Poster #0499

PREDICTORS OF VIROLOGIC OUTCOME WHILE CONTINUING A PI-BASED ART REGIMEN IN ACTG A5288

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Introduction

A5288 was an open-label phase IV, prospective interventional strategy study at 19 urban sites in 10 countries* evaluating a treatment strategy for individuals experiencing virologic failure on their 2nd-line regimen. As part of this strategy, participants with no lopinavir/ritonavir (LPV/r) resistance and susceptibility to at least one NRTI were enrolled in **Cohort A** of the study and **continued their 2nd-line PI-based regimen** with possible change in NRTIs.

* 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

Objective

Antiretroviral (ARV) choices are challenging in resource-limited settings (RLS) after failure of 2nd-line therapy because of accumulated resistance. Many failing 2nd-line therapy without resistance remain on their 2nd-line therapy.

Our objective was to evaluate demographic and clinical predictors of virologic outcomes in this subgroup (Cohort A) of the A5288 study population.

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 (Figure 1). Participants at most sites were also randomized to receive a cellphone adherence support intervention in addition to standard of care (CPI+SOC) or SOC adherence support.

These analyses focus on participants enrolled to **Cohort A**. Logistic regression models were used to evaluate sex, age, baseline HIV-1 RNA, CD4 count, presence of resistance to at least one NRTI, and randomized adherence support intervention (CPI+SOC vs SOC) as **predictors of failing to meet** the study's primary endpoint: suppression of HIV-1 RNA ≤200 c/mL at week 48 (ITT, irrespective of ART changes). Similarly, proportional hazards models were used to assess predictors of time to confirmed virologic failure (VF) ≥ 1000 c/mL. Kaplan-Meier plots show results for time to VF by categories of age, HIV-1 RNA, CD4 count and NRTI resistance. Based on similarity of outcomes, some categories of age and CD4 count were then combined in the models [Table 1].

Cohort Allocation

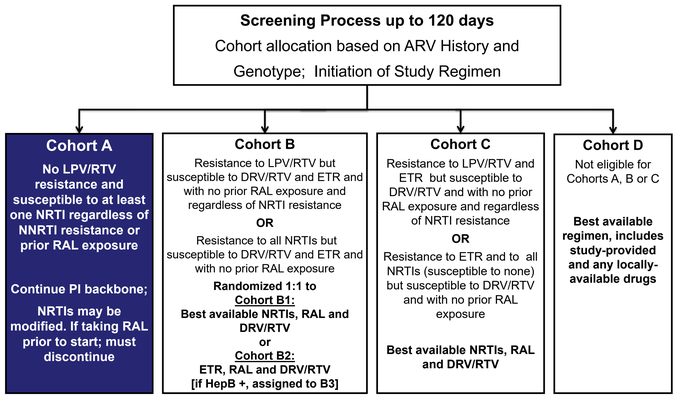

Figure 1 (above) displays the criteria used by the study team to determine a participant's cohort at screening

Results

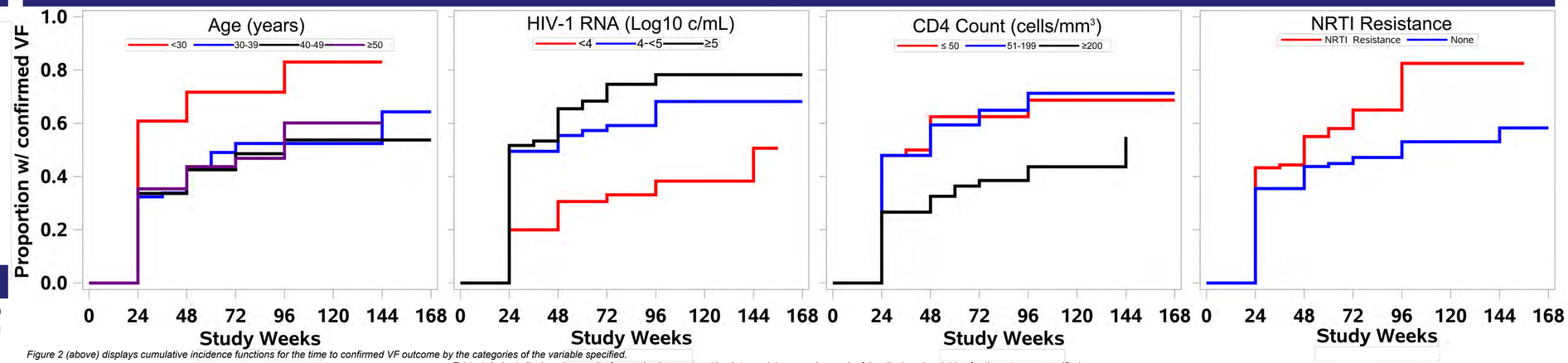

Figure 2 (above) displays cumulative incidence functions for the time to confirmed VF outcome by the categories of the variable specified.

Table 1 (below) displays the results from univariate and multivariate models assessing each of the displayed variables for the outcome specified.

