3rd Line ART Regimens

Dr Leon Levin

ADReC

What is a Viral Load?

What does the viral load tell us?

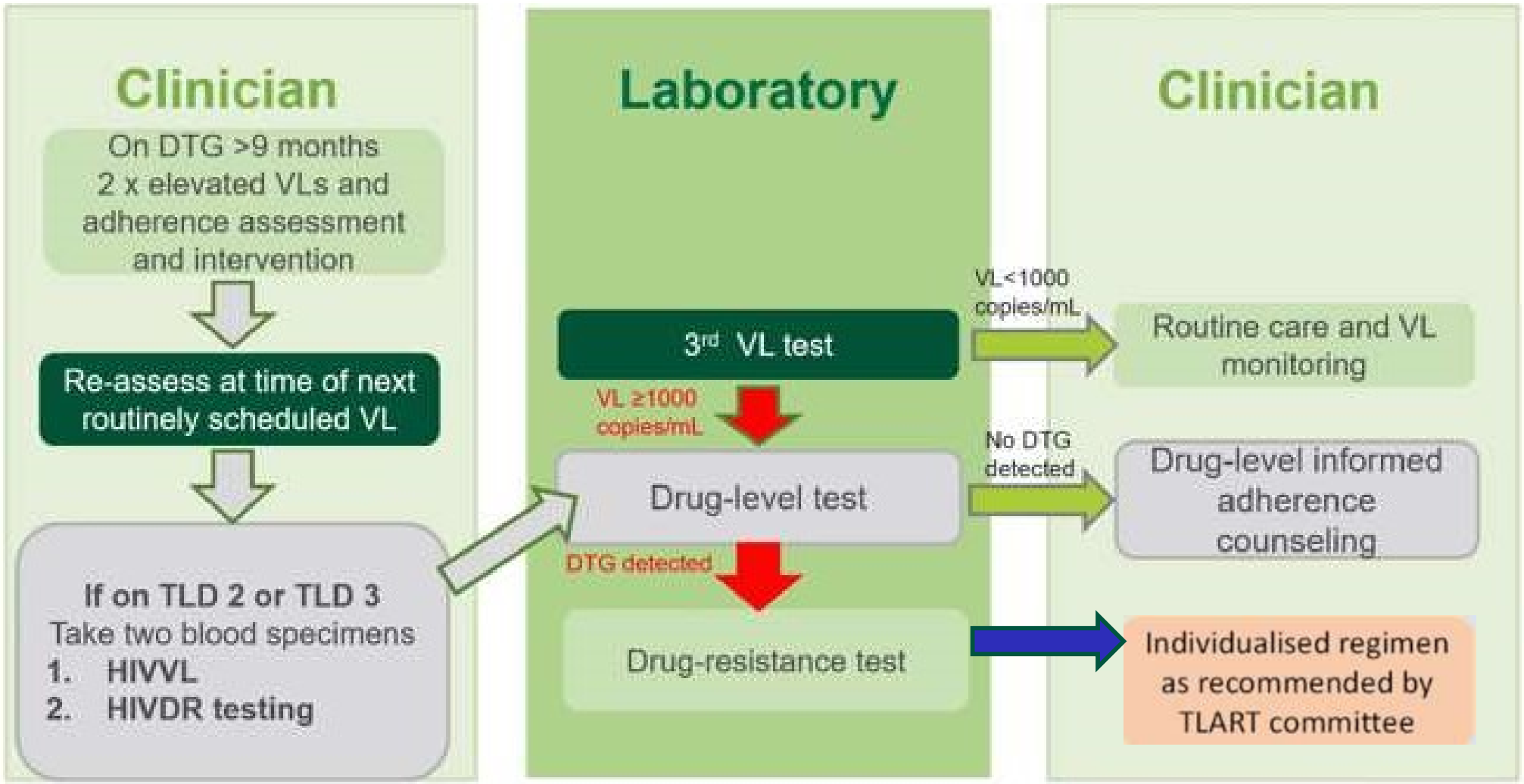
- Where does the virus live?
- In the Blood?
- No
- In the liver
- Yes
- Spleen?
- Yes
- Lymph nodes?
- Yes
- So what does it mean if we find it in the blood?

So what does the viral load tell us?

