

# Understanding virological failure

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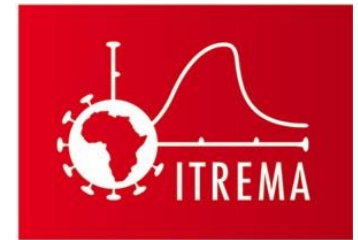
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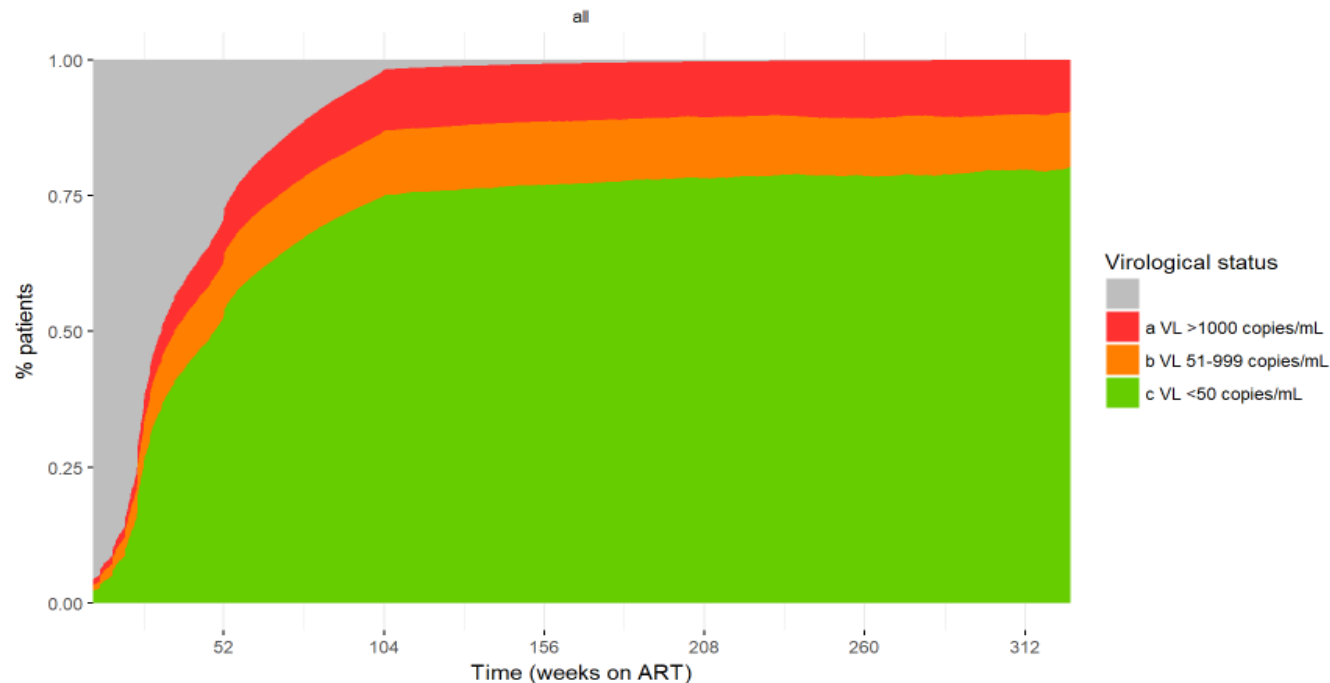
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# Virological suppression of individuals in care in South-Africa



Viral suppression in 56,589 SA patients with 1st VL <2 years after starting 1st line ART

