Rationale behind the New 2023 ARV Treatment Guidelines

Yunus Moosa
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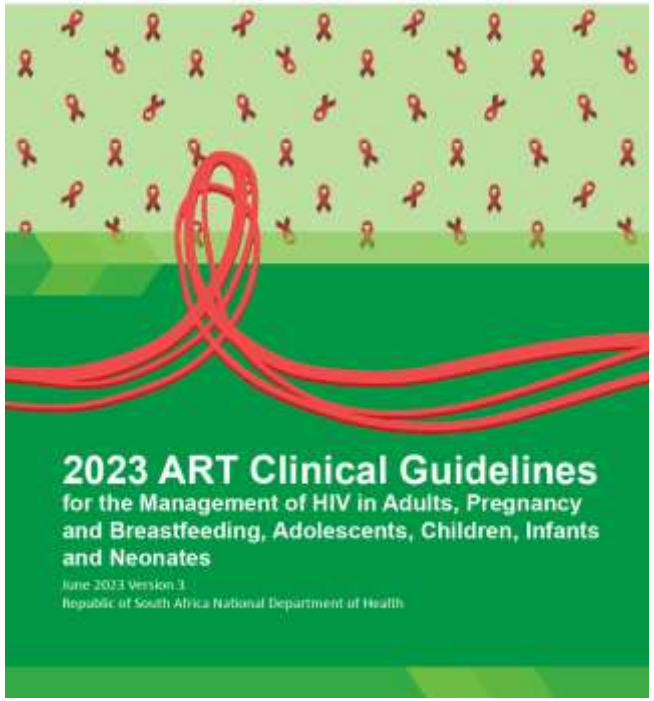
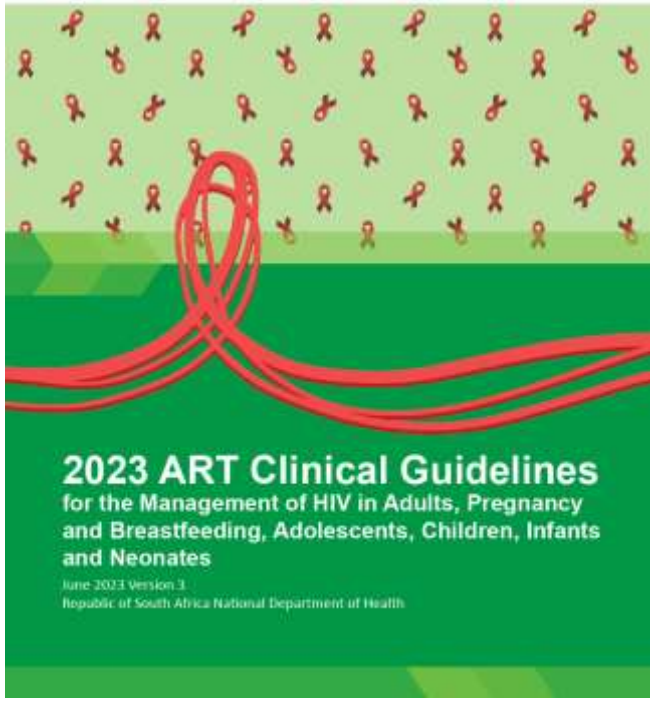
19 October 2023

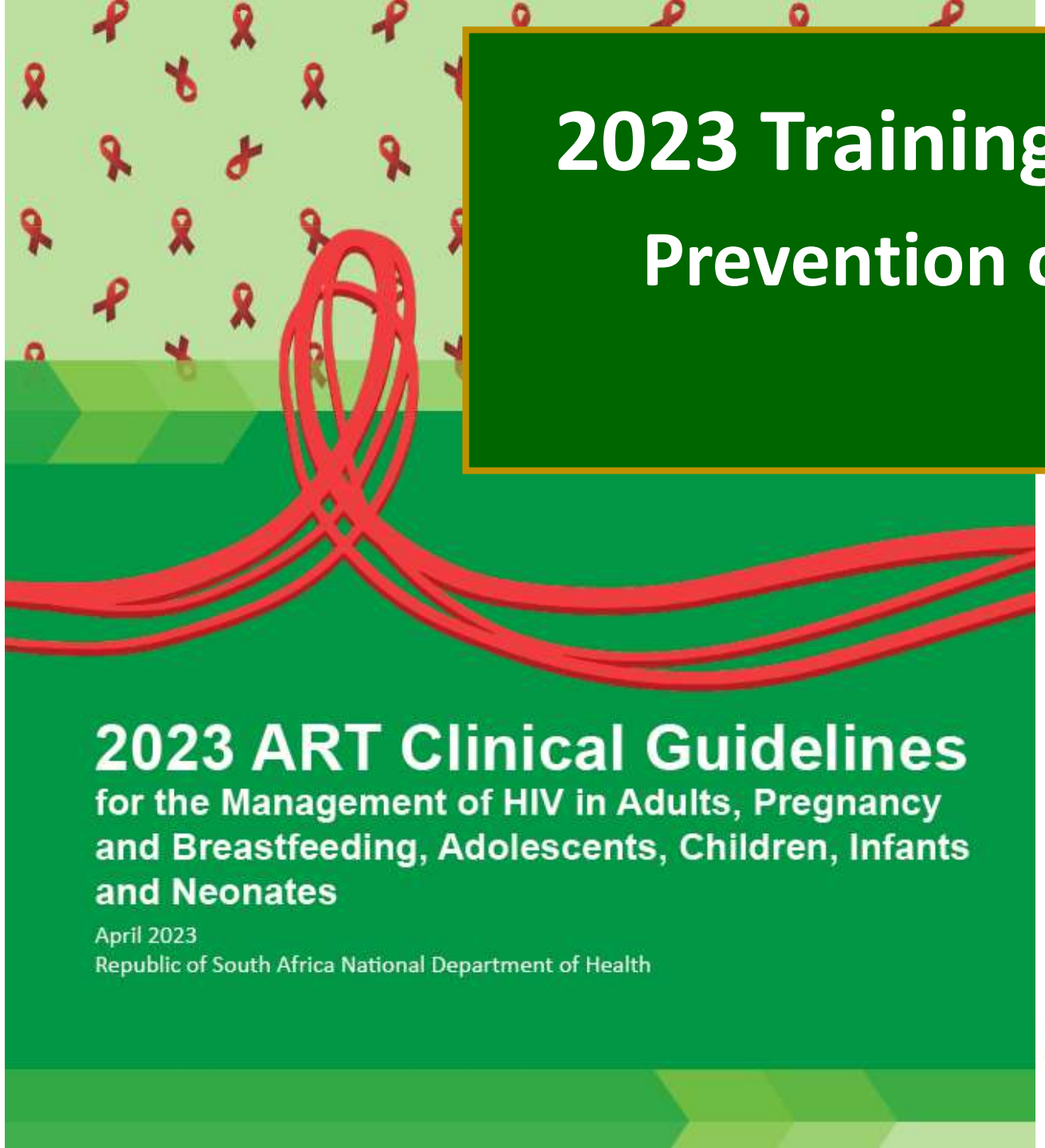




How many people have read the guideline: Spent a total of at least total of 30 min on it

- Yes
- No
- Not sure
- What are you talking about! 

