

Integrated adherence counselling using biomedical and socio-economic information

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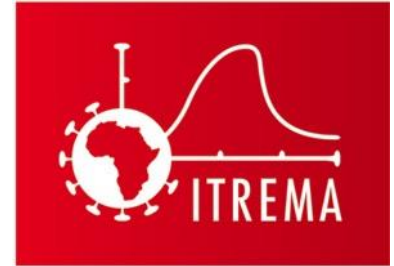
UMC Utrecht



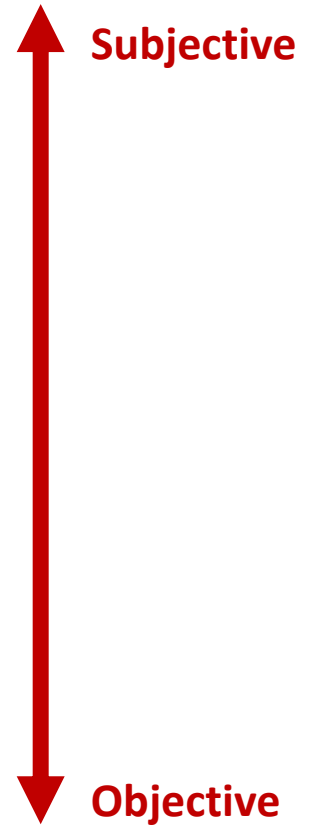
Universiteit Utrecht

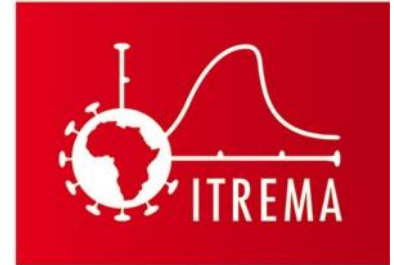
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Insight in adherence



- Measure self-reported adherence
- Perform pill counts, review clinic attendance
- Repeat viral load
- Specialized adherence testing, drug level testing





Case #1

17 year old female

Vertical transmission, presented to clinic at 8 years old (ART naïve), CD4 20 cells/mL, mother passed away shortly after birth, father taking care of his child alone.

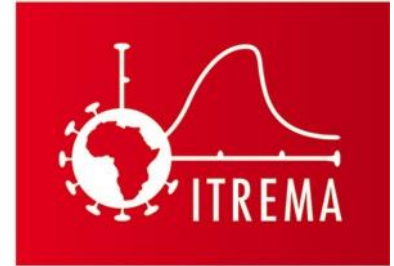
Initiated ART: AZT/3TC/NVP. Viral rebound after 24 months of ART. Switched to 2nd line ART (AZT/3TC/LPVr) at 10 years old.

Virological suppression on 2nd line until 16 years old, then intermittently defaults treatment. Visits clinic irregularly.

Brought to clinic by father, who is now extremely worried:

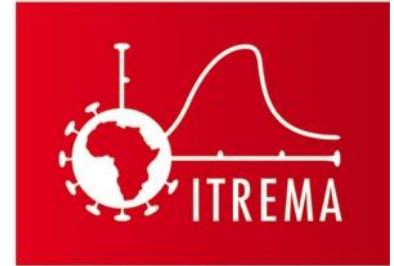
- Virological failure for one year: last VL 57540 copies/mL
- 26 weeks pregnant

Case #1 (ctd)



- Drug resistance testing was urgently requested (t=0)
 - Intensified adherence support while awaiting test results
 - Results (now 29 weeks pregnant): **No resistance, wild-type virus**
 - VL repeated (32 weeks pregnant): <50 copies/mL
- Delivered healthy HIV-negative boy

Retrospective drug level test during failure: NEGATIVE



Case #2

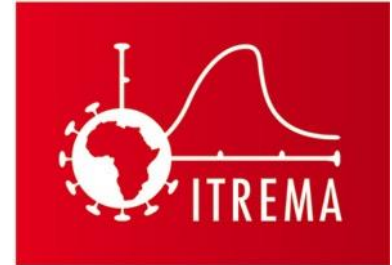
46 year old male

Initiated on ART 38 years old, transferred in with 1st line failure after 24 months of ART (3TC/AZT/EFV).