- **It tells us that the HIV virus is replicating**

New Resistance testing algorithm

Process of "Reflex Testing"



Slide Courtesy of Dr Jeannette Wessels

New Resistance testing algorithm

- Drug level testing will screen out patients who have not taken their meds in the previous week before doing the test.
- How do we ensure that the patient is adherent to their meds before doing the test

How to do resistance testing

- Therefore make certain that patient is adherent before doing resistance testing
- Maintain patient on current antiretroviral therapy - resistance testing **must** be performed whilst the patient is taking the antiretroviral therapy regimen they are failing
- Ask patient to take ARVs regularly for 1 month and then do resistance testing

3rd Line ART Regimens

Previously

TEE **AZT/3TC/LPV/r** **TLD+DRV/r**

Now

TLD

New Name for 3rd Line Committee

ARV Drug Resistance Committee (ADReC)

Definition of Third Line*

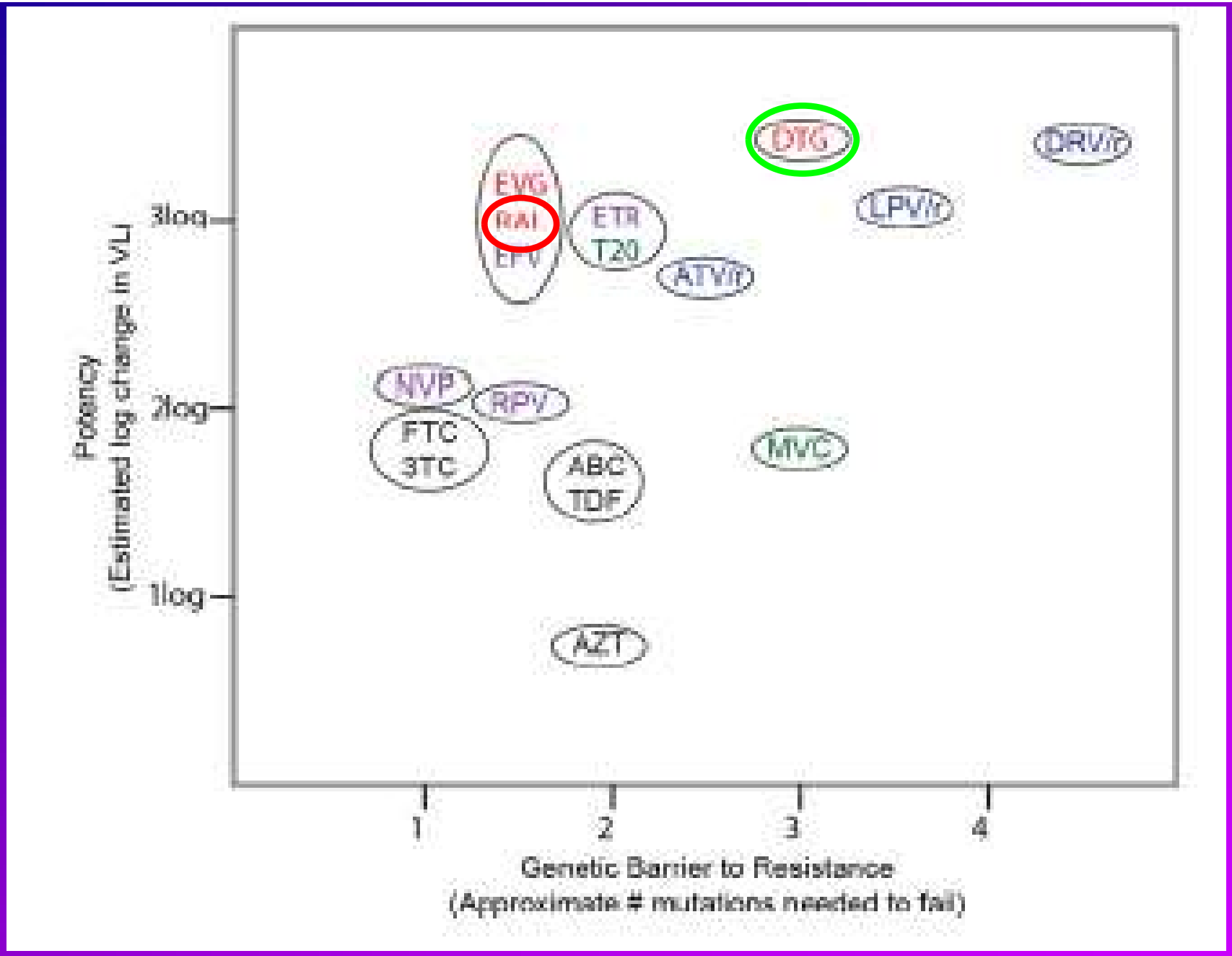
- Any patient with PI resistance
- Any patient with INSTI resistance

