

Integrated adherence counselling using biomedical and socio-economic information

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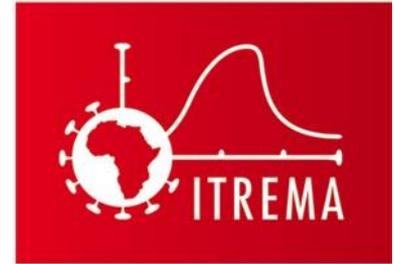
UMC Utrecht



Universiteit Utrecht

Radboudumc

Adherence, a daily concern...



13:07 TelkomSA 3G 22%
I have 35 yr old female
Started HAART June :
CD4 02 WT 50Kg
Tolerating meds well.
Now c/o weight loss
Gud appetite, food av
No other symptoms. C
investigations cxr-Nac
radiologist report. Hb
dl plt 764 WBC 0.66 C
20. LFTs basically nor
Creative 152. VL 8 32
Clinically wasted but i
distress Ambulant.
What next can I do for
lady?

13:06 TelkomSA 3G
+27 [redacted]
I have just spoken to the nu
who referred the pt. He see
believe the pt was adheren
With a VL of 8320 000
don't believe the patie
was taking
treatment ,patients wit
resistance don't have
kind of VL

13:05 TelkomSA E 22%
+27 [redacted]
You
So it means that this instan
failure is adherence relate
likely not caused by resista

13:03 TelkomSA E 22%
+27 [redacted]
Even the viral load of
234000 before even l
at the resistance patte
indicates that the pati
has poor complianc

+27 [redacted]
What's the PI score? What
from the results, Ur patien
doesn't have PI resistance

+27 [redacted]
I agree

+27 [redacted]
This is poor adherenc

05 Feb 2018
+27 [redacted]
The urine LAM was po
so I startef her on TB
treatment

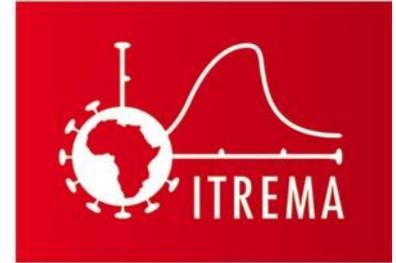
16:46

which ART was she ta
Are you sure she was
compliant?

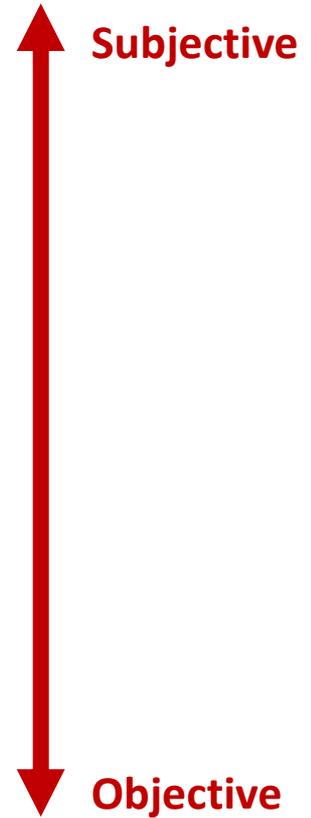
Evidence of poor
adherence... 😭😭😭
...we spent so much time
educating patient...then

A photograph showing several white plastic medicine bottles of various sizes on a wooden table. Some bottles have their caps removed, and some are open. There are also some papers and a green folder in the background.

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.

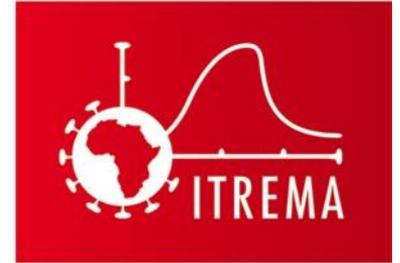
Initiated ART: AZT/3TC/NVP. Viral rebound after 24 months of ART. Switched to 2nd line ART (AZT/3TC/LPVr) at 10 years old.