Switched to 2nd line (3TC/AZT/LPVr), but never suppressed. Viral loads:

m6	44309 c/mL
m12	6790 c/mL
m24	4798 c/mL
m36	3981 c/mL
m48	44136 c/mL

Case #2 (ctd)



- Drug resistance testing requested

PI Major Resistance Mutations: **M46I, I54V, L76V, V82A**
PI Accessory Resistance Mutations: **L10F**
Other Mutations: K14R, I15V, G16E, L19I, K20R, E35D, M36I, R41K, R57K, D60E, Q61N, L63T, H69K, L89I, I93L

Protease Inhibitors

atazanavir/r (ATV/r) High-Level Resistance
darunavir/r (DRV/r) Low-Level Resistance
lopinavir/r (LPV/r) High-Level Resistance

NRTI Resistance Mutations: **M41L, E44D, D67N, M184V, L210W, T215Y, K219N**
NNRTI Resistance Mutations: **E138A, V179D, M230L**
Other Mutations: I2V, P4S, V35T, T39E, S48T, V60I, K103R, K104R, V106I, V111I, V118I, K122E, D123S, I135V, T139A, S162F, K173T, Q174K, T200A, E203V, Q207E, H208Y, R211K, L228H, V245Q, E248D, A272S, L283I, R284K, I293V, P313Q

Nucleoside Reverse Transcriptase Inhibitors

abacavir (ABC) High-Level Resistance
zidovudine (AZT) High-Level Resistance
emtricitabine (FTC) High-Level Resistance
lamivudine (3TC) High-Level Resistance
tenofovir (TDF) High-Level Resistance



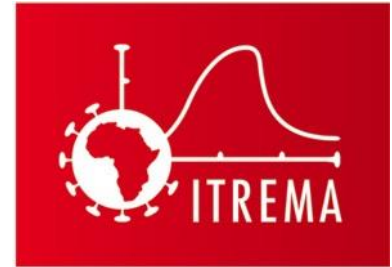
Stanford University

HIV DRUG RESISTANCE DATABASE

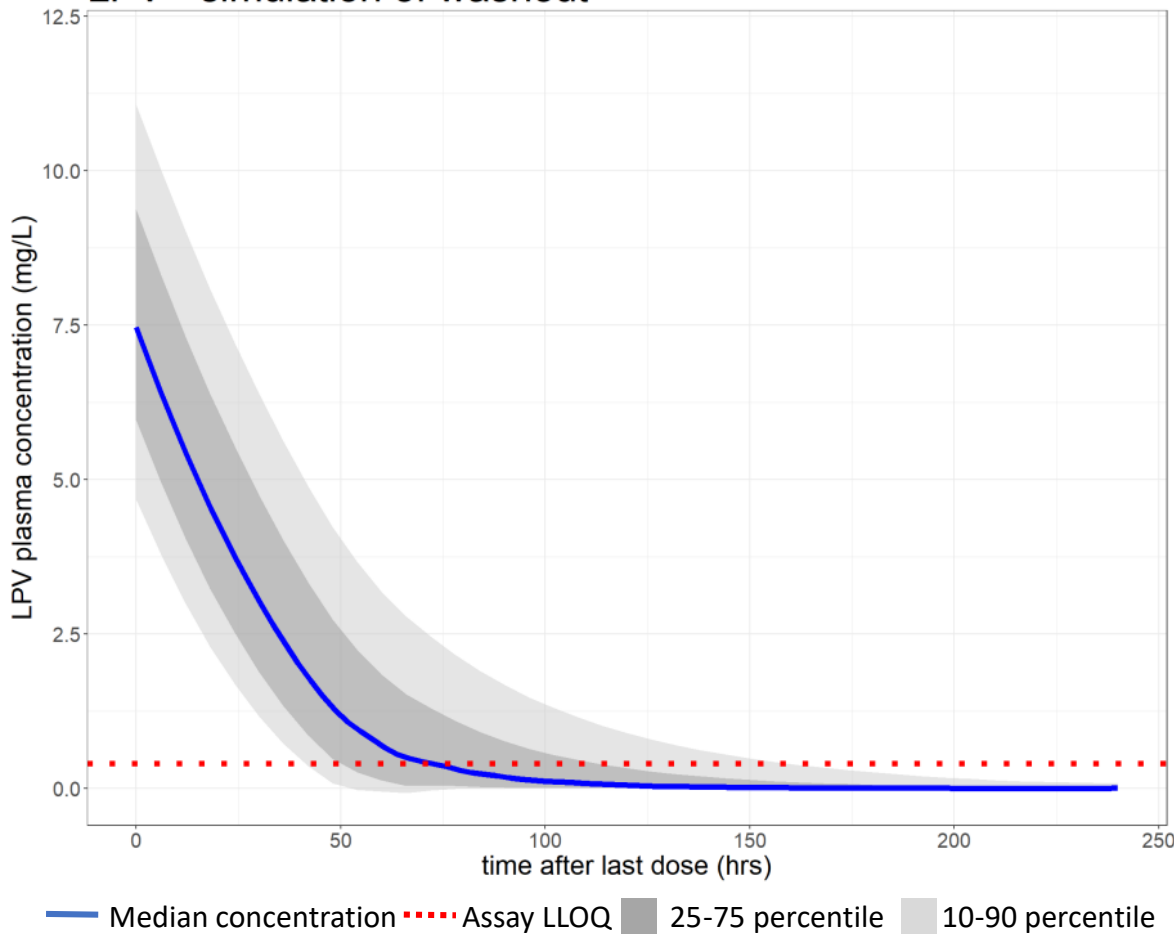
A curated public database to represent, store and analyze HIV drug resistance data.

