HIV Resistance Patterns in a Cohort of Adults Living with HIV Failing First-line Efavirenz-based Antiretroviral Therapy in South Africa

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Background

Human immunodeficiency virus (HIV) drug resistance poses a serious threat to antiretroviral therapy (ART) regimens. The ADORE study was designed to assess the efficacy of doravirine-based ART in people living with HIV (PLWH) experiencing virological failure on efavirenz-based first-line ART in Johannesburg, South Africa. This paper reviews the resistance patterns obtained thus far, with particular reference to doravirine, in participants screened for the aforementioned study.

Method

We are in the process of conducting a single-arm, phase 3, switch study to assess the efficacy of doravirine/lamivudine/tenofovir disoproxil fumarate in PLWH experiencing virological failure on first-line efavirenz-based ART with non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance. HIV genotypic drug resistance profiles are obtained at screening visits and major drug resistance mutations (DRMs) scored using the Stanford University HIV Drug Resistance Database, with the corresponding algorithm used to predict drug susceptibility.

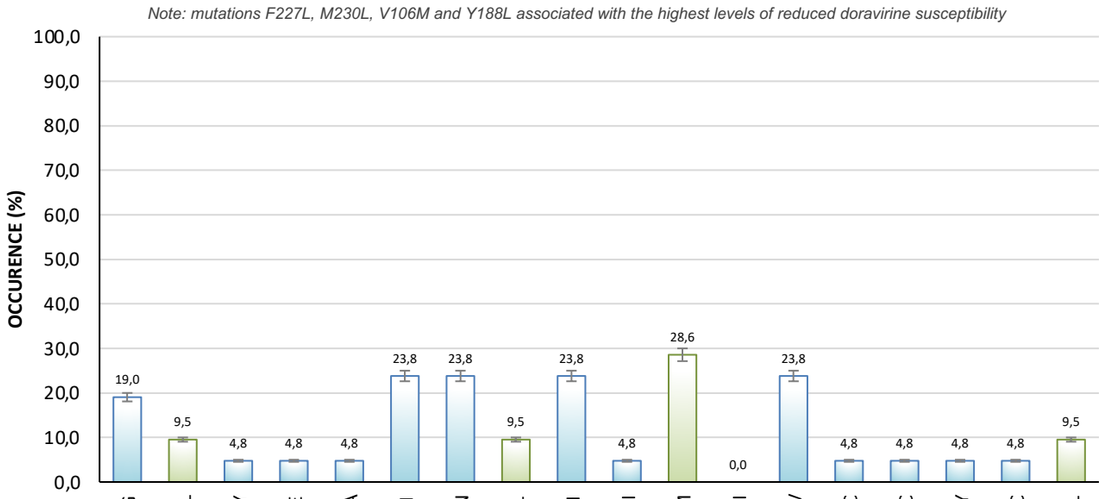
Results

A total of 40 individuals have been screened to date, with HIV genotypic drug resistance profiles obtained in 21 of those with unsuppressed viral loads. Of these participants, all were black, and 76.1% were female. The mean age was 35 years, and the mean baseline viral load 64 350 cp/mL with participants on ART for an average of 6 years.

At screening, major NNRTI resistance mutations associated with the highest levels of reduced susceptibility to doravirine (i.e., M230L, F227L, V106M and Y188L) were present in 57.1% (95% CI [35.9 – 78.3]) of participants, although 95.2% (95% CI [86.1 – 100.0]) exhibited varying levels of resistance to doravirine.

