HIV Drug Resistance Mutations Associated with Virologic Failure in Women on Efavirenz-based ART following PROMISE Study

CL Boyce[1,2], T Sils[2], R Milne[2], D Ko[2], A Wong-on-Wing[2], M Mackey[2,3], N Higa[2], IA Beck[2], S Styrchak[2], P DeMarrais[4], C Tierney[4], MG Fowler[5], LM Frenkel[1,2,6], for the PROMISE Study Team

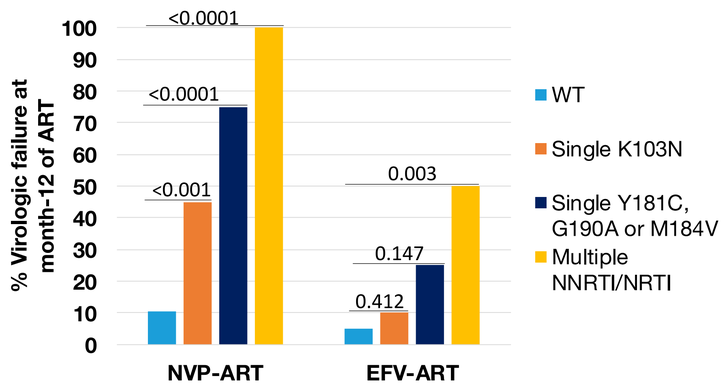
1 University of Washington, Department of Global Health, Seattle, WA, USA; 2 Seattle Children's Research Institute, Seattle, WA, USA; 3 Cornell University, Ithaca, NY, USA; 4 Harvard T. H. Chan School of Public Health, Center for Biostatistics in AIDS Research, Boston, MA, USA; 5 Johns Hopkins University, Department of Pathology, Baltimore, MD, USA; 6 University of Washington, Department of Pediatrics and Laboratory Medicine, Seattle, WA, USA

Introduction

BACKGROUND

- Efavirenz-based antiretroviral therapy (EFV-ART) is a WHO-recommended 1st-line ART
- Pre-treatment HIV-drug resistance (PDR) to 1st-line non-nucleoside reverse transcriptase inhibitor (NNRTI) is increasing in low-resource communities due to transmitted and selected mutations, particularly in women, in part from treatment to prevent mother-to-child HIV transmission (PMTCT)
- Studies of Kenyans initiating NNRTI-ART from 2006-14:
  - PDR increased to 11% and to >20% in women 18-24yo
  - In 2014, drugs switched: NVP to EFV and ZDV to TDF
- Virologic failure (VF) varied by ART regimen (Figure 1):

Figure 1. VF at month-12 of NVP+ZDV- or EFV+TDF-ART by number of pre-ART DR mutations detected by OLA vs. wild type



OBJECTIVE OF THIS STUDY

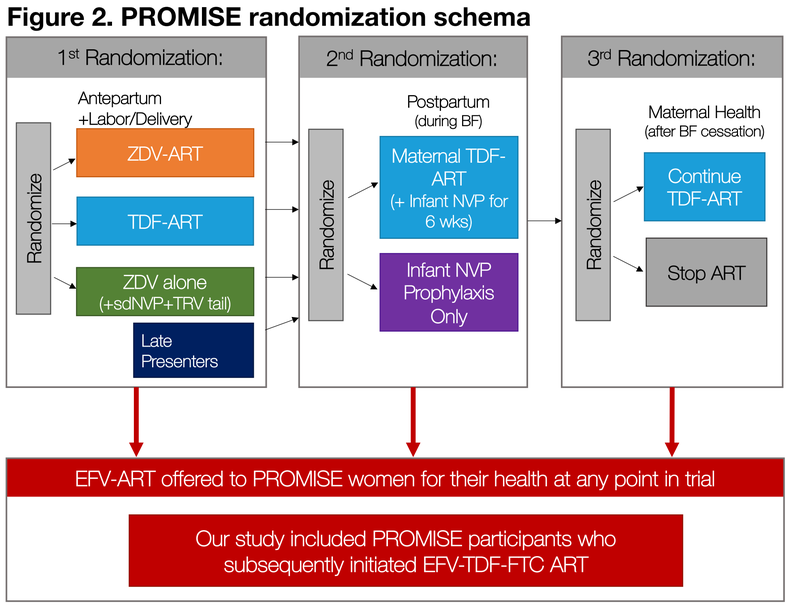
Assess if pre-EFV-ART DR in PROMISE Study participants who subsequently initiated EFV-ART is associated with VF

Methods

SUBJECTS

Participants in PROMISE study 1077BF (of strategies for PMTCT; Figure 2) who subsequently started EFV-ART for their own health; initiated EFV-ART at any point during the study

Figure 2. PROMISE randomization schema



INCLUSION CRITERIA

PROMISE women who initiated EFV-ART and had:

- Enrollment plasma HIV RNA ≥400c/mL available
- Plasma available just prior to EFV-ART initiation
- Plasma HIV RNA known at month-6 and -12 of EFV-ART

