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

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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.

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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 ≥1000 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, .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

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

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

[a] Regardless of race.

[b] Asian, Pacific Islander, Native American, or >1 race; excluded from analysis.
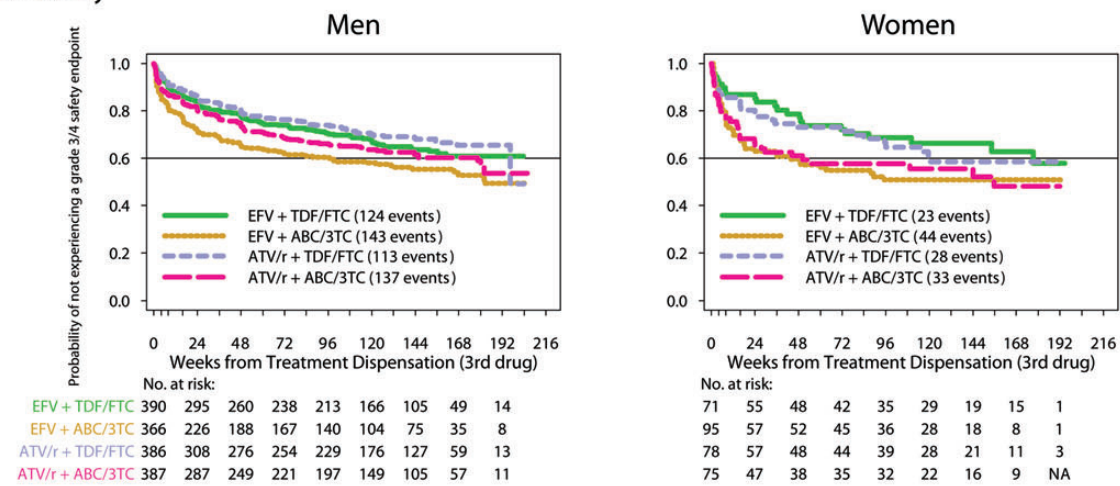
[c] Genotype was not required at screening, unless recently infected; creatinine clearance calculated based on Crockcoft-Gault equation.