Image 1: Frequency of Baseline Doravirine-specific Mutations in ADORE Patients

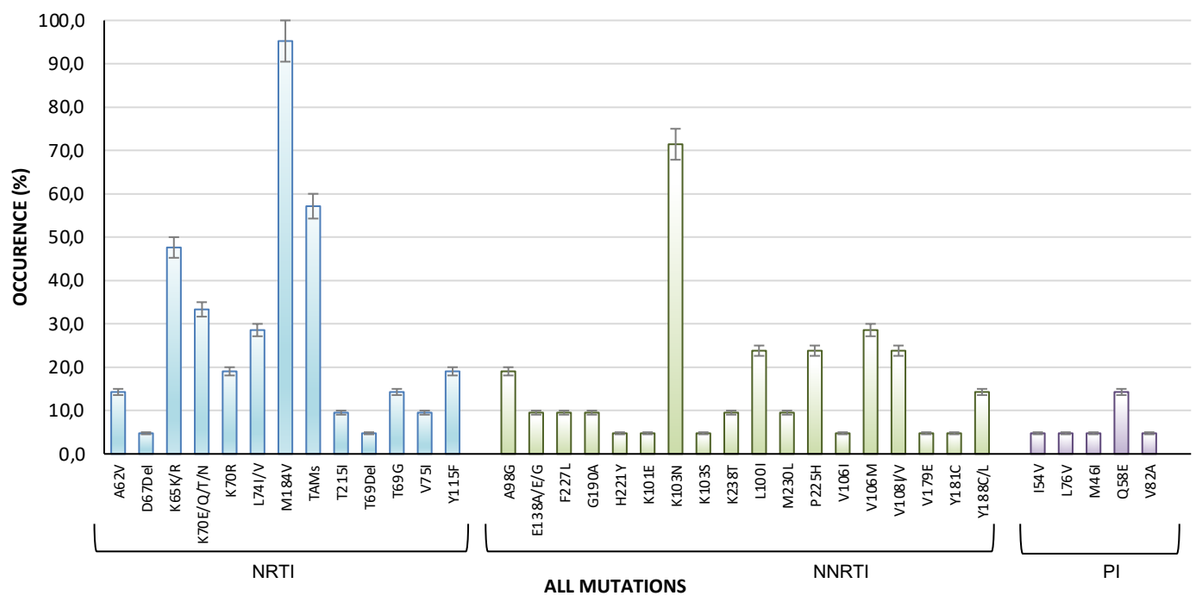
Note: mutations F227L, M230L, V106M and Y188L associated with the highest levels of reduced doravirine susceptibility



Results Cont.

Overall, the most common mutations present included M184V (95.2%, n=20), and K103N (71.4%, n=15). High-level resistance to both efavirenz and nevirapine was detected in 90.5% of participants, and full rilpivirine susceptibility maintained in 33.3% (n=7).

Image 2: Frequency of Significant HIV Resistance Mutations in ADORE Patients



Conclusion

Despite a small sample size, these insights offer valuable information into the resistance patterns of PLWH in South Africa, failing NNRTI-based first-line ART regimens. Cross-resistance within NNRTIs may be more prevalent with doravirine than recorded in previous clinical trials, this potentially compromising their role as an option for patients failing efavirenz-based regimens, particularly with the introduction of dolutegravir into ART programmes in South Africa. However, the clinical significance of this genotypic resistance is still poorly understood.

Regulatory approvals

We obtained ethical clearance from the University of the Witwatersrand Human Research Ethics Committee (191109B), Approval was granted by the South African Health Products Regulatory Authority (20200324).

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Table 1: Significant NNRTI Drug Resistance Mutations Per Participant

	AD-001	AD-004	AD-005	AD-006	AD-007	AD-008	AD-011	AD-012	AD-013	AD-014	AD-015	AD-016	AD-019	AD-023	AD-027	AD-028	AD-030	AD-033	AD-037	AD-039	AD-040
DOR Specific Drug Resistance Mutations	L100I L100I+K103N	**V106M**	A98G K101E K101E+G190A	**V106M Y188L**	**F227L V106M**	**V106M** Y188C	V108I/V	**M230L** V106I	**V106M** H221Y V108I/V V108IV+Y181C Y181C Y181C+H221Y	L100I L100I+K103N	**M230L**	L100I L100I+K103N	P225H	**F227L V106M**	P225H V108I/V	L100I L100I+K103N	A98G P225H V108I/V	A98G K103N+P225H P225H V108I/V	L100I L100I+K103N	**Y188L** A98G	P225H
DOR Stanford Score	30	50	35	110	100	60	15	70	110	30	60	30	30	100	45	30	60	55	30	75	30
EFV Stanford Score	120	120	75	120	120	120	70	105	110	120	105	120	115	120	145	120	130	130	120	145	135
RPV Stanford Score	60	0	90	60	0	0	0	70	70	60	60	60	10	15	0	60	15	15	60	90	0
VL at Genotyping (cp/mL)	17100	231000	14400	12500	89100	18900	4010	178000	28800	33600	65600	465000	16000	16100	41900	51000	11300	6940	20200	12500	17400
Time on ART (years)	7.9	1.8	9.2	1.4	15.0	2.3	1.5	3.0	2.9	1.3	11.3	2.1	2.1	7.9	11.2	13.1	18.1	8.4	2.8	2.8	5.5

Susceptible – low-level resistance
Intermediate resistance
High-level resistance

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