IMPACT OF PRE-EXISTING DRUG RESISTANCE ON RISK OF VIROLOGIC FAILURE IN SOUTH AFRICA

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Background

- There is conflicting evidence on the impact of pre-existing HIV drug resistance mutations (DRMs) in individuals infected with non-B subtype virus.
- Also, the clinical impact of drug-resistant minority variants (DRMVs) is not clear.

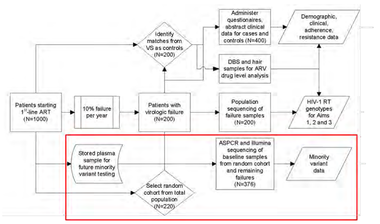
Objectives

- To assess the impact of both majority and minority HIV drug resistance mutations on the risk of virologic failure (VF) in those initiating a first-line NNRTI-based ART regimen.

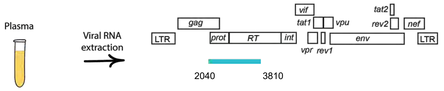
Methods

Study population & next-generation sequencing

- Case-cohort substudy of the HIV/AIDS Drug Resistance Surveillance Study (ADReSS), enrolling 1,000 patients initiating first-line efavirenz/emtricitabine/tenofovir (EFV/FTC/TDF) in KwaZulu-Natal, South Africa.



- Nested *pol* PCR was performed on plasma viral RNA followed by Illumina based NGS sequencing.



- Pre-ART DRMs were detected by multiplexed Illumina sequencing of HIV *pol* and sequence analysis performed using PASeq software.
- DRMs present at >20% of viral population were defined as "majority" while those at <20% were labeled as "minority variants" (MVs).
- Personalized genotypic susceptibility scores (GSS) at varying minority variant (MV) thresholds (0.5-20%) calculated using the Stanford HIV database.
- GSS of each antiretroviral medication (ARV) was defined as the following: 1 (Stanford score 0-9), 0.75 (Stanford score 10-14), 0.5 (Stanford score 15-29), 0.25 (Stanford score 30-59), and 0 (Stanford score ≥60).

Statistical Analysis

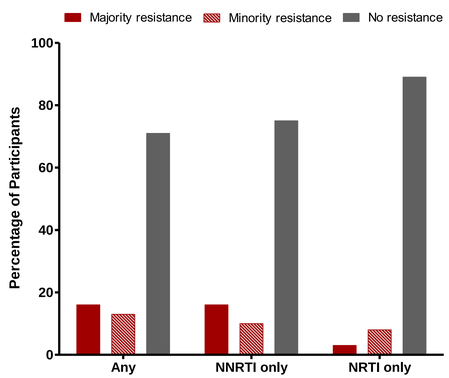
- Weighted stratified Cox proportional hazards model were used to estimate the association between pre-ART DRMs and risk of VF.
- Weights were based on the inverse sampling fraction; all cases assigned a weight of 1.

Results

Table 1: Baseline characteristics of parent and subcohort population

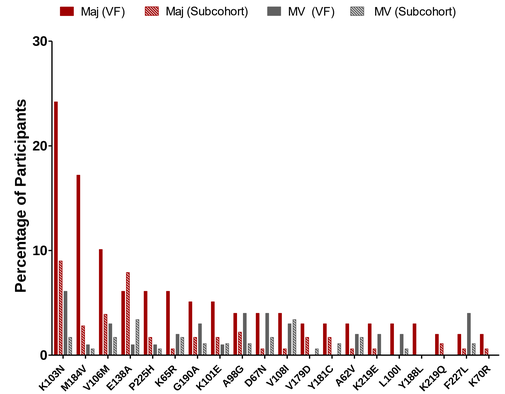
			Random Subcohort		
		Non-Cohort Case (N=83)	Case (N=16)	Non-Case (N=162)	Total (N=178)
Enrollment site	RKK	43 (52%)	5 (31%)	85 (52%)	90 (51%)
	BTD	40 (48%)	11 (69%)	77 (48%)	88 (49%)
Age at enrollment	Mean (s.d.)	31.33 (8.67)	33.94 (12.30)	35.12 (10.84)	35.02 (10.95)
	Median (Q1, Q3)	30 (24, 38)	29.50 (23.50, 39.00)	32 (27, 42)	32 (27, 42)
	Min, Max	18, 53	21, 61	20, 66	20, 66
Sex	Female	45 (54%)	10 (63%)	104 (64%)	114 (64%)
	Male	38 (46%)	6 (38%)	58 (36%)	64 (36%)
ARV Regimen	EFV/FTC/TDF	78 (94%)	15 (94%)	161 (99%)	176 (99%)
	EFV/3TC/ABC	1 (1%)	1 (6%)	1 (1%)	2 (1%)
	EFV/3TC/AZT	1 (1%)	0 (0%)	0 (0%)	0 (0%)
	NVP/FTC/TDF	2 (2%)	0 (0%)	0 (0%)	0 (0%)
	NVP/3TC /TDF	1 (1%)	0 (0%)	0 (0%)	0 (0%)

