<td>312 (17)</td>
<td>.195</td>
</tr>
<tr>
<td>Creatinine clearance &lt;90 mL/min, No. (%)</td>
<td>240 (16)</td>
<td>74 (23)</td>
<td>314 (17)</td>
<td>.002</td>
</tr>
</tbody>
</table>

Abbreviations: HIV, human immunodeficiency virus; SD, standard deviation.

a Regardless of race.

b Asian, Pacific Islander, Native American, or >1 race; excluded from analysis.

c Genotype was not required at screening, unless recently infected; creatinine clearance calculated based on Crockcroft-Gault equation.

** $P$ value based on Wilcoxon and $\chi^2$ test for continuous and categorical variables, respectively.
Figure 1. Time to virologic failure (A), safety (B), and tolerability (C) endpoints by sex. Abbreviations: ABC/3TC, abacavir/lamivudine; ATV/r, atazanavir/ritonavir; EFV, efavirenz; TDF/FTC, tenofovir/emtricitabine.
With TDF/FTC

Whereas overall ATV/r and EFV performed similarly (HR, 1.01 [95% CI, .70–1.46]) [9], there was a significant treatment effect interaction by sex (P = .028). The hazard of VF was higher among women randomized to ATV/r compared to EFV (HR, 2.16 [95% CI, .52–8.33]). There was no significant difference in VF hazard in men on ATV/r vs EFV (HR, 1.16 [97–4.08]). Comparing women to men, in multivariable models, women randomized to ATV/r had a higher risk of VF (HR, 2.36 [95% CI, 1.30–4.26]; Figure 2C). There was no significant evidence for increased VF in women compared to men randomized to EFV in univariate or multivariable models.

Safety

With ABC/3TC

Overall, subjects treated with ATV/r had a longer time to a safety endpoint than those treated with EFV (HR, 0.81 [95% CI, .66–1.00]) [9], and there was no significant evidence that this effect differed by sex (P = .49); IRs were 31.71 vs 33.96 for women and 20.81 vs 28.51 for men (Figure 2A).

Overall, compared to men, women had a shorter time to safety endpoint (HR, 1.32 [95% CI, 1.03–1.70]; Figure 2B). However, the risk of a safety endpoint for women compared to men on ATV/r (HR, 1.44 [95% CI, .98–2.10]) or EFV (HR, 1.20 [95% CI, .86–1.68]) did not differ statistically (Figure 2B).

Women assigned to ABC/3TC with ATV/r had a slightly higher incidence of grade 3–4 gastrointestinal safety endpoint compared to men on ATV/r (13% vs 7%) and to women receiving EFV (13% vs 6%) (Table 2).
**With TDF/FTC**

Overall, the time to a safety endpoint was not significantly different for subjects treated with ATV/r compared with those treated with EFV (HR, 0.91 [95% CI, 0.72–1.15]), [9] with no evidence of a difference by sex (Figure 2C); for women and men, the IRs were 21.36 vs 18.27 and 15.31 vs 18.01, respectively. Likewise, time to safety endpoint was not significantly different between women and men (Figure 2D). Safety endpoints are summarized by type in Table 2.

Grade 3–4 gastrointestinal events occurred with similar frequency in women (4%) and men (6%) receiving ATV/r with TDF/FTC (Table 2).

**Tolerability**

Primary tolerability endpoints (modification of ATV/r or EFV) data for AS202 have been published elsewhere [8, 9]. In summary, time to modification was significantly longer with ATV/r than EFV when combined with ABC/3TC (Figure 2A); there was no significant difference in time to modification with ATV/r or EFV plus TDF/FTC (Figure 2C). The third drug effect did not significantly differ by sex with either NRTI (Figure 2B and 2D). Comparing women to men, with either set of NRTIs, there was no apparent difference in time to discontinuation of either third drug (Figure 2B and 2D).

The most common reason for modification of a third drug was noncompliance with study medications or visits, which was identified in 7% of women and 10% of men.

**Pharmacokinetics Analyses for ATV**

The population model included 2195 ATV concentration values from 815 of 926 (88%) participants who initiated ATV. Parameter estimates for ATV obtained from the structural population pharmacokinetic model were clearance equal to 7.9 L/hour (95% CI, 7.6–8.2 L/hour), volume of distribution equal to 86 L (95% CI, 78–94 L), and absorption rate constant equal to 0.46 hour-1 (95% CI, 0.37–0.56 hour-1). ATV concentration trough (C24h) data were available from 358 of 926 subjects (39%). ATV oral clearance and trough concentrations were different for subjects treated with ATV/r compared with those treated with EFV (HR, 0.91 [95% CI, .72–.89]; however, there were no significant interactions between dual NRTIs and sex (P ≥ .10; Table 3).