METHODS & ANALYSES

- Genotyped PR & RT by consensus sequencing (CS)
- Illumina sequencing with "Primer ID" technology for minority variants
- Phylogenetic and bioinformatic analyses used for quality assurance
- Virologic failure was defined as HIV RNA >400c/mL
- NRTI- & NNRTI-associated mutations with Stanford Database score >10 were analyzed (Table 1)
- Rates of EFV-ART VF compared by pre-EFV genotype and PROMISE antepartum (AP) treatment arm (Fisher's Exact test)

Table 1. Mutations included as DRMs in the analyses

NRTI:	M41L, K65R*, D67N, K70_, L74I*, V75I, M184_, T215_, K219_
NNRTI:	A98G, L100I, K101_, K103_, V106_, V108I, Y181C, Y188_, G190_, H221Y, P225H, M230L*, K238T

*DRMs not found in any of the women in this study

Results

Figure 3. Pre-EFV DR and VF by month-6 or -12 of EFV-ART by clinical site and overall

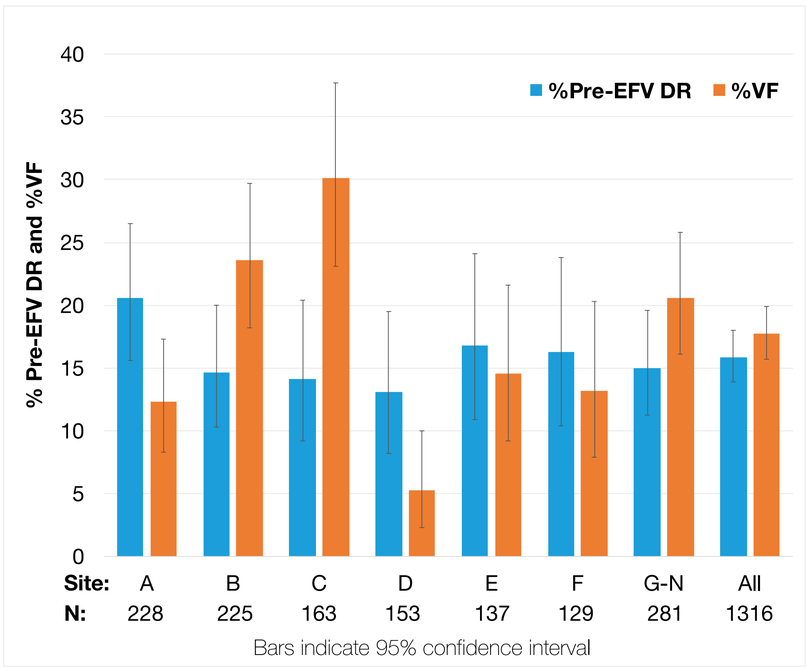


Figure 4. VF by pre-EFV genotype across clinical sites and overall

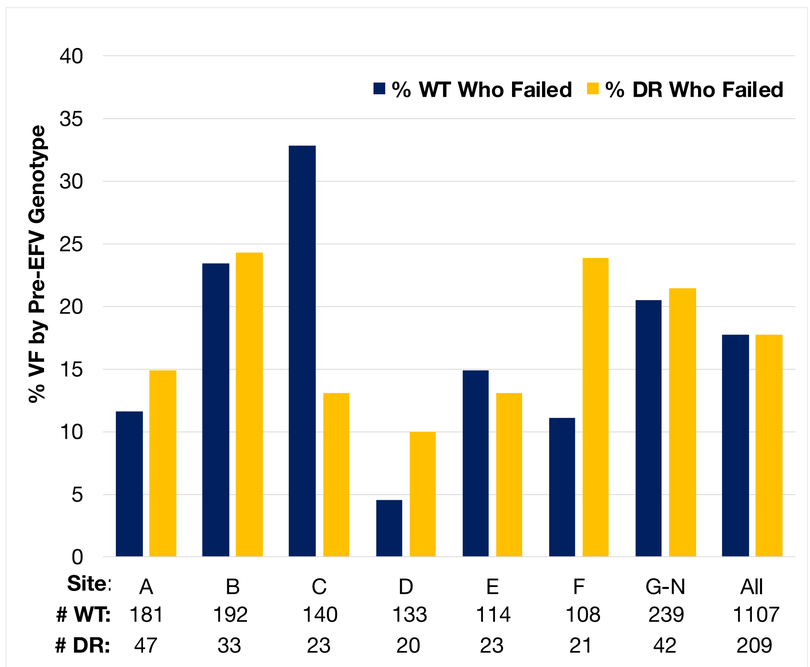


Table 3. VF by pre-EFV genotype

Pre-EFV Genotype	Total # Women	# (%) VF	p-value
WT	1,107	196 (17.7)	reference
1 NRTI only	13	0 (0)	0.2362
K65R only	0	0 (--)	N/A
K70R only	4	0 (0)	1.0000
M184V only	1	0 (0)	1.0000
≥ 2 NRTI only	0	0 (--)	N/A
1 NNRTI only	169	26 (15.3)	0.5897
K103N only	97	18 (18.6)	0.8918
Y181C only	8	1 (12.5)	1.0000
G190A only	5	0 (0)	1.0000
≥ 2 NNRTI only	19	4 (21.1)	0.7674
NRTI & NNRTI	**8**	**7 (87.5)**	**<0.0001**

