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Differences in Antiretroviral Safety and Efficacy by Sex in a Multi-national Randomized Clinical Trial

Cynthia Firnhaber, MD, MS, DTM&H[1,2,*], **Laura M. Smeaton, MS**[3], **Beatriz Grinsztejn, MD, PhD**[4], **Umesh Lalloo, MBChB, FCP, MD**[5], **Sharla Faesen, MBBCh**[1], **Wadzanai Samaneka, MBChB, MSc**[6], **Rosa Infante**[7], **Aadia Rana, MD**[8], **Nagalingeswaran Kumarasamy, MBBS, PhD**[9], **James Hakim, MBChB, FRCP**[6], **Thomas B. Campbell, MD**[10], and **for the PEARLS study team^**

[1]Department of Internal Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

[2]Right to Care Johannesburg, South Africa

[3]Center for Biostatistics in AIDS Research, Harvard School of Public Health, Boston, United States of America

[4]Evandro Chagas Clinical Research Institute, Fiocruz, Rio de Janeiro, Brazil

[5]Durban University of technology, Durban, South Africa

[6]University of Zimbabwe College of Health Sciences, Harare, Zimbabwe

[7]IMPACTA Peru, San Miguel, Peru

[8]Alpert Medical School of Brown University, Providence, Rhode Island, United States of America

[9]YRGCARE Medical Centre, VHS, Chennai, India

[10]Division of Infectious Diseases, Department of Medicine, University of Colorado School of Medicine, Aurora, United States of America

INTRODUCTION

Approximately half of the 35 million people living with human immunodeficiency virus type 1 (HIV-1) are women and the majority live in resource-limited settings (RLS) [1]. Although women account for a substantial proportion of the global population infected with HIV, they are underrepresented in clinical trials of antiretroviral therapy and current HIV-1

*Corresponding author. Mailing Address: Helen Joseph Hospital Perth Road, Westdene 2092, cindy.firnhaber@righttocare.org.
^Additional members of the AIDS Clinical Trials Group PEARLS Team are listed after the text.

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Consent and manuscript consort check list:

Informed consent was obtained from all participants and the human experimentation guidelines of the U.S. Department of Health and Human Services were followed. The study was approved by local site institutional review boards and ethics committees. CONSORT check list was used in the preparation of this manuscript.

Three authors have declaration none which influence the outcome of this analysis. Ms Laura Smeaton worked as a consultant for Pfizer within a different population and disease. Dr Thomas Campbell is a consultant for Gilead and Dr Umesh Lalloo has either active or pending grants with Astra—Zeneca, Cipla and Rambaxy.

treatment practices are based largely on data from Caucasian male populations [2, 3]. Women pass through different stages during their lives such as pregnancy and menopause which could affect drug metabolism and consequently therapeutic response [4, 5]. Unfortunately, little is known about sex difference associated with responses to antiretroviral therapy, especially for women from diverse racial and ethnic groups in resource limited countries.

Existing studies of whether there are sex-based differences in antiretroviral therapy outcomes have had different conclusions. Some published literature suggest differences between women and men in the pharmacokinetics, efficacy and safety of antiretroviral therapy [6, 7]. Post hoc and secondary analyses of other studies have not identified sex-based differences in the efficacy and safety of antiretrovirals [8, 9]. Other, mainly observational studies have reported a higher frequency of antiretroviral-related adverse effects in women, such as increased risk for lactic acidosis, nevirapine-associated rashes and fat redistribution [10–15].

Additional data from large randomized clinical trials with study populations representative of the worldwide epidemic of HIV-1 infection are needed to better inform guidelines for antiretroviral use in men and women. The objective of this post-hoc analysis was to investigate the effects of sex on antiretroviral efficacy and safety, and participant retention in a randomized clinical trial of initial antiretroviral therapy, the Prospective Evaluation of Antiretrovirals in Resource Limited Settings (PEARLS) study of the AIDS Clinical Trials Group (ACTG study A5175), which a high proportion of women from diverse settings with randomized assignment of antiretroviral regimens [16].

METHODS

Design Overview and Patient Setting/ Participation

The parent PEARLS study enrolled 1,571 antiretroviral-naïve participants with CD4+ lymphocyte count <300 cells/mm^3 from nine countries (Brazil, Haiti, India, Malawi, Peru, South Africa, Thailand, the United States and Zimbabwe) from May 2005 to August 2007 and followed participants until May 2010 [16]. Women who received prior single dose nevirapine or zidovudine for prevention of mother-to-child transmission of HIV-1 (pMTCT) were included. Women who used two or more antiretroviral drugs for pMTCT for more than seven days within the prior six months were excluded. Potential participants were also excluded if they had an acute illness, opportunistic infection with less than two weeks of treatment, pregnant, chemotherapy or radiation therapy or a laboratory values > grade 2 per the DAIDS toxicity table 2004 within the prior 45 days [17]. Informed consent was obtained from all participants and the human experimentation guidelines of the U.S. Department of Health and Human Services were followed. The study was approved by local site institutional review boards and ethics committees. The CONSORT check list was used in the preparation of this manuscript.

