Pretreatment drug resistance and virological failure in South African patients on first-line ART

findings from the ITREMA trial

Lucas Hermans, MD

NDLOVU CARE GROUP
UMC Utrecht
WITS REPRODUCTIVE HEALTH & HIV INSTITUTE
Universiteit Utrecht
Radboudumc

Background

- Pretreatment drug resistance (PDR) in LMIC is increasing[1]
  - Infection with viral strains that are already resistant to ART
  - Resistance selection during previous (undisclosed) exposure to ART
- NNRTI mutations are predominant
- PDR increases linked to roll-out of first-line treatment [1]

1: Gupta R, LID 2017

PDR and treatment failure

- Effect of PDR on treatment failure in LMIC established in previous studies[2]

- Limited evidence of effect of PDR on treatment outcomes in currently available first-line regimens

- One recent study did not find association between PDR and outcome (viral rebound >1000 c/mL at week 48 of ART)[3]

2: Bertagnolio S, WHO PDR guidelines 2017, 3: Derache A, CROI 2017

Methods

- ITREMA open-label RCT (NCT03357588)
  - Adult HIV-1 infected patients
  - Either initiating first-line ART or stable on first-line ART (last viral load <1000 c/mL)
  - Control arm: Viral load (VL) monitoring according to SA/WHO guidelines
  - Intervention arm: Intensified VL monitoring, and drug level and resistance testing. Interventions only initiated upon rebound
- Implemented as pragmatic RCT at a rural clinical site (Limpopo, South Africa)
- Previous ART exposure was assessed systematically using a questionnaire
- Current status
  - 501 participants recruited: 207 enrolled while initiating first-line ART
  - Year 1 (week 48) follow-up completed

Laboratory testing procedures

- Viral load (VL) testing
  - ART initiation: batch-wise retrospective
  - Week 24 of ART
  - Week 48 of ART

- Population-based RT sequencing (plasma)
  - ART initiation: batch-wise retrospective
  - At viral rebound (ongoing)

- Efavirenz & lopinavir drug level testing (plasma)
  - ART initiation: retrospective, in patients with pretreatment VL<1000 c/mL or established PDR, to assess potential undisclosed current ART