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

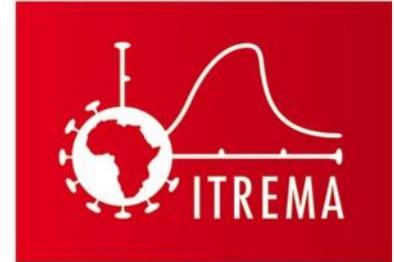
46 year old male

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



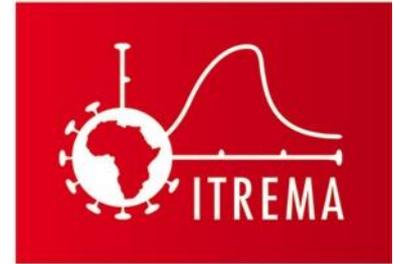
Stanford University

HIV DRUG RESISTANCE DATABASE

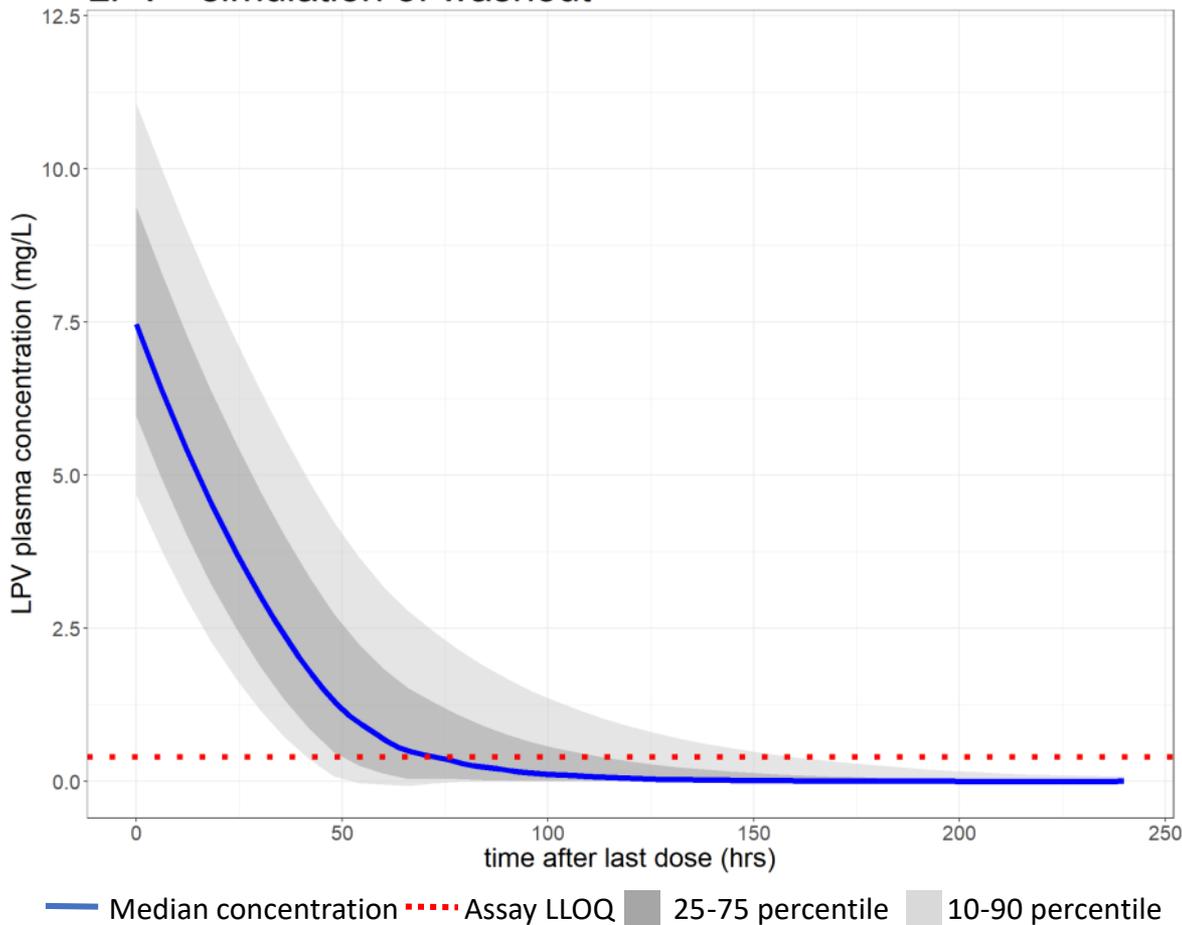
A curated public database to represent, store and analyze HIV drug resistance data.