2023 Training on updates to ART and Prevention of Vertical Transmission Guidelines



Jeannette Wessels
Lynne Wilkinson

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

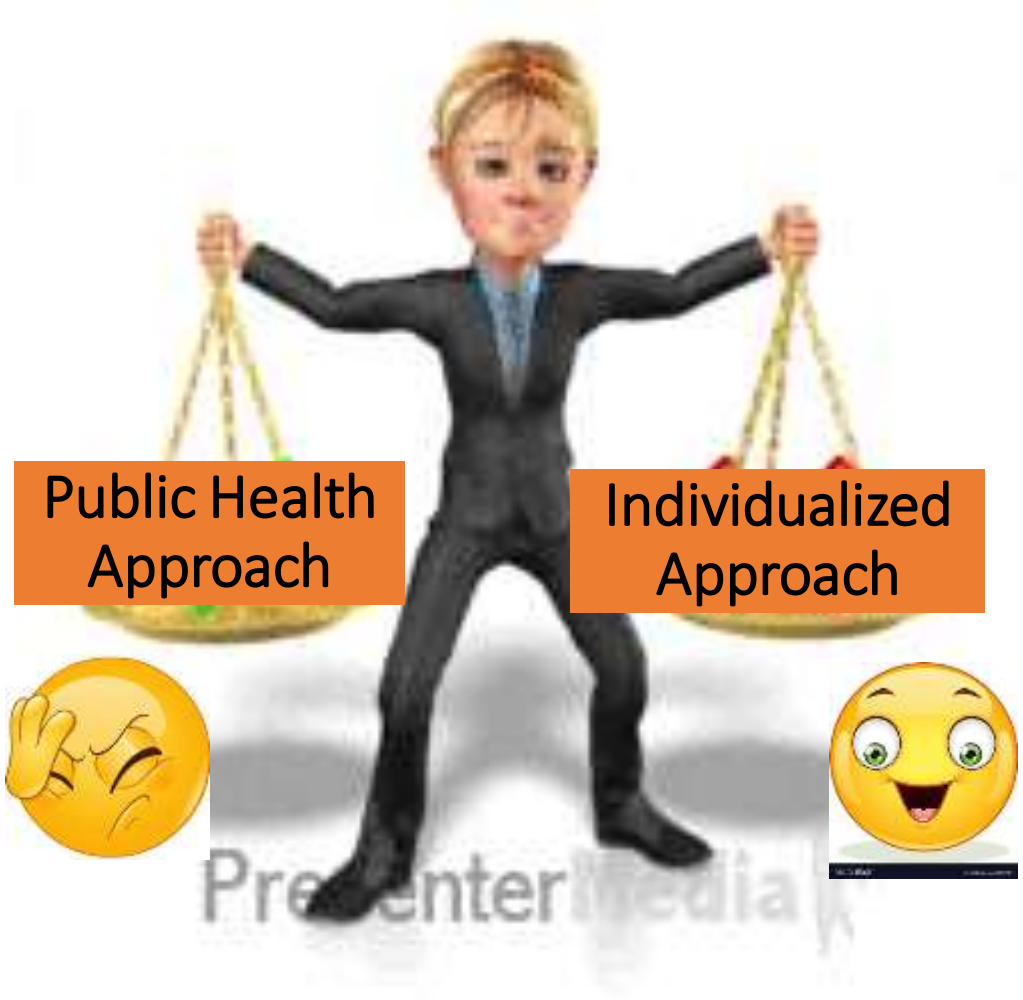
CLINTON HEALTH ACCESS INITIATIVE

World Health Organization

unicef

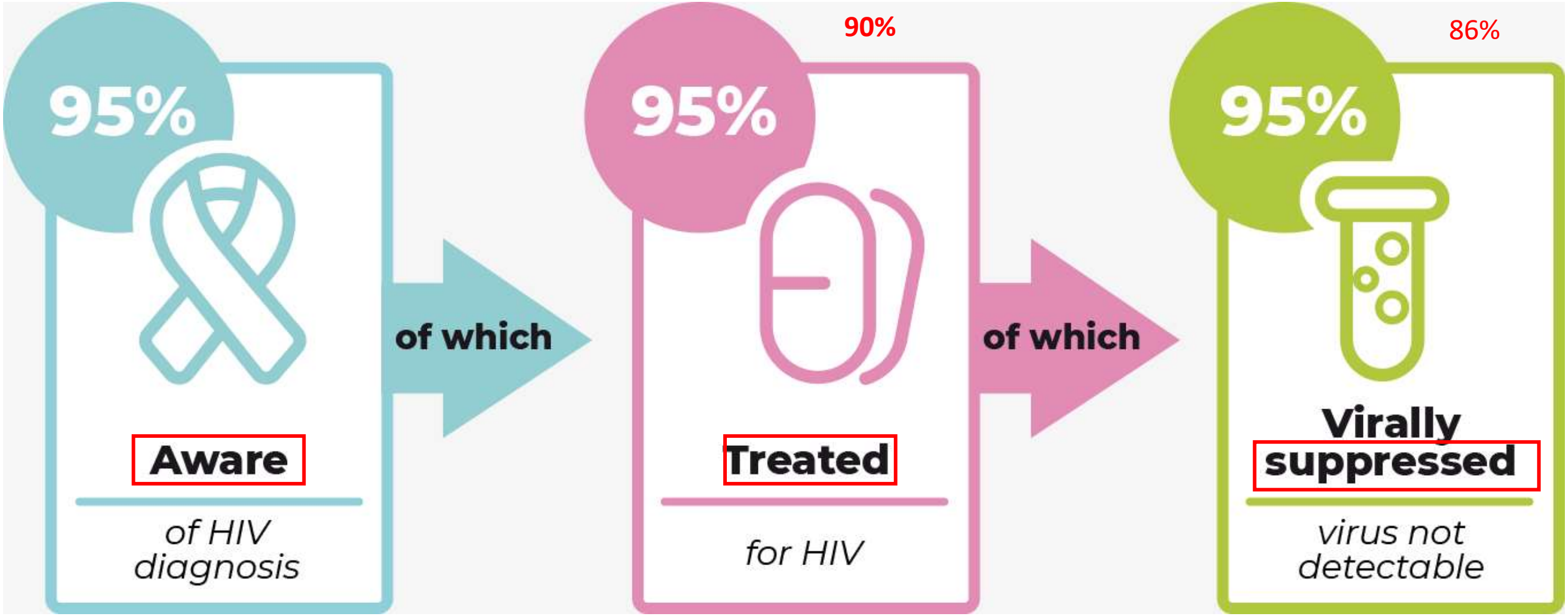
Facts to note

- South Africa has the largest HIV epidemic in the world
- 7.9 million out of 58 million (14%)
- Largest ART programme in the world
- 5 out of 8 million on ART (62.5%) (2017)
- ~200 000 on second line (4%),
- ~ 3000 third line



Any discussion on drugs/treatment/monitoring translates to hundreds to thousands to millions of patients for lives.

UNAIDS HIV/AIDS Targets for 2030



South African HIV program big challenges….

Sub-optimal retention

especially in the first 12 year on ART

(including for returning clients)

Sub-optimal VL suppression

(<50 copies/ml)

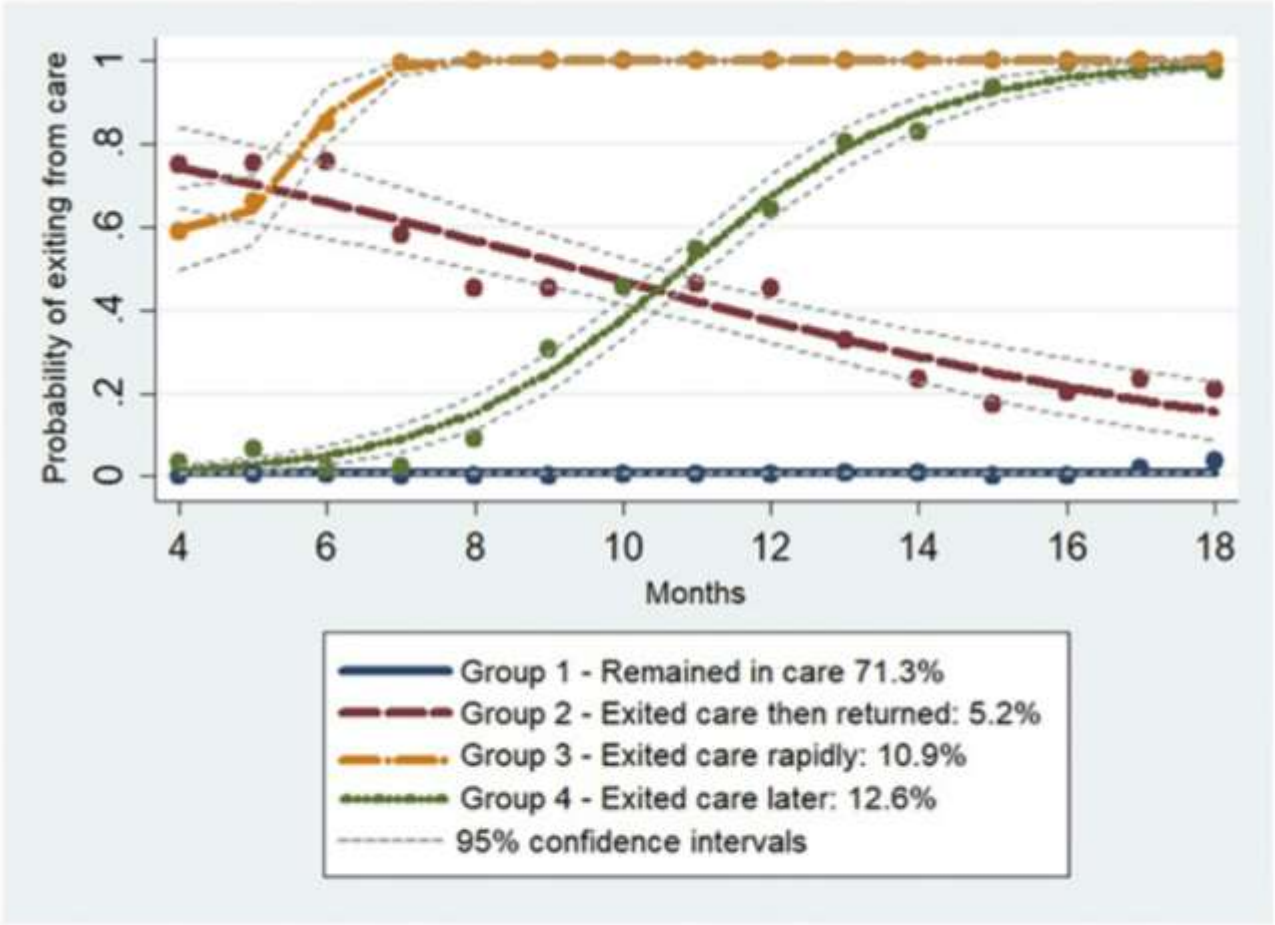
Massive health system burden

high number of people living with HIV and people at risk of acquiring HIV requiring ongoing **HIV treatment and prevention services**

Disengagement:

~15% by mth 6 of ART

~24% by mth 12



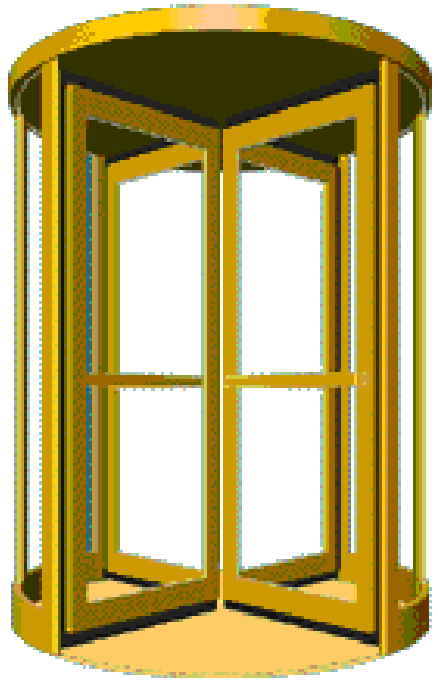
Care trajectories in trial clinics over 18 months of clinical follow-up among patients eligible for ART initiation at the first visit (ANRS 12249 TasP trial, n = 777).

Gosset, Andréa MSc[a,b]; Protopopescu, Camelia PhD[a]; Larmarange, Joseph PhD[c,d]; Orne-Gliemann, Joanna PhD[e,f]; McGrath, Nuala PhD[g,c,h]; Pillay, Deenan PhD[c,i]; Dabis, François PhD[e,f]; Iwuji, Collins MRCP[j,c,h]; Boyer, Sylvie PhD[a]. Retention in Care Trajectories of HIV-Positive Individuals Participating in a Universal Test-and-Treat Program in Rural South Africa (ANRS 12249 TasP Trial). JAIDS Journal of Acquired Immune Deficiency Syndromes 80(4):p 375-385, April 1, 2019.

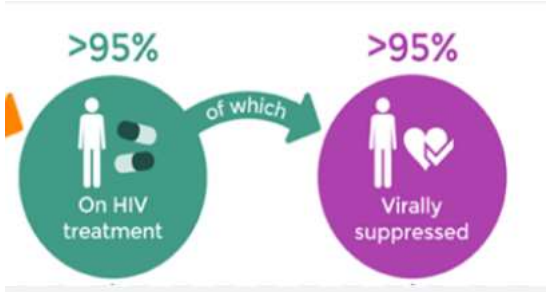
Important considerations to reduce disengagement

- Length of the wait
- Quality of the care
- Overall experience
- Reason for visit- just another script?
- Reason for return?
- Cost of visit? – **competing priority**, time off work?

How responsive and kind are you to your patient?