* In the South African setting

Background on 3rd line Drugs

Raltegravir(RAL)

- INSTI just like DTG
- Twice daily dosing
- Low genetic barrier to resistance
- Resistance to RAL can cause cross resistance to DTG
- AVOID RAL at all costs!
- Patients on RAL should be switched to DTG with expert guidance



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Dolutegravir

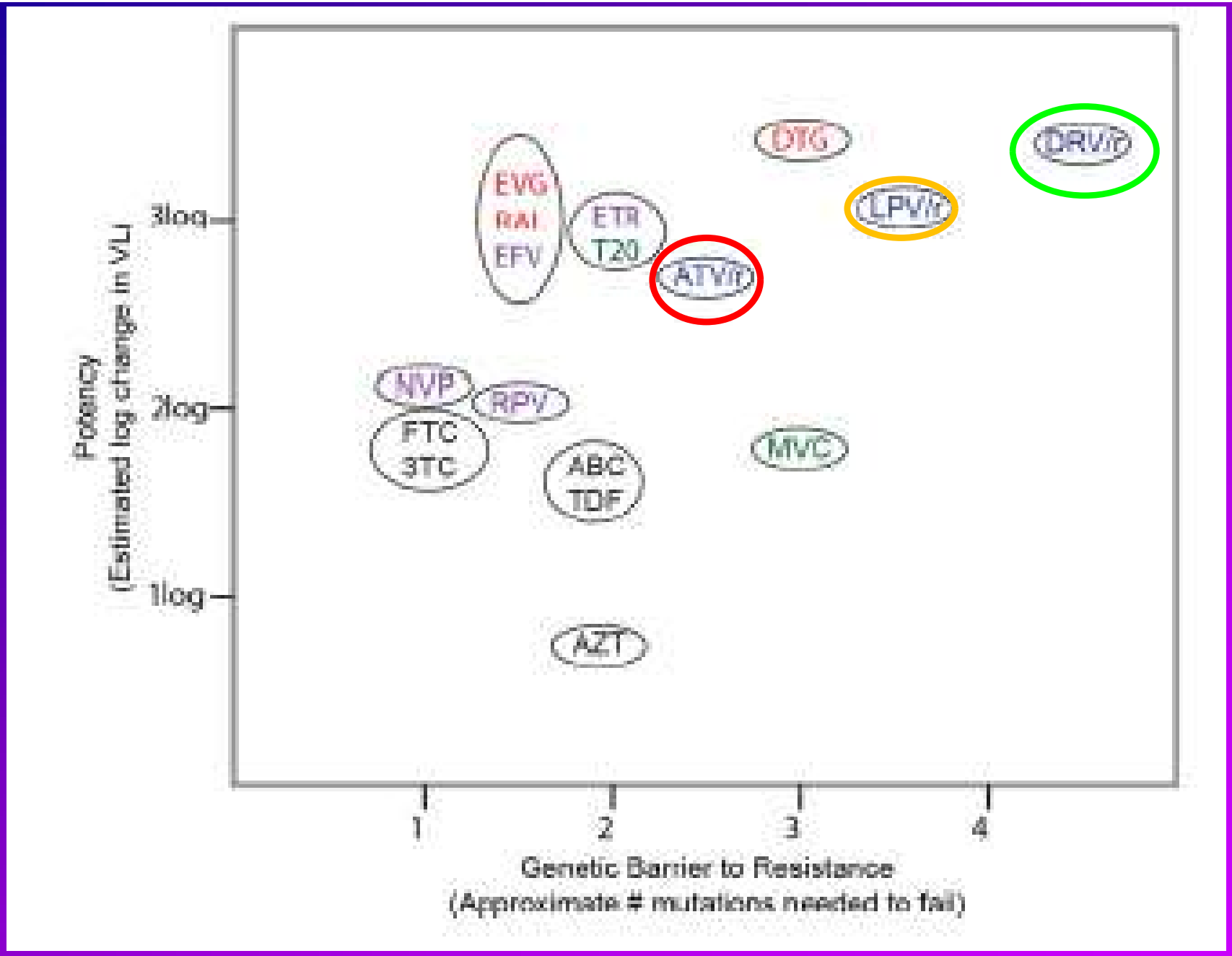
- Well known ARV used in 1st 2nd and 3rd line regimens
- High potency and genetic barrier to resistance.
- If patient is INSTI experienced, or has INSTI resistance, DTG should be dosed at 50mg twice a day.