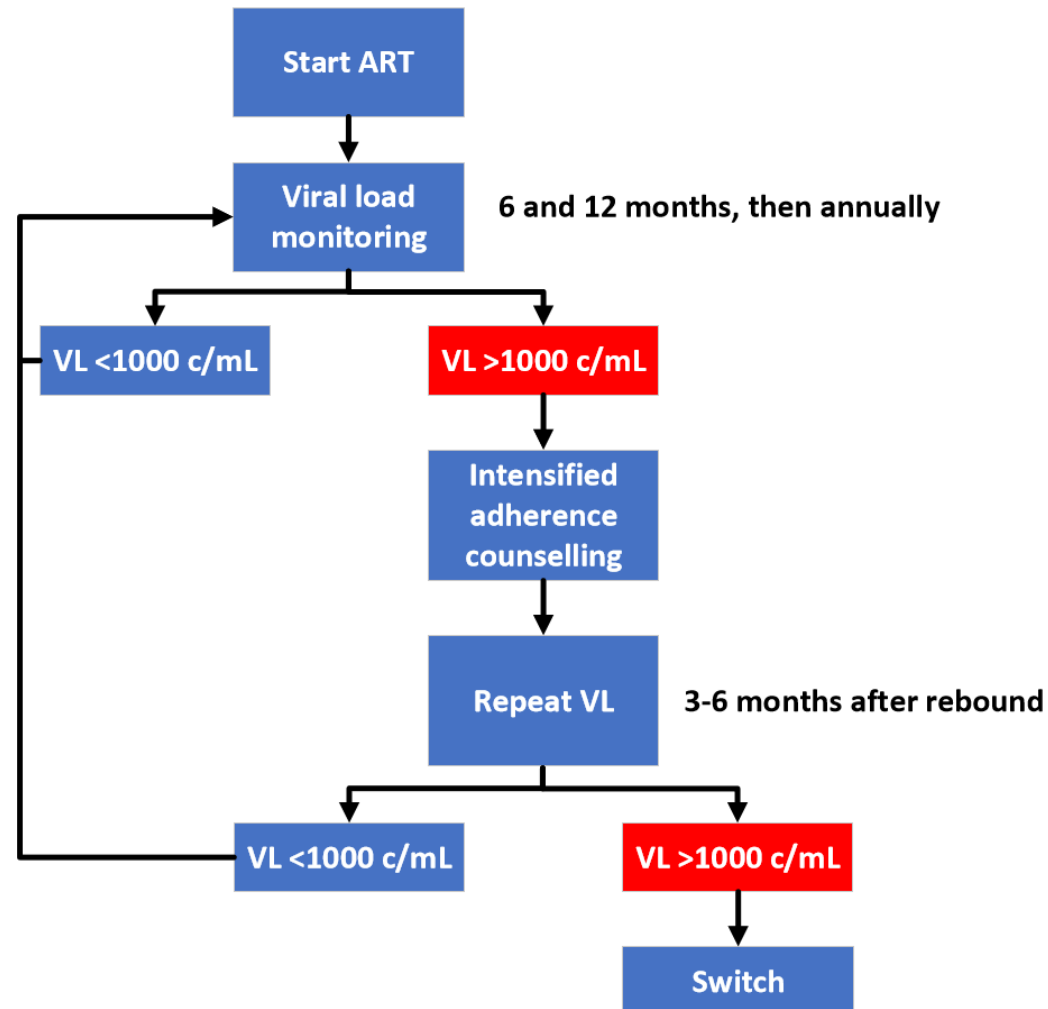
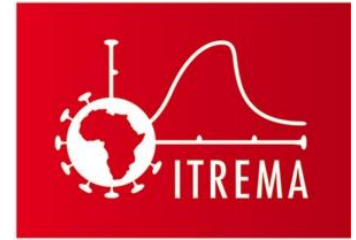
*Cumulative incidence curves of multistate competing risks model*