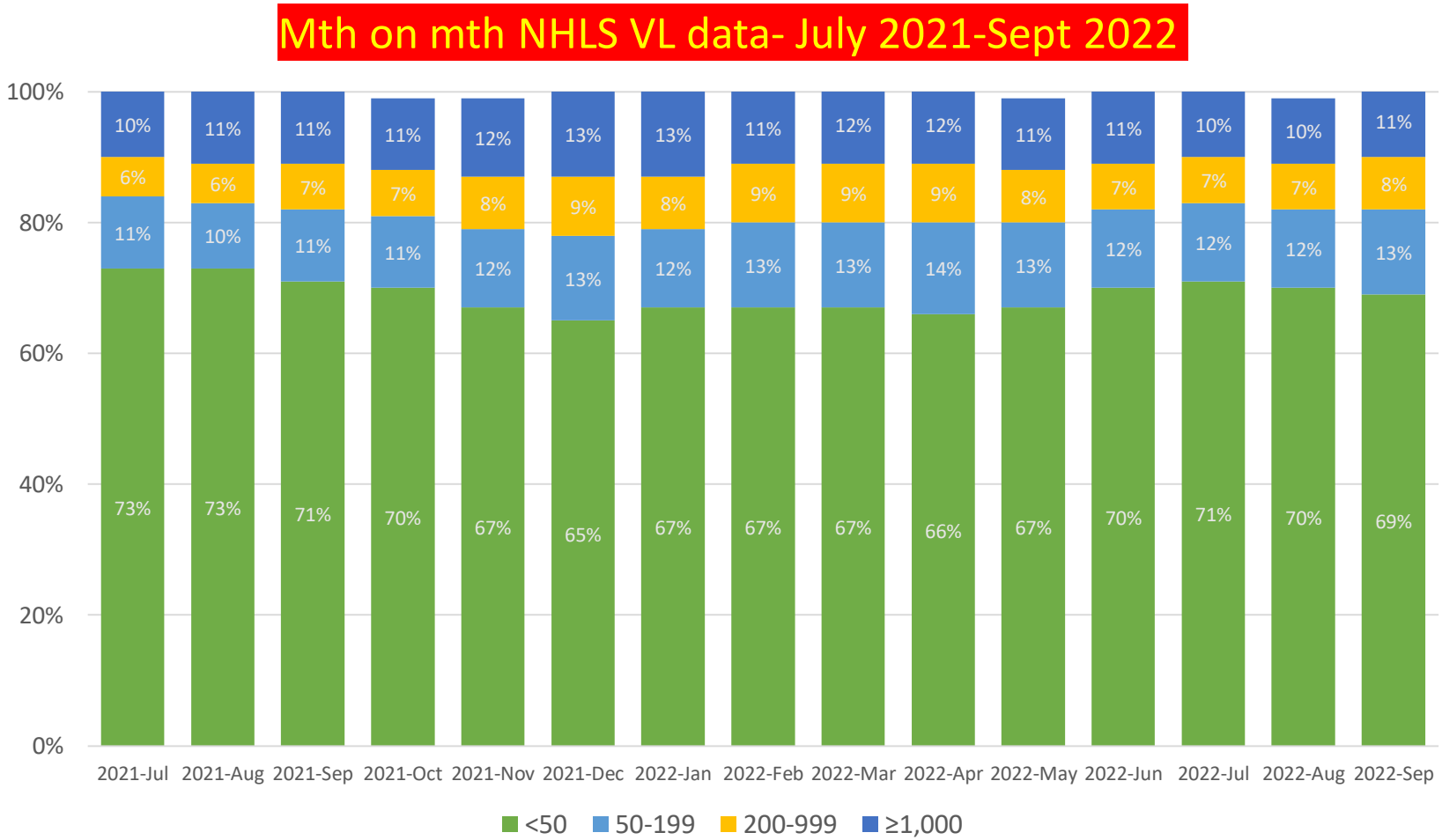
Important: improving long-term viral suppression



95% of engaged clients on treatment should be virally suppressed

VL>50: 26-35%

VL<50 ~70%



Public health problem

- Need to simplify treatment:
- Lower-level health care workers
- Pharmacy:
  - Cost
  - Procurement – one regimen
  - Storage- one small box
  - Dispensing – reduced error
- Patient factor adherence

New guidelines recommend TLD as the simplified optimum regimen and should be used as:

A First-line regimen

A Second-line regimen

Part of Third-line regimens

This means that:

All new clients should be initiated on TLD, or…

Clients already on ART should have been switched to TLD, or…

…be IN THE PROCESS of switching to TLD

All Adult and Adolescent Males and Females, including Pregnant Women ≥ 30 kg and ≥ 10 years of Age

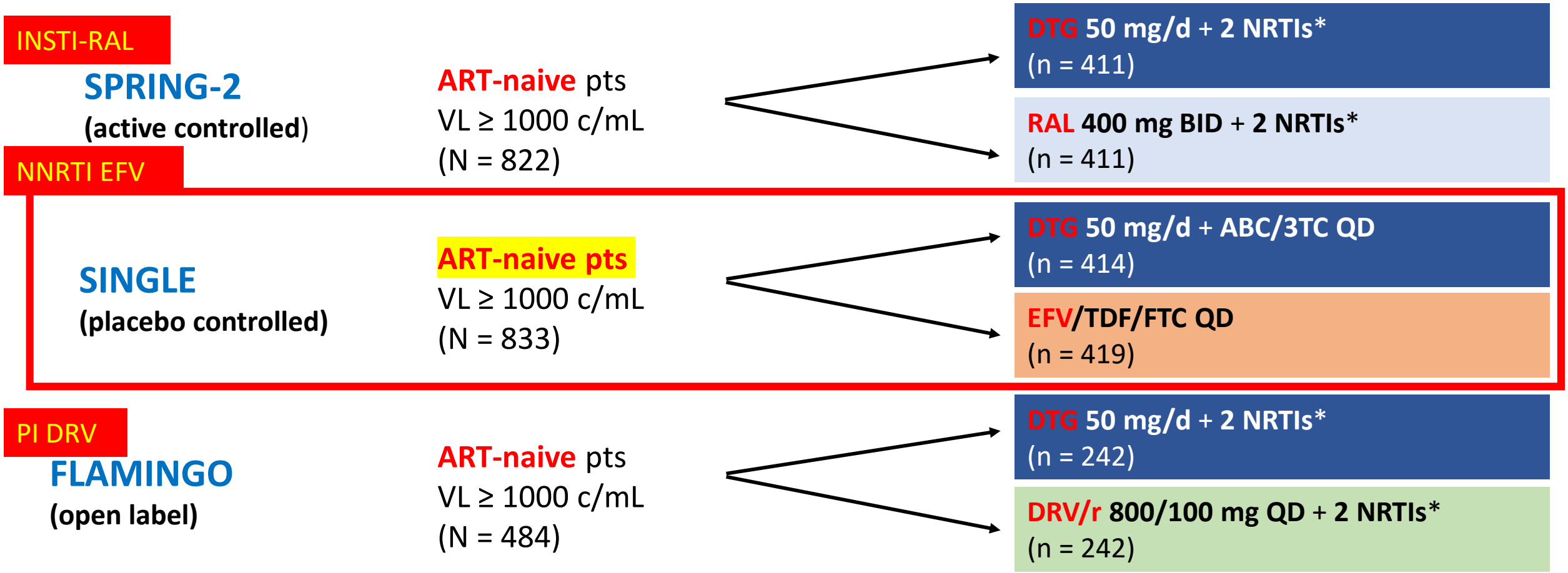
TDF + 3TC + DTG (TLD)

What is the evidence that supports DTG based ART as the most optimum regimen

Regimen of choice for **ART naïve-patient**

DTG regimen of choice for ART naïve

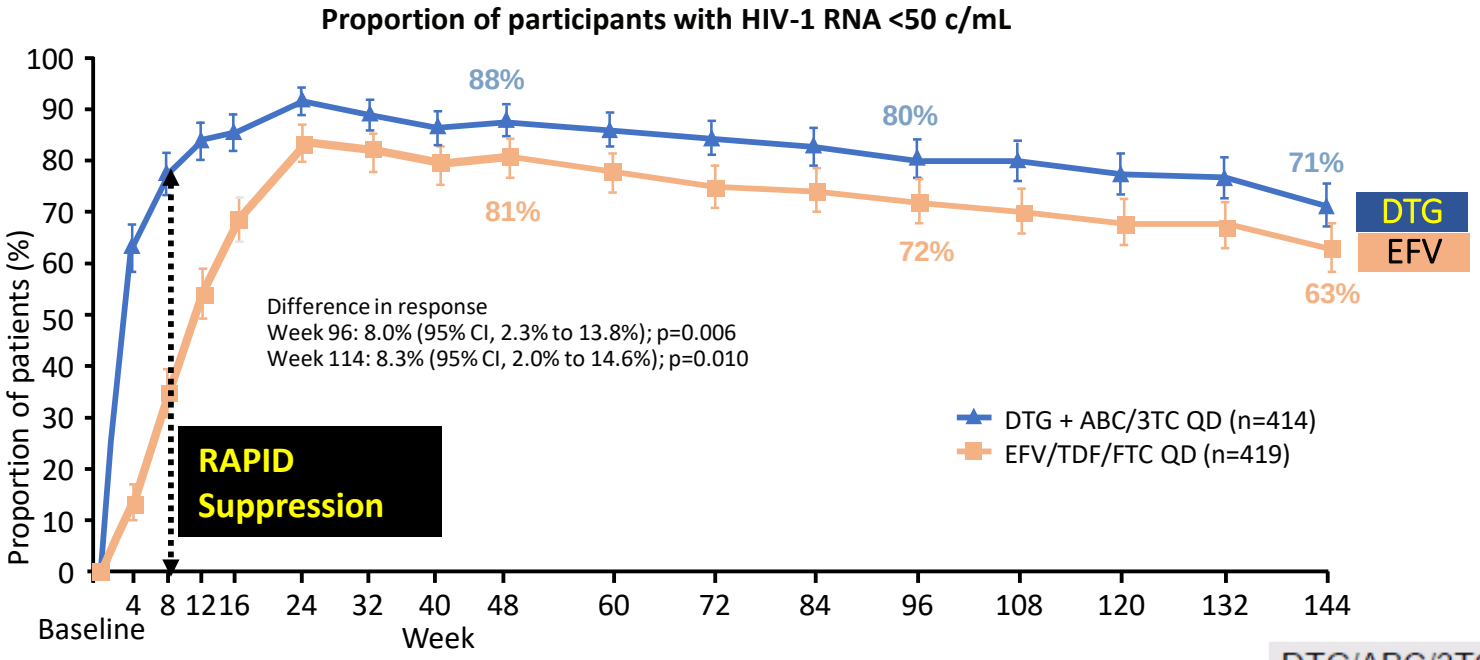
- **3 registrational studies**: RCT - non-inferiority phase 3 studies
- Primary endpoint: HIV RNA < 50 at 48wk.