Randomization and Intervention

Study participants were randomly assigned with equal probability within country and HIV-1 viral load strata (<100,000 copies/ml versus ≥100,000 copies/ml) to one of three open-label antiretroviral regimens: efavirenz plus co-formulated lamivudine-zidovudine (EFV+3TC-ZDV), atazanavir plus didanosine-EC plus emtricitabine (ATV+DDI-EC+FTC), or efavirenz plus co-formulated emtricitabine-tenofovir-DF (EFV+FTC-TDF). Atazanavir without boosting was used in naïve patients as this was an approved use of Atazanavir during the time the study was conducted.

Outcomes and Follow-up

The primary endpoint of the parent PEARLS study was treatment failure defined as the time from randomization to first occurrence of one of the following: 1) virologic failure defined as two successive measurements of plasma HIV-1 RNA ≥1000 copies/mL starting at study visit week 16 or later, 2) HIV-1 disease progression; or 3) death due to any cause. The primary safety endpoint was time from randomization to first occurrence of one of the following: 1) onset of first grade ≥3 (at least one grade higher than entry) sign/symptom, 2) first laboratory abnormality grade ≥ 3 (at least one grade higher than entry), or 3) last dose of antiretrovirals before regimen change. Hyperbilirubinemia from atazanavir was not considered in the study as a safety endpoint as this is an expected effect of this drug. Participants who did not meet the efficacy or safety endpoint were censored at the earliest of the last study visit that the following occurred: viral load measured, last study visit for safety endpoint assessment or final medication dose. Premature study discontinuation occurred when the last study visit occurred prior to the study close-out period (April – May 2010) [16].

Study Oversight and Monitoring

The United States National Institute of Allergy and Infectious Diseases (NIAID) Multinational Data Safety Monitoring Board reviewed safety and efficacy at least yearly. During a routine review (May 22, 2008), the ATV+DDI-EC+FTC regimen was found to be significantly inferior in efficacy compared to EFV+3TC-ZDV, participants receiving ATV +DDI-EC+FTC were placed on an alternative antiretroviral regimen and followed [16].

Statistical Analysis

A secondary analysis of the primary study was performed to evaluate sex-based comparisons on the primary efficacy, safety, and retention outcomes, and their components. For evaluation of virologic failure on the arm that was stopped early (ATV+DDI-EC+FTC), participants who had not already experienced virologic failure became at risk for this outcome at the 16 week visit following initiation of the subsequent antiretroviral regimen, and respective failure/censoring times were calculated from randomization. Distributions of pretreatment/entry characteristics were compared between sexes using Wilcoxon rank sum test for continuous variables and Chi-Square tests for categorical variables.

Sex differences for time-to-event outcomes were assessed using Cox proportional hazard models stratified by country and screening HIV RNA group. Direction and magnitude of sex differences were estimated with hazard ratios (HR) and associated 2-sided, 95% confidence

intervals (CI). Other covariates, including age at entry, race, ethnicity, pretreatment (screening) CD4+ cell count, entry HIV-1 RNA viral load, weight, body mass index (BMI), AST, ALT, history of antiretroviral use, Karnofsky score and body measurements were added to the basic model and tested to be retained in the model using a backward selection method (using a significance level of .05 to remain in the model), in order to arrive at a multivariable model with adjusted hazard ratios (aHR). In all analyses, treatment arm was included by randomized allocation and analyzed using intent-to-treat principle.

Among women, Fisher's exact test explored the association between treatment failure outcome and each of its three components, between those who had prior antiretroviral experience for pMTCT versus those who did not. Among the subgroup of women with reproductive potential, Fisher's exact test evaluated the association of treatment failure, virologic failure and safety outcome, between women who became pregnant post study entry but before the outcome of interest (and regardless of pregnancy outcome), versus those who did not. Pregnancy absolute incidence rate and relative ratio among categories of entry age, randomized regimen and screening CD4 groups were explored by the event count data model (i.e. Poisson regression). Piecewise (2-phase with knot at week 24) linear longitudinal models of CD4+ cell count levels over time were estimated in order to examine if sex effects on CD4+ counts over time persisted after adjusting for the randomized regimen, pretreatment CD4+ count, and country.