- Third-line ART requested from third-line committee.
 - Patient switched to third-line ART and currently suppressing
- Retrospective drug level test at time of failure: POSITIVE**

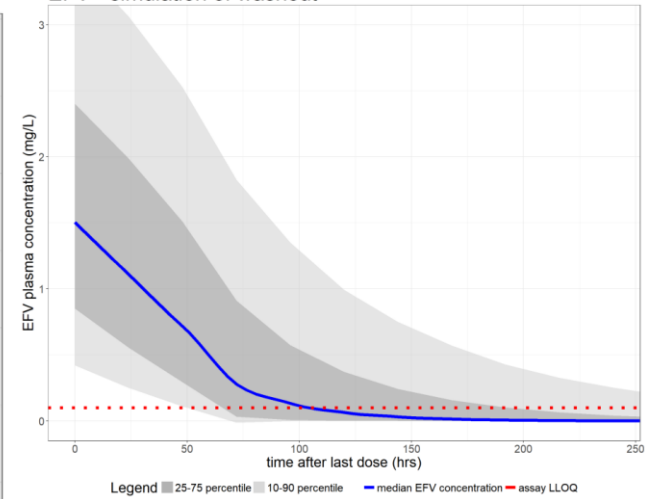
Significance of a negative drug level test



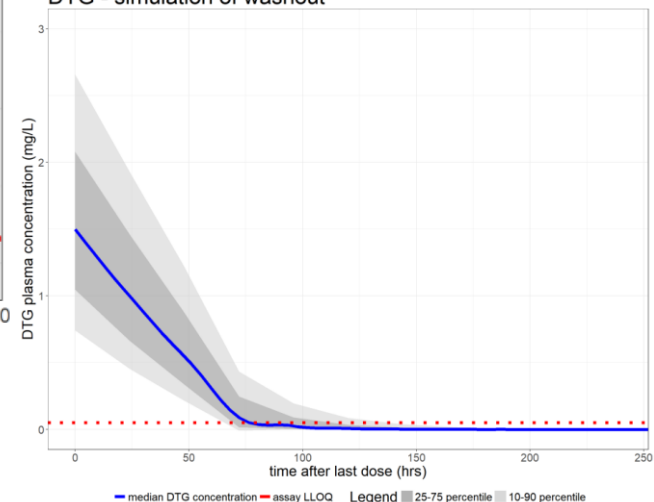
LPV - simulation of washout



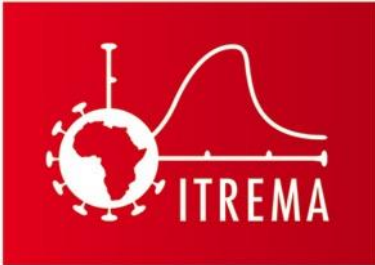
EFV - simulation of washout



DTG - simulation of washout

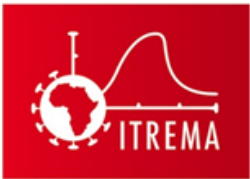


Evaluation of ITREMA strategy



First-line ART

Prospective evaluation
(ITREMA Open-label RCT)