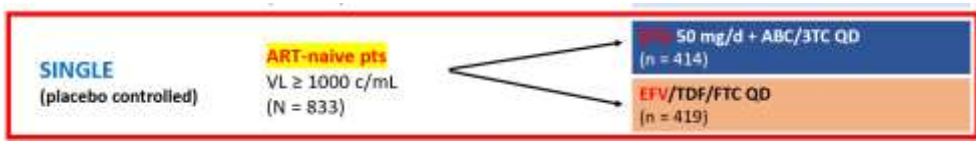


*Investigator-selected NRTI backbone: either TDF/FTC or ABC/3TC.

Clinical Care Options 2014; Raffi et al. Lancet Infect Dis 2013, Walmsley et al. N Engl J Med 2013; Clotet et al. Lancet 2014

SINGLE Study: DTG vs. EFV





DTG better tolerated than EFV

DTG/ABC/3TC (n=414)vs. EFV/TDF/FTC (n=419)	DTG based regimen superior[3,4]
	48 wks: 88% vs. 81% (P=0.003)
	96 wks: 80% vs. 72% (P=0.006)
	144 wks: 71% vs. 63% (P=0.010)

Table 1. Selected Adverse Events and Laboratory Abnormalities That Developed during Treatment.*

Event	Dolutegravir and Abacavir–Lamivudine (N=414)	Efavirenz–Tenofovir DF–Emtricitabine (N=419)
	no. of participants (%)	
Adverse event leading to discontinuation of study drug†	10 (2)	42 (10)
Psychiatric disorder	2 (<1)	15 (4)
Nervous system disorder	0	13 (3)
Skin and subcutaneous-tissue disorder	2 (<1)	8 (2)
Gastrointestinal disorder	0	8 (2)
General disorder or administration-site condition	0	7 (2)

Superior to EFV
1.Less toxicity
2.Greater efficacy

Walmsley et al. NEJM 2013; Walmsley et al. JAIDS 2015

Dolutegravir vs. Efavirenz

Systematic review of 156 publications
Concluded that:

- DTG had **improved odds of viral suppression**
- DTG was **high barrier to resistance**
- DTG led to **fewer discontinuations** due to **better tolerance** and low side effect profile
- Evidence supported dolutegravir use among TB-HIV co-infected persons and **pregnant women.**

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Research Paper

Comparative efficacy, tolerability and safety of dolutegravir and efavirenz 400mg among antiretroviral therapies for first-line HIV treatment: A systematic literature review and network meta-analysis

Steve Kanters[a,*], Marco Vitoria[b], Michael Zoratti[c], Meg Doherty[b], Martina Penazzato[b], Ajay Rangaraj[b], Nathan Ford[b], Kristian Thorlund[c], Prof. Aslam H. Anis[a,d], Mohammad Ehsanul Karim[a,d], Lynne Mofenson[e], Rebecca Zash[f,g], Alexandra Calmy[h], Tamara Kredo[i], Nick Bansback[a,d]

[a] School of Population and Public Health, University of British Columbia, Vancouver, British Columbia, Canada
[b] Department of HIV/AIDS, WHO, Geneva, Switzerland
[c] Departments of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Canada
[d] Centre for Health Evaluation and Outcome Science, University of British Columbia, Vancouver, Canada
[e] Elizabeth Glaser Pediatric AIDS Foundation, Washington, DC, USA
[f] Division of Infectious Diseases, Beth Israel Deaconess Medical Center, Boston, USA
[g] Botswana - Harvard AIDS Institute Partnership, Gaborone, Botswana
[h] HIV/AIDS Unit, Division of Infectious Diseases, Geneva University Hospital, Geneva, Switzerland
[i] South African Medical Research Council, Cape Town, South Africa

No additional risk of NTDs!!

DTG based ART is the most optimum first line:

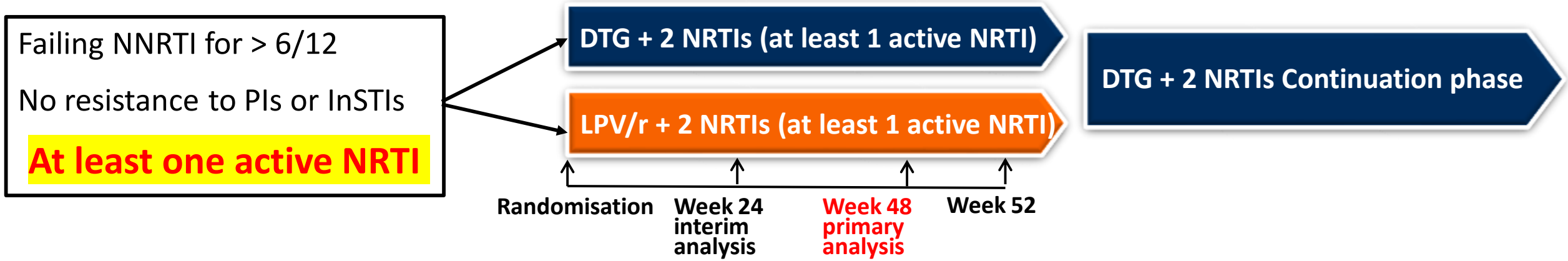
- Simplifies management
- Reduces pill burden (FDC)
- Once daily dosing
- Well tolerated
- Reduced toxicity
- Reduced/manageable drug-drug interactions
- High barrier to resistance
- Cost effective

What about patients failing NNRTI-based first line ART? Does DTG have a role as **second-line treatment**

- **DAWNING**
- **NADIA**
- **VISEND**
- **ARTIST**
- **D²EFT**

DAWNING: Study design
DTG as option for First-Line Failure

Open-label randomised noninferiority phase 3b study - randomized 1:1



- **Stratification:** by HIV-1 RNA (≤ or >100,000 copies/mL), number of fully active NRTIs in the investigator-selected study background regimen (2 or < 2)
- **Primary endpoint:** proportion with **HIV-1 RNA < 50 copies/mL at Week 48** using the FDA snapshot algorithm (12% noninferiority margin)

Aboud M, et al. AIDS 2018. Abstract THPEB040.

Dawning Study- Outcome

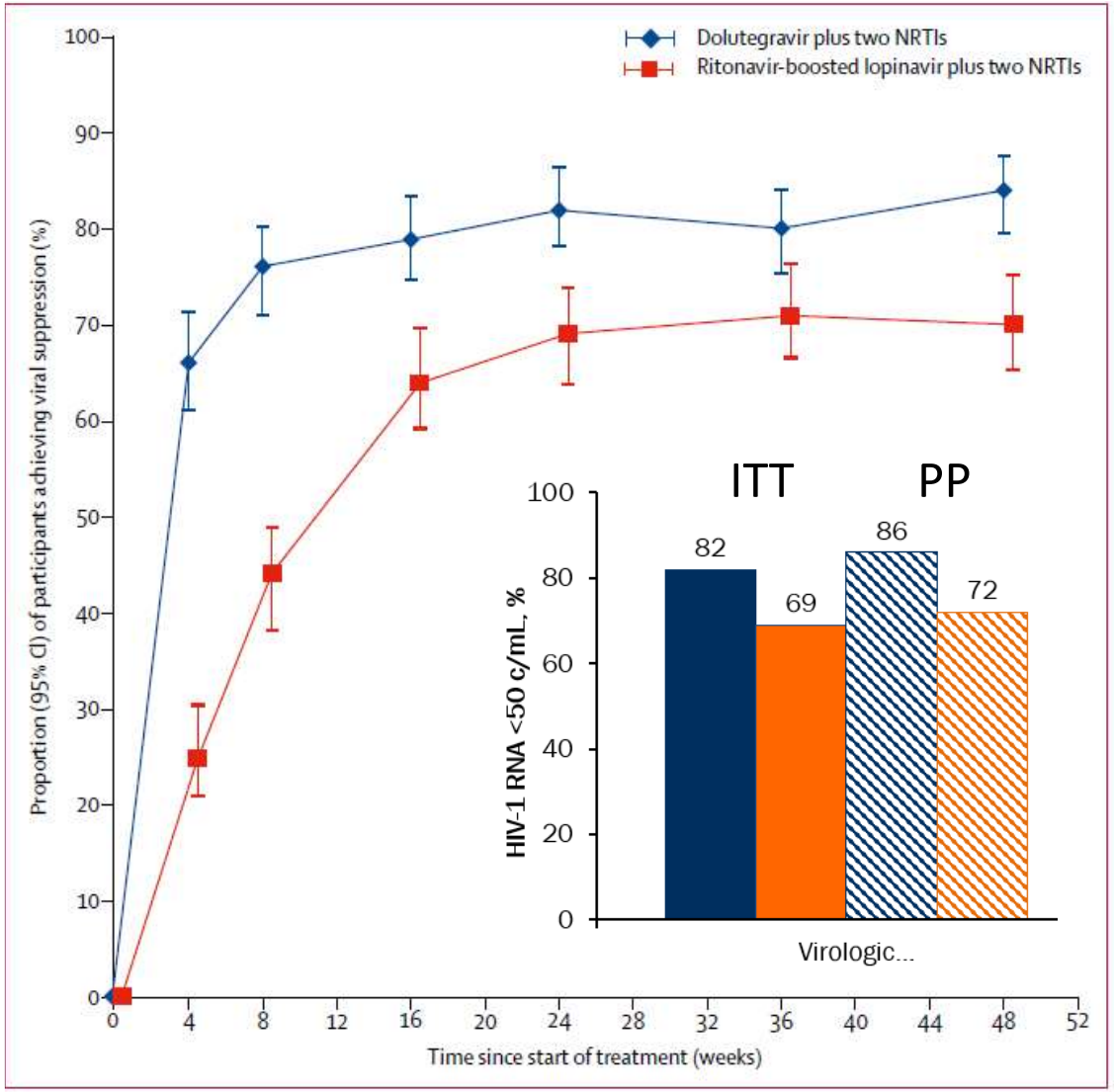


Figure 3: **Participants achieving viral suppression over the course of the study**
Analysis is in the intention-to-treat-exposed population. Viral suppression is defined as plasma HIV-1 RNA less than 50 copies per mL. NRTI=nucleoside reverse transcriptase inhibitor.

Stopped early by DSMB

Second-line DTG superior to LPV/r with at least **one fully active NRTI**

Aboud et al, IAS, 2017

Current public health approach

Switch to PI based second-line without HIV resistance test!

Can we do the same with DTG?