| time             | 26.0    | 52.0    | 78.0    | 104.0   | 130.0   | 156.0   | 182.0   | 208.0   | 234.0   | 260.0  | 286.0  | 312.0  |
|------------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|--------|--------|--------|
| n_at_risk        | 17340.0 | 28360.0 | 30713.0 | 30190.0 | 25852.0 | 21966.0 | 17875.0 | 14256.0 | 11097.0 | 8975.0 | 6881.0 | 5502.0 |
| VL_below_50_OT   | 70.0    | 74.2    | 75.8    | 76.4    | 77.1    | 77.5    | 78.1    | 78.5    | 79.1    | 78.7   | 79.0   | 79.9   |
| VL_51_999_OT     | 18.9    | 14.5    | 12.6    | 12.2    | 11.9    | 11.8    | 11.3    | 11.3    | 10.9    | 10.6   | 10.5   | 10.2   |
| VL_above_1000_OT | 11.2    | 11.3    | 11.6    | 11.5    | 11.0    | 10.7    | 10.5    | 10.3    | 10.1    | 10.7   | 10.5   | 10.0   |

Hermans et al.  
CROI 2018

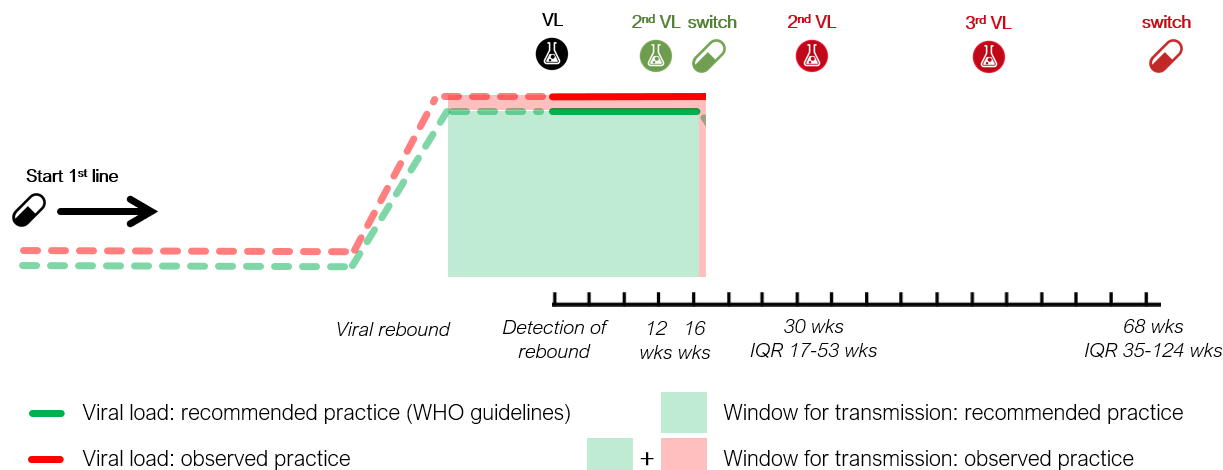
# Current recommendations for management of viral rebound for LMIC