RESULTS

Patient Enrollment and Follow-up

Of 1,571 participants enrolled, 47.0% (N=739) were women. Women were younger than men (median 33 vs. 35 years P<0.001). Womens 'median pretreatment CD4 count (182 cells/mm^3) was higher and HIV plasma HIV-1 RNA (4.9 $\log_{10}$ copies/mL) lower when compared to men (165 cells/mm^3; P<0.001 and 5.2 $\log_{10}$copies/mL; P<0.001, respectively). Proportion with a prior or current AIDS defining illness was lower in women (6.6% versus 14.5%; P<0.001) (see Table 1 and reference 18 for more entry characteristics by sex).

Premature study discontinuation occurred in (9.5%, N=150/1571) of the participants. The most common reason for leaving the study before treatment failure was not being able to return to clinic (37.3% N=56/150) (Figure 1). Women were less likely to prematurely discontinue study treatment (aHR =0.74; 95% CI 0.56–0.98, adjusted for age, plasma HIV RNA and Karnofsky score) or study participation (aHR=0.75; 95% CI 0.56–1.00, adjusted for age, Karnofsky score and ethnicity) and the risk of premature treatment discontinuation and premature participation discontinuation did not vary significantly by treatment arm (p=0.70 and 0.90 respectively).

Efficacy Outcomes

While approximately 20% of both women and men experienced a treatment failure outcome, this significantly differed among the three treatment groups (interaction p = 0.020; Table 2) Within ATV+DDI-EC+FTC there was a statistically significant longer time to treatment

failure in women compared to men aHR 0.59 (CI 0.40, 0.87). However, there was no difference in time to treatment failure within the other two ARV treatment arms (Table 2).

From further evaluation of the three components of treatment failure, women assigned to ATV+DDI-EC+FTC arm had lower and slower rates of virological failure as compared to men (aHR =0.56; 95% CI 0.36, 0.86; Table 2). These estimated effects for virological failure were similar in adjusted models controlling for possible confounding factors including age, screening CD4 and self-reported race (Table 2). There was not a significant sex difference (or evidence of sex by treatment interactions) for the two other definitions of treatment failure: Time to HIV disease progression or Time to death (Table 2). There were a relative small number of events for each of these two outcomes.

Without adjustment for treatment arm, pretreatment CD4+ count or country, the estimated (or modeled) mean absolute CD4+ cell counts were 16 cells/mm^3 (95% CI 8, 25) higher in women compared to men over time. However, when pretreatment CD4+ cell count was added to the model, the sex effect on absolute CD4+ count over follow-up was no longer statistically significant (mean difference between sexes <1 cell/mm^3 per week; p=0.80; Figure 2).

Safety Outcomes

For the primary safety outcome, differences by sex varied significantly by treatment arm (interaction p=0.002). Within the EVF+3TC-ZDV arm, women had a significantly higher rate and shorter time to a primary safety event (aHR= 1.49; 95% CI 1.18, 1.88). This effect remained after adjusting for potential confounders such as entry AST value, self-reported ethnic group and anthropometric measurement (Table 2). However, in the other two arms, there was not a difference in the primary safety outcome by sex: ATV+DDI-EC+FTC (aHR=0.82; 95% CI 0.64, 1.05), EFV+FTC/TDF (aHR= 0.91; 95% CI 0.70, 1.19) (Table 2). There was not a difference by sex (or sex by treatment interaction) for either the sign or symptom component (aHR= 1.05; 95% CI 0.82, 1.35), or overall laboratory abnormality component (HR=0.8; 95% CI 0.7, 1.1) of the primary safety outcome (Table 2). Therefore, the effect in the primary safety outcome appeared to be a result of a sex by treatment difference in the first dose modification component of the outcome (interaction p=0.060). Adjusting for screening CD4, age and entry Karnofsky score, within EVF+ZDV-3TC, women were more likely to have a dose modification compared to men (HR =1.4; 95% CI 1.0, 1.8) most likely due to neutropenia caused by ZDV. However, among the other arms, there was not a difference in risk of dose modification by sex EVF+FTC-TDF (HR = 0.9; 95% CI 0.68, 1.35) / ATV+DDI-EC+FTC (HR= 0.84; 95% CI 0.62, 1.14).