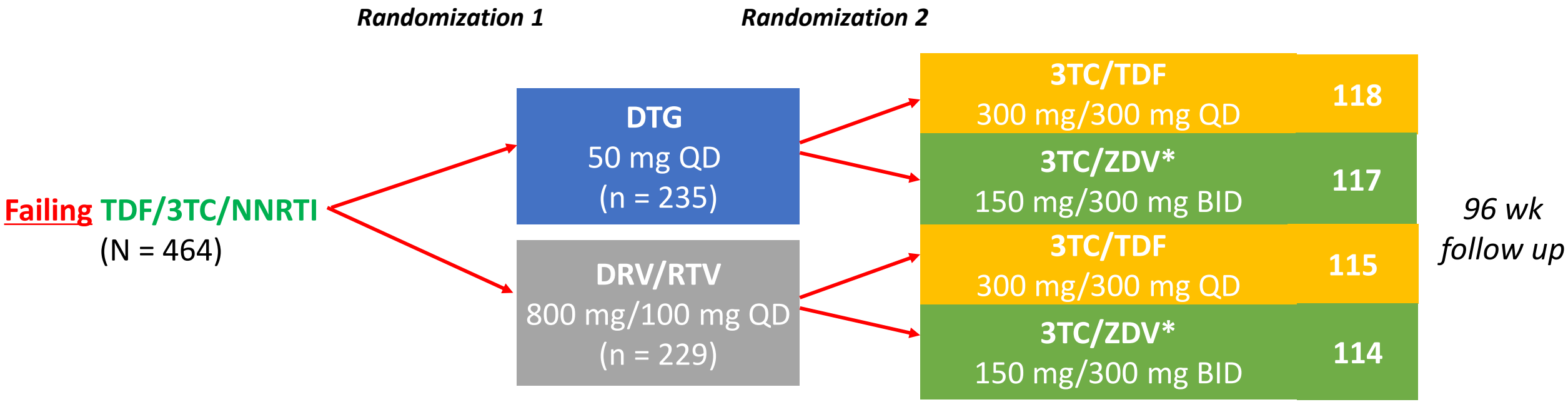
NUCLEOSIDES AND DARUNAVIR/DOLUTEGRAVIR IN AFRICA (NADIA)

Nicholas Paton[1], Joseph Musaazi[2], Cissy M. Kityo[3], Stephen I. Walimbwa[2], Anne Hoppe[2], Apolo Balyegisawa[2], Arvind Kaimal[2], Grace Mirembe[4], James Hakim[5], Henry Mugerwa[3], Abraham Siika[6], Barbara Castelnuovo[2], Agnes Kiragga[2], Andrew D. Kambugu[2], for the Nucleosides and Darunavir/Dolutegravir in Africa (NADIA)

CROI 2021 Abstract 94

NADIA: DTG vs DRV/RTV and TDF vs ZDV - Second-line Therapy

- Multicenter, **2 x 2 factorial**, randomized, open-label, noninferiority phase III trial



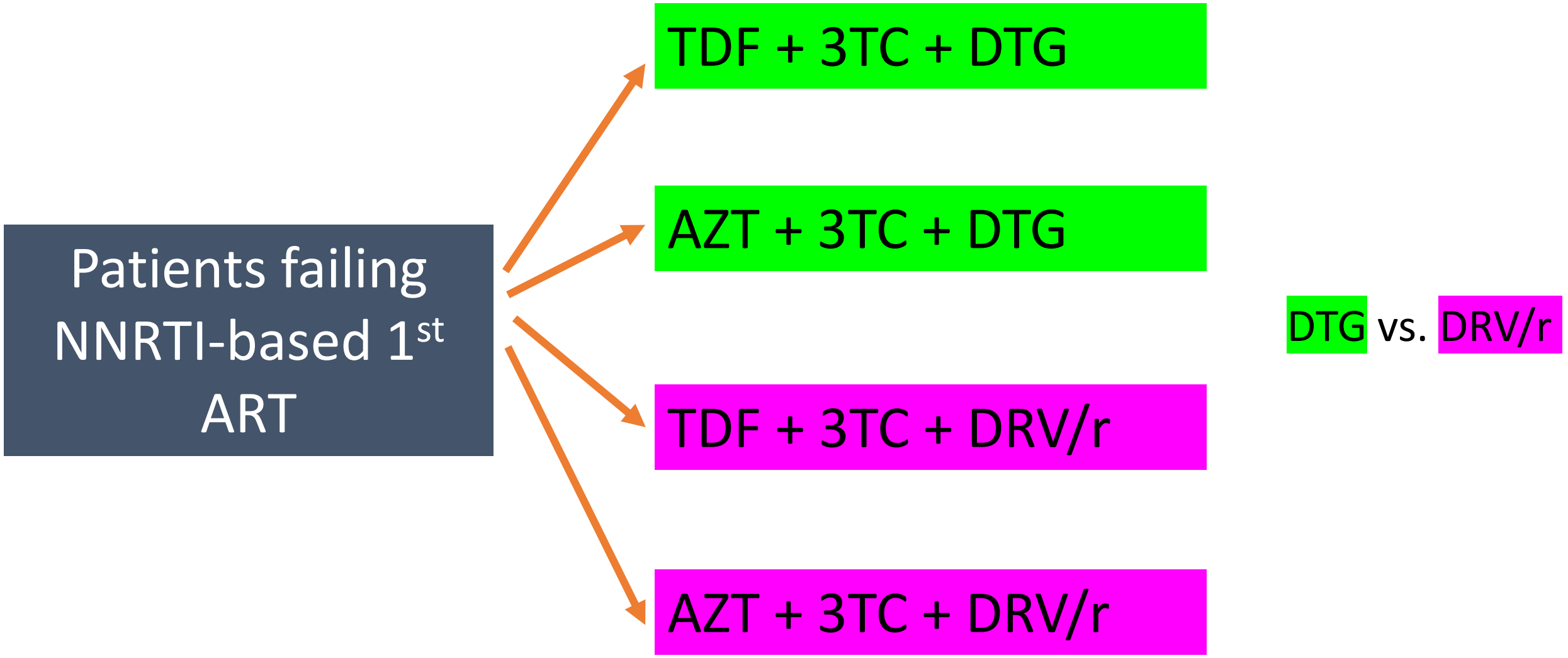
Aim: Evaluate noninferiority of DTG to DRV/RTV and 3TC/TDF to 3TC/ZDV in second line

Primary outcome: HIV-1 RNA <400 c/mL at Wk 96 by FDA snapshot

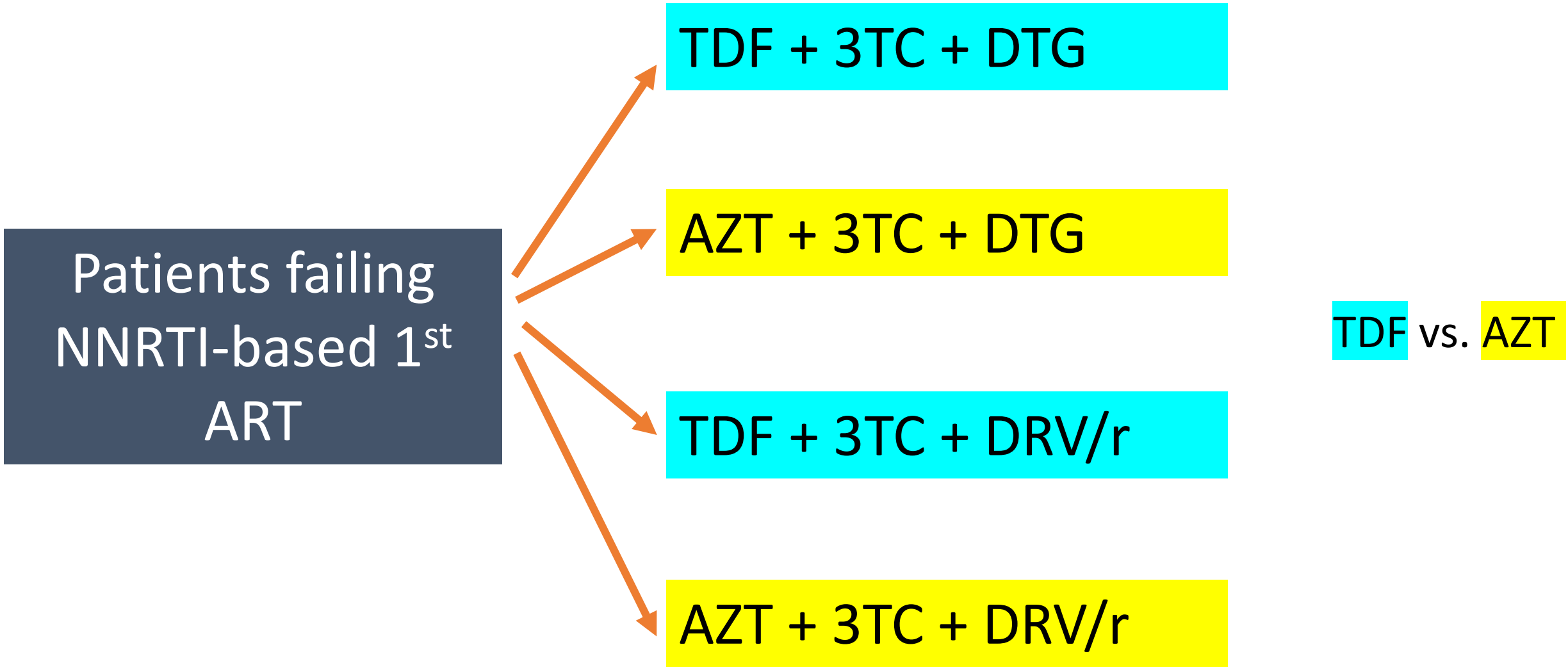
Slide credit: clinicaloptions.com

Paton. NEJM. 2021;385:330. NCT03988452.

Factorial design



Factorial design



NADIA: Distribution of NRTI Resistance at Baseline

Characteristic	DTG (n = 235)	DRV/RTV (n = 226)	3TC/TDF (n = 233)	3TC/ZDV (n = 231)
Baseline resistance, n/N (%)				
▪ Intermediate- or high-level resistance by Stanford algorithm to, n/N (%)				
– Tenofovir	139/228 (**61.0**)	126/225 (**56.0**)	133/230 (**57.8**)	132/223 (**59.2**)
– ZDV	45/228 (**19.7**)	38/225 (**16.9**)	41/230 (**17.8**)	42/223 (**18.8**)
– 3TC	213/228 (**93.4**)	203/225 (**90.2**)	213/230 (**92.6**)	203/223 (**91.0**)

Same proportion of NRTI resistance in all groups

- TDF ~58%
- AZT ~18%
- 3TC ~90%

Note: treatment allocation was random: not influenced by resistance pattern

Paton. NEJM. 2021;385:330. NCT03988452.