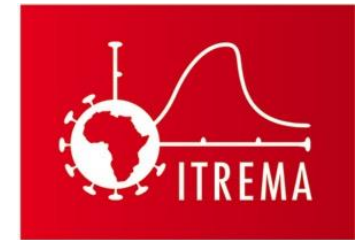


# Management of viral rebound in clinical practice

- Management according to the guidelines

Clinical follow-up of viral rebound: Observed versus recommended practice

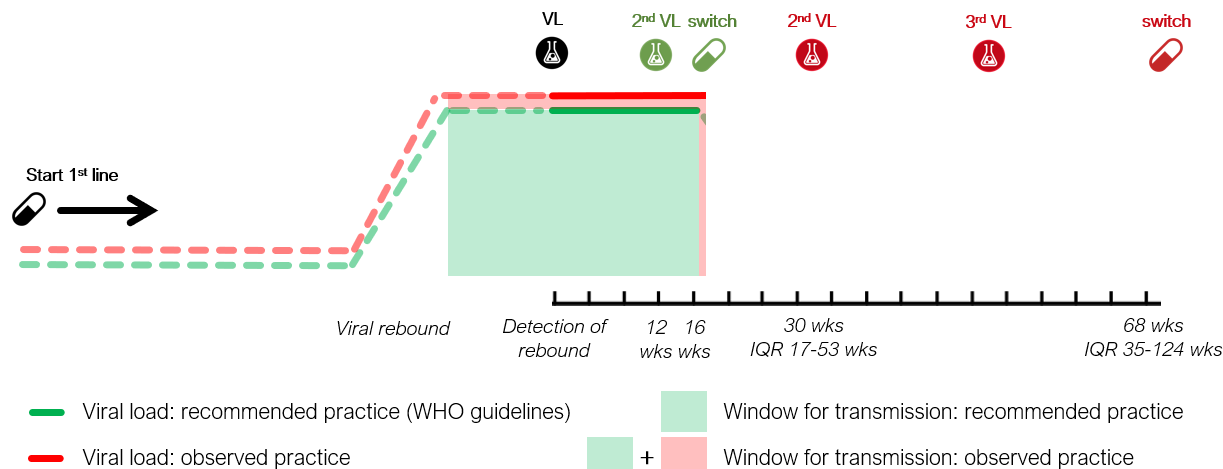




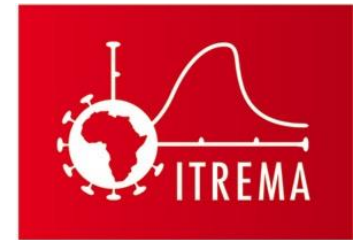
# Management of viral rebound in clinical practice

