LOW-FREQUENCY NNRTI MUTATIONS CORRELATE WITH HIV ART FAILURE IN PREGNANT WOMEN 0577

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Background

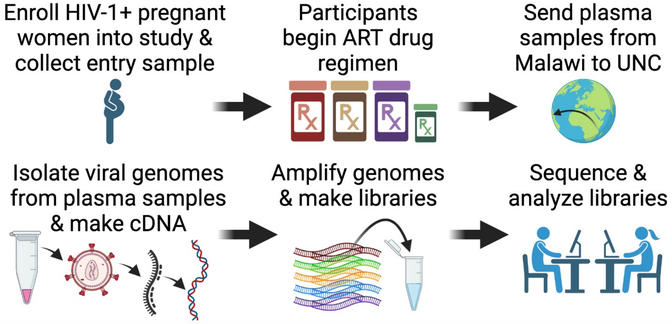
Do low-frequency drug resistance mutations increase likelihood of treatment failure?

❖ HIV-1 drug resistance mutations (DRMs) can be acquired at transmission, during untreated infection, or from poor adherence to antiretroviral therapy (ART) regimen.

❖ High frequency DRMs increase chances of treatment failure, but it is unclear if there is an association between **low frequency DRMs** and treatment failure.

❖ Low frequency DRMs are hard to distinguish from sequencing errors. We used **Primer ID** to establish viral population sampling depth in order to define sensitivity of detection and to reduce the error rate to accurately detect low frequency DRMs.

Methods





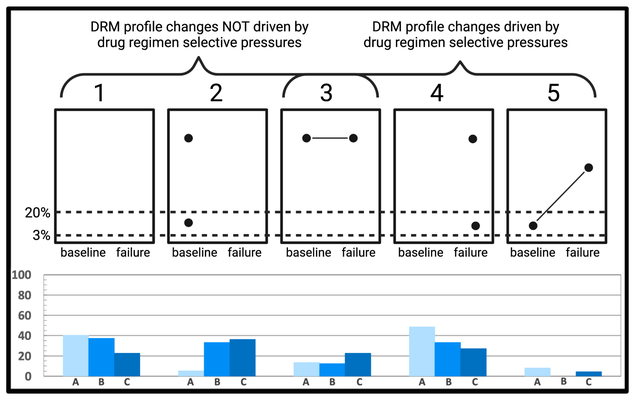
Participant characteristics at entry and outcome statistics

	A (N=193)	B (N=74)	C (N=73)	Total (N=340)	p value
Participant age: Median (Q1, Q3)	26.0 (22.0, 30.0)	30.0 (26.0, 33.0)	26.0 (23.0, 32.0)	27.0 (23.0, 31.0)	< 0.001
Viral Load, log10 copies/mL: Median (Q1, Q3)	4.36 (3.86, 4.76)	4.28 (3.65, 4.66)	4.41 (3.86, 4.87)	4.35 (3.79, 4.76)	0.284
Followup days tracked in study: Median (Q1, Q3)	1200 (1100, 1231)	968 (673, 1186)	750 (474, 1009)	1156 (812, 1218)	< 0.001
Treatment failure: % success % failure	143 (74.1%) 50 (25.9%)	44 (59.5%) 30 (40.5%)	41 (56.2%) 32 (43.8%)	228 (67.1%) 112 (32.9%)	0.012

The drug resistance mutation K103N can increase risk of ART treatment failure at both low and high frequencies

Due to high background of K103N and other NRTI and NNRTI drug resistance mutations in the population, Malawi's ongoing switch to an INSTI/NRTI 1st line ART regimen is well supported

Results

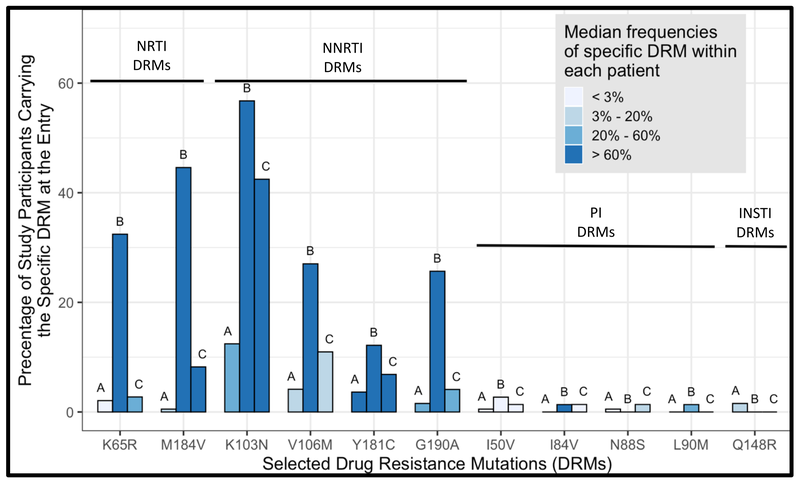


K103N significantly increases TF risk at both high and low frequencies	Hazard Ratio (Univariable)	Hazard Ratio (Multivariable) *stratified by vital load*
DRM is absent: 94 participants (75.8%)	*	*
High frequency: 18 participants (14.5%)	**3.29** (1.58-6.83)	**3.26** (1.52-6.98)
Low frequency: 12 participants (9.7%)	**2.44** (1.00-5.95)	**2.53** (1.00-6.37)

K103N: The K103N DRM increases treatment failure risk when present at ART initiation at either low frequency (<20% in the viral population) or high frequency (>20%).

DRM changes before / after treatment: Participants commonly ended the study with a different DRM profile than they started with. DRM changes were either consistent with drug regimen selective pressure, suggesting good adherence, or not, suggesting poor adherence.

Cohorts A, B, and C entered the study with different levels of resistance DRMs against several ART drug classes: Cohort B participants were more likely than Cohort A or C participants to carry more DRMs at higher frequency against a range of ART drug classes.



Conclusions

❖ The K103N drug resistance mutation can increase risk of treatment failure even at low frequency.

❖ Malawi's ongoing switch from an NNRTI/NRTI 1st line ART regimen to an INSTI/NRTI 1st line ART regimen is well supported.

❖ ART-experienced participants have greater risk of treatment failure and are more likely to carry more DRMs against previous ART drugs at higher frequency.

Acknowledgements

❖ Bwaila Family Health Unit in Lilongwe and UNC Project Malawi for sample collection

❖ Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) S4 project, Clinical Trial NCT02249962)

❖ This work was supported by NIAID (R01-AI140970).

❖ This research received infrastructure support from the UNC CFAR (P30-AI050410) and the UNC Lineberger Comprehensive Cancer Center (P30-CA016086).

❖ The support of the UNC High Throughput Sequencing Facility is also acknowledged