N/A = not analyzed

Table 4. VF by previous PMTCT treatment arm: ZDV alone vs ART

Antepartum Treatment Arm	Total # Women	# (%) VF	p-value
ZDV Alone	553	87 (15.7)	Reference
ART (TDF or ZDV)	763	146 (19.1)	0.1941

Table 5. VF within previous antepartum treatment arm by pre-EFV genotype

AP Treatment Arm	Pre-EFV Genotype	Total # (%) Women	# (%) VF on EFV-ART	p-value
ZDV-ART (ZDV-3TC/LPV-RTV) Median EFV-ART Initiation: 836 days post-delivery (IQR: 509-1113 days)	Total	582	119 (20.5)	N/A
	WT	496 (85.4)	104 (21.0)	Reference
	Any DRM	85 (14.6)	15 (13.8)	0.5618
	NRTI DRM only	5 (0.9)	0 (0.0)	0.5888
	NNRTI DRM(s) only	75 (12.9)	11 (14.7)	0.2786
	NRTI & NNRTI	**5 (0.9)**	**4 (80.0)**	**0.0086****
TDF-ART (TDF-FTC/LPV-RTV) Median EFV-ART Initiation: 441 days post-delivery (IQR: 271-616 days)	Total	181	27 (14.8)	N/A
	WT	149 (81.9)	16 (10.7)	Reference
	Any DRM	**33 (18.1)**	**11 (31.3)**	**0.0024****
	NRTI DRM only	0 (0.0)	0 (--)	1.0000
	NNRTI DRM(s) only	**31 (17.1)**	**10 (32.3)**	**0.0043****
	NRTI & NNRTI	**1 (0.6)**	**1 (100)**	**0.1133**
ZDV Alone (+sdNVP+TRV tail) Median EFV-ART Initiation: 857 days post-delivery (IQR: 491-1110 days)	Total	553	87 (15.7)	N/A
	WT	461 (83.3)	76 (16.5)	Reference
	Any DRM	92 (16.6)	11 (10.0)	0.3468
	NRTI DRM only	8 (1.4)	0 (0.0)	0.3649
	NNRTI DRM(s) only	82 (14.8)	9 (11.0)	0.2493
	NRTI & NNRTI	**2 (0.4)**	**2 (100)**	**0.0281***

*p < 0.05; **p < 0.01; N/A = not analyzed

Summary & Conclusions

SUMMARY

- Pre-EFV-ART DR was detected in 209/1,316 women (15.9%, 95% CI: 13.9-18%)
- VF was detected in 233/1,316 women (17.7%, 95% CI: 15.7-19.9%)
- Pre-EFV DR prevalence and rates of VF varied across the 14 clinical sites (IQR = 11.2-18.8% and IQR = 12.4-28.5%, respectively)
- Rates of VF by 6-12 months of EFV-ART (Table 2) did not differ by pre-EFV genotype by CS (17.7% vs. 17.7%, p=1.0)
- Single or multiple NRTI or NNRTI DRMs were not associated with VF compared to no DRM (p=0.40 and p=0.77, respectively)
- Pre-EFV DR to multiple drug classes (≥1 NRTI & ≥1 NNRTI DRMs) was associated with increased VF (p<0.0001)
- Past randomization to ART vs ZDV in PROMISE did not significantly impact rates of VF (p=0.1941)
- Any Pre-EFV DR found after past randomization to TDF-ART was associated with VF whereas only multi-class PDR was associated with VF for ZDV-ART
- Illumina sequencing analyses of minority variants in women with wild-type pre-EFV genotype and VF is ongoing

CONCLUSIONS

- Pre-EFV-ART drug resistance data from PROMISE trial aligns with previous observations in Kenya:
  - ➢ Single NRTI or NNRTI DRMs do not significantly impact rates of VF to EFV-ART
  - ➢ EFV-ART does not appear to suppress replication of multi-class drug-resistant HIV
- This study suggests:
  - ➢ EFV-ART is a more potent regimen compared to NVP-ART
  - ➢ Detection of multi-class PDR could extend the effective use of EFV-ART in resource limited settings

Acknowledgements

Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) was provided by the National Institute of Allergy and Infectious Diseases (NIAID) with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH), all components of the National Institutes of Health (NIH), under Award Numbers UM1AI068632 (IMPAACT LOC), UM1AI068616 (IMPAACT SDMC) and UM1AI106716 (IMPAACT LC), and by NICHD contract number HHSN2752018000011. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

IMPAACT International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Seattle Children's HOSPITAL · RESEARCH · FOUNDATION

Presented at the XXVII International Workshop on HIV Resistance and Treatment Strategies Johannesburg, October 22-23, 2018