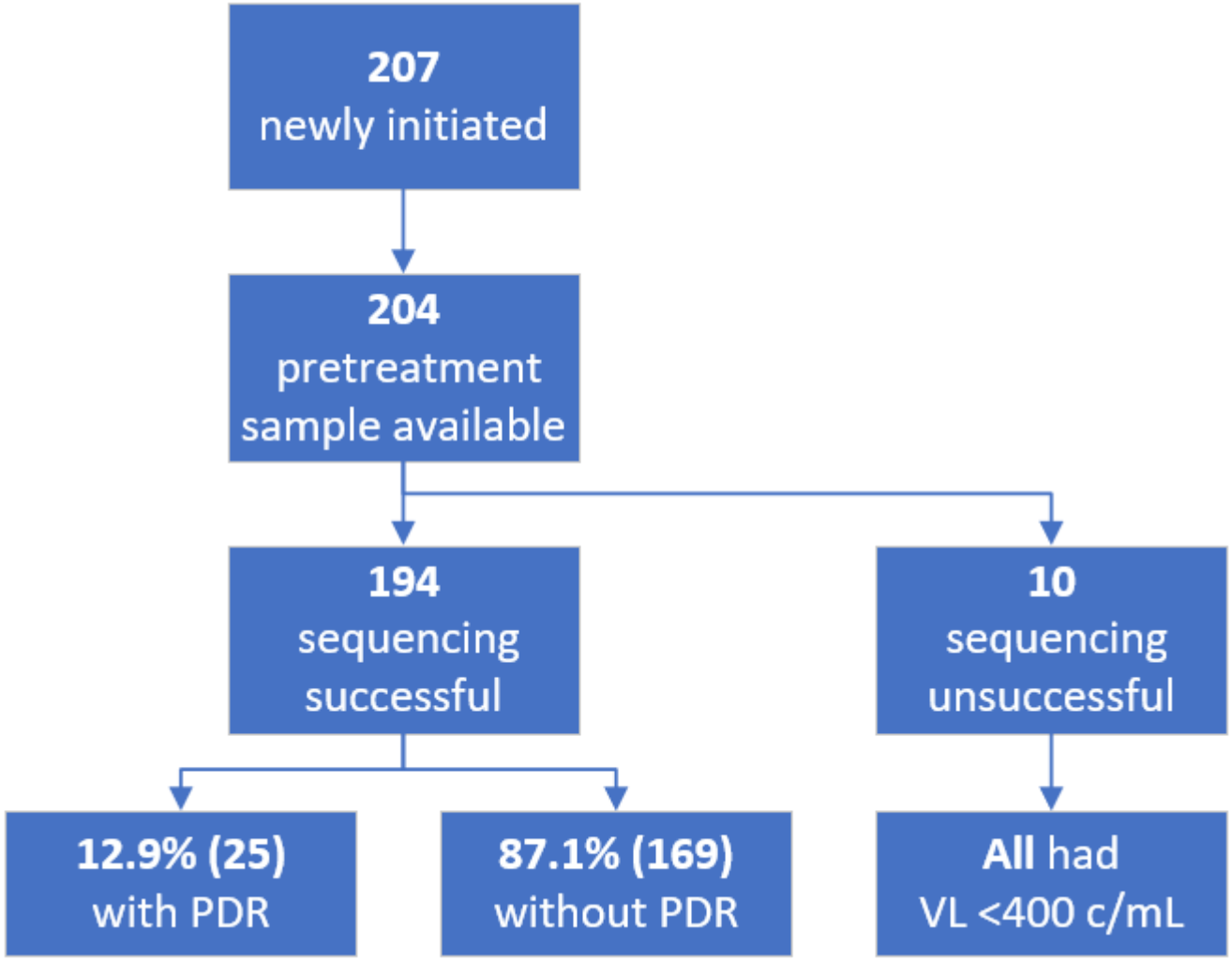
Participant characteristics

207 patients newly initiated on ART

Sex	*% female*	60.4% [125/207]
Age	*median [IQR]*	38.8 years [31.4 – 46.7]
CD4 count at start ART		191 cells/uL [70 - 355]
First-line ART		
	TDF/FTC/EFV (%)	96.6% (200/207)
	ABC/3TC/EFV (%)	3.4% (7/207)
Reported prior ART		
	Overal (n)	6.3% (13/207)
	TDF/FTC/EFV (%)	46.2% (6/13)
	As part of PMTCT, regimen unkown (%)	15.4% (2/13)
	Regimen unkown (%)	38.5% (5/13)

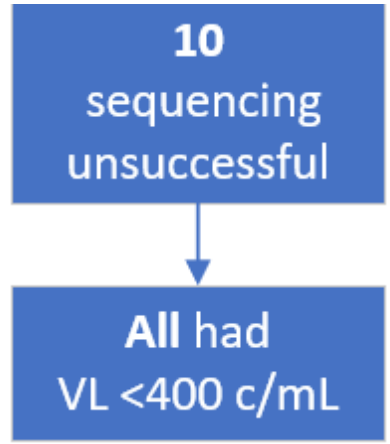
Note: *ART = Antiretroviral therapy; CD4 count = CD4+ T-lymphocyte count; cells/uL = cells per microliter; IQR = Interquartile range*

Pretreatment drug resistance



Pretreatment drug resistance

χ^2-test



Reported prior ART	20% (5)	32% (8)	4.1% (7)	p = 0.009	10% (1)	50% (5)
Detectable EFV at ART initiation	20% (5)		*NA*	*N/A*	40% (4)	
VL >1000 c/mL within 48 wks of ART	56.3% (9/16)		17.4% (24/138)	p = 0.001		
Confirmed failure within 48 wks of ART	37.5% (6/16)		5.8% (8/138)	p = 0.0002		
LTFU within 24 wks of ART	32.0% (8/25)		15.0% (22/147)	P = 0.03		

NNRTI resistance (19/25)

NNRTI-mutations	Frequency	Reported prior ART	drug level	rebound >1000 c/mL
K103N	53.6% (10)	**20% (2)**	**20% (2) EFV**	**37.5% (3/8)**
V106M	10.5% (2)	None	None	**0.0% (0/1)**
Y181C	10.5% (2)	**50% (1)**	None	**100.0% (1/1)**
Y188L	5.3% (1)	None	None	**100.0% (1/1)**
K103N/S + V106M	5.3% (1)	None	None	***N/A***
K101E + K103N	5.3% (1)	None	None	**0.0% (0/1)**
L100I + K103N	5.3% (1)	None	None	***N/A***
K103N + P225H	5.3% (1)	None	None	***N/A***

