Poster # 547

Randomized Comparison of Anthropometric Outcomes on EFV-Based Antiretroviral Therapies

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ABSTRACT

Background: ACTG A5175/PEARLS was a randomized trial undertaken in diverse geographic settings that showed similar outcomes for the primary endpoint of time to virologic failure, new AIDS event or death in the comparison of tenofovir/emtricitabine or zidovudine/lamivudine with efavirenz (TDF/FTC+EFV or ZDV/3TC+EFV). We present results for a secondary objective comparing the effects of these regimens on anthropometric outcomes.

Methods: Antiretroviral naïve subjects with nadir CD4 counts <300/mm^3 were enrolled in Brazil, Haiti, India, Malawi, Peru, South Africa, Thailand, United States and Zimbabwe, and randomized to TDF/FTC+EFV (n=526) or ZDV/3TC+EFV (n=519). We compared changes in weight, body mass index (BMI), and mid-arm, waist, hip and mid-thigh circumferences, from baseline to 48, 96 and 144 weeks using repeated measures intent to treat analysis.

Results: 46% of subjects were female; median age, CD4 count and HIV-1 RNA were 34y, 159/mm^3 and 5.0 log$_{10}$ c/mL. Mean (sd) baseline anthropometric measures were: weight kg: 63 (14); BMI kg/m^2: 23 (4); circumferences, cm: mid-arm 28 (4), waist 80 (10), hip 92 (10), mid-thigh 48 (7). 9% had BMI<18.5 (underweight); 26% had BMI≥25 (overweight). At weeks 48, 96 and 144: n=973, 941 and 902 had measurements; 35 subjects died and 106 were lost to follow-up before week 144. In both arms, there were significant increases in all anthropometric measures at each of weeks 48, 96 and 144 (figure). The increases from baseline were, however, significantly larger for TDF/FTC+EFV vs ZDV/3TC+EFV (repeated measures p<0.001 except p=0.037 for waist) with mean change at week 144: weight kg: 4.8 vs 3.0; BMI kg/m^2: 1.8 vs 1.1; circumferences, cm: mid-arm 1.7 vs 0.7, waist 5.2 vs 4.3, hip 3.8 vs 1.4, mid-thigh 3.1 vs 0.9. Difference in mean BMI change between arms did not vary significantly by baseline BMI: at week 144*, 2.0 vs 1.7 kg/m^2 for baseline BMI <18.5, 1.8 vs 1.3 for BMI 18.5-<25; 1.8 vs 0.6 for BMI≥25. There were 7 clinical diagnoses of lipoatrophy in the ZDV/3TC+EFV arm but none in the TDF/FTC+EFV arm.

Conclusions: Although the primary efficacy outcome was similar for TDF/FTC+EFV and ZDV/3TC+EFV, increases in weight, BMI and body circumferences were larger for TDF/FTC+EFV. While these findings and the lower rate of clinical lipoatrophy for TDF/FTC+EFV support current guideline recommendations for TDF/FTC+EFV as initial therapy, the greater BMI increases and hence potential for increased cardiovascular risk among overweight subjects needs consideration.

*mean changes corrected from submitted abstract.

BACKGROUND

ACTG A5175/PEARLS was a randomized trial undertaken in diverse geographic settings that included comparison of two EFV-based antiretroviral therapies as initial treatment: for HIV infection, TDF/FTC+EFV and ZDV/3TC+EFV

During a median follow-up of 184 weeks, for the primary outcome measure of time to virologic failure, new AIDS event or death, the two regimens were similar: 95 (18%) of 526 participants assigned TDF/FTC+EFV versus 98 (19%) of 519 participants assigned ZDV/3TC+EFV (hazard ratio 0.95, 95% CI 0.72–1.27; p = 0.74) [Campbell et al., 2012).

OBJECTIVE

We present results for a secondary objective of the PEARLS study: to compare the effects of these regimens on anthropometric outcomes.

METHODS

Study population: HIV-1-infected individuals were enrolled in nine countries: India, Brazil, Malawi, S Africa, USA, Peru, Haiti, Zimbabwe and Thailand. The participants were ≥18 years old, had received no more than 7 days of cumulative prior ART (prior use of single-dose NVP or ZDV for any duration to prevent mother-to-child HIV transmission was allowed), and had a CD4 cell count <300 cells/mm^3 within 90 days prior to study entry. Written informed consent was obtained from all participants, and the study was approved by local Ethics Committees at each participating institution.

Anthropometric measurements: Weight and body circumferences (mid-arm, waist, hip and mid-thigh) were evaluated at baseline (immediately before starting antiretroviral therapy) and, at the time of study closure, all subjects could have had measurements at weeks 48, 96 and 144 after randomization. Body circumferences were measured using a standard protocol including three measurements at each visit; the median of the three measurements was used in analyses.

Statistical methods: Change from baseline in anthropometric outcomes at weeks 48, 96 and 144 were analyzed using intention-to-treat repeated measures analysis. P-values less than 0.05 were considered statistically significant. No adjustment was made for multiple comparisons across anthropometric outcomes.

RESULTS

Baseline Characteristics and Associations

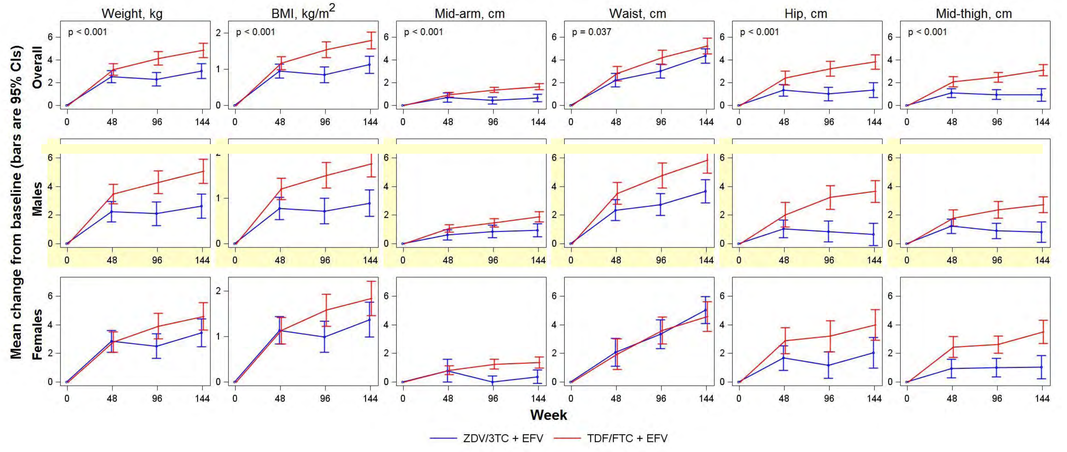
Table: Characteristics of study participants at baseline

Characteristic		Overall study population (n=1045*)	Males (n=562 [54%])	Females (n=483 [46%])
Age (years): median (quartiles)		34 (29, 41)	35 (25, 48)	33 (25, 46)
Country:	India	16%	17%	15%
	Brazil	15%	18%	11%
	Malawi	14%	8%	21%
	S. Africa	13%	9%	19%
	USA	13%	20%	6%
	Peru	8%	11%	5%
	Zimbabwe	7%	5%	9%
	Haiti	7%	8%	5%
	Thailand	6%	5%	8%
CD4 count (cells/mm^3): median (quartiles)		167 (89, 228)	158 (28, 270)	175 (51, 268)
HIV-1 RNA (log$_{10}$ copies/mL): median (quartiles)		5.0 (4.6, 5.4)	5.2 (4.3, 5.8)	4.9 (3.9, 5.7)
Anthropometric measures: mean (sd)				
Weight (kg)		62.9 (14.0)	66.2 (13.2)	59.0 (14.0)
BMI (kg/m^2)		23.2 (4.4)	22.7 (3.7)	23.8 (5.2)
	< 18.5 (underweight)	9%	9%	9%
	18.5 - < 25 (normal)	65%	69%	61%
	25+ (overweight)	26%	22%	31%
Mid-arm circumference (cm)		28.0 (4.0)	28.2 (3.8)	27.9 (4.3)
Waist circumference (cm)		79.5 (10.2)	81.0 (9.3)	77.8 (10.9)
Hip circumference (cm)		92.5 (10.2)	91.1 (8.4)	94.2 (11.7)
Mid-thigh circumference (cm)		47.9 (6.6)	47.0 (5.7)	49.0 (7.3)

*up to 26 subjects had missing circumference measurements at baseline

- Enrollment of men vs women varied among sites: USA, India and Brazil were the top three enrolling countries for men versus Malawi, South Africa and India for women.
- At baseline, 9% of participants were underweight (BMI < 18.5 kg/m^2) and 26% were overweight (BMI ≥ 25 kg/m^2).
- There was high correlation between BMI and each of the body circumferences (men: 0.79 to 0.85; women: 0.85 to 0.87).
- Multivariable analysis (including adjustment for age, sex and country) showed that baseline BMI was significantly lower among subjects with higher HIV-1 RNA and lower CD4 count, but was not significantly associated with a prior AIDS diagnosis. Specifically, BMI was 0.69 kg/m^2 lower on average for each 1 log$_{10}$ copies/mL higher HIV-1 RNA (95% CI: 0.34 to 1.05 kg/m^2), and 0.35 kg/m^2 lower for each 100 cells/μL lower CD4 count (95% CI: 0.07 to 0.63 kg/m^2 lower).

Changes from Baseline in Anthropometric Outcomes



- Of the 1045 subjects, 973, 941 and 902 subjects had weight measurements at weeks 48, 96 and 144, respectively. Thirty-five subjects died and 106 were lost to follow-up before week 144 (2 subjects did not have weight measured at week 144). At each visit, a few subjects did not have body circumference measurements, usually due to lack of time at the visit.
- In both treatment arms, there were significant increases from baseline in all measures at each of weeks 48, 96 and 144 (Figure). Increases were, however, significantly larger for TDF/FTC+EFV vs ZDV/3TC+EFV (p<0.001 for each measure except p=0.037 for waist).
- Mean increase in BMI at week 144 was 1.8 vs 1.1 kg/m^2 for TDF/FTC+EFV vs ZDV/3TC+EFV. Among subjects in follow-up at week 144, the proportion overweight (BMI≥25) increased from 26% at baseline to 38% at week 144 for TDF/FTC+EFV and from 25% to 42% for ZDV/3TC+EFV.
- Waist circumference increases at week 144 (5.2 vs 4.3cm) were larger than limb circumference increases (mid-arm, 1.7 vs 0.7cm; hip 3.8 vs 1.4cm; and mid-thigh 3.1 vs 0.9cm).
- For waist circumference, but not for other measures, there was significant evidence that the difference between treatments varied by sex: for men, the mean increases were larger for TDF/FTC+EFV versus ZDV/3TC+EFV, whereas for women, the mean increases were similar for the two treatments (interaction p=0.038). This finding, however, needs to be interpreted with caution given the multiplicity of outcomes considered and the potential for other differences between men and women (e.g. country of enrollment).
- The difference between treatments in change in BMI (and in other measures) did not vary significantly by baseline BMI group: at week 144, 2.0 vs 1.7 kg/m^2 for TDF/FTC+EFV vs ZDV/3TC+EFV among subjects with baseline BMI <18.5kg/m^2; 1.8 vs 1.3 kg/m^2 for BMI 18.5-<25kg/m^2; and 1.8 vs 0.6 kg/m^2 for BMI≥25kg/m^2.

Clinical outcomes

- There were 7 clinical diagnoses of lipoatrophy in the ZDV/3TC+EFV arm but none in the TDF/FTC+EFV arm.

CONCLUSIONS

Although the primary efficacy outcome (virologic failure/AIDS progression/death) was similar for TDF/FTC+EFV and ZDV/3TC+EFV, increases in weight, BMI and body circumferences were larger for TDF/FTC+EFV. While these findings and the lower rate of clinical lipoatrophy for TDF/FTC+EFV support current guideline recommendations for TDF/FTC+EFV as initial therapy, the greater BMI increases and hence potential for increased cardiovascular risk among overweight subjects needs consideration.

REFERENCE

Campbell TB, Smeaton LM, KumarasamyN, et al. Efficacy and safety of three antiretroviral regimens for initial treatment of HIV-1: a randomized clinical trial in diverse multinational settings. PLOS Medicine 2012. 9(8):e1001290.

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