- 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**

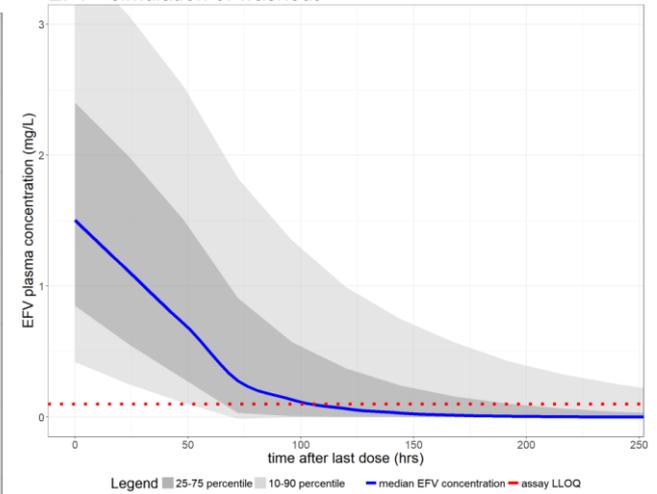
Significance of a negative drug level test



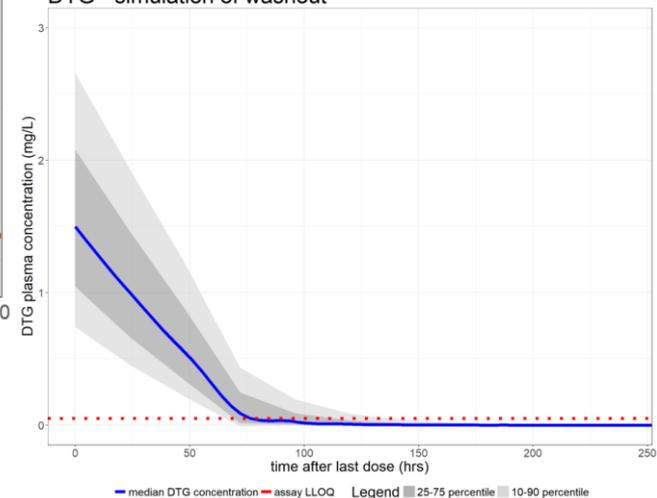
LPV - simulation of washout



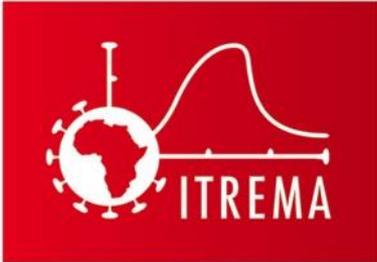
EFV - simulation of washout



DTG - simulation of washout



Evaluation of ITREMA strategy



First-line ART

Prospective evaluation
(ITREMA Open-label RCT)

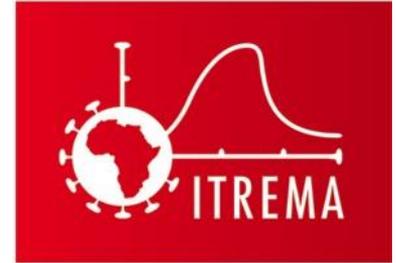


Second-line ART

Retrospective evaluation
(Single centre clinic-based)



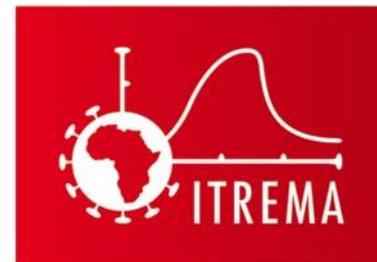
Retrospective evaluation
(Multicentre lab-based)



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

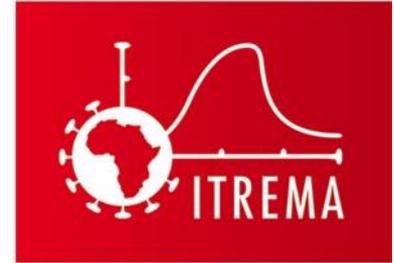


Characteristics of patients (*n* = 60)

