Pre-Treatment HIV Drug Resistance and Virologic Outcomes in the ADVANCE Trial

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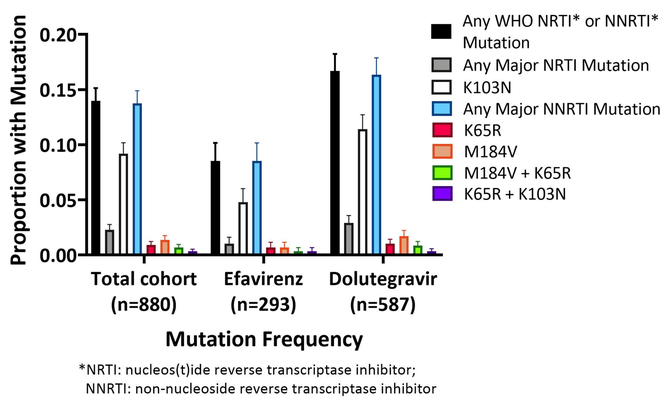
BACKGROUND

- Pre-treatment drug resistance (PDR) is rapidly increasing in sub-Saharan Africa[1]
- In response, Dolutegravir (DTG)-based ART has become first-line in much of the region
- **Hypothesis: PDR has a small but significant effect on outcomes with efavirenz (EFV)-based therapy and no effect on DTG-based therapy**

METHODS

- Data from the ADVANCE Study[2]
- Next-generation sequencing of pre-treatment plasma specimens
- **Primary Outcome** failure defined as any of:
  - Viral load > 1,000 copies/mL at 12 weeks or later
  - Viral load > 200 copies/mL at 24 weeks or later
  - Viral load > 50 copies/mL at 48 weeks or later
- **Secondary Outcome** failure defined as:
  - Consecutive visits viral load >200 copies/mL at ≥24 weeks
  - Detectable viral load at last study visit
- **Other Outcomes**
  - FDA 48-week snapshot analysis
  - FDA 96-week snapshot analysis
- **Primary Exposure of Interest**
  - PDR, defined as presence of any WHO-defined drug mutation at study visit prior to ART initiation[3]
- **Statistical Methods**
  - Described PDR in both groups (EFV vs DTG-based ART)
  - Estimated outcomes by group and presence of PDR
  - Fit multivariable regression models, with and without adjustment for demographic and clinical factors, and self-reported ART adherence

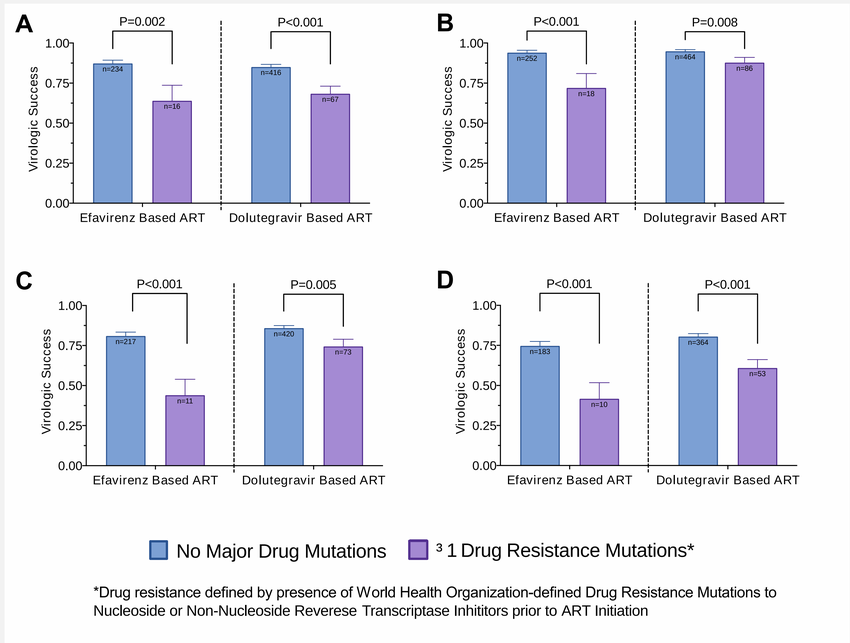
Figure 1. Prevalence of pre-treatment resistance in ADVANCE (n=880)



*NRTI: nucleos(t)ide reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor

Pre-treatment resistance to NRTIs and/or NNRTIs predicted virologic failure *for <u>both EFV and DTG-based regimens</u>*, before and after adjusting for clinical factors and ART adherence.