Etravirine (ETR)

- 2nd Generation NNRTI
- Higher genetic barrier than EFV or NVP
- Big pill burden
- Don't know if it will really work because patients aren't on a NNRTI in 2nd line so could miss ETR resistance
- TLD +DRV/r so good that virtually never need ETR anymore
- Etravirine is no longer on contract and is being removed from the South African market
- Contact the ADReC for advice on stopping your patient's ETR

Darunavir/ritonavir (DRV/r)

- Very potent PI
- Very high barrier to resistance
- Previously dosed at 600mg bd + 100mg RTV bd
- Now, dosing depends on if there is DRV/r resistance or not



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Appropriate clinical use of darunavir 800 mg

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Indication

Darunavir 400 mg tablets were recently approved by the South African Health Products Regulatory Authority (SAHPRA) for the following indication:

> PREZISTA, in combination with low dose ritonavir (DRV/r) and with other antiretroviral medicines, is indicated for the treatment of human immunodeficiency virus (HIV) infection in antiretroviral treatment experienced adult patients who are protease-inhibitor-naïve or after exclusion of darunavir resistance associated mutations (DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V). Genotypic or phenotypic testing should guide the use of DRV/r. (Prezista package insert)

There is no information on the use of darunavir in combination with ritonavir in the paediatric population for the once-daily dose.

Southern African HIV Clinicians Society guidelines

Southern African HIV Clinicians Society adult antiretroviral therapy (ART) guidelines currently recommend ritonavir-boosted atazanavir (ATV/r) 300/100 mg as preferred boosted protease inhibitor (PI/r) for second-line ART. It was noted in the guidelines that once a suitable tablet for DRV/r 800/100 mg dosing became available, DRV/r 800/100 mg would be a feasible option in second-line ART, with fewer side effects than the DRV/r 600/100 mg twice-daily dosing.

Using darunavir/ritonavir 800/100 mg in third-line antiretroviral therapy

Currently, patients on DRV/r on third-line ART receive DRV/r 600/100 mg bid. However, a small proportion of third-line patients have no DRV resistance-associated mutations (RAMs), and in such patients it may be possible to use DRV/r 800/100 mg daily instead of DRV/r 600/100 mg bid to reduce pill burden, dosing frequency and side effects.

For patients initiating third-line ART, if the composite DRV score (Stanford) is zero on *all* genotypes, DRV/r 800/100 mg daily may be initiated (see Figure 3).

For those patients who are already on a third-line regimen, their VL must be checked. If the VL is undetectable, and the composite DRV score (Stanford) on *all* genotypes is zero, the patient may switch from DRV/r 600/100 mg twice daily to DRV/r 800/100 mg once daily. The rest of the regimen should not be changed (see Figure 4). If the VL is detectable, manage further as appropriate according to current guidelines.

Darunavir/ritonavir (DRV/r) Dosing

- **If No DRV/r mutations**
  - Dosed at DRV 800mg and Ritonavir 100mg **ONCE** daily
  - 2 X DRV/r 400/50 tabs once a day
- **If DRV/r resistance**
  - Dosed at DRV 600mg and ritonavir 100mg **TWICE** daily

Tenofovir Alafenamide (TAF)

- Prodrug of Tenofovir similar to TDF
- Less effect on kidneys and bones than TDF.
- TAF 25mg can be given from 25kg irrespective of the age of the child.
- TAF 25mg +3TC/FTC can be given together with NNRTIs, INSTIs or PIs
- TAF + FTC can be used from an EGFR of 30ml/min (15ml/min if TAF used on its own)
- Does have some effect on lipids (LDL, HDL, Total cholesterol)

Tenofovir Alafenamide (TAF)

- Has been **associated** with weight gain especially in black women but doesn't necessarily cause weight gain.
- On New 2025 Tender
- In Primary Healthcare STGs, TAF is indicated for patients with chronic Hepatitis B and EGFR 30-50ml/min
- ADReC may recommend TAF for paediatric patients 25-30kg requiring Tenofovir or Patients >25kg with an EGFR 30-50ml/min requiring Tenofovir.