- Observed clinical practice is not as per guidelines

Clinical follow-up of viral rebound: Observed versus recommended practice

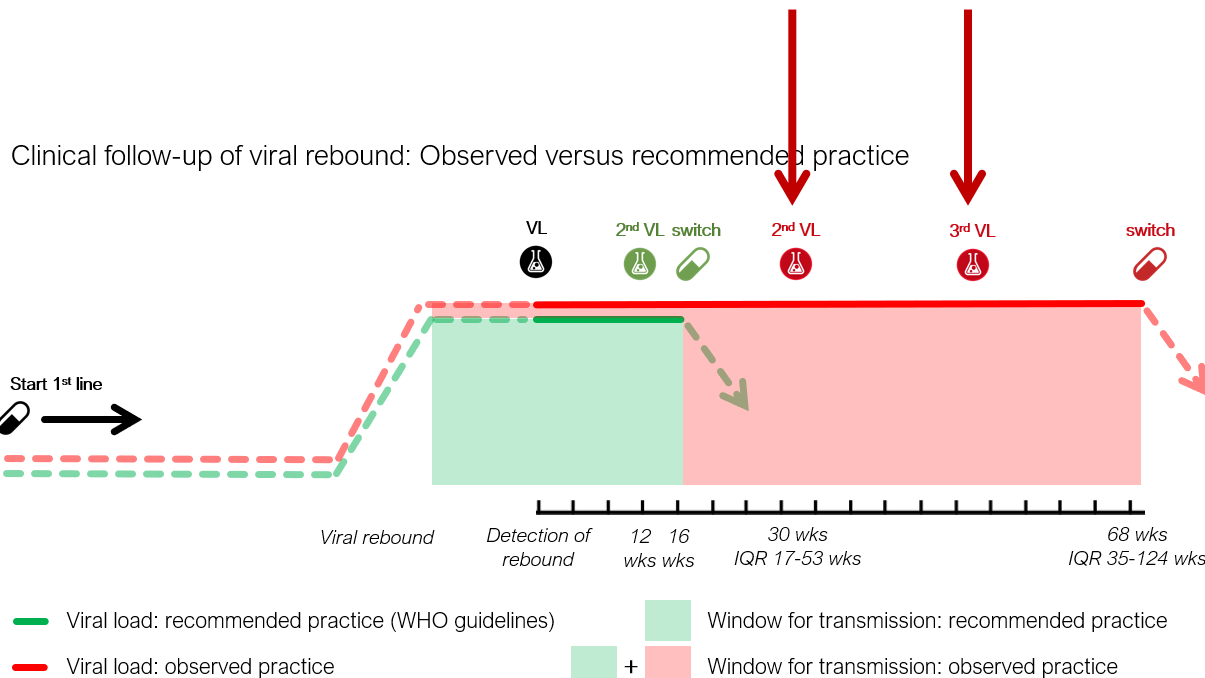


Hermans et al.  
CROI 2018



# Management of viral rebound in clinical practice

- Observed clinical practice is not as per guidelines
- VL is measured repeatedly despite  $> 1000$  cp result
- Switch is often postponed or not performed at all



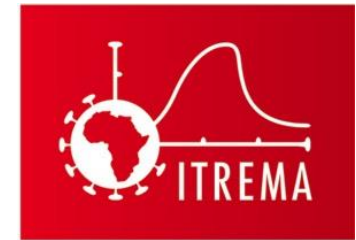


# Why not to switch:

- No clinical urge, patient's preference
  - Suspected non-adherence
  - Evidence of non-adherence despite intervention
    - Patient-reported/Poor clinic attendance/defaulting
- In case of non-adherence, low or no risk of resistance

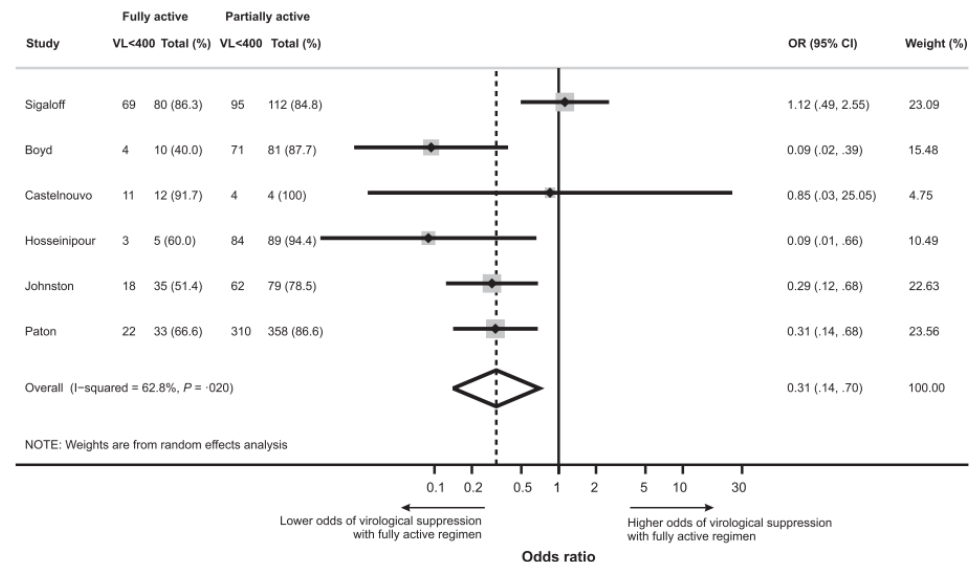
**Prevalence studies of virological failure cases without detected drug resistance**

| Author   | Journal             | Year | Setting           | % without resistance | n=  |
|----------|---------------------|------|-------------------|----------------------|-----|
| Kantor   | AIDS Res Hum Retrov | 2002 | Zimbabwe          | 19%                  | 21  |
| Marconi  | CID                 | 2008 | SA (KZN)          | 17%                  | 124 |
| Murphy   | AIDS                | 2010 | SA (KZN)          | 13%                  | 115 |
| Van Zyl  | J Med Virol         | 2011 | SA (W Cape)       | 17%                  | 167 |
| Manasa   | PLoS ONE            | 2013 | SA (KZN)          | 14%                  | 222 |
| Aghokeng | CID                 | 2014 | various countries | 21%                  | 433 |



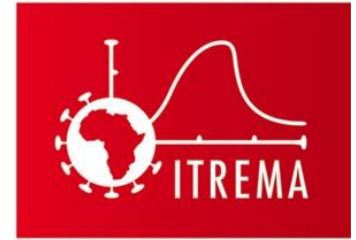
# Why not to switch (contin.)