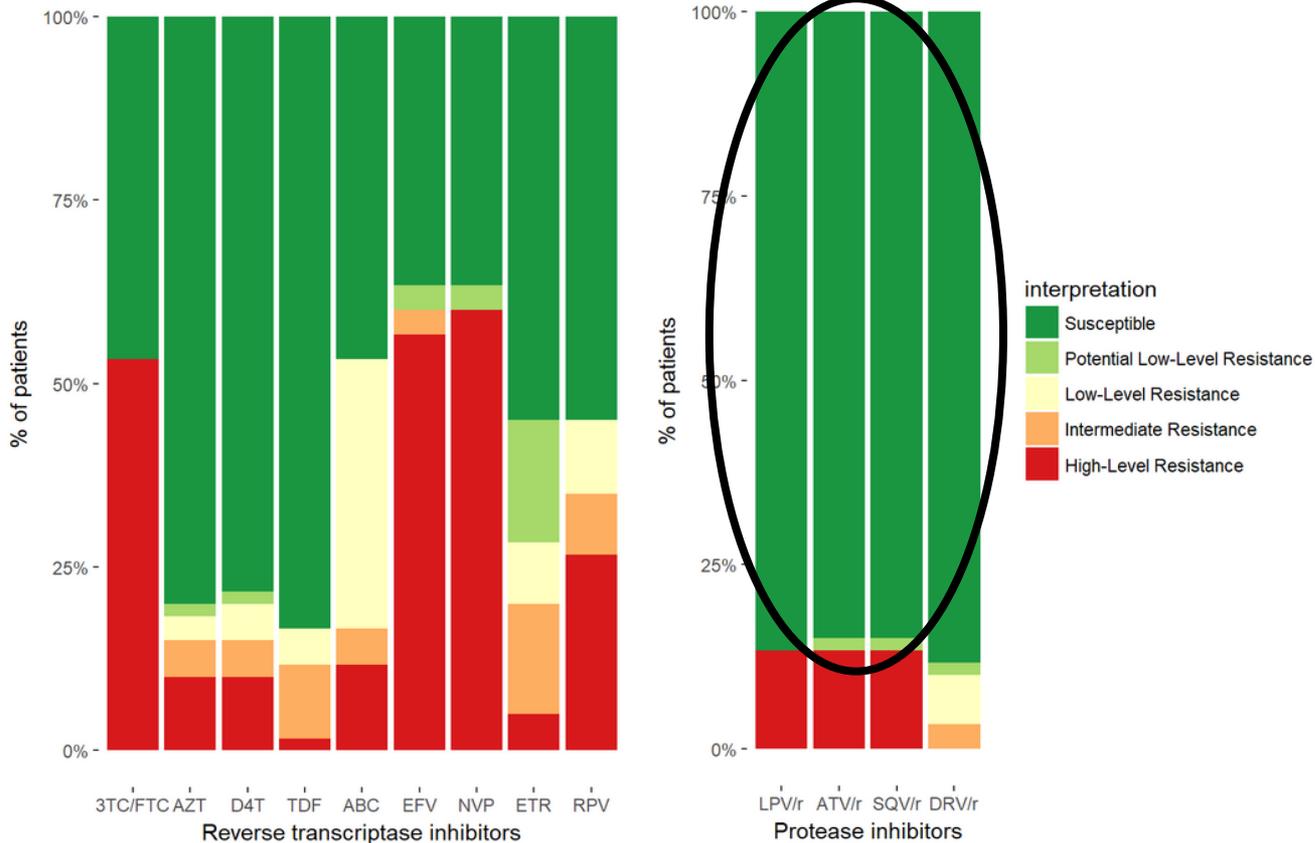
| | | |
|----------------------------------|---------------------|-------------------------------|
| Gender | <i>% female</i> | 56.7% |
| Age | <i>median [IQR]</i> | 36.6 years [31.7 - 46.4] |
| Duration of ART | | 5.0 years [2.7 - 6.2] |
| Duration of second-line ART | | 2.4 years [1.2 - 4.1] |
| CD4 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