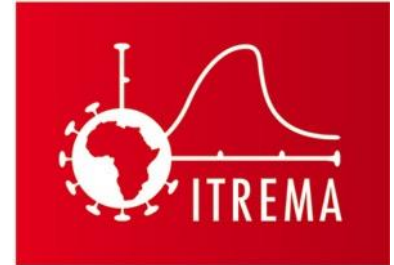
Second-line ART

Retrospective evaluation
(Single centre clinic-based)



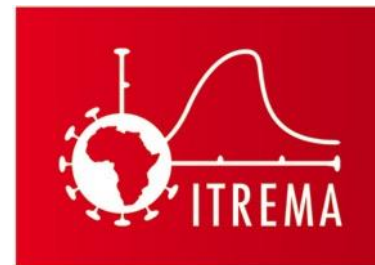
Retrospective evaluation
(Multicentre lab-based)

Pilot study



- Clinical implementation project
 - Adults on second-line ART at Ndlovu Medical Centre (Limpopo, SA)
 - Confirmed VL >1000 copies/mL >12 months of second-line ART
- DBS-based population-based sequencing of PR-RT at WHO reference laboratory (UMCU)
 - Drug susceptibility interpreted according to Stanford
- DBS-based LPV drug testing (UMCU)
 - DBS-based liquid chromatography-tandem mass spectrometry
 - ≥ 0.25 mg/L \rightarrow “positive” result
 - Batch-wise retrospective

Pilot study - patients

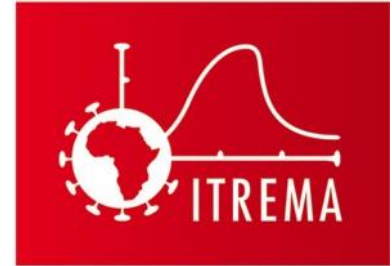


Characteristics of patients (*n* = 60)

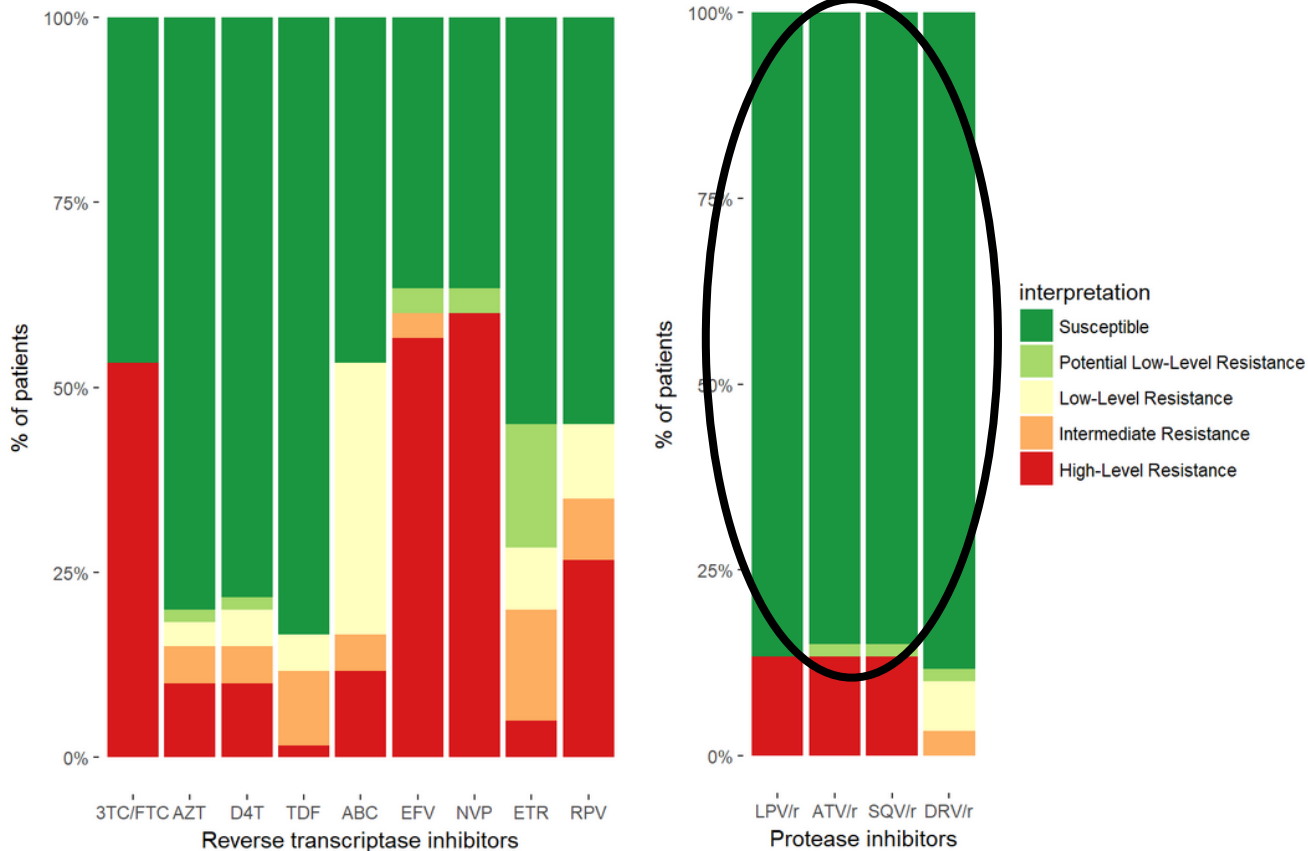
Gender	<i>% female</i>	56.7%
Age	<i>median [IQR]</i>	36.6 years [31.7 - 46.4]
Duration of ART		5.0 years [2.7 - 6.2]
Duration of second-line ART		2.4 years [1.2 - 4.1]
CD4 count at start ART		98 cells/uL [47 - 1912]
CD4 count at second-line failure		226 cells/uL [104 - 357]
log HIV-RNA at 2nd line failure		4.6 log copies/ml [3.9 - 5.2]
Current ART treatment	<i>LPV/r (%)</i>	60/60 (100%)
	<i>3TC/AZT (%)</i>	41/60 (68.3%)
	<i>FTC/TDF (%)</i>	10/60 (16.7%)
	<i>other (%)</i>	9/60 (15%)