Figure 2. Virologic Suppression by Treatment Regimen and Presence or Absence of WHO-Defined Pre-treatment Drug Resistance. (A) Primary Outcome; (B) Secondary Outcome; (C) 48-week FDA Snapshot; (D) 96-week FDA Snapshot



*Drug resistance defined by presence of World Health Organization-defined Drug Resistance Mutations to Nucleoside or Non-Nucleoside Reverese Transcriptase Inhibitors prior to ART Initiation

Table 1. Participant Characteristics	Efavirenz Arm (n=293)	Dolutegravir Arms (n=587)	*P*-value
Female sex, n (%)	169 (58%)	362 (62%)	0.25
Age, median (IQR)	32 (27-37)	32 (27-37)	0.99
Married, n (%)	64 (22%)	114 (19%)	0.41
Tertiary or higher education, n (%)	21 (7%)	56 (10%)	0.23
Employed, n (%)	178 (61%)	365 (63%)	0.55
Baseline CD4, n (%)			
<200 cells/µL	87 (30%)	187 (32%)	0.69
201-350 cells/µL	89 (30%)	176 (30%)	
351-500 cells/µL	62 (21%)	106 (18%)	
>500 cells/µL	55 (19%)	118 (20%)	
Baseline viral load, n (%)			
<10k copies/ml	100 (34%)	186 (32%)	0.40
10k-100k copies/ml	124 (42%)	276 (47%)	
>100k copies/ml	69 (24%)	124 (21%)	
Any poor adherence	115 (39%)	255 (43%)	0.23
WHO-defined PDR, n (%)*	**25 (9%)**	**98 (17%)**	**0.001**

Table 2. Logistic Regression Models for Primary Outcome*	Univariable Models		Multivariable Model	
	OR (95% CI)	*P*-value	AOR (95% CI)	*P*-value
Female sex	0.85 (0.61- 1.19)	0.34	0.83 (0.55-1.26)	0.38
Age (per year)	**1.05 (1.03-1.07)**	**<0.001**	**1.03 (1.00-1.06)**	**0.05**
Married	1.61 (1.03-2.51)	0.04	1.09 (0.65-1.83)	0.74
Tertiary education	1.03 (0.58-1.84)	0.92	0.83 (0.44-1.60)	0.58
Employed	**2.02 (1.46-2.82)**	**<0.001**	**1.62 (1.09-2.42)**	**0.017**
Baseline CD4				
<200 cells/µL	REF		REF	
201-350 cells/µL	1.20 (0.80-1.81)	0.38	1.12 (0.72-1.96)	0.50
351-500 cells/µL	1.21 (0.76-1.91)	0.43	0.91 (0.51-1.63)	0.76
>500 cells/µL	1.20 (0.76-1.90)	0.43	1.01 (0.56-1.84)	0.96
Baseline viral load				
<10k copies/mL	REF		REF	
10k-100k copies/mL	**0.56 (0.38-0.84)**	**0.005**	**0.50 (0.30-0.83)**	**0.008**
>100k copies/mL	**0.48 (0.30-0.75)**	**0.002**	**0.35 (0.19-0.64)**	**0.001**
Any poor adherence	**0.34 (0.24-0.47)**	**<0.001**	**0.34 (0.23-0.50)**	**<0.001**
Study Group				
EFV arm	REF		REF	
DTG arms	0.71 (0.49-1.01)	0.056	0.88 (0.56-1.39)	0.59
Arm*WHO PDR	--		1.82 (0.61-5.42)	0.28
WHO PDR	**0.32 (0.21-0.48)**	**<0.001**	**0.24 (0.09-0.61)**	**0.003**

***Similar estimates for PDR observed with all four outcomes**

REFERENCES

1. Gupta et al, *Lancet HIV*, 2018
2. Venter et al, *NEJM*, 2019
3. https://hivdb.stanford.edu/page/who-sdrm-list

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