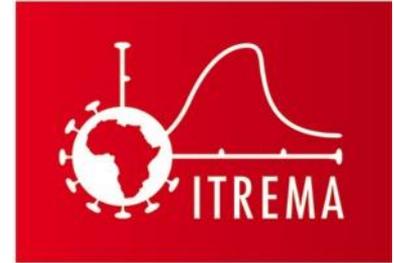
Pilot study – Drug resistance



- **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

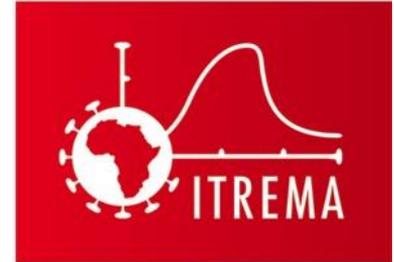
Positive LPV level →

35.3% chance of PI-resistance

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

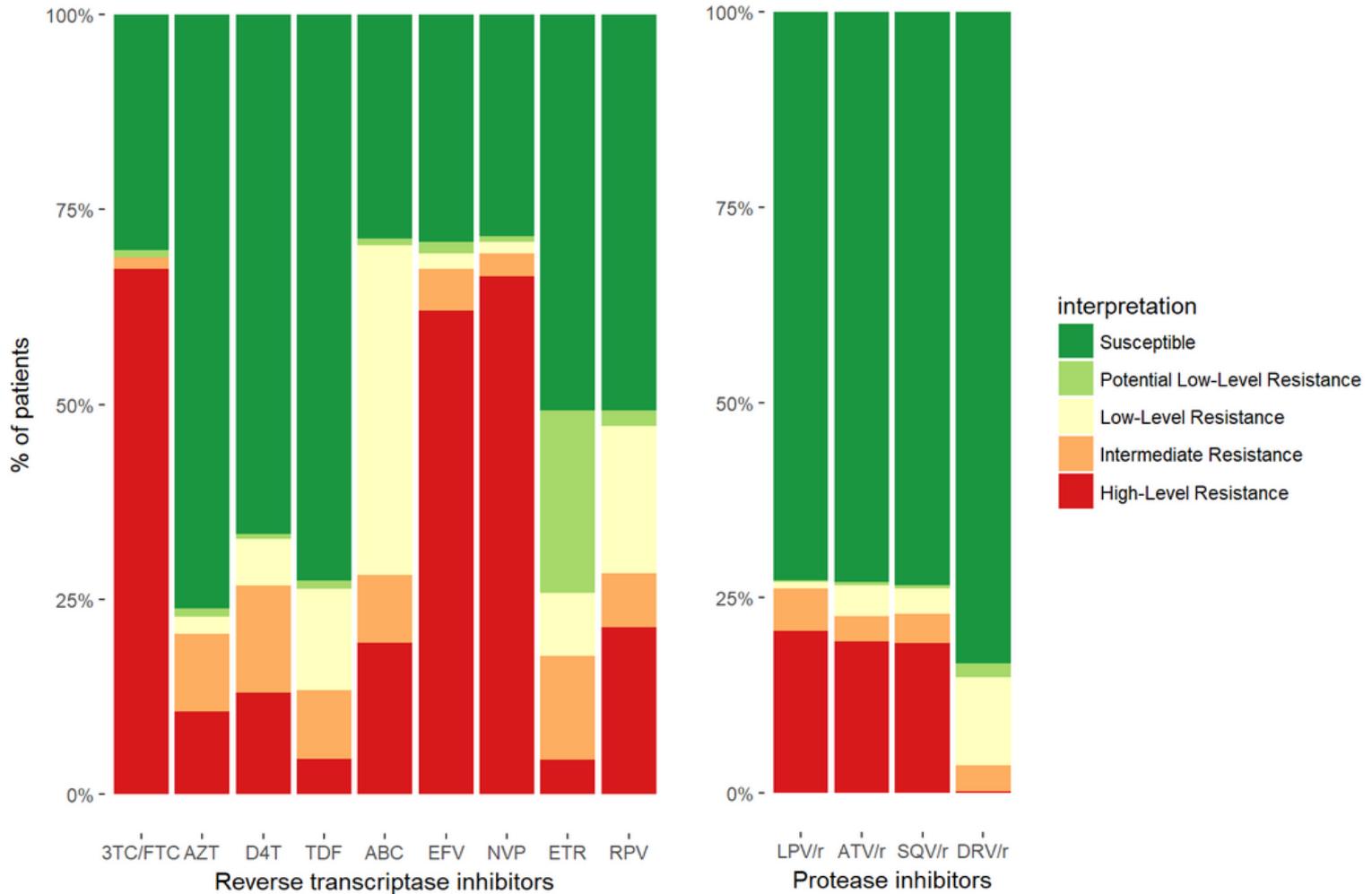
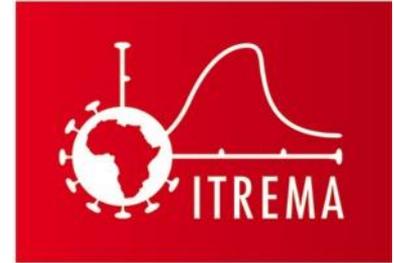
| N = 49 | LPV-resistance PRESENT | LPV-resistance ABSENT | |
|---------------------------|---------------------------|--------------------------|------------|
| LPV drug test POSITIVE | 6 (12.2%) | 11 (22.5%) | 17 (34.7%) |
| LPV drug test NEGATIVE | 0 (0%) | 32 (65.3%) | 32 (65.3%) |
| | 6 (12.2%)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