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

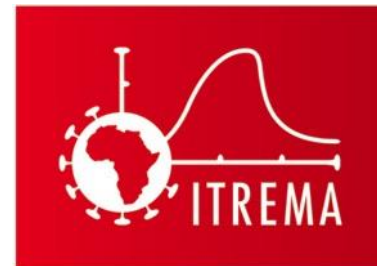
Pilot study – Drug resistance



- **34/59 (57.6%)** harbored DRMs to NRTI backbone
- **8/59 (13.6%)** harbored DRMs conferring major PI resistance



Pilot study – Drug level testing



65.3% of patients had a negative LPV level

Negative LPV level →

0.0% chance of PI-resistance

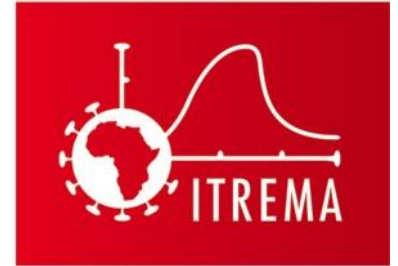
Positive LPV level →

35.3% chance of PI-resistance

Sens:	100%	[54% - 100%]
NPV:	100%	[89% - 100%]
Spec:	76%	[60% - 88%]
PPV:	38%	[15% - 65%]

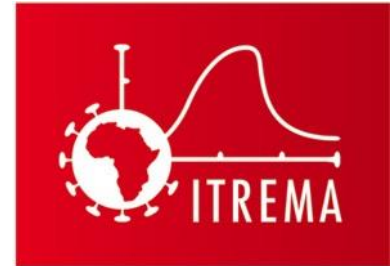
N = 49	LPV-resistance PRESENT	LPV-resistance ABSENT	
LPV drug test POSITIVE	6 (12.2%)	11 (22.5%)	17 (34.7%)
LPV drug test NEGATIVE	0 (0%)	32 (65.3%)	32 (65.3%)
	6 (12.2%)	43 (87.8%)	49 (100%)

Conclusions



- Non-adherence is a major concern in HIV treatment
- The ITREMA strategy uses qualitative drug level testing to gain insight into adherence
- In second-line ART the ITREMA strategy has the potential to prevent unnecessary costly resistance testing

Acknowledgements



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