Pregnancy/Prevention Mother to Child Transmission (PMTCT)

Among women with reproductive potential, the incidence of pregnancy was 2.7 per 100 women years (95% CI 2.2, 3.4). Women who were randomly assigned to an efavirenz containing study regimen were required to use two forms of birth control, which may have decreased the overall pregnancy incidence in this study. Women were tested for pregnancy at every study visit; therefore early pregnancy which may have resulted in miscarriage may have been over-represented in this study. Pregnancy outcomes from this study have been

reported elsewhere [19]. There was not a significant difference in pregnancy incidence among the three regimen arms (p=0.38) nor an association between pregnancy and CD4+ cell count (p>0.30). Primary efficacy or primary safety outcomes were not significantly associated with a proceeding pregnancy diagnosis (data not shown). There was no difference in treatment failure between the small subgroup of women who had limited PMTCT (17.2%; 10 of 58), as allowed by the protocol, and those women who did not have PMTCT experience (19.4%; 132 of 681; p=0.86).

CONCLUSIONS

PEARLS evaluated the efficacy and safety of initial antiretroviral therapy in a prospective clinical trial conducted in high-, medium- and low-income countries in Africa, Asia, the Caribbean and North and South America. To our knowledge, PEARLS is the only randomized clinical trial to recruit a near equal number of men and women from these diverse cultural, socioeconomic and geographic settings. The randomized assignment of initial antiretroviral therapy to a large and equal number of women and men in PEARLS provided a unique opportunity to evaluate potential associations between sex and antiretroviral therapy efficacy and safety outcomes. In this context, we found significant differences in both antiretroviral efficacy and safety, and in study retention, between women and men.

Among participants assigned to an antiretroviral regimen of ATV+DDI-EC+FTC, women had decreased risk of treatment failure compared to men. In contrast, the risk of treatment failure did not differ by sex for participants assigned to initial antiretroviral regimens of efavirenz with either co-formulated lamivudine or emtricitabine-tenofovir-DF. Several previous studies with smaller sample sizes conducted in developed country settings have not shown sex-related differences in immunological and virological outcomes of antiretroviral therapy [20–24]. In contrast to the findings in PEARLS, a large randomized study of antiretroviral naive men and women in the United States (A5202), found that women randomized to ritonavir-boosted atazanavir had poorer efficacy outcomes, with a 2.5 times higher rate of virological failure to atazanavir/ritonavir compared to women taking efavirenz. An important difference between PEARLS and A5202 is that atazanvir was not boosted with ritonavir in PEARLS. Since protease inhibitor clearance may be lower among women [25–27], women in the A5202 study may not have tolerated the adverse effects related higher systemic concentrations of this drug brought about by ritonavir inhibition of atazanavir metabolism [28]. Better adherence to the ATV+DDI-EC+FTC regimen among women than men could also explain sex differences in efficacy. An adherence analysis from the PEARLS study demonstrated overall better adherence in women compared to their male counterparts. However, this adherence analysis was not stratified by ARV treatment arms [29]. Analysis plasma antiretroviral drug levels in the PEARLS study have been analyzed and manuscript in press. Pharmacokinetic analysis showed a significant association between sex and ATV C_{24} where males tended to have a lower C_{24}estimates compared to females (*Adriana Andrade, personal communicatio, December 2014*).

A second key finding in PEARLS was that women assigned to a regimen of efavirenz with co-formulated lamivudine-zidovudine had a higher risk of a primary safety outcome and

regimen discontinuation, compared to men. Since this safety difference was driven by an increased rate of neutropenia among women, it seems likely that the safety difference may be due to the zidovudine component of this regimen. Sex differences in adverse drug reactions between men and women have been noted previously. Other studies have also found that women are more likely to have lactic acidosis, gastro-intestinal symptoms and significant drug reactions to nevirapine [8–15, 30, 31]. In PEARLS sex differences in antiretroviral safety were not detected among participants assigned to either ATV+DDI-EC +FTC, or EFV+FTC-TDF.

A sex effect was also observed on retention outcomes in this study, with men having a higher risk of premature study discontinuation or stopping antiretroviral therapy. The most frequent reasons for discontinuation were inability to come to the clinic and loss to follow up. Other studies in low-income countries have found higher rates of treatment failure in men due to non–adherence and loss to follow-up. An evaluation from the Tanzanian government treatment cohort showed that compared to women, men were 19% more likely to be lost to follow-up HR=0.74; 95% CI 0.56, 0.98) [32]. Two large studies in Kenya and South Africa also showed that HIV-infected men were more likely to become lost to follow-up and non-adherent than women, both before and after starting antiretrovirals [33, 34]. Moreover, women are more adapted to daily medication, such as contraceptive pills or iron/folic acid supplementation during pregnancy [35]. Alcohol abuse, which is more frequent among African HIV-infected men than women may also be a factor to the significant increase of lost to follow up in men in this study [36].

