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Genotypic assessment of the viability of second-generation NNRTIs as an alternative therapy for ART-experienced individuals with multi-class HIV drug resistance in Botswana

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Background

- An increase in multi-class drug resistant (MDR) HIV variants substantially limits future antiretroviral therapy (ART) options
- There is constant need to monitor the emergence and spread of drug resistance to avoid selection of ineffective regimens
- **The study investigated the prevalence of MDR HIV-1 strains within ART experienced individuals in Botswana, and evaluated the susceptibility of these strains to second-generation non-nucleoside reverse transcriptase inhibitors (NNRTIs), doravirine (DOR), etravirine (ETR), and rilpivirine (RPV).**

Methods

Study Population

- This study included **4769** plasma derived HIV sequences from ART experienced individuals who had enrolled for the Botswana Combination Prevention Project (BCPP), 2013-2018, (n = 4747) and the Bosele study, 2015-2018, (n = 22)

Methods

- Sequences were aligned using the Los Alamos HIVAlign tool and adjusted for hypermutations according to the Hypermut tool
- Major HIV drug resistance mutations (DRMs) were analysed according to the Stanford HIV drug-resistance database.
- Participants harbouring MDR (resistance to ≥2 ARV classes), with at-least NNRTI resistance, were further evaluated for resistance to DOR, ETR, and RPV.
- The Stanford "DRM penalty scores" were utilised to predict resistance levels and interpretation (individuals with low-level, intermediate-level and high-level resistance were considered to have resistance) **[Figure 1]**