**Self-reported Adherence and Virologic Failure by Sex**

**With ABC/3TC**

Reported rates of short-term 100% adherence at follow-up visits week 8 through 96 with EFV ranged from 87% to 93% in women and 89%–92% in men. Reported rates of 100% adherence in the ATV/r arm ranged from 80% to 92% in women and 87%–93% in men.

**With TDF/FTC**

Reported rates of 100% adherence at follow-up visits week 8 through 96 with EFV ranged from 85% to 97% in women and 92%–93% in men. Reported rates of 100% adherence with ATV/r with TDF/FTC ranged from 87% to 93% in women and 91%–92% in men.

**Association With Adherence**

Repeated measures analyses adjusted for third drug assignment and stratified by screening viral load showed no significant association between sex and reported adherence (100% vs <100%) over weeks 8, 24, 48, 72, and 96 with ABC/3TC (odds ratio [OR] for women vs men, 1.15 [95% CI, .83–1.60]; P = .42) or with TDF/FTC (OR, 1.19 [95% CI, .84–1.67]; P = .35), and no significant evidence that adherence differed by the third drug (P = .63 and .47 with ABC/3TC, P = .99 and .92 with TDF/FTC).

Subjects who reported <100% adherence and subjects not on ART at week 8 had increased risk of VF compared to those reporting 100% adherence: HR, 2.20 (95% CI, 1.35–3.56) and 4.85 (95% CI, 2.53–9.31), respectively, for ABC/3TC (P ≤ .0002); HR, 2.67 (95% CI, 1.54–4.62) and 4.89 (95% CI, 2.08–11.48), respectively, for TDF/FTC (P ≤ .0004), with no evidence that this adherence association differed by third drug (P = .26 for ABC/3TC, P = .35 for TDF/FTC).

**Table 2. Most Common Types of Grade 3–4 Safety Endpoints by Sex (While Initially Receiving Efavirenz or Atazanavir/Ritonavir)**

<table>
<thead>
<tr>
<th>Category</th>
<th>EFV + TDF/FTC</th>
<th>EFV + ABC/3TC</th>
<th>ATV/r + TDF/FTC</th>
<th>ATV/r + ABC/3TC</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men n = 390</td>
<td>Women n = 71</td>
<td>Men n = 366</td>
<td>Women n = 95</td>
<td></td>
</tr>
<tr>
<td>General body</td>
<td>35 (9%)</td>
<td>11 (15%)</td>
<td>54 (15%)</td>
<td>17 (18%)</td>
<td></td>
</tr>
<tr>
<td>Hematology</td>
<td>8 (2%)</td>
<td>6 (8%)</td>
<td>2 (1%)</td>
<td>5 (5%)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>21 (5%)</td>
<td>1 (1%)</td>
<td>17 (5%)</td>
<td>6 (6%)</td>
<td></td>
</tr>
<tr>
<td>Metabolic</td>
<td>23 (6%)</td>
<td>2 (3%)</td>
<td>45 (12%)</td>
<td>10 (11%)</td>
<td></td>
</tr>
<tr>
<td>Neuropsychologic</td>
<td>26 (7%)</td>
<td>2 (3%)</td>
<td>22 (6%)</td>
<td>6 (6%)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ABC/3TC, abacavir/lamivudine; ATV/r, atazanavir/ritonavir; EFV, efavirenz; TDF/FTC, tenofovir plus emtricitabine.
with ABC/3TC, \( P = .98 \) with TDF/FTC) or by sex (\( P = .32 \) with ABC/3TC, \( P = .27 \) with TDF/FTC).

**DISCUSSION**

This is the first randomized clinical trial (RCT) to identify a higher risk of VF in women assigned to an ATV/r-containing regimen compared to a regimen with EFV. In addition, we found that women in the ATV/r arms had higher VF risk and slower ATV clearance than men assigned to ATV/r.

Several meta-analyses of clinical trials and cohort studies have evaluated responses to ART comparing women and men. Some studies have suggested that women have higher rates of VF due to poorer adherence and complex socioeconomic factors, whereas other studies report comparable responses [5–7].

Few RCTs have had adequate enrollment of women to provide statistical power to allow comparisons of responses to specific antiretroviral agents between and within sex groups. ACTG A5202 enrolled 1857 participants, of whom 322 (17%) were women, making this the largest US-based randomized comparison of different antiretroviral regimens in HIV-1–infected women. Furthermore, this is one of the largest clinical trials comparing responses to specific modern antiretroviral regimens between HIV-1–infected women and men.