Interestingly women participating in North American based studies were more likely to discontinue study treatment than men. In the GRACE and REALMRK Studies, which were powered to specifically evaluate sex differences, women were more likely to discontinue study treatment and follow-up [37–38]. The characteristics of the HIV-infected populations in resource-limited and -rich settings are quite different, reflecting patterns of concentrated and generalized epidemics. How cultural, educational and economic differences might differentially affect retention of women relative to men deserves further investigation.

The strengths of PEARLS for evaluating sex differences in antiretroviral efficacy and safety were the relative and absolute numbers of women enrolled from nine countries in four continents; a median follow up of 3.8 years (maximum five years) with regular visits for adverse events, HIV disease and adherence monitoring; birth control accessibility and a low pregnancy rate. Although, sex-based analysis was not the primary objective of the PEARLS and the study was not designed to evaluate sex effects or differences in treatment effect by sex, the analysis present herein was prompted by the statistically significant treatment by sex interactions in the primary analysis.

Limitations of this study were that collection of socio-demographic data such as housing, education and income level was limited and the lack of this information may have precluded a better understanding of the factors that influence patients' motivation for study follow-up. While the large absolute and relative sample size of women within this single clinical trial provided an opportunity to explore these associations without the added heterogeneity of combining data across different clinical studies via meta-analyses, statistical power for

detecting sex associations with rare outcomes (like AIDS progression or death), or small subgroups within women (i.e. pregnancy or previous antiretroviral exposure for pMTCT), was limited by small numbers of events.

Women have been under-represented in clinical trials of antiretroviral therapy and current antiretroviral treatment guidelines are based largely on the clinical trial populations that primarily included male subjects [2, 3]. The sex discrepancy in clinical trial populations, relative to the global burden of HIV-1 infection, has raised concerns that the evidence base for informing antiretroviral treatment recommendations for women is inadequate. PEARLS provides evidence that these concerns are realistic and both antiretroviral efficacy and safety can differ between men and women. The implications of these findings are twofold: First, researchers must continue to strive to improve the evidence base for antiretroviral safety and efficacy in women. Future clinical trials should be designed to include sufficient numbers of women to define, with greater precision, the risk/benefit ratio for both individual antiretroviral drugs and drug combinations in women. Second, antiretroviral treatment guidelines should be updated to reflect new information from clinical trials with greater numbers of women. Recommendations should take into account, that both antiretroviral safety and efficacy can be different in non-pregnant women, and sex should influence choice of antiretroviral regimens.

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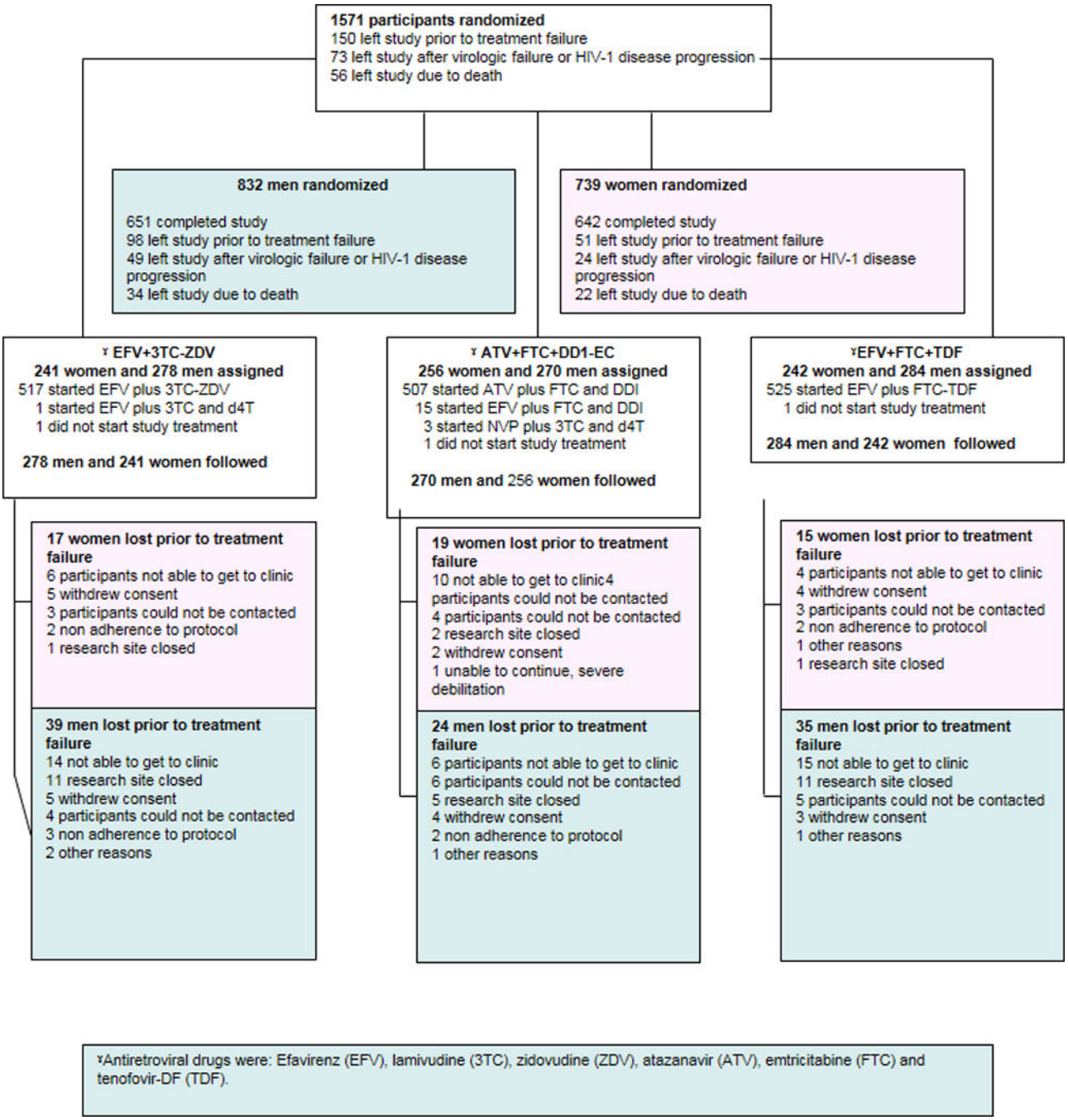