- Increased drug costs
- A more complex and more toxic regimen for a patient who already struggles with one pill a day
- Patients with no resistance at first-line failure more likely to fail second-line: non-medical barriers should be explored.

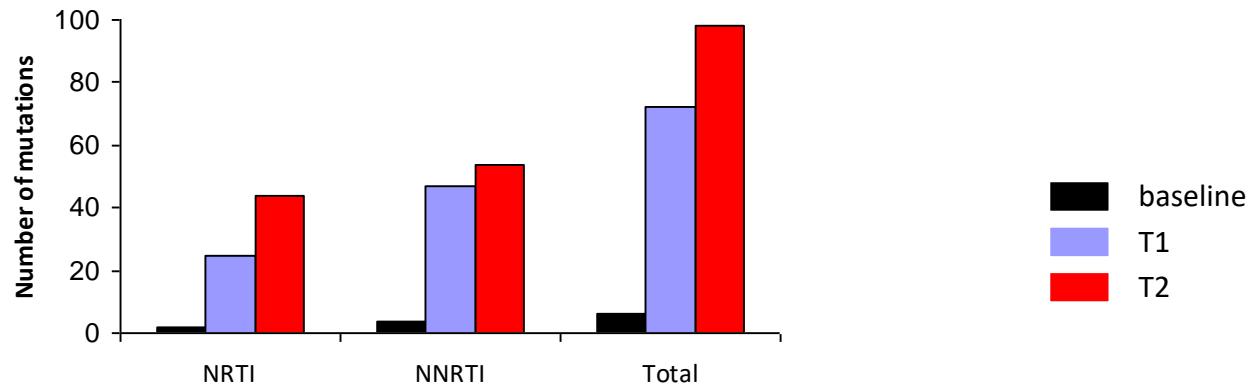




# Why to switch promptly



- Prolonged virological failure may lead to CD4-count decline and clinical deterioration<sup>1,2</sup>
- Increases risk of transmission of HIV
- May allow for accumulation of resistance<sup>3,4</sup>



1: Orrell C, AIDS Res Treat, 2011.

2: Keiser O, Trop Med Int Health, 2010

3: Barth et al, 2012

4: Aitken et al, 2013

# Viral rebound results in HCW dilemma: “To switch or not to switch?”

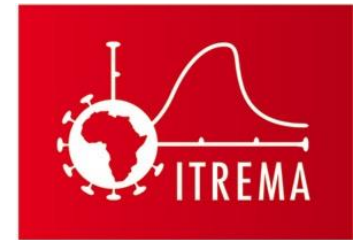
## Switch

- Best option if resistance is present
- Unnecessary if resistance is absent

## No switch

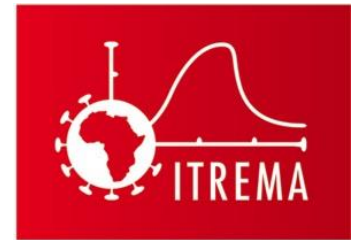
- One pill per day
- Limited toxicity
- Accumulation of resistance if present





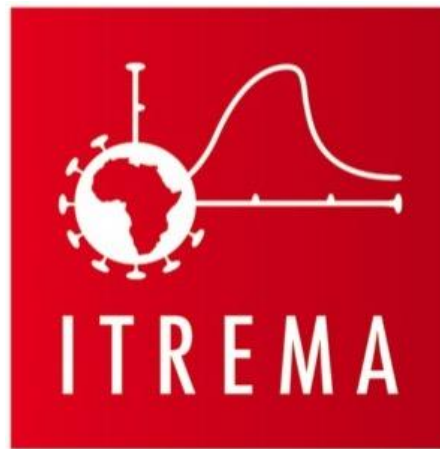
# Insight in failure

- Rapid decision-making requires additional insight into adherence and resistance
- Resistance testing is costly and complex
  - Results are frequently unreliable if a patient non-adherent



So..