The finding of higher VF rates among women on ATV/r compared to EFV was unexpected. Previous clinical trials that compared virological responses with EFV-based regimens to PI-based regimens have had variable results by sex. For example, ACTG 384 randomized 980 persons to zidovudine plus 3TC, or stavudine plus didanosine, each combined with EFV, nelfinavir (NFV), or EFV plus NFV. Eighteen percent (n = 176) of participants were women. This study found no evidence of significantly different virologic responses by sex [12,13].

ACTG 5142 was an open-label randomized study that compared 3 regimens for initial therapy: EFV plus 2 NRTIs; lopinavir/ritonavir (LPV/r) plus 2 NRTIs; and LPV/r plus EFV [14]. The study enrolled 757 subjects, of whom 20% (n = 151) were women. In a multivariable Cox proportional hazards model stratified by baseline factors, women had a greater risk of VF than men (HR, 1.38 [95% CI, 1.01–1.89]) [14]. However, no significant differences were found in time to VF when comparing EFV to LPV/r in women [15].

We hypothesized that the higher VF rate in A5202 was related to lower adherence or tolerability of ATV/r in women. However, we found no evidence suggesting lower adherence in women on ATV/r compared to women on EFV or compared to men on ATV/r based upon a validated self-report questionnaire [16]. However, the adherence measure used has limitations as it is based upon self-report and was limited to the week preceding its completion.

We did not find a significant difference in safety or tolerability endpoints comparing ATV/r to EFV between men and women. There was trend evidence of higher frequency of grade 3–4 gastrointestinal events among women compared to men on ATV/r with ABC/3TC (Table 2), yet this pattern was not seen with TDF/FTC. Of note, not all grade 1 and 2 adverse events were collected in this study, so we cannot assess their contribution to adherence or virologic outcomes. Previous studies have demonstrated higher rates of gastrointestinal side effects in women than in men on ritonavir-boosted PIs. For example, in the Abbott study M98-863 (that compared LPV/r vs NFV, each

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### Table 3. Atazanavir Plasma Pharmacokinetics by Sex, and Nucleoside/Nucleotide Reverse Transcriptase Inhibitor Treatment Arms

<table>
<thead>
<tr>
<th>Group</th>
<th>Model-Based ATV CL/F</th>
<th>Observed ATV Ctrough (22–25 h Postdose)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>*aMean ATV CL/F, L/h (± SD)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>680</td>
<td>8.4 (2.4)</td>
</tr>
<tr>
<td>Women</td>
<td>135</td>
<td>7.6 (2.8)</td>
</tr>
<tr>
<td>TDF/FTC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>338</td>
<td>8.6 (2.3)</td>
</tr>
<tr>
<td>Women</td>
<td>68</td>
<td>8.0 (2.8)</td>
</tr>
<tr>
<td>ABC/3TC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>342</td>
<td>8.2 (2.4)</td>
</tr>
<tr>
<td>Women</td>
<td>67</td>
<td>7.2 (2.8)</td>
</tr>
</tbody>
</table>

*Abbreviations: ABC/3TC, abacavir/lamivudine; ATV, atazanavir; CL/F, oral clearance; Ctrough, trough serum concentration; SD, standard deviation; TDF/FTC, tenofovir/emtricitabine.

\(^a\) Arithmetic mean.

\(^b\) Geometric mean.

\(^c\) Satterthwaite t-test.

\(^d\) Interaction (sex nucleoside reverse transcriptase inhibitor treatment arm) \( P \) value.
with 2 NRTIs), women had similar response rates to men, but rates of nausea and dyspepsia were higher in women [17].

Although the cause of higher VF rates among women on ATV/r in our study is uncertain, our pharmacokinetic study findings that women had slower ATV clearance and higher mean before-dose ATV concentration suggests a hypothesis that higher ATV levels may lead to higher rates of low-level (unmeasured) toxicity that could affect outcomes. An exploratory analysis of A5202 pharmacokinetics trended in the direction of a greater risk of safety endpoint among subjects with slower ATV clearance, but this association did not reach statistical significance [18].

It is notable that in A5202 a greater proportion of women reported black race compared to men. It is possible that pharmacogenetic differences between racial groups could contribute to drug metabolism differences attributed to differences by sex. If this were the case, one would expect this difference to be demonstrated most significantly among the EFV-treated participants, as a higher prevalence of low EFV clearance has been described among blacks and Hispanics than whites [19]. However, we did not see differences in virologic outcomes or safety endpoints comparing women on EFV to men on EFV in our study. Pharmacokinetic differences in ATV/r metabolism among racial groups are less well described. In our pharmacokinetic substudy, there was evidence that ATV/r clearance was associated with VF and this association differed by sex and race; however, there was no significant evidence that the differential association of ATV/r clearance with VF by sex differed by race/ethnicity [18].