Figure 1.

Distribution of study participants and reasons for premature discontinuation from study before treatment failure

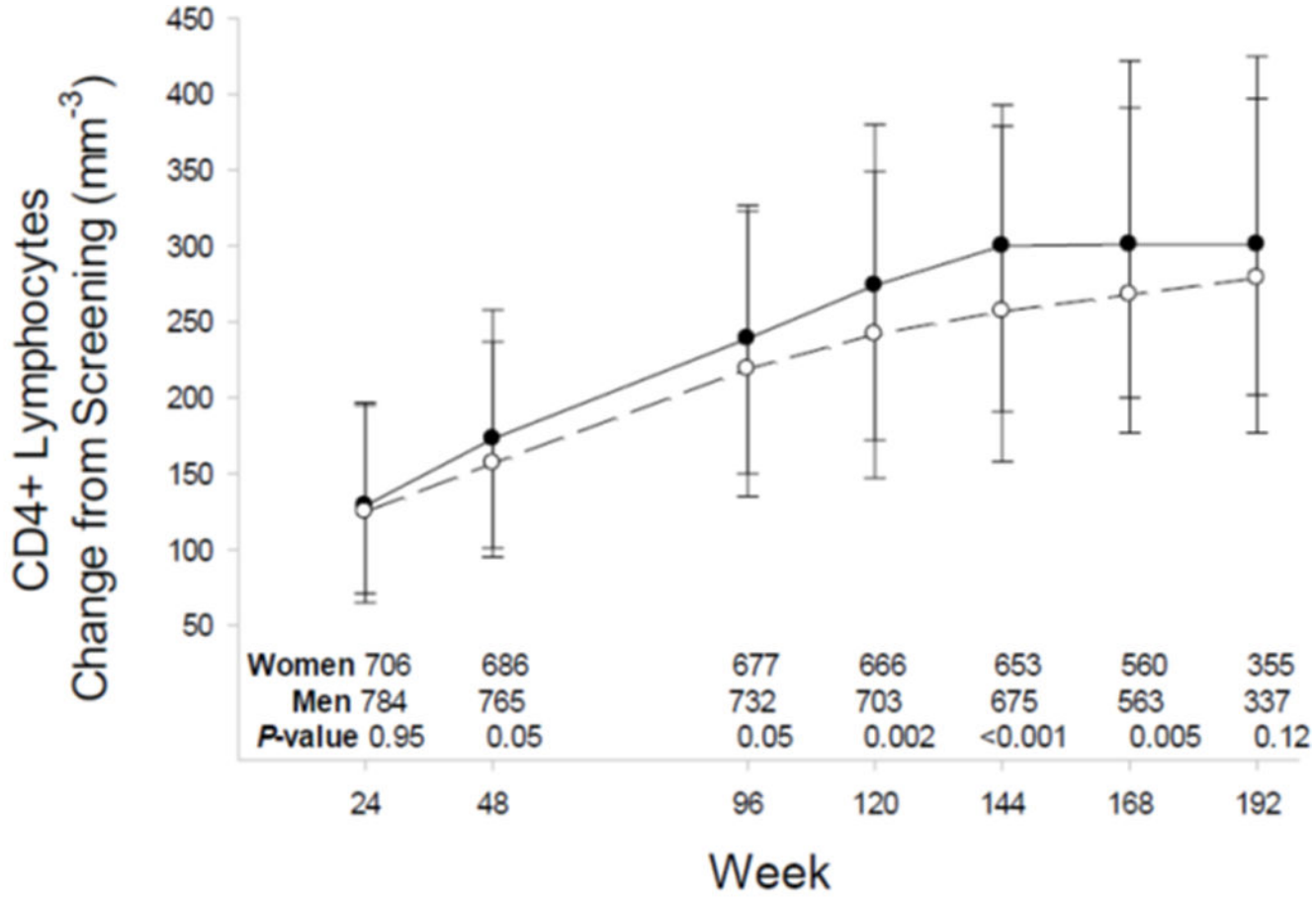

Figure 2.
Comparison of CD4 change from pretreatment between men and women

- Women
- Men

Table 1

Entry Participant Characteristics by Sex

Variable	Description	Sex		*p*-value*
		Female (n=739)	Male (n=832)	
Age, years†		33 (30, 41)	35 (28, 39)	<0.001
Race (%)	Asian	166 (22.5%)	192 (23.1%)	<0.001
	Black/ African American	458 (62.0%)	329 (39.5%)	
	White	58 (7.8%)	193 (23.2%)	
	Other/unknown	57 (7.7%)	118 (14.2%)	
Ethnicity (%)	Hispanic	90 (12.2%)	232 (27.9%)	<0.001
Site location; country (%)	Brazil	82 (11.1%)	149 (17.9%)	<0.001
	Haiti	48 (6.5%)	52 (6.3%)	
	India	111 (15.0%)	144 (17.3%)	
	Malawi	149 (20.2%)	72 (8.7%)	
	Peru	45 (6.1%)	89 (10.7%)	
	South Africa	141 (19.4%)	69 (8.3%)	
	Thailand	55 (7.4%)	45 (5.4%)	
	United States	38 (5.1%)	172 (20.7%)	
	Zimbabwe	70 (9.5%)	40 (4.8%)	
Weight; kg‡		58.5 (13.3)	66.3 (13.6)	<0.001
Body mass index ;kg/m^2‡		23.6 (5.0)	22.7 (3.7)	0.002
Anthropometric measurements†	Mid arm (cm)	27.2 (25.0, 30.0)	27.8 (25.7, 30.0)	0.013