*Diagnostic tools to establish the cause of viral rebound are urgently required to perform targeted adherence interventions and informed timely switches to second-line ART*



Evaluation of an intensified **t**reatment  
**m**onitoring strategy to prevent **a**ccumulation  
of HIV-1 drug resistance in resource limited  
settings

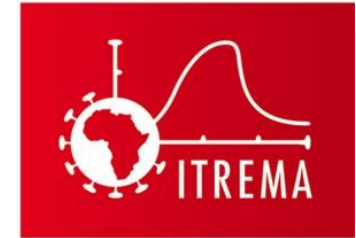


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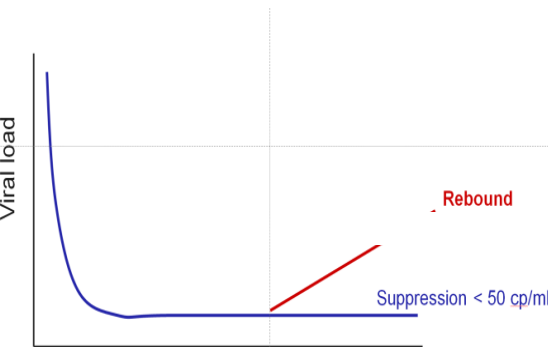


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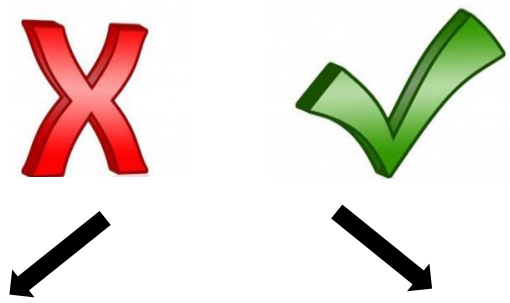
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# The ITREMA strategy



Point-of-care drug level assessment



Drug level informed adherence counselling  
Actively exploring non medical issues as well



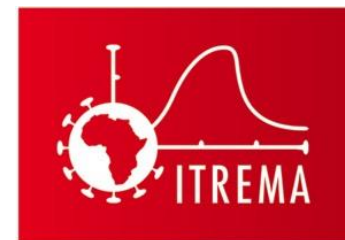
|     | IRVAD 072017     |              | IRVAD 072017     |              | IRVAD 072017     |
|-----|------------------|--------------|------------------|--------------|------------------|
|     | Algorithm Result | IRVAD 072017 | Algorithm Result | IRVAD 072017 | Algorithm Result |
| EPV | Intermediate     | Intermediate | Intermediate     | Intermediate | Intermediate     |
| ETR | Intermediate     | Intermediate | Intermediate     | Intermediate | Intermediate     |
| MPV | Intermediate     | Intermediate | Intermediate     | Intermediate | Intermediate     |
| MPV | Intermediate     | Intermediate | Intermediate     | Intermediate | Intermediate     |

|     | IRVAD 072017     |              | IRVAD 072017     |              | IRVAD 072017     |
|-----|------------------|--------------|------------------|--------------|------------------|
|     | Algorithm Result | IRVAD 072017 | Algorithm Result | IRVAD 072017 | Algorithm Result |
| EPV | Intermediate     | Intermediate | Intermediate     | Intermediate | Intermediate     |
| ETR | Intermediate     | Intermediate | Intermediate     | Intermediate | Intermediate     |
| MPV | Intermediate     | Intermediate | Intermediate     | Intermediate | Intermediate     |
| MPV | Intermediate     | Intermediate | Intermediate     | Intermediate | Intermediate     |