96 weeks

Regimen	VL <400
TDF/3TC/DTG (n=118)	92%
TDF/3TC/DRV/r (n=115)	92%
AZT/3TC/DTG (n=117)	88%
AZT/3TC/DRV/r (n=114)	82%

Outcomes with **TDF** superior to outcomes with **AZT** (92% vs. 85%)

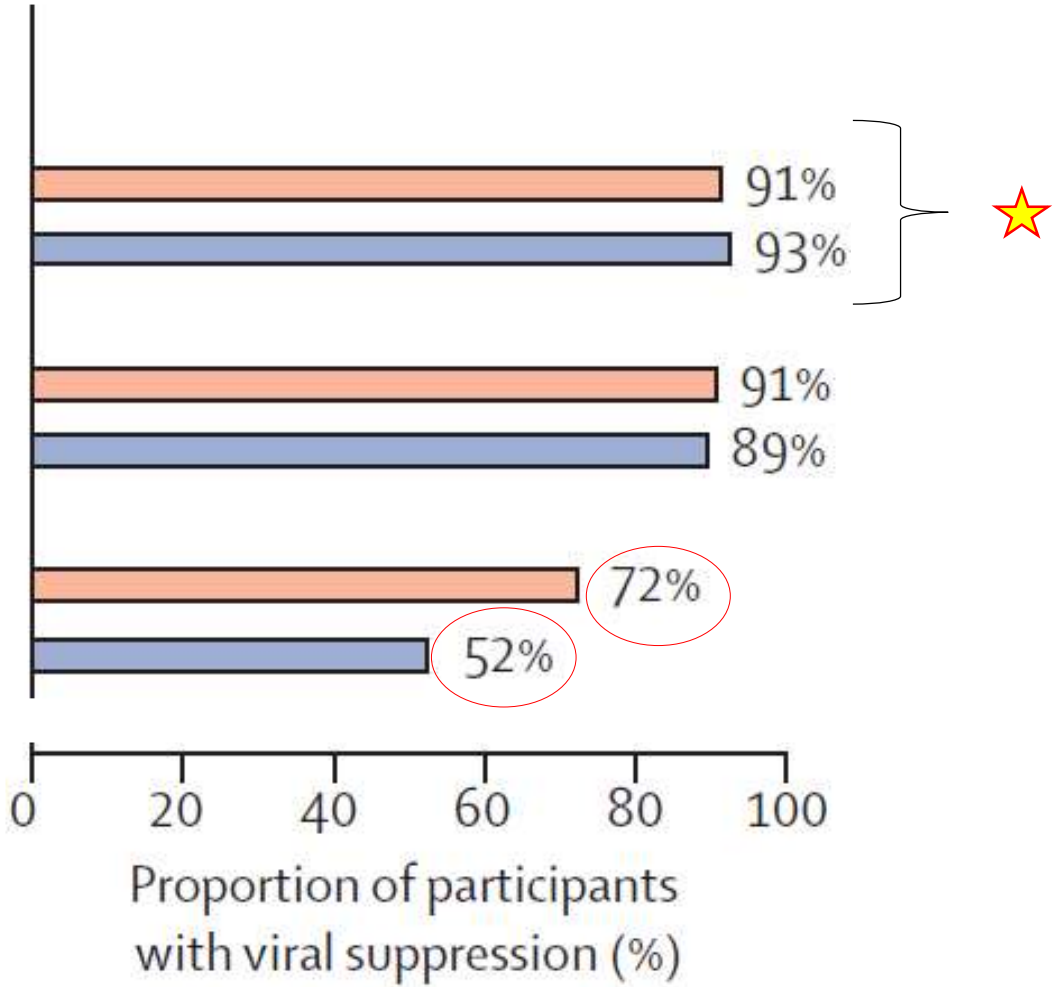
Outcomes with **DTG** equivalent to **DRV/r** (90% vs 87%)

Paton. NEJM. 2021;385:330. NCT03988452.

Subgroup analysis at 96 weeks breakdown by NRTI activity

Good suppression despite 0 predicted NRTIs activity

Number of predicted-active NRTIs	
0 No NRTIs predicted active	
Dolutegravir	84/92
Darunavir	74/80
1 One NRTI predicted active	
Dolutegravir	107/118
Darunavir	109/122
≥2 All NRTIs predicted active	
Dolutegravir	13/18
Darunavir	12/23

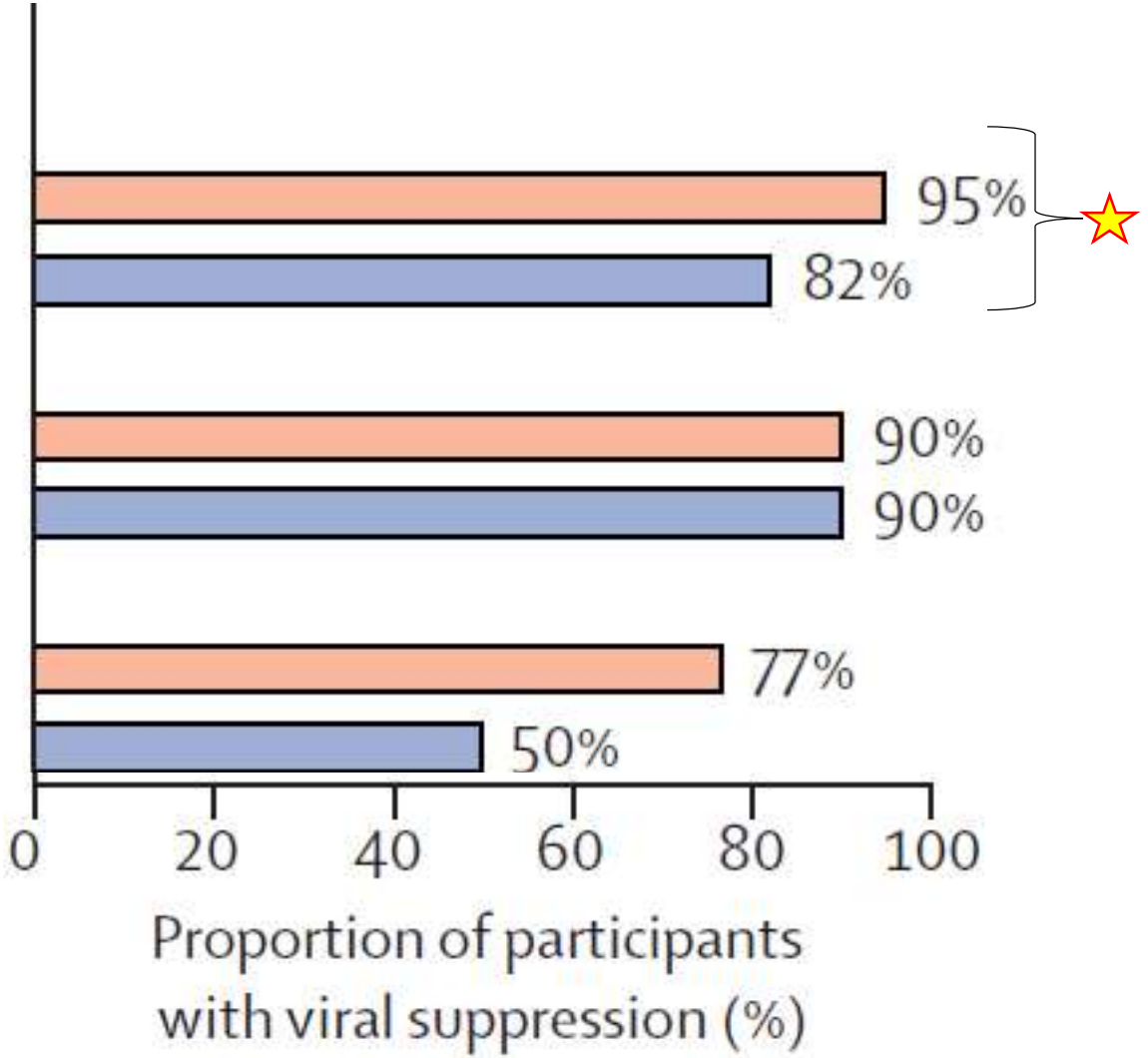


Paton. NEJM. 2021;385:330. NCT03988452.

Subgroup analysis at 96 weeks breakdown by NRTI activity

Activity is better with TDF vs. AZT with no full activity of NRTIs.

Number of predicted-active NRTIs	
0 No NRTIs predicted active	
Tenofovir	126/133
Zidovudine	32/39
1 One NRTI predicted active	
Tenofovir	72/80
Zidovudine	144/160
≥2 All NRTIs predicted active	
Tenofovir	13/17
Zidovudine	12/24



Paton. NEJM. 2021;385:330. NCT03988452.

NADIA trial conclusions:

DTG in combination with NRTIs is as effective as DRV/r

Irrespective of presence of extensive NRTI resistance.

No need for VL or resistance test prior to switch

TDF can be effectively recycled and is superior to AZT in second-line therapy.

Same outcomes

VISEND

ARTIST

D^{2}EFT

Recycling TDF in 2nd line in place of AZT

- Simplification with distinct benefits:
  - Better viral suppression
  - Better tolerated
  - Less intense monitoring
  - Lower pill burden
  - Less frequent dosing
  - Available as FDC
  - Lower cost

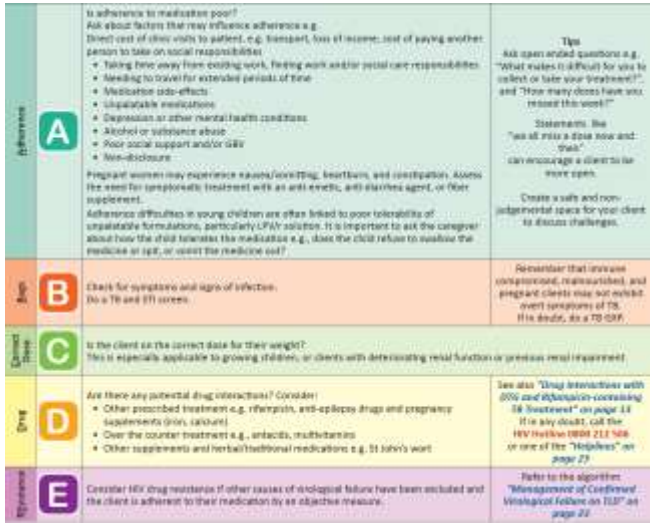
Back to the guideline

Why GL recommends Regimen switches independent of VL as follows:

- **TDF/FTC**/EFV
- **ABC/3TC**/EFV (or NVP)
- **AZT/3TC**/EFV (or NVP)
- **Any LPV/r or ATV/r** for **< 2 years**

Regardless of VL or resistance to NRTIs → **TLD ABC/LD AZT/LD**

- Review VL in last 12 months:
  - Suppressed
  - Not suppressed – switch – ABCDE and EAC
  - Not done - do it - do not wait for the result to switch



South Africa ART Guidelines 2023

Why GL recommends VL-dependent switches- for PI regimens >2yrs

Probability of PI resistance

- **VL <1000-** switch to TLD (LLV) – low probability PI resistance mutations
- **VL >1000 for** ≥2 consecutive tests – **need adherence information**
  - **Adherence <80%**- switch to TLD – low probability PI resistance mutations
  - **Adherence >80%**- resistance test/expert opinion – high probability PI resistance mutations

Clients who meet the definition of confirmed virological failure and have confirmed adherence more than 80% may need a resistance test.
These clients do not qualify for a same-day switch.
Discuss with an HIV expert[4] to authorise and interpret a resistance test.