Implementation study (*preliminary results*)

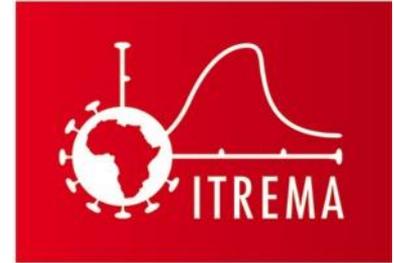


- What would be the effect of broad implementation of drug level testing?
- Collaboration with NHLS HIV genotyping lab JHB
 - Random representative sample of resistance testing requests in 2017 (Gauteng, NW, Limpopo, Mpumalanga)
- 500 unique patient samples selected
 - Adult patients
 - On LPV/r-based second-line ART
 - Last VL >1000 c/mL
- Drug level testing: batch-wise retrospective LCMS on plasma

Drug resistance *(preliminary results)*



Drug level testing (*preliminary results*)



47.3% of patients had a negative LPV level

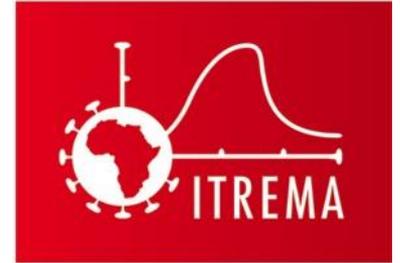
Negative LPV level →
Positive LPV level →

5.9% chance of PI-resistance
45.4% chance of PI-resistance

| | | |
|-------|------------|------------------|
| Sens: | 89% | [83 - 94] |
| NPV: | 94% | [90 - 97] |
| Spec: | 61% | [55 - 66] |
| PPV: | 45% | [39 - 52] |

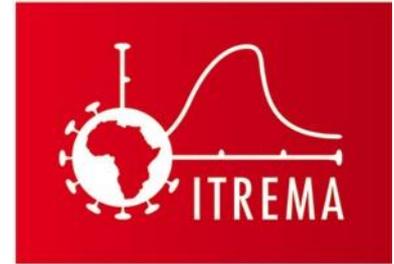
| N = 49 | LPV-resistance PRESENT | LPV-resistance ABSENT | |
|---------------------------|---------------------------|--------------------------|--------------------|
| LPV drug test POSITIVE | 23.9% (119) | 28.8% (143) | 52.7% (262) |
| LPV drug test NEGATIVE | 2.8% (14) | 44.5% (221) | 47.3% (235) |
| | 26.8% (133) | 73.2% (364) | 100% (497) |

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



RCT investigator team

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



Hugo Tempelman



Francois Venter



WITS REPRODUCTIVE HEALTH & HIV INSTITUTE

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Ndlovu Research
Consortium



All participants, clinical and research staff at Ndlovu Care Group

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