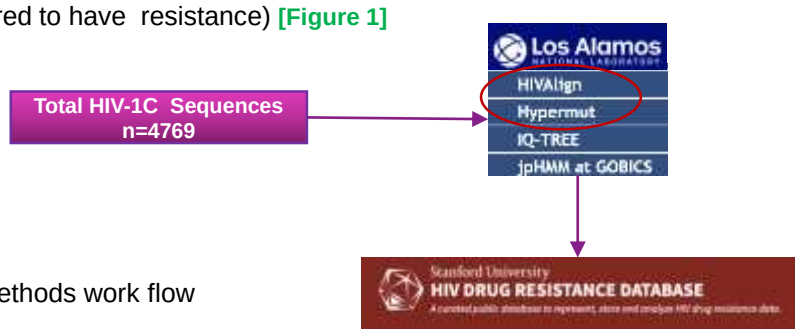

Figure 1: Methods work flow

Results

- 511 (45.5%) of 1122 individuals with NNRTI resistance had MDR **[Figure 2]**

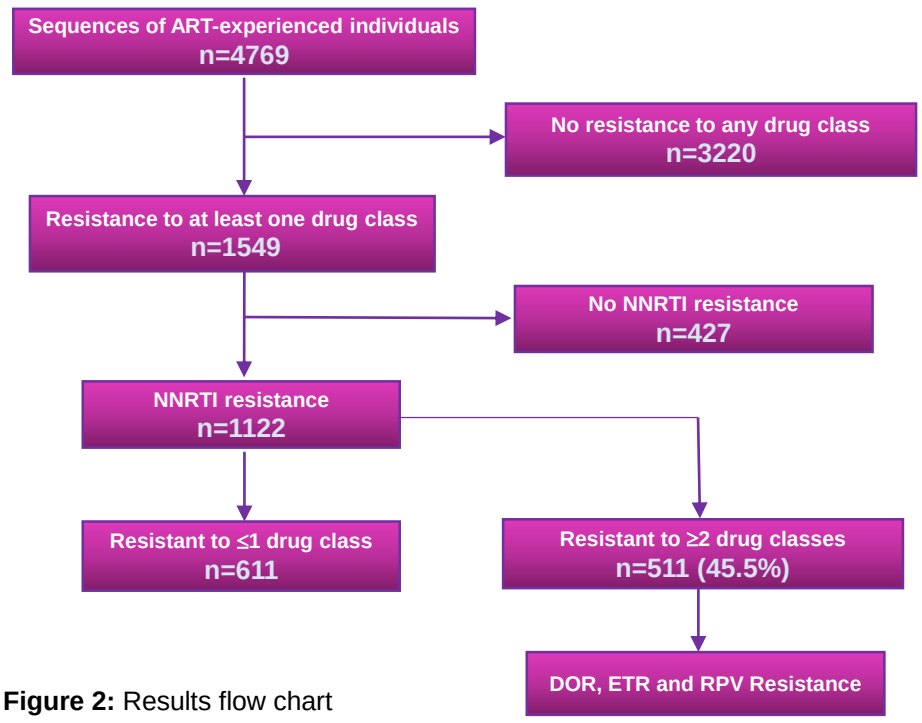

Figure 2: Results flow chart

DOR,ETR and RPV Resistance

- Overall, 495/511 (96.9%; 95% CI: 95.1-98.2) had resistance to at least one second-generation NNRTI
- 99/511 (19.4%) had resistance to 1 second-generation NNRTI: either RPV (81.9%) or ETR (18.9%)
- 30/511 (5.9%) had resistance to 2 second-generation NNRTIs: either RPV and ETR (53.3%) or RPV and DOR (46.7%)
- 366/511 (71.6%) were resistant to all three ARVs DOR, ETR and RPV

Results

- Majority of participants had low-level DOR (78.1%) and ETR (80.4%) resistance
- Mutations M230I (64.4%) and E138K (12.2%) both associated with high level RPV resistance were the most predominant **[Table 1]**
- MDR individuals failing second-generation NNRTIs had a high prevalence of resistance to NRTIs (399/495; 80.6%) and PIs (255/495; 51.5%) **[Figure 3]**

Table 1: Resistance to DOR, ETR and RPV, and prevalence of RAMs

	DOR (%) n=398	ETR (%) n=382	RPV (%) n=477
Overall (n=495)	80.4	77.2	96.4
Level of resistance			
Low Level	78.1	80.4	14.9
Intermediate	9	15.4	65
High Level	12.8	4.2	20.1
Specific Mutations			
A98G	-	-	3.6[a]
L100I	0.8[a]	0.8[b]	0.6[c]
K101E	3.5[a]	3.7[a]	2.9[b]
K101P	-	0.3[c]	0.2[c]
V106A	0.5[c]	-	-
V106M	4.0[b]	-	-
E138K	-	-	12.2[b]
E138Q	-	-	0.8[a]
Y181C	-	6.8[b]	5.5[b]
Y181I	-	0.3[c]	0.2[c]
Y188F	0.3[b]	-	0.2[b]
Y188L	1.5[c]	-	1.3[c]
G190E	7.8[c]	8.1[b]	6.5[c]
G190S	0.5[b]	-	-
H221Y	-	-	1.0[a]
P225H	2.3[b]	-	-
F227C	0.3[c]	0.3[b]	0.2[b]
F227L	0.8[c]	-	-
M230I	-	-	64.4[b]
M230L	0.5[c]	0.5[b]	0.4[c]
Y318F	0.3[c]	-	-

[a] Mutation associated with intermediate resistance
[b] Mutation associated with high-level resistance
[C] Mutation associated with low-level resistance
[-] Mutation associated with susceptibility to the drug

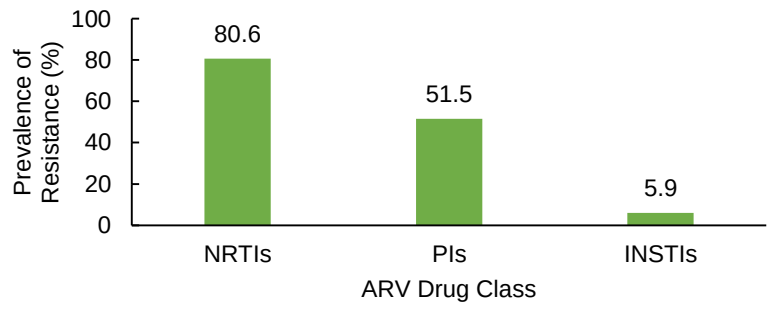

Figure 3 : Prevalence of resistance to NRTIs, PIs and INSTIs within MDR ART experienced individuals

Conclusion

- We observed high proportion of resistance to second-generation NNRTIs among treatment-experienced individuals with MDR HIV variants who had no prior exposure to second-generation NNRTIs.
- This limits their potential use as an alternative therapy for treatment experienced MDR individuals with MDR
- Our results strongly suggest genotypic resistance testing prior to ART use among treatment-experienced individuals.

Acknowledgments

BCPP and Bosele Study Participants

References

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