Provide individualised regimen as recommended by HIV expert.
Repeat VL 3 months after the regimen change to confirm re-suppression, as per the ***"Management of Confirmed Virological Failure on TLD" on page 23***

Objective measures of good adherence include at least one of:
Pharmacy refills > 80% in last 6-12 mths.
Attendance of > 80% of clinic visits - last 6-12 mths.
Detection of ARVs in blood or urine

Rationale for more intense interrogation of PI based treatment failure

- Why should PI resistance matter? Why should you care?
- Main reason- preparing the next regimen should DTG fail ⇒PI based regimen?
- To construct an informed regimen, one needs to know the presence & nature of PI resistances mutations.
- **Best information from a resistance test is when done on a failing regimen**
- **Once switched away from a PI, without a resistance test – this missed opportunity to detect PI resistance is lost.**
- This is not only preparing for the future but might also dictate the regimen you propose now!

XXX INTERNATIONAL WORKSHOP ON HIV DRUG RESISTANCE AND TREATMENT STRATEGIES
20 - 22 September 2023 • Cape Town, South Africa

The use of atazanavir limits cross resistance to darunavir in the South African Public Sector

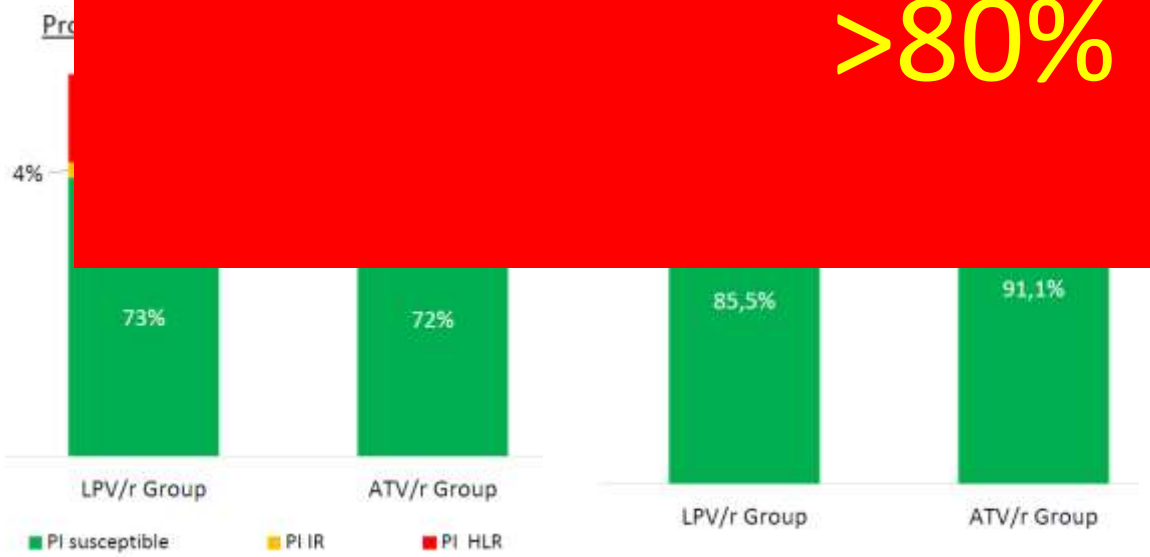
HJ Coetser, L Hans, DP Magubane, LR Gaelejwe, EL Letsoalo, K Steegen

Do Genotypic Resistance test:

PI > 2 years

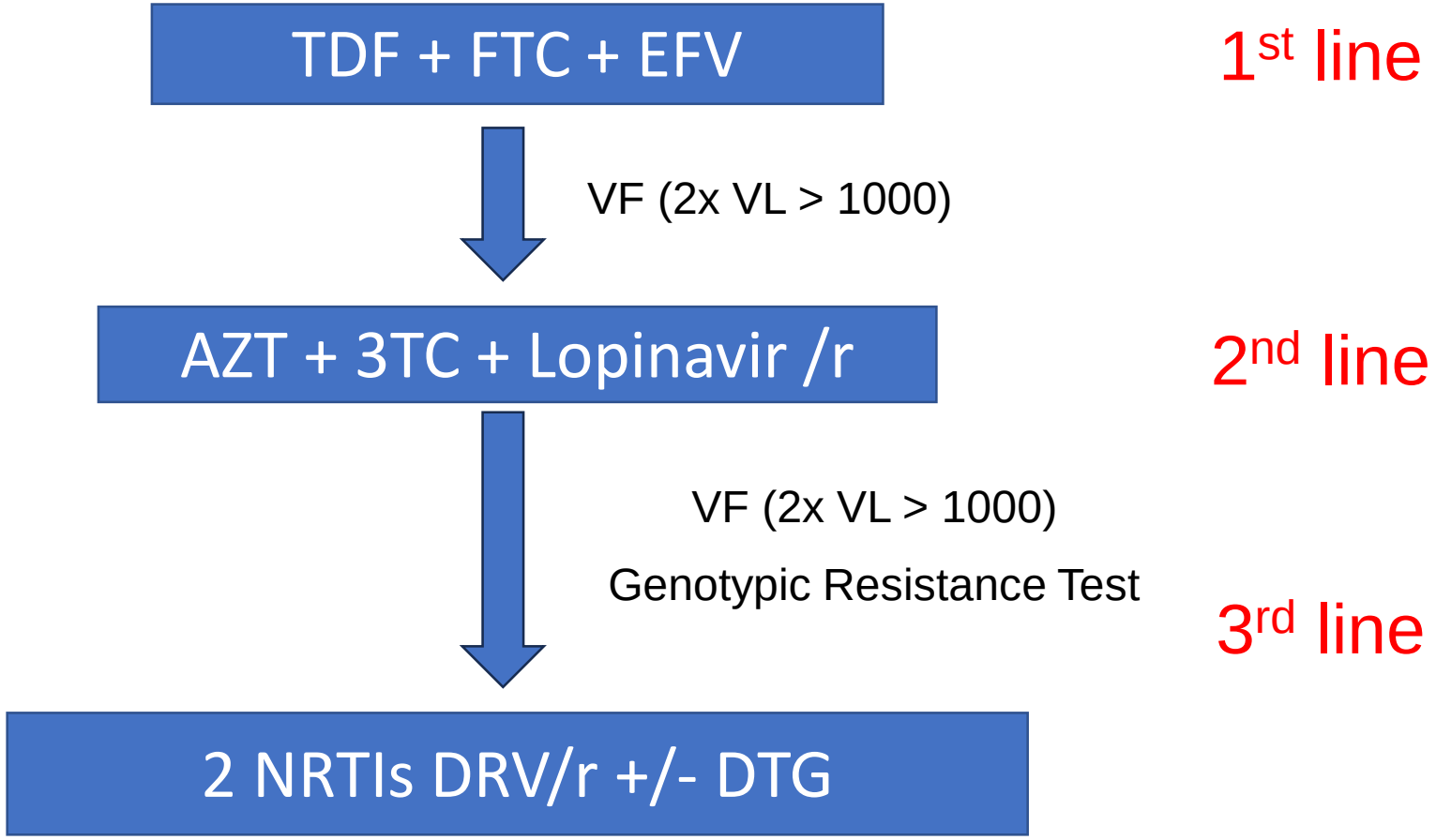
≥ 2 consecutive VL >1000

>80% adherent



May not have DRV/r + 2NRTIs as a reliable rescue regimen

Previous Paradigm

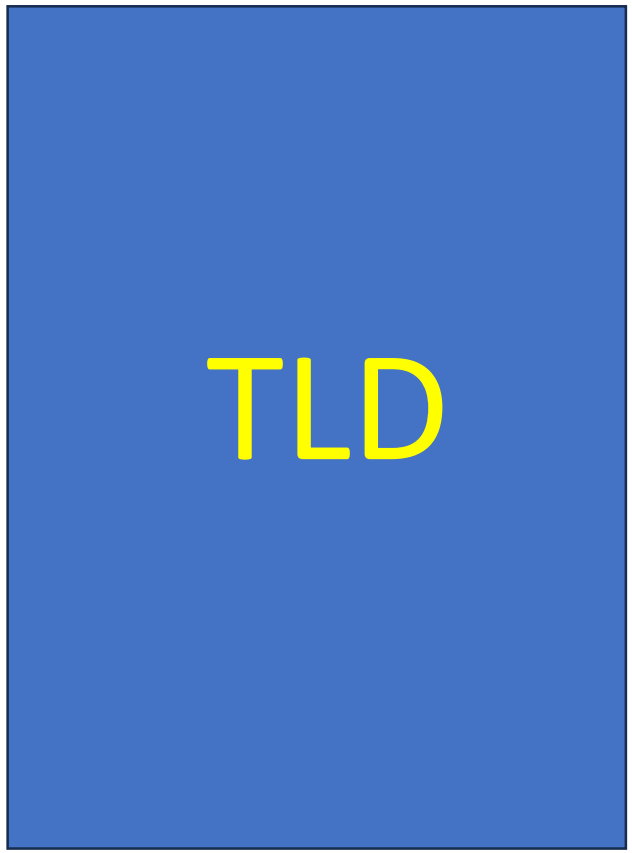


New paradigm

ART Naïve

On NNRTI based first line

On PI based second line



Paradigm shift in terminology of DTG regimens

All TLD is NOT equal

Patients on TLD never having failed a regimen.

(Very low DTG resistance risk)

TLD 1

Patients on TLD previously failed a regimen (1-3% risk of DTG resistance)

TLD 2

What about DTG resistance!
Is there a need to be concerned?