Resistance testing

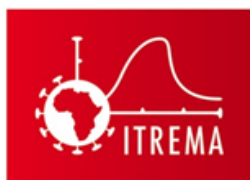


# Evaluation of the ITREMA strategy



**First-line ART**

Prospective evaluation  
(ITREMA Open-label RCT)

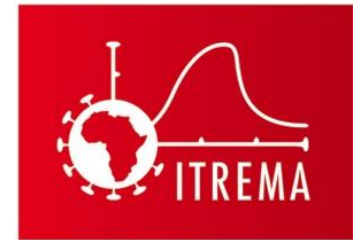


**Second-line ART**

Retrospective evaluation  
(Single centre clinic-based)



Retrospective evaluation  
(Multicentre lab-based)

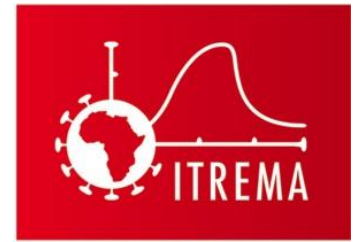


# Prospective assessment during 1<sup>st</sup> line ART

- 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: Monitoring according to SA/WHO guidelines
  - Intervention arm: ITREMA intensified monitoring strategy
- Implemented as pragmatic RCT at a rural clinical site (Ndlovu Care Group, Limpopo, South Africa)
  - 501 participants included, follow-up ends Q1 2019

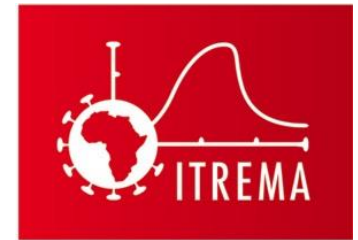


# Preliminary results of the ITREMA trial (1<sup>st</sup> line ART)



Preliminary trial results presented this week

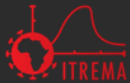
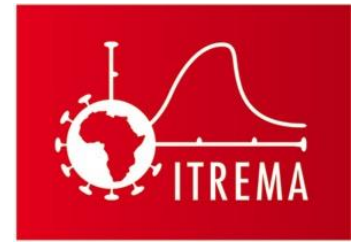
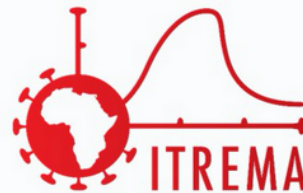
- Pretreatment dual class drug resistance, increases risk of poor treatment outcomes (Abstract #2, IDRW)
- Predictive value of pill counts for treatment outcomes is poor, but baseline psychosocial factors do predict outcomes (Abstract #97, SA HIV Clin Soc)
- Qualitative drug level testing for LPV/EFV/DTG can be implemented and reliably performed a resource-limited setting as a point-of-care test (Abstract #98, SA HIV Clin Soc)



# Conclusions

- On-treatment virological suppression rates in SA are high
- Clinical response to viral rebound and switch to second-line ART is delayed
- The ITREMA project is an integrated platform
  - to gain insight in reasons for treatment failure
  - to evaluate the use of tools to empower healthcare workers and patients

# www.itrema.org

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Aiming to improve the effectiveness of HIV treatment



Low level viremia  $\neq$   
treatment success



Delayed response to viral  
rebound puts individuals  
and society at risk



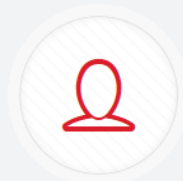
Use tools to generate  
insight in virological failure



Public health  
officials



Scientists



People living with HIV

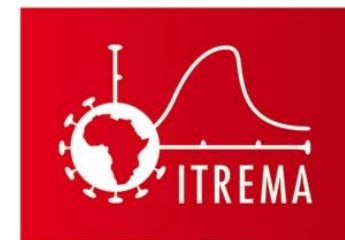


Laboratory staff



Health care  
workers

# Acknowledgements



## RCT investigator team

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Hugo Tempelman



Francois Venter



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Kim Steegen

Ndlovu Research  
Consortium



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