493LB

DIVERGENT ARV RESISTANCE AT SCREENING FOR ACTG A5288 STUDY OF 3RD-LINE ART IN RLS

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INTRODUCTION

To date, over 13 million individuals have obtained treatment for HIV in resource limited settings (RLS) from large public health based programs. A population based approach has been used to design first- and second-line regimens expected to be most effective in decreasing viremia. Recent studies (SECOND-LINE; EARNEST; SELECT [A5273]) have shown that HIV drug resistance associated to first-line failure does not impact second-line ART outcomes and therefore HIV drug resistance testing after first-line may not be a useful tool to incorporate into large national roll-out programs.

Currently, there is limited data on the optimal third-line regimen to be used in these settings and the impact of first and second-line accumulated drug resistance might have on third line outcomes. Studies of second-line failure show very low rates (10%) of protease resistance, however, the majority of these data are from older protease based second-line regimens from small not well-characterized cohorts. The A5288 study is an open-label phase IV, prospective interventional, strategy study in RLS for HIV-infected participants with triple-class experience or resistance to (nucleoside reverse transcriptase inhibitors [NRTIs], non-NRTIs [NNRTIs], and protease inhibitors [PIs]) who are failing their current second-line regimen. Eligible participants were allocated in four cohorts based on real-time resistance testing.

In this analysis, we present the resistance profiles of volunteers screening for enrollment into A5288.

METHODS

- 665 participants with confirmed viral failure on a protease based second-line regimen were eligible for resistance testing and screened for A5288.
- The participants were from 20 sites in 10 countries: Real-time HIV drug resistance testing was performed using a NIAID virology quality assessment (VQA)-certified laboratory developed assays at FIOCRUZ, YRGcare and BARC-SA/Lancet Laboratories. This RT-initiated assay sequenced the full protease and partial reverse transcriptase regions of HIV-1.
- Subtype was determined by phylogenetic analysis.
- Resistance mutations and scores were determined using the Stanford algorithm (v6.2).
- Associations of drug class resistance with HIV-1 subtype, screening HIV RNA, and nadir CD4 were evaluated.

RESULTS

Of the 683 plasma samples available for analysis sequences were obtained for 665. The 665 sequences were from: 171 from Asia (26%); 138 from Latin America (21%); 180 from Eastern Africa (27%); 170 from Southern Africa (26%) and 6 from other locations (<1%). The median age of participants was 41 years and the majority of samples were from black (65%) males (52%). The median HIV RNA and CD4 were 4.5log$_{10}$copies/ml and 65 cells/mm^3, respectively (Table 1). HIV subtype C (48%), B (20%) and A1 (18%) were the most common, followed by D (7%), AE (3%) and other (3%).

Table 1: Screening Demographics

		Total (N=665)
Age	Median (Q1, Q3)	41 (35, 47)
Sex	Male	348 (52%)
Country	India	149 (22%)
	South Africa	98 (15%)
	Uganda	98 (15%)
	Kenya	82 (12%)
	Brazil	60 (9%)
	Haiti	54 (8%)
	Malawi	45 (7%)
	Other*	79 (12%)
Screening log10 HIV-1 RNA	Median (Q1, Q3)	4.5 (4.0, 5.1)
Nadir CD4 count	Median (Q1, Q3)	65 (25, 141)

* Zimbabwe, Peru, Thailand, missing

Table 2: High-level or Intermediate Resistance to Antiretroviral Drug Classes (Stanford Algorithm v 6.2)

Number of classes with resistance	Total (n=665)
Susceptible/Low resistance to 3 drug classes	146 (22%)
Resistance to 1 drug class	137 (21%)
Resistance to 2 drug classes	207 (31%)
Resistance to 3 drug classes	175 (26%)

All participants had been exposed to NRTIs with the most common NRTIs being 3TC/FTC (100%); TDF (84%) and AZT (76%). Ninety nine percent had prior exposure to NNRTIs. NVP (63%) was more common than EFV (56%). At time of screening, TDF (67%) and 3TC (90%) were the most commonly prescribed NRTIs with either LPV/r (55%) or ATV/r (43%). Six percent of participants had had RAL exposure.

96% (638 out of 665) had at least one mutation. High-level or intermediate resistance was common (Table 2): 519 candidates (78%) had resistance to one or more drugs. 137 samples (21%) had resistance to 1 drug class, 207 (31%) to 2 drug classes, and 175 (26%) to all 3 drug classes (NRTI, NNRTI, PI). The majority of the participants had NRTI resistance to 3TC/FTC (58%); with TDF having the lowest level of resistance (18%); very few participants had DRV resistance (2%; Figure 1).

The most common NRTI, NNRTI and PI mutations are shown in Figure 2. Sixty percent had no TAMS and 22% had three or more TAMs and the most common TAM pathway was TAM-1.