Signals of DTG resistance from 2nd line DTG (TLD2)
RCT and **observational studies**

Dawning:	6/314 at 3 years
NADIA:	9/235 (4%)- 6 AZT, 3 TDF at 2 years
ARTIST:	2/192 at 1- 3 years
ODYSSEY B:	4/196 at 3 years
Malawi MSF program:	2/101 at 6 months (viraemic at switch)

Best estimate : 1-3% with 2nd line TLD over 6 months – 3 years

Emergent Resistance to Dolutegravir Among INSTI-Naïve Patients on First-line or Second-line Antiretroviral Therapy: A Review of Published Cases

Muge Cevik,[1,2] Chloe Orkin,[3,4] and Paul E. Sax[5,6] **May 2020**

Contextualizing Risk of DTG Resistance

- Rare but important - :
- 5 cases - ART naïve
- 10 cases - ART experienced
- **Risk factors:**
  - Poor adherence**
  - Drug interactions
  - High baseline VL and active OI

- Risk of resistance:
  - *TLD after 1st line VF – 1-4% at 96wks 1:100
  - *DTG monotherapy - 3% at 24-48wks 1:33
  - TLD in ART naïve - ~ 0.1% 1:1000
- Early days: Lack of data
  - ATT/other D/D interactions
  - Transitioning to TLD without VL testing.

Close monitoring of dolutegravir resistance in patients with laboratory confirmed dolutegravir exposure:

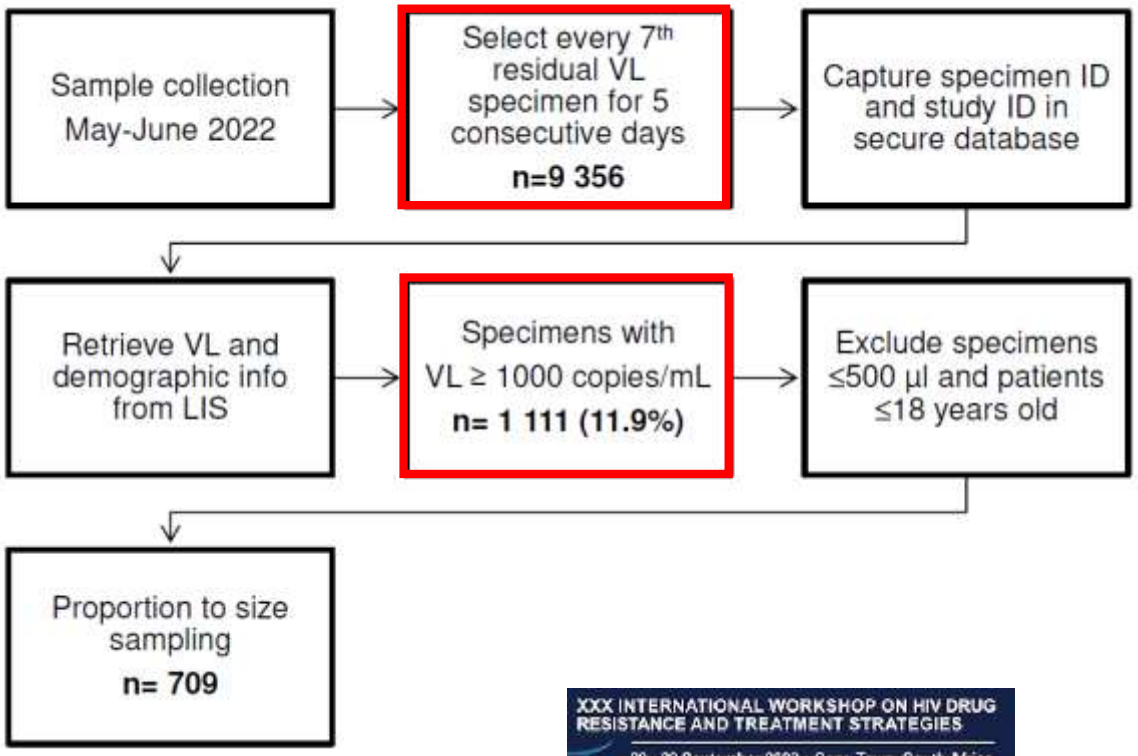
Observations from the 2022 national HIV drug resistance survey in South Africa

K Steegen, WB MacLeod, L Hans, V Kana, MN Kalimashe, H Zwane, C van der Walt, E Cutler, G Hunt, N Cassim, S Currin, K Ayalew, E Raizes

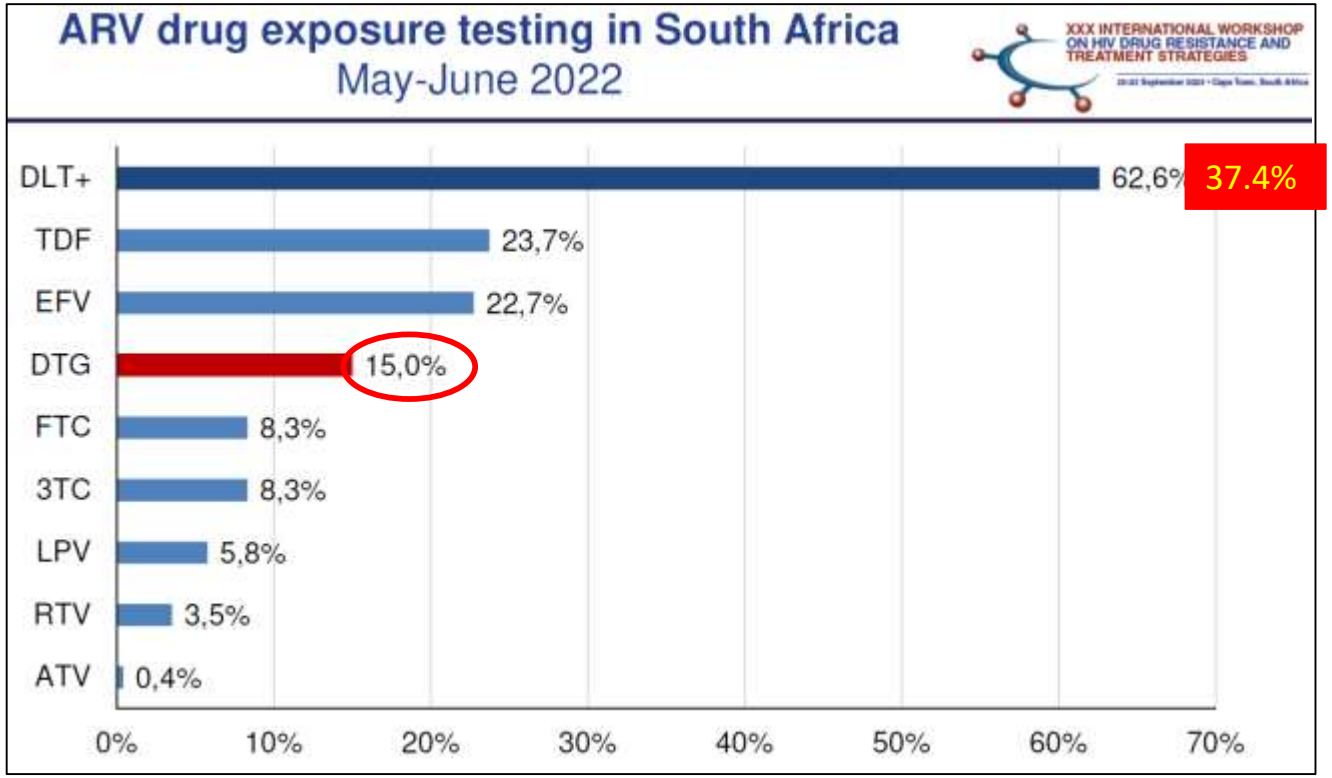
Laboratory based surveillance:

***ARV drug exposure testing**

***HIVDR genotyping**



In every 7th sample sent for VL that had residual volume and VL>1000



XXX INTERNATIONAL WORKSHOP ON HIV DRUG RESISTANCE AND TREATMENT STRATEGIES
20 - 22 September 2023 • Cape Town, South Africa

Close monitoring of dolutegravir resistance in patients with laboratory confirmed dolutegravir exposure:

Observations from the 2022 national HIV drug resistance survey in South Africa

K Steegen, WB MacLeod, L Hans, V Kana, MN Kalimashe, H Zwane, C van der Walt, E Cutler, G Hunt, N Cassim, S Currin, K Ayalew, E Raizes

Overall resistance

- ✓ 57.9% ≥1 DRM (95% CI: 54.1% - 61.6%)
- ✓ 1.6% ≥1 major INSTI DRM (95% CI: 0.8% - 3.0%)

Any drug level detected

- ✓ 2.4% ≥1 major INSTI DRM (95% CI: 1.1% - 4.7%)

No drug level detected

- ✓ 0.7% ≥1 major INSTI DRM (95% CI: 0.0% - 2.8%)

- Viraemic
- **No** drug in blood
- Successful INSTI genotype

NNRTI drug level detected

- ✓ 90.1% ≥1 NNRTI DRM (95% CI: 84.0% - 94.1%)

PI drug level detected

- ✓ 28.6% ≥1 major PI DRM (95% CI: 17.1% - 43.7%)

INSTI drug level detected

- ✓ 11.9% ≥1 major INSTI DRM (95% CI: 5.9% - 22.1%)

- Viraemic
- DTG in blood
- Successful INSTI genotype

DTG resistance in laboratory confirmed DTG exposed increased- **2.7%** in 2021 to **11.9%** in 2022

DTG resistance is here and likely to become the next major challenge.

Need to be vigilant!!!

Genotypic resistance test expensive

Approach to VF on TLD

Regimen	Definition	Resistance testing	Recommendation
TLD-1	2 VL ≥1000 c/mL	Not recommended	Most likely poor adherence ABCDE & AAC -monitor
TLD-2 **< 2 years**	2 VL ≥1000 c/mL	Not recommended	Too soon to expect resistance mutations ABCDE & AAC -monitor
TLD-2 > 2 years	2 VL ≥1000 c/mL	Discuss with HIV expert	Genotype based individualized regimen

South Africa ART Guidelines 2023

Rationalizing DTG resistance tests: Strong Gate keeping

- Most common cause of DTG failure:
  - Poor adherence
  - D/D interactions
- Expecting low levels of resistance esp. TLD1
- Must confirm DTG resistance before switch
- Use best objective measures of adherence

Objective measures of good adherence include at least one of:
Pharmacy refills > 80% in last 6-12 mths.
Attendance of > 80% of clinic visits - last 6-12 mths.
Detection of ARVs in blood or urine

KEH ID Dept will serve as contact for Authorization of resistance Tests and ART advice

0800 111 740 – toll free on Telkom lines

063 682 5888 (calls and WhatsApp)

Gosnell@ukzn.ac.za

Conclusion: New Guideline

- Optimizes the management of HIV
  - ART naïve – TLD1
  - ART experience – TLD2
  - Failing PI (*) – TLD3+
- Simplifies the public health approach.
- Heavily reliant on DTG- **robust** nature and **high genetic barrier for resistance**.
- Most treatment failures expected to be related adherence.
- 2 main scenarios for resistance testing: Failing PI based 2nd line and suspicion for DTG resistance
- Critical to be vigilant for resistance
- Use genotypic resistance tests sparingly through established approval processes