** P value based on Wilcoxon and χ^2 test for continuous and categorical variables, respectively.

A Virologic Failure
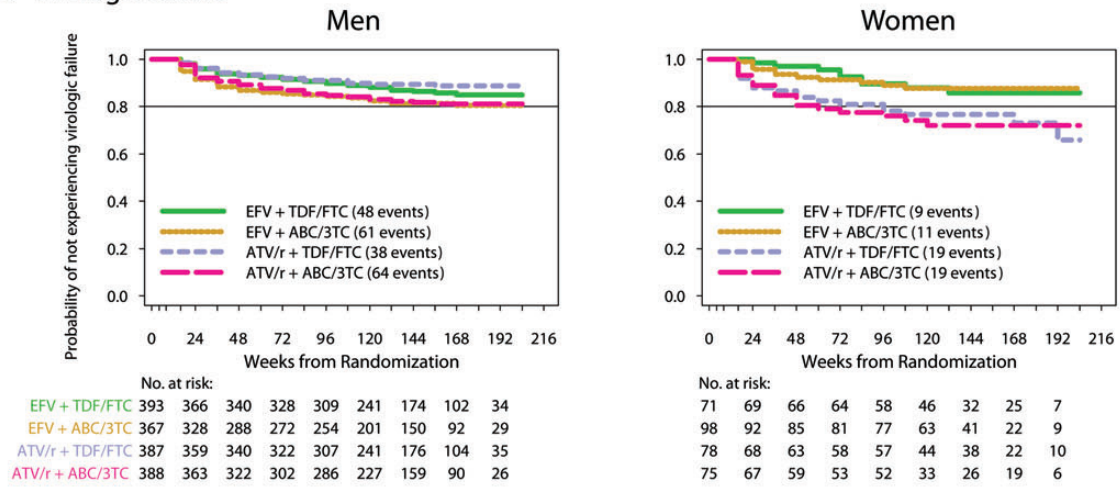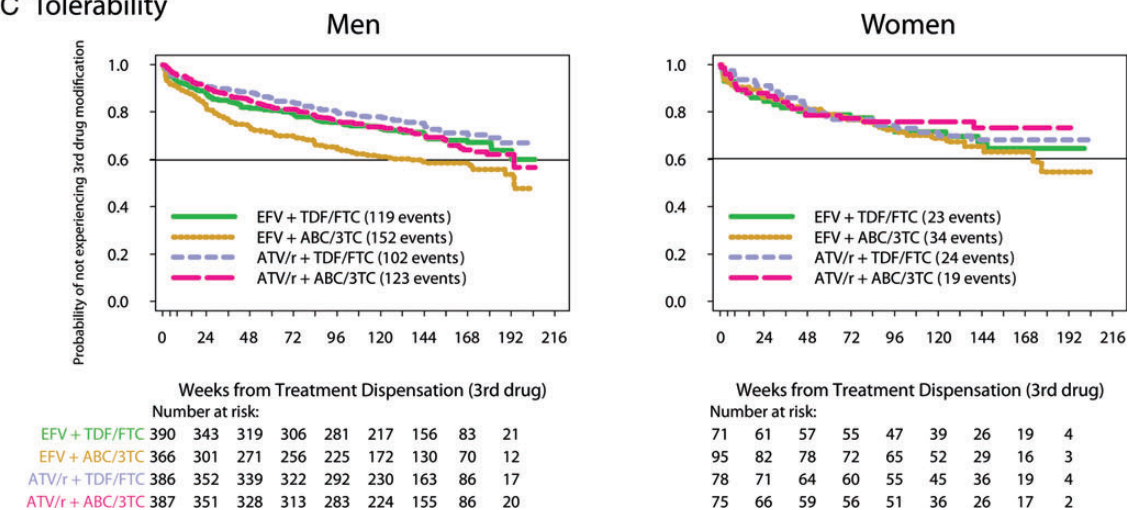