TAF Formulations available in NDoH

- **FTAF-** TAF 25mg/FTC 200mg

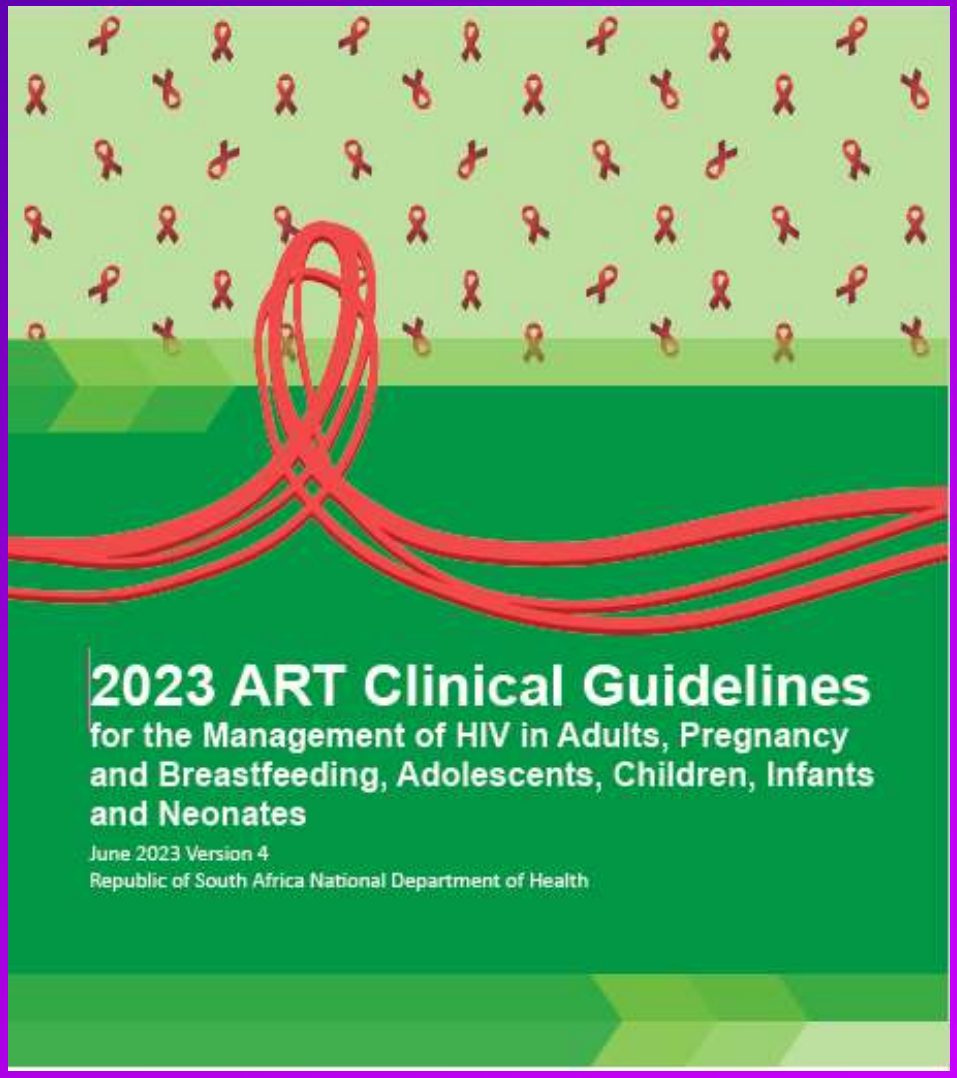
- **TAFLD** - TAF 25mg/3TC 300mg /DTG 50mg- Similar to TLD but with TAF instead of TDF

- **TAFED-** TAF 25mg/FTC 200mg /DTG 50mg- basically interchangeable with TAFED

DRV/r and TB treatment

- In certain situations, can stop the DRV/r and just use TLD + DTG
- Can use Rifabutin 150mg daily instead of Rifampicin
  - Other TB drugs must be given individually
- Can use a quinolone instead of rifampicin eg levofloxacin
  - Course of TB treatment much longer
- Please discuss with the ADReC

New 2023 NDoH ART Guidelines



Nadia Trial

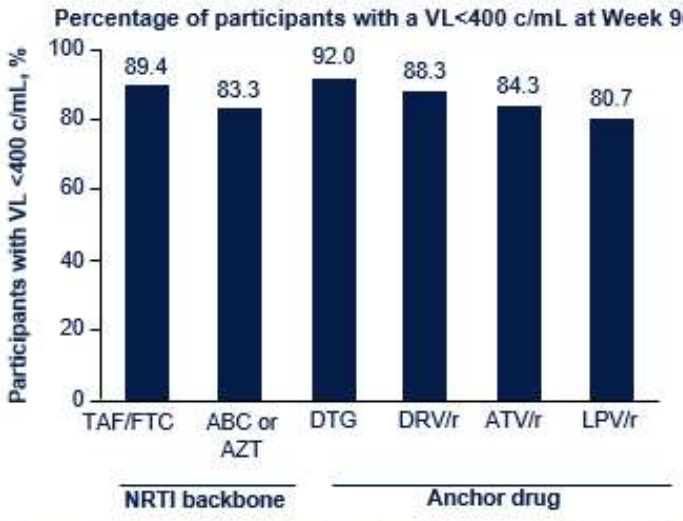
- In Patients failing TDF/3TC/NNRTI regimen TDF/3TC/DTG (TLD)was superior to AZT/3TC/DTG in 2nd line
- ARTIST, VISEND and D²EFT Trials show similar results
- We don't know if this would apply to ABC ie can patients failing an ABC/3TC/NNRTI regimen be switched to ABC/3TC/DTG?