Note: *NRTI = Nucleos(t)ide Reverse Transcriptase inhibitor; NNRTI = non-NRTI; EFV = Efavirenz; c/ml = copies/milliliter*

NNRTI+NRTI resistance (6/25)

NRTI-mutations	NNRTI-mutations	Reported prior ART	drug level	Outcome
K65R + Y115F + M184V + K219E	K103S + Y181C	No	Neg	**virological failure**
K65R + K70T + M184V	K103N + V108I + E138A + P225H + K238T	No	**EFV pos**	**virological failure**
M184V	V106M + E138A + V179E	No	Neg	**virological failure**
M184V + T215I	A98G + K103N + V108I + P225H	No	Neg	**virological failure**
M184V	K103S + V106M	**Yes, stopped >1yr**	**EFV pos**	**LTFU**
M184V + K219E	K103N + P225H + K238T	**Yes, stopped >4yr**	**EFV pos**	**LTFU**

Note: *NRTI = Nucleos(t)ide Reverse Transcriptase inhibitor; NNRTI = non-NRTI; EFV = Efavirenz; c/ml = copies/milliliter*

PDR & viral rebound week 48 - OT

	Dependent variable: **Viral rebound >1000 c/mL**	
	model 1	*model 2*
Pretreatment drug resistance	8.5*** [2.5 - 30.6]	*N/A*
NNRTI monoresistance	*N/A*	4.1(ns) [0.96 - 16.8]
NNRTI+NRTI resistance	*N/A*	*4/4 virological failure*
Reported prior ART	0.4(ns) [0.04 - 2.7]	0.6(ns) [0.06 - 3.9]
Sex: male	2.9* [1.2 - 7.4]	3.1* [1.2 - 8.1]
Age at start ART	0.8(ns) [0.5 - 1.2]	0.8(ns) [0.5 - 1.2]
CD4 at start ART		
<50 cells/mL	*Ref*	*Ref*
50-200 cells/mL	0.99(ns) [0.33 - 3.17]	1.16(ns) [0.37 - 4.01]
>200 cells/mL	0.35(ns) [0.10 - 1.24]	0.39(ns) [0.10 - 1.45]

Note: *Results are displayed as adjusted odds ratios [95% confidence intervals]. LLV = Low-level viremia; CD4 = CD4+ T-lymphocyte count; (ns) = p≥0.05; * = p<0.05; ** = p<0.01; *** = p<0.001.*

PDR & confirmed failure week 48 - OT

	Dependent variable: **Confirmed virological failure**	
	model 1	*model 2*
Pretreatment drug resistance	14.6*** [3.4 - 70.7]	*N/A*
NNRTI monoresistance	*N/A*	3.7(ns) [0.3 - 26.3]
NNRTI+NRTI resistance	*N/A*	*4/4 virological failure*
Reported prior ART	1.1(ns) [0.1 - 7.4]	2.1(ns) [0.2 - 14.3]
Sex: male	1.2(ns) [0.3 - 4.4]	1.3(ns) [0.3 - 5.4]
Age at start ART	0.9(ns) [0.5 - 1.8]	0.8(ns) [0.4 - 1.6]
CD4 at start ART		
<50 cells/mL	*Ref*	*Ref*
50-200 cells/mL	0.14* [0.02 - 0.67]	0.14* [0.02 - 0.84]
>200 cells/mL	0.18* [0.03 - 0.79]	0.20* [0.04 - 0.96]

Note: *Results are displayed as adjusted odds ratios [95% confidence intervals]. LLV = Low-level viremia; CD4 = CD4+ T-lymphocyte count; (ns) = p≥0.05; * = p<0.05; ** = p<0.01; *** = p<0.001.*

Conclusions

- PDR prevalence of 13% was found in this population
  - 8/25 patients evidence suggesting acquired drug resistance
- PDR was significantly associated with poor treatment outcomes
- Association mainly driven by dual NNRTI+NRTI resistances
- Efforts to uncover prior ART exposure are indicated in clinical practice

Acknowledgements

Annemarie Wensing
Monique Nijhuis
Rob Schuurman
Marije Hofstra
Mirjam Kretzschmar
Kiki Tesselaar
Sigrid Vervoort

Hugo Tempelman

Francois Venter

John de Wit

David Burger
Rob ter Heine

Supported by The Netherlands Organisation for Scientific Research (ZonMW) and NOW-WOTRO Science for global development