B Safety

C Tolerability

Figure 1. Time to virologic failure (*A*), safety (*B*), and tolerability (*C*) endpoints by sex. Abbreviations: ABC/3TC, abacabir/lamivudine; ATV/r, atazanavir/ritonavir; EFV, efavirenz; TDF/FTC, tenofovir/emtricitabine.
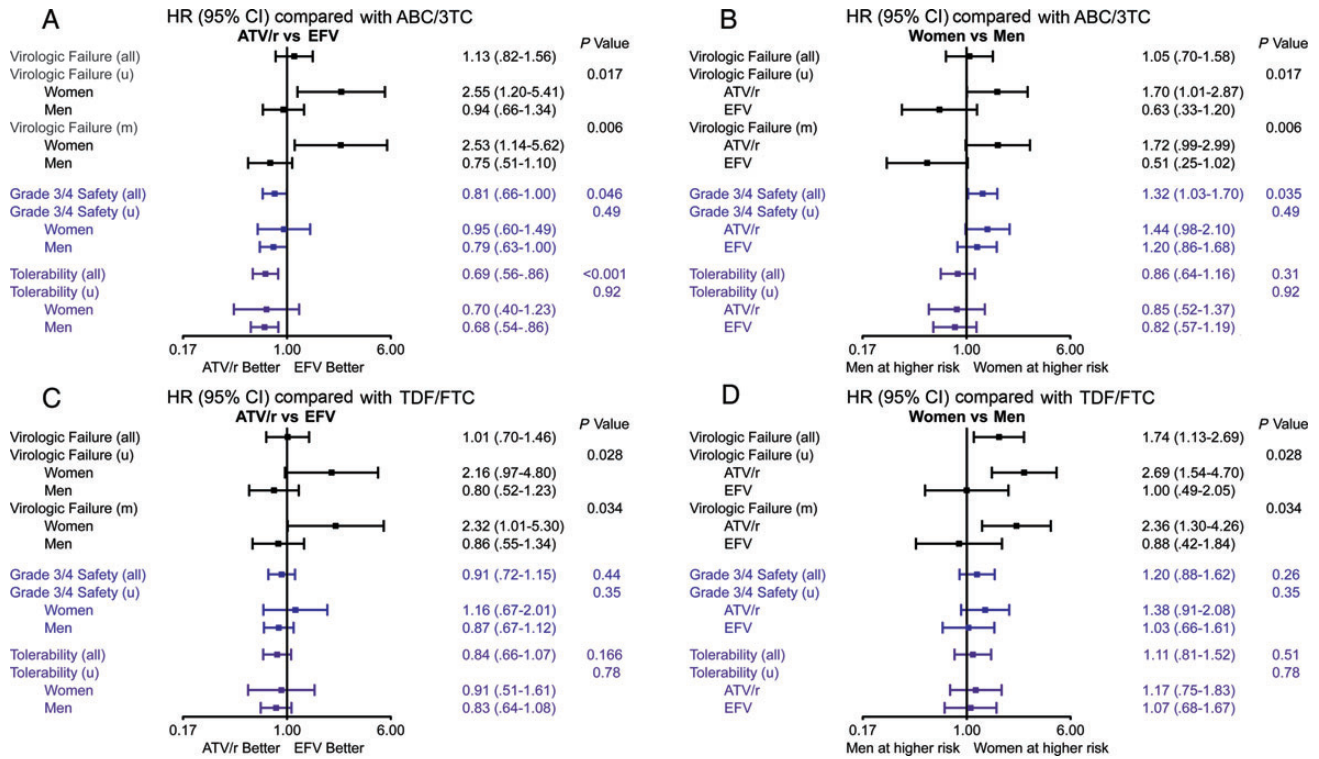
Figure 2. Treatment and sex comparisons for virologic failure, safety, and tolerability endpoints. *A*, Subjects on abacavir and lamivudine (ABC/3TC), comparing atazanavir (ATV) vs efavirenz (EFV). *B*, Subjects on ABC/3TC, comparing women vs men. *C*, Subjects on tenofovir and emtricitabine (TDF/FTC), comparing ATV vs EFV. *D*, Subjects on TDF/FTC, comparing women vs men. Univariate analysis (u) stratified by screening human immunodeficiency virus type 1 (HIV-1) RNA, and based on all available data for the covariate. Multivariable (m) analyses were adjusted for race/ethnicity (white, black, Hispanic), intravenous drug use, HIV-1 drug resistance genotype screening, age quartiles, CD4 cell count (4 categories), HIV-1 RNA level (4 categories), history of AIDS-defining event, and hepatitis B or C. Multivariable analysis excluded participants of "other" race/ethnicity due to small numbers. *P* value: likelihood ratio test, for main effect in "overall" results, and interaction tests otherwise. All models are stratified by screening HIV-1 RNA group (<100 000 or ≥100 000 copies/mL); univariate and multivariable adjusted estimates are based on interaction model; treatment effects by sex and sex associations by treatment are derived from the same model. Abbreviations: ABC/3TC, abacabir; lamivudine; ATV/r, atazanavir/ritonavir; CI, confidence interval; EFV, efavirenz; HR, hazard ratio; 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 (IR, 10.90 vs 5.06 per 100 person-years; HR, 2.16 [95% CI, .97–4.80]). There was no significant difference in VF hazard in men on ATV/r vs EFV (IR, 4.17 vs 5.23 per 100 person-years; HR, 0.80 [95% CI, .52–1.23]); the adjusted model showed similar results (Figure 2*C*).

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 2*D*). 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 2*A*).