The results of this study offer new insight into potentially important sex-based differences in treatment outcomes with modern regimens for HIV treatment–naïve patients. This is the first RCT to identify a significantly greater risk of VF among women treated with ATV/r vs EFV in combination with ABC/3TC or TDF/FTC. These findings may have important clinical implications given that ritonavir-boosted PIs are often favored over EFV for women of childbearing potential. Moreover, ATV/r is currently a preferred treatment for pregnant women, and although EFV is listed under pregnancy risk category D, ATV/r is currently a preferred treatment for pregnant women, over EFV for women of childbearing potential.

Other investigators and contributors included the following: Hector H. Bolivar, MD, and Sandra Navarro, MD, University of Miami (Site 901) CTU Grant #AI069477; ACTG Grant #A27675, CFAR Grant #AI073961; Susan L. Koletar, MD, and Diane Gochnour, RN, The Ohio State University (Site 2301) CTU Grant #AI069474; Edward Seefried, RN, and Julie Hoffman, RN, UCSD (Site 701) CTU Grant #AI069432; Judith Feinberg, MD, and Michelle Saemann, RN, University of Cincinnati (Site 2401) CTU Grant #AI069513; Kristine Patterson, MD, Donna Pittard, RN, and David Currin, RN, University of North Carolina (Site 3201) CTU Grant #AI069423, CFAR Grant #AI054907, Grant #RR00051; Bartolo Santos, RN, and Connie A. Funk, RN, MPH, University of Southern California (Site 1201) CTU Grant #S01 AI069428; Michael Morgan, FNP, and Brenda Jackson, RN, Vanderbilt Translational Therapeutics CRS (Site 3652) CTU Grant #AI069439; Pablo Tesas, MD, and Aleshia Thomas, RN, University of PA, subunit of Children’s Hospital of Philadelphia (Site 6201) CTU Grant #U01 AI069467-03, CFAR Grant #5P30 AI045008-10; Ge-Hyoul Kim, RN, BSN, and Michael K. Klebert, PhD, RN, ANP-BC, Washington University (Site 2101) CTU Grant #AI069495; Jorge L. Santana and Santiago Marrero, University of Puerto Rico (Site 5401) CTU Grant #S03 AI069415-03; Jane Norris, PA-C, and Sandra Vallee, PA-C, Stanford University (Site 501) CTU Grant #AI069556; Gary Matthew Cox, MD, and Martha Silberman, RN, Duke University Medical Center (Site 1601) CTU Grant #S03 AI069484-02; Sadia Shaik and Ruben Lopez, Harbor-UCLA Medical Center (Site 603) CTU Grant #AI069424; Margie Vasquez, RN, and Demetres Daskalakis, MD, New York University/ NYCHC at Bellevue Hospital Center (Site 401) CTU Grant #AI069532; Christina Megill, RPA-C, and Todd Strober, RN, Cornell Chelsea (Site 7804) CTU Grant #AI069419; CTC Grant #RR024996; Jessica Shore, BSN, and Babafemi Taiwo, MBBS, Northwestern University CRS (Site 2701) CTU Grant #AI069471; Mitchell Goldman, MD, and Molly Bostom, RN, Indiana University (Site 2601) CTU Grant #U01 AI025859; Dr Jeffrey Lennox and Dr Carlos del Rio, The Ponce de Leon Center (AS082) CTU Grant #S03 AI069418,CFAR Grant #S03 AI050490; Timothy W. Lane, MD, and Kim Epperson, RN, Moses H. Cone Memorial Hospital (Site 3203) CTU Grant #S01 AI069423-01; Annie Luetkenmeyer, MD, and Mary Payne, RN, UCSF (Site 801) CTU Grant #S01 AI069502-01; Barbara Gripshover, MD and Dawn Antosh, RN, Case Western Reserve University (Site 2501) CTU Grant #AI069501; Jane Reid RN, MS, APN-BC, and Mary Adams, RN, MPH, University of Rochester (Site 1101) CTU Grant #U01 AI069511, GCRC Grant #UL1 RR024160; Sheryl S. Storey, PA-C, Sheila B. Dunaway, MD- University of Washington (Site 1401) CTU Grant #AI069434; Joel Gallant, MD, and Ilene Wiggins, RN, Johns Hopkins University (Site 201) CTU Grant #AI069465; Kimberly Y. Smith, MD, MPH, and Joan A. Swiatek, RN, AP, Rush University Medical Center (Site 2702) CTU Grant #S03 AI069471; Joseph Timpong, MD, and Princy Kumar, MD, Georgetown University (Site 1008) CTU Grant #S03 AI069494-01; Ardis Moe, MD, Maria Palmer PA-C, UCLA Care Center (Site 601) CTU Grant #AI069424; Jon Gowing, RN, BSN, ACRN, and Joanne Delaney, RN, BSN, Brigham and Women’s Hospital Boston MA (Site 107) CTU Grant #AI069472; Kim Whitley, RN, and Ann Marie Anderson, RN, Metro Health Center (Site 2503) CTU Grant #AI069501; Scott M. Hammer and Michael T. Yin, HIV Prevention & Treatment (Columbia University) (Site 30329) CTU Grant #S01 AI069470, Grant #S01 UL1 RR024156; Manta Jain, MD, and Tianna Petersen, MSUT Southwestern Medical Center at Dallas (Site 3751) CTU Grant #S01 AI046376 05S4; Roberto Coresales, DO, and Christine Hurley, RN, AIDS Community Health Center (Site 1108) CTU Grant #U01 AI069511, GCRC Grant #UL1 RR024160; Keith Henry, MD, and Bette Bordenave, RN, and Babafemi Taiwo, MBBS, Northwestern University CRS (Site 2701) CTU Grant #U01 AI069472; Richard B. Pollard, MD, and Abimbola Olusanya, NP, University of California, Davis Medical Center (Site 3851) CTU Grant #AI38885;
Paul R. Skolnik, MD, and Betty Adams, RN, Boston Medical Center CRS (Site 104) CTU Grant #A1069472; Karen T. Tashima and Helen Patterson, The Miriam Hospital–Brown University (Partners/Harvard) (Site 2951) CTU Grant #U101 A1069472-01; Michelle Ukewu and Lauren Rogers, Peabody Health Center (Site 31443) CTU Grant #A1069471; Henry H. Balfour Jr, MD, and Kathy A. Fox, RN, MBA, University of Minnesota (Site 1501) CTU Grant #AI27661; Susan Swindells, MBBS, and Frances Van Meter, APRN, University of Nebraska Medical Center (Site 1505) CTU Grant #AI27661; University of Hawaii (Site 5201) CTU Grant #AI134853; Gregory Robbins, MD, and APRN, Burgett-Yandoo, RN, BSN, Massachusetts General Hospital from the Partners/Harvard/BMC ACTU (Site 101) CTU Grant #U101 A1069472-01; Dr Charles E. Davis Jr and Colleen Boyce, RN, IHV Baltimore Treatment Center (Site 4651) CTU Grant #U101 A1069447 03; William A. O’Brien, MD, and Gerianne Casey, University of Texas Medical Branch (Site 6301) CTU Grant #A1032782; Dr Gene D. Morse, PharmD, and Dr Chiu-Bin Hsiao, MD, SUNY-Buffalo (Site 1102) CTU Grant #U101 A1027658; San Mateo County AIDS Program (Site 505) CTU Grant #AI27666; Jeffrey L. Meier and Jack T. Stapleton, University of Iowa Healthcare (Site 1504) NIAID Grant #AI27661 and Grant #AI58740; Donna Maldovan, MD, and Manuel Revuelta, MD, Beth Israel Medical Center ACTU (Site 2851) CTU Grant #AI46370; David Currin, RN, Wake County HHS (Site 30076) CTU Grant #AI25868; Wafaa El Sadr, MD, MPH, MPA, and Avelino Loquere, RN, Harlem ACTG CRS (Site 31483) CTU Grant #U101 A1069470-03; Nyef El-Daher, MD, and Tina Johnson, RN, McCree McCuller Wellness Center (Site 1107) CTU Grant #U101 A1069511, GCR Center #UL1 RR024160; Robert Ross GD, MSCE, and Kathryn Maffei, RN, BSN, University of Pennsylvania Health (Site 6206) CTU Grant #U101 A109467-01; Valery Hughes, FNP, and Glenn Sturge, BS, Cornell Uptown (Site 7803) CTU Grant #U101 A1069419-01; Deborah McMahon, MD, and Barbara Rutecki, CRNP, MHP, University of Pittsburgh (Site 1001) CTU Grant #U101 A1069494-01; Michael Wulfsohn, MD, PhD, Andrew Cheng, MD, PhD, Norbert Bischofberger PhD, Gilead Sciences; Lynn Dix, PhD, and Qiming Liao, PhD, GileadSmithKline, Inc.

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