Figure 1: Prevalence of HIV drug resistance mutations by antiretroviral class and frequency in the subcohort



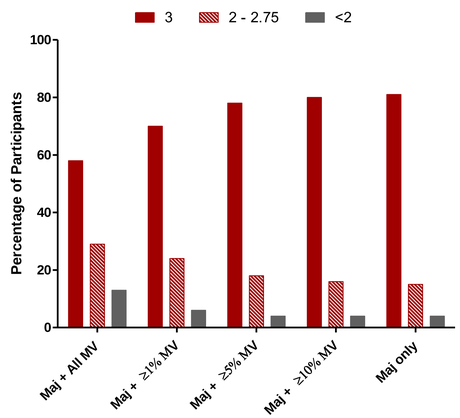
- Within the random subcohort, 16% of participants harbored at least one majority drug-resistance mutation (present at ≥20% of the viral population) that conferred intermediate or greater ART resistance (Stanford score ≥30).

Figure 2: Percentage of participants with the most common ART resistance mutations



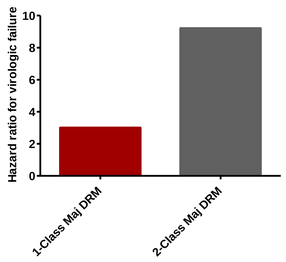
- The most common baseline resistance mutations in participants with eventual VF were K103N (24%), M184V (17%), V106M (10%), E138A (6%), P225H (6%), and K65R (6%). In the subcohort, it was K103N (9%), E138A (8%), V106M (4%) and M184V (3%).
- Most commonly detected high-level majority DRMs (e.g., K103N, V106M, M184V) were less commonly detected as MVs.

Figure 3: Proportion of subcohort participants at each genotypic susceptibility score level



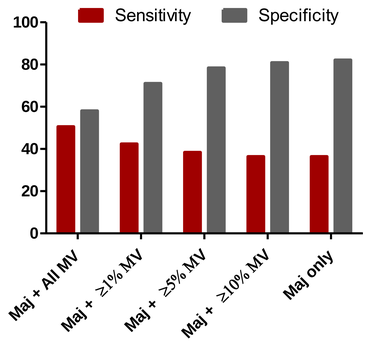
- Taking into account the majority mutations, 81% of participants had a GSS of 3, 15% had a GSS of 2 to 2.75, and 4% had a GSS<2, corresponding to less than 2 fully-active antiretroviral drugs.
- Incorporating minority variants decreased the expected GSS scores.

Figure 4: Majority resistance mutations significantly increase risk of virologic failure



- Any majority DRM was associated with a 3-fold greater risk of VF (p=0.002), increasing to 9.2-fold (p<0.001) in those with <2 active drugs.

Figure 5: Sensitivity and specificity of predicting virologic failure based on presence of at least one majority and/or minority drug resistance mutations



- Inclusion of pre-ART MVs with majority DRMs improved the sensitivity but reduced the specificity of predicting VF.

Conclusions

- In a South African cohort, the presence of majority DRMs increased the risk of VF, especially in the presence of dual-class resistance.
- The detection of drug-resistant minority variants alone did not significantly increase the risk of VF, but their inclusion with majority DRMs affected the sensitivity/specificity of predicting VF.

Acknowledgements

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