Of the 665 sequences, population based sequencing found that 461 (69%) showed susceptibility to 2nd-line regimens (2 NRTI + ATV/r or LPV/r; Figure 3) and the majority were susceptible or only low-level resistant to DRV/r (97%) and ETR (79%).

Nadir CD4 count but not screening HIV RNA was significantly associated with the number of resistant drug classes but quantitative differences were small and unlikely to be helpful clinically (Table 3).

Table 3: Association of Nadir CD4 and screening plasma HIV RNA with the number of ARV classes with resistance.

	Nadir CD4 count (cells/mm^3)				Screening HIV-1 RNA (log$_{10}$ copies/mL)				
Number of classes with resistance	N=656	≤200 N=564	>200 N=92	P-value*	N=653	<4.00 N=172	4.00-4.99 N=279	≥5.0 N=202	P-value**
Susceptible/Low resistance to all 3 drug classes	142 (22%)	114 (20%)	28 (30%)	0.006	145 (22%)	35 (20%)	67 (24%)	43 (21%)	0.209
Resistance to 1 drug class	137 (21%)	118 (21%)	19 (21%)		134 (21%)	32 (19%)	60 (22%)	42 (21%)	
Resistance to 2 drug classes	206 (31%)	176 (31%)	30 (33%)		202 (31%)	62 (36%)	93 (33%)	47 (23%)	
Resistance to 3 drug classes	171 (26%)	156 (28%)	15 (16%)		172 (26%)	43 (25%)	59 (21%)	70 (35%)	

* P-value adjusted for screening log$_{10}$HIV-1 RNA and subtype; ** P-value adjusted for screening nadir CD4 count and HIV-1 subtype

Figure 1: Predicted level of intermediate/high level resistance to NRTI (blue); NNRTI (yellow) and PI (green). After second-line failure, the majority of the participants would be susceptible to TDF; ETR, RVP and DRV (Y axis: % intermediate/high level resistance).

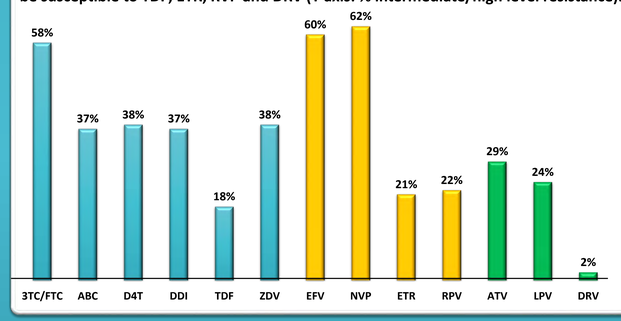


Figure 2: NRTI (blue); NNRTI (yellow) and PI (green) resistance mutations that occurred above 10%. The most common NRTI mutation was M184V, followed by K103N (Y axis: % intermediate/high level resistance).

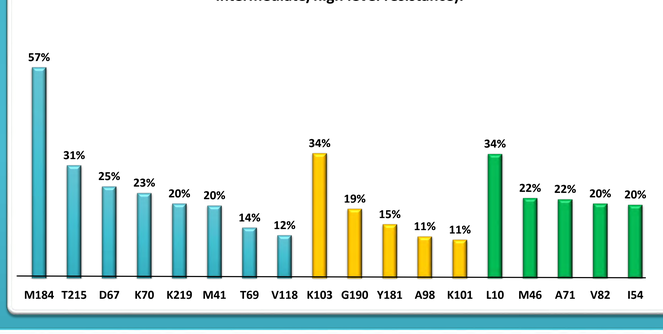
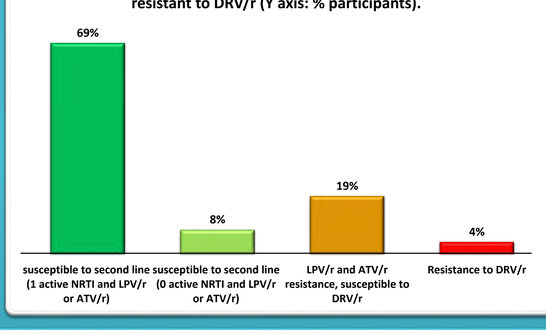


Figure 3 Predicted level of susceptibility to LPV/r, ATV/r and DRV/r; 77% of participants were still susceptible to PIs used in second-line regimens; however, 23% were resistant to LPV/r and ATV/r of that 4% were also resistant to DRV/r (Y axis: % participants).



CONCLUSION

- Highly divergent resistance profiles were observed among study candidates being evaluated for 3rd-line ART in RLS.
- The majority remained susceptible to 2nd-line regimens (69%) but others had high level resistance to 2 (31%) and 3 drug classes (26%).
- Routine clinical parameters were not discriminatory for the extent of resistance.
- These results indicate that objective measures of ART adherence and access to both resistance testing and newer ARVs are needed to guide 3rd-line ART in RLS.

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