Lancet HIV 2022

CHAPAS-4: Increasing second-line ART options for children with HIV in Africa

Study objective and design[1,2]

- **Objective:** To investigate second-line ART options for children, by evaluating long-term outcomes for those switching from first-line (NNRTI-based) to second-line ART
- **Study design:** Randomised clinical trial (ISRCTN22964075) conducted in Uganda, Zambia and Zimbabwe. Participants aged 3–15 years (N=919) were randomised to receive TAF/FTC, or 3TC + ABC or AZT as an NRTI backbone, in combination with either DTG, DRV/r, ATZ/r or LPV/r as an anchor drug



Results[1,2]

- Virologic suppression (VL <400 c/mL) was high across study arms at Week 96
  - TAF/FTC demonstrated superior virologic suppression versus ABC or AZT + 3TC (89.4% vs 83.3%; treatment difference 6.3%; 95% CI: 2.0, 10.6; p=0.004)
  - DTG demonstrated superior virologic suppression versus LPV/r or ATV/r (92.0% vs 82.5%, treatment difference 9.7%; 95% CI: 4.8, 14.5; p<0.0001)
- $CD4^+$ T-cell counts increased from BL in all groups, with no differences between groups observed
- Rates of AEs were low overall, with similar AE profiles between NRTI backbones, and fewer Grade 3/4 AEs reported for DTG versus other anchor drugs
- From BL to Week 96, weight-for-age z scores significantly increased for all anchor drugs except LPV/r
  - Weight increased by 7.0 kg for TAF, 6.2 kg for ABC or AZT, 5.6 kg for LPV/r, 6.7 kg for ATV/r and DRV/r, and 7.2 kg for DTG

TAF/FTC and DTG were virologically superior to other backbone and comparator regimens, with a favourable safety profile in children

Slide Courtesy of Prof Helena Rabie and Viiv

1. Musiime V, et al. IAS 2023. Oral OALBB0503
2. Bwakura-Dangarembizi M. IWHP 2023. Abstract 1

Principles of Switching to DTG regimens in 2023 NDOH Guidelines

- **NADIA**
  - **TEE to TLD**
- **Non NADIA Switches**
  - **Ensure there is a viable future regimen (usually PI regimen)**

Third line Regimens

3rd Line Committee

- **New Name:**
- **ARV Drug Resistance Committee (ADReC)**

- **Dr Ruth Lancaster**
- **TLART@health.gov.za**
- **ADReC will only authorize 3rd line drugs where there is PI resistance, or INSTI resistance**

- **WC, KZN and FS have their own provincial 3rd line committees**

Third line Algorithm

Why the need for a 3rd line Algorithm?

- To ensure consistency between the different 3rd line committees
- To ensure consistency within the same 3rd line committee
- To ensure transparency

Previous 3rd line Algorithm

- The more resistance, the more ARVS
- Options included
  - 2 NRTIs +DRV/r
  - 2NRTIs + DTG + DRV/r
  - 2NRTIs + DTG + DRV/r + Etravirine

SA Adult 3rd line committee Algorithm

- Eligibility to 3rd line requires at least low level resistance to either LPV or ATV, depending on what patient is taking – **all get DRV-r**
- All get either 3TC or FTC plus either TDF or AZT (whichever has the least resistance)
- If there is intermediate resistance (or worse) to TDF or AZT OR low level resistance to DRV or worse **ADD DTG**
- If there is intermediate resistance (or worse) to TDF or AZT AND low level resistance to DRV or worse **ADD ETR** (unless there is intermediate resistance (or worse) to ETR

OPEN

Third-Line Antiretroviral Therapy Program in the South African Public Sector: Cohort Description and Virological Outcomes

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Background: The World Health Organization recommends that antiretroviral therapