Poster #0518

IMPORTANT SEX DIFFERENCES IN OUTCOMES FOR INDIVIDUALS PRESENTING FOR THIRD LINE ART

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Introduction

Important sex differences in ART drug exposure and tolerability that lead to treatment discontinuation and unfavorable outcomes for women have been reported.

- Ritonavir's clearance is decreased in women leading to increased levels
- Nevirapine is associated with a fatal hepatitis in women
- Atazanavir is associated with poorer viral outcomes in women compared to Efavirenz potentially due to PK differences.

A5288 was an open-label phase IV, prospective interventional strategy study at 19 urban sites in 10 countries* evaluating third-line treatment options for individuals experiencing virologic failure on their second regimen. This analysis evaluated differences in safety and tolerability between men and women taking third-line ART regimens.

* Kenya, Malawi, South Africa, Uganda, Zimbabwe, Brazil, Haiti Peru, India and Thailand

Key inclusion/exclusion criteria:

- HIV-infected adults age ≥18 years
- Two prior ARV regimens, including one NNRTI-based regimen replaced by a PI-based regimen; with the change due to toxicity or failure
- Current receipt of a PI based regimen for a minimum of 24 weeks prior to screening, with confirmation of virologic failure at screening

Methods

Real-time HIV drug resistance results, treatment history and, if available, any historical resistance results, were used to assign participants to one of four treatment cohorts. Ritonavir boosting was part of every cohort.

This analysis combined cohorts B, C and D (BCD) as all three involved newer ART regimens as third-line therapy and numbers were too small in individual cohorts for meaningful analysis. Sex differences were evaluated using logistic regression and proportional hazards models adjusted for cohort (A or BCD), and were further evaluated in multivariate models adjusted for cohort; baseline age, weight, HIV-1 RNA and CD4 count; and country of enrollment.

Results

Event	All Cohorts (n=545)		Cohort A (n=287)		Cohorts B, C and D (n=258)		Difference between M and F*	Difference between M and F: model** adjusted for Cohort Group (95% CI)	Difference between M and F: model** adjusted for Cohort Group; country and categorized age, weight, CD4, and $\log_{10}$ HIV-1 RNA (95% CI)
	Male (n=287)	Female (n=258)	Male (n=127)	Female (n=160)	Male (n=160)	Female (n=98)			
HIV-1 RNA ≤200 c/mL at week 48	205 (71%)	144 (56%)	62 (49%)	63 (39%)	143 (89%)	81 (83%)	P=0.029	OR 0.64 (0.43, 0.96) P=0.030	OR 0.87 (0.54, 1.39) P=0.56
Confirmed VF (≥1000 c/mL)	66 (23%)	100 (39%)	54 (43%)	91 (57%)	12 (8%)	9 (9%)	P=0.018	HR 1.48 (1.08, 2.03) P=0.014	HR 1.37 (0.97, 1.93) P=0.075
Grade ≥3 signs and symptoms	**27 (9%)**	**52 (20%)**	**18 (14%)**	**37 (23%)**	**9 (6%)**	**15 (15%)**	**P=0.002**	**HR 1.87 (1.17, 2.99) P=0.009**	**HR 1.67 (1.01, 2.74) P=0.044**
Grade ≥3 laboratory abnormalities	90 (31%)	73 (28%)	50 (39%)	52 (33%)	40 (25%)	21 (21%)	P=0.18	HR 0.76 (0.56, 1.04) P=0.088	HR 0.90 (0.64, 1.28) P=0.57
Grade ≥3 diagnoses	48 (17%)	58 (22%)	26 (20%)	42 (26%)	22 (14%)	16 (16%)	P=0.21	HR 1.23 (0.84, 1.81) P=0.29	HR 1.01 (0.67, 1.52) P=0.95
Serious Adverse Events	40 (14%)	58 (22%)	20 (16%)	41 (26%)	20 (13%)	17 (17%)	P=0.024	HR 1.48 (0.98, 2.23) P=0.060	HR 1.16 (0.76, 1.79) P=0.50
AIDS-defining events	12 (4%)	19 (7%)	7 (6%)	14 (9%)	5 (3%)	5 (5%)	P=0.19	HR 1.47 (0.71, 3.04) P=0.30	Not Fitted‡
Deaths	11 (4%)	12 (5%)	8 (6%)	10 (6%)	3 (2%)	2 (2%)	P=0.98	HR 0.97 (0.42, 2.21) P=0.94	Not Fitted‡

Table displays the N(%) and results from models assessing each of the outcomes and groups specified.
Males were used as the reference group for analyses
‡ Multivariate proportional hazards models were not fitted for some outcome measures with too few events
* Cochran-Mantel-Haenszel Test of Sex stratified by Cohort Group (A vs. B/C/D);
** Proportional hazards model for time to first event (except logistic regression model for HIV-1 RNA ≤200 c/mL at week 48)

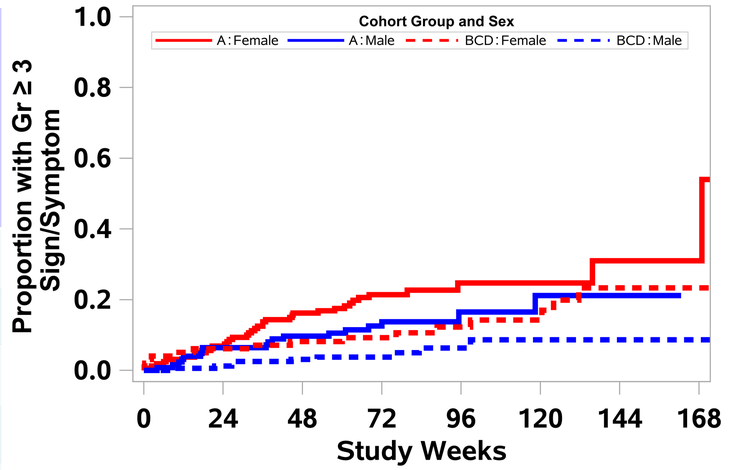
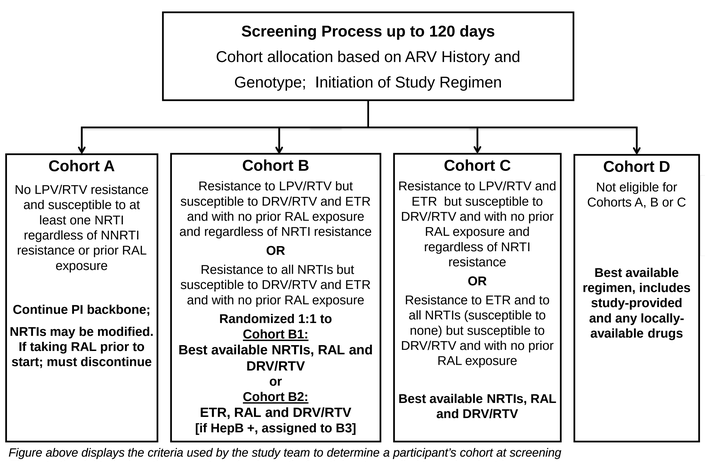


Figure above displays the cumulative incidence function for the Gr ≥3 Sx outcome by Cohort Group and Sex

Discussion

- More women than men entered Cohort A after treatment failure of both NNRTI- and PI-based regimens
  - Cohort A participants had resistance profiles suggesting they could be suppressed on their current 2nd-line regimen
- Both among those who continued their 2nd-line regimen and those who started a new regimen:
  - More women than men experienced grade ≥3 signs and symptoms
  - More women than men had suboptimal virologic responses

Cohort Allocation



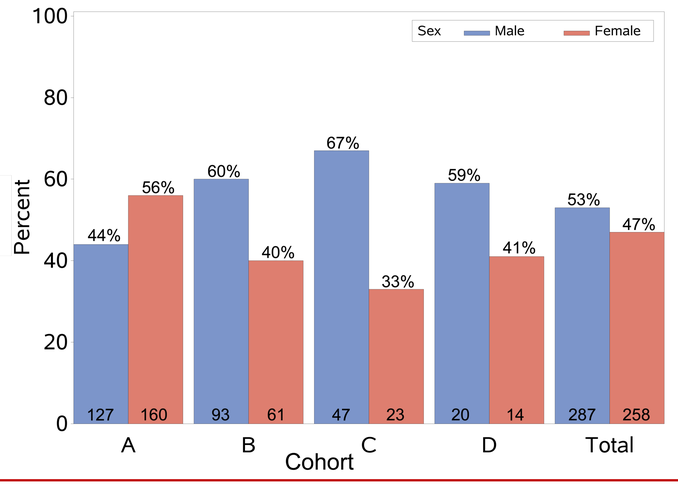


Figure above displays the criteria used by the study team to determine a participant's cohort at screening
Figure to the right displays the percentage (and count) of participants enrolled to each cohort by sex

Implications

- **Women failed therapy without resistance on a regimen containing a boosted PI more commonly than men**
- **Women experienced grade ≥3 signs and symptoms more frequently than men without concomitant diagnoses or laboratory values**
- **Subjective tolerability may be different for women and men, and interventions designed to improve tolerability may improve adherence and clinical outcomes**

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