	Mid thigh (cm)	48.0 (44.0, 53.2)	46.5 (43.0, 50.6)	<0.001
	Waist/hip ratio	0.8 (0.8, 0.9)	0.9 (0.9, 0.9)	<0.001
Karnofsky Score Median		90 (90, 100)	90 (90, 100)	0.080
Any prior/current binge drinking		80 (10.8%)	249 (29.9%)	<0.001
CD4+ lymphocyte count (mm^{-3})†		182 (113, 232)	165 (81, 230)	<0.001
Plasma HIV-1 RNA (log$_{10}$copies/mL)†		4.9 (4.5, 5.4)	5.2 (4.7, 5.5)	<0.001
Screening plasma HIV RNA stratum	< 100,000 c/mL	382 (51.7%)	339 (40.7%)	<0.001
	> 100,000 c/mL	357 (48.3%)	493 (59.3%)	
Prior or current AIDS diagnosis		46 (6.6%)	121 (14.5%)	<0.001
Prior or current tuberculosis		129 (17.2%)	150 (17.6%)	0.690
Hepatitis B surface antigen positive		35 (4.7%)	55 (6.6%)	0.110
Liver transaminases†	AST, IU/L	28 (23, 38)	31 (24, 41)	<0.001
	ALT, IU/L	22 (16, 32)	29 (20, 45)	<0.001
Creatinine clearance, mL/min†,//		94 (78, 117)	101 (84, 123)	<0.001
Randomized treatment assignment§	EFV+3TC/ZDV	241 (32.6%)	278 (33.4%)	0.65
	ATV+FTC+DDI-EC	256 (34.6%)	270 (32.5%)	
	EFV+FTC/TDF	242 (32.7%)	284 (34.1%)	

*Wilcoxon Rank Sum test for continuous variables; Chi-square test for categorical variables.

† Median (25th and 75th percentiles)

‡ Mean (standard deviation)

§ Antiretroviral drugs were: Efavirenz (EFV), lamivudine (3TC), zidovudine (ZDV), atazanavir (ATV), emtricitabine (FTC) and tenofovir-DF (TDF).

// Crockoft-Gault calculation.

Table 2

Efficacy and Safety Outcomes by Sex and Treatment Arm

Outcome	Assigned treatment group[Y]	Female N (%)	Male N (%)	Hazard Ratio (95% CI)[*] comparing females to males	*P* Value[†]	Adjusted Hazard Ratio (95% CI)
Efficacy Endpoints						
Treatment failure	Overall	142 (19.2)	169 (20.3)		0.018	
	ZDV/3TC + EFV	49 (20.3)	49 (17.6)	1.14 (0.76, 1.72)		1.13 (0.75, 1.71)[‡]
	ATV + FTC + DDI-EC	45 (17.6)	73 (27.0)	0.60 (0.41, 0.87)		0.59 (0.40, 0.87)[‡]
	EFV + TDF/FTC	48 (19.8)	47 (16.5)	1.21 (0.80, 1.83)		1.25 (0.82, 1.92)[‡]
Virologic failure	Overall	113 (15.2)	137 (16.5)		0.013	
	ZDV/3TC +EFV	39 (16.2)	39 (14.0)	1.18 (0.75, 1.86)		1.10 (0.69, 1.74)[§]
	ATV + FTC + DDI-EC	34 (13.2)	60 (22.2)	0.57 (0.37, 0.88)		0.56 (0.36, 0.86)[§]
	EFV + TDF/FTC	40 (16.5)	38 (13.3)	1.33 (0.84, 2.11)		1.38 (0.86, 2.21)[§]
Disease progression	Overall	19 (2.6)	27 (3.2)	0.78 (0.42, 1.47)	0.45	0.84 (0.44, 1.58)[//]
Death	Overall	22 (3.0)	34 (4.1)	0.59 (0.34, 1.04)	0.600	0.85 (0.47, 1.54)[¶]
Safety Endpoints						
Primary safety	Overall	393 (53.4)	444 (53.6)		0.002	
	EFV + ZDV/3TC	160 (66.4)	153 (55.2)	1.4 (1.1, 1.8)		1.49 (1.18, 1.88)[***]
	ATV + FTC + DDI-EC	126 (49.6)	155 (57.8)	0.82 (0.64, 1.04)		0.82 (0.64, 1.05)[***]
	EFV + TDF/FTC	107(44.4)	136 (47.9)	0.88 (0.68, 1.14)		0.91, (0.70, 1.19)[***]
Sign/symptom	Overall	147 (20.0)	184 (22.2)	0.95 (0.75, 1.19)	0.50	1.05 (0.82, 1.35)
[****]Abnormal laboratory	Overall	164 (22.3)	181 (21.8)	0.84 (0.67, 1.06)	0.090	
	ZDV/3TC + EFV	56 (23.2)	61 (22.0)			1.28 (0.89, 1.83)
	ATV + FTC + DDI-EC	56 (22.0)	60 (22.4)			0.90 (0.61, 1.33)
	EFV + TDF/FTC	35 (14.5)	54 (19.0)			0.66 (0.43, 1.04)
Initial regimen change	Overall	249 (33.8)	299 (36.1)	1.03 (0.86, 1.24)	0.060	
	ZDV/3TC+EFV	109 (45.2)	113 (40.8)			1.35 (1.03, 1.79)
	ATV + FTC + DDI-EC	79 (31.1)	107 (39.9)			0.84 (0.62, 1.14)
	EFV + TDF/FTC	61 (25.3)	79 (27.8)			0.96 (0.68, 1.35)

[*]Basic model adjusted for country and plasma HIV-1 RNA stratification factors, and treatment arm.

† P value for interaction term between sex and treatment arm.

‡ Adjusted model included age, race, pretreatment CD4+ lymphocytes and body measurements.

§ Adjusted model included age, race and pretreatment CD4+ lymphocytes.

// Adjusted model included pretreatment CD4+ lymphocytes and body measurements.

¶ Adjusted model race, pretreatment CD4+ lymphocytes, body measurements, prior AIDS diagnosis and serum ALT.

*** Adjusted model included serum AST, body measurements, and ethnicity

**** Adjusted model included baseline weight, body measurement, and serum AST

ɣ Antiretroviral drugs were: Efavirenz (EFV), lamivudine (3TC), zidovudine (ZDV), atazanavir (ATV), emtricitabine (FTC) and tenofovir-DF (TDF).