Overall, compared to men, women had a shorter time to safety endpoint (HR, 1.32 [95% CI, 1.03–1.70]; Figure 2*B*). 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 2*B*).

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, .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 A5202 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, .37–.56 hour-1). ATV concentration trough (C_{24h}) data were available from 358 of 926 subjects (39%). ATV oral clearance and trough concentrations were different by sex, with women having a higher exposure to ATV

than men (Table 3). The average CL/F of ATV in men was 0.8 L/hour (95% CI, .3–1.3 L/hour) faster than in women. The geometric mean ratio of the ATV C_{24h} for men to women was 0.72 (95% CI, .58–.89); however, there were no significant interactions between dual NRTIs and sex ($P \geq .10$; 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 ($P \leq .0002$); HR, 2.67 (95% CI, 1.56–4.62) and 4.89 (95% CI, 2.08–11.48), respectively, for TDF/FTC ($P \leq .0004$), with no evidence that this adherence association differed by third drug ($P = .26$

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

Category	EFV + TDF/FTC Men n = 390	EFV + TDF/FTC Women n = 71	EFV + ABC/3TC Men n = 366	EFV + ABC/3TC Women n = 95	ATV/r + TDF/FTC Men n = 386	ATV/r + TDF/FTC Women n = 78	ATV/r + ABC/3TC Men n = 387	ATV/r + ABC/3TC Women n = 75	Total Men n = 1529	Total Women n = 319
General body	35 (9%)	11 (15%)	54 (15%)	17 (18%)	45 (12%)	14 (18%)	56 (14%)	8 (11%)	190 (12%)	50 (16%)
Hematology	8 (2%)	6 (8%)	2 (1%)	5 (5%)	11 (3%)	4 (5%)	6 (2%)	0 (0%)	27 (2%)	15 (5%)
Gastrointestinal	21 (5%)	1 (1%)	17 (5%)	6 (6%)	22 (6%)	3 (4%)	28 (7%)	10 (13%)	88 (6%)	20 (6%)
Metabolic	23 (6%)	2 (3%)	45 (12%)	10 (11%)	20 (5%)	6 (8%)	41 (11%)	8 (11%)	129 (8%)	26 (8%)
Neuropsychologic	26 (7%)	2 (3%)	22 (6%)	6 (6%)	10 (3%)	0 (0%)	8 (2%)	6 (8%)	66 (4%)	14 (4%)

Abbreviations: ABC/3TC, abacavir/lamivudine; ATV/r, atazanavir/ritonavir; EFV, efavirenz; TDF/FTC, tenofovir plus emtricitabine.

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

Group	Model-Based ATV CL/F			Observed ATV C_{trough} (22–25 h Postdose)		
	No.	[a]Mean ATV CL/F, L/h (± SD)	P Value	No.	[b]Mean ATV C_{trough}, ng/mL (Range)	P Value
Overall						
Men	680	8.4 (2.4)	.004[c]	299	562 (108–3782)	.003[c]
Women	135	7.6 (2.8)		59	783 (638–960)	
TDF/FTC						
Men	338	8.6 (2.3)	.3[d]	147	574 (108–3782)	.1[d]
Women	68	8.0 (2.8)		26	670 (125–2500)	
ABC/3TC						
Men	342	8.2 (2.4)		152	550 (125–3391)	
Women	67	7.2 (2.8)		33	886 (124–4985)	

Abbreviations: ABC/3TC, abacavir/lamivudine; ATV, atazanavir; CL/F, oral clearance; C_{trough}, 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 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 response rates 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

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 slow 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–naive 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, the recent perinatal guidelines have been modified to allow women who become pregnant while taking EFV to remain on this agent as the greatest teratogenicity risk appears to be in the early first trimester. EFV is also a now recommended as a treatment option for pregnant women who initiate ART after the first trimester [20]. The findings of the current study should warrant additional investigation of antiretroviral regimens in RCTs and cohorts with large enrollment of women.

Notes

References

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