Analysis Population and Findings

- **The analysis included 277 participants:**
  - 56% were Female
  - Median age was 40 years old
  - Median baseline HIV-1 RNA was 4.3 log10 c/mL
  - Median baseline CD4 count was 167 cells/mm^3
  - 103 (37%) had resistance to at least one NRTI
- **10 participants were excluded:**
  - 9 had resistance to both NRTIs or to the PI received (e.g. due to toxicity to the susceptible NRTI; on atazanavir with minor resistance; or sample mix-up)
  - 1 had no follow-up
- **All participants received 3TC or FTC**
- **The second NRTI received was:**
  - TDF for 255 (92%)
  - ZDV for 20 (7%)
  - ABC for 1 (<1%)
  - 1 participant received both TDF and ZDV
- **134 of the 138 with confirmed VF had a genotype available from the failure time point:**
  - Of the 57 who had VF and NRTI resistance at screening, 25% gained new mutation(s)
  - Of the 81 who had VF and no resistance at screening, 35% gained new mutation(s)

Variable	Categories	N (%)	HIV-1 RNA > 200 c/mL At Week 48 Outcome: N (%) with HIV-1 RNA >200 c/mL at week 48	HIV-1 RNA > 200 c/mL At Week 48 Outcome: Odds ratio (95% CI) HIV-1 RNA >200 c/mL at week 48	HIV-1 RNA > 200 c/mL At Week 48 Outcome: Odds ratio, adjusted for other variables shown (95% CI)	Confirmed Virologic Failure Outcome: N (%) with Confirmed VF (≥1000 c/mL)	Confirmed Virologic Failure Outcome: Hazard ratio (95% CI) Confirmed VF (≥1000 c/mL)	Confirmed Virologic Failure Outcome: Hazard ratio, adjusted for other variables shown (95% CI)
Sex	**Female**	155 (56%)	94 (61%)	1.49 (0.92, 2.41)	1.31 (0.76, 2.24)	87 (56%)	1.55 (1.10, 2.20)	1.42 (0.99, 2.05)
	Male	122 (44%)	62 (51%)	Reference		51 (42%)	Reference	
Age at study entry (years)	**<30**	46 (17%)	35 (76%)	2.89 (1.40, 5.97)	3.10 (1.41, 6.81)	35 (76%)	2.17 (1.46, 3.21)	2.15 (1.43, 3.23)
	≥30	231 (83%)	121 (52%)	Reference		103 (45%)	Reference	
Bsl HIV-1 RNA (Log_{10} c/mL)	**<4.00**	107 (39%)	44 (41%)	Reference		35 (33%)	Reference	
	4.00-<5.00	103 (37%)	62 (60%)	2.17 (1.25, 3.76)	1.69 (0.92, 3.10)	60 (58%)	2.30 (1.51, 3.50)	1.95 (1.26, 3.03)
	≥5.00	67 (24%)	50 (75%)	4.21 (2.15, 8.24)	2.85 (1.35, 6.03)	43 (64%)	2.93 (1.87, 4.61)	2.60 (1.60, 4.24)
Bsl CD4 count (cells/mm^3)	**<200**	154 (56%)	109 (71%)	3.92 (2.37, 6.48)	3.15 (1.79, 5.54)	93 (60%)	2.12 (1.48, 3.04)	1.64 (1.11, 2.42)
	≥200	123 (44%)	47 (38%)	Reference		45 (37%)	Reference	
Resistance to any NRTI	**No**	174 (63%)	92 (53%)	Reference		81 (47%)	Reference	
	Yes	103 (37%)	64 (62%)	1.46 (0.89, 2.40)	1.93 (1.10, 3.39)	57 (55%)	1.45 (1.03, 2.05)	1.76 (1.23, 2.51)
Adherence Support Intervention	**CPI+SOC**	127 (46%)	70 (55%)	Reference		57 (45%)	Reference	
	SOC	132 (48%)	78 (59%)	1.18 (0.72, 1.92)	1.27 (0.73, 2.20)	71 (54%)	1.31 (0.92, 1.86)	1.28 (0.90, 1.84)
	Site opted out	18 (6%)	8 (44%)	0.65 (0.24, 1.76)	0.56 (0.20, 1.60)	10 (56%)	1.15 (0.59, 2.27)	1.13 (0.56, 2.26)

Conclusions

- Less than half of the participants who remained on 2nd-line ART (44%) achieved HIV-1 RNA suppression ≤ 200 c/mL at 48 weeks in this analysis of participants in RLS, failing 2nd-line PI-containing ART with no LPV resistance and susceptibility to at least one NRTI
- Participants of younger age, higher baseline HIV-1 RNA, lower baseline CD4 count, and resistance to any NRTI (multivariate only) were less likely to meet the study's primary endpoint of HIV-1 RNA ≤200 c/mL at week 48 [Table 1]
- Participants of younger age, higher baseline HIV-1 RNA, lower baseline CD4 count, and resistance to any NRTI were more likely to experience confirmed virologic failure during study follow up (median 72 weeks). Sex was statistically significant in univariate analyses and not significant in the multivariate models [Table 1]
- **Individuals who are younger and/or have more advanced disease as indicated by higher baseline HIV-1 RNA and lower CD4 count, and those with NRTI resistance-associated mutations, are at higher risk of negative virologic outcomes when continuing their 2nd-line regimen and therefore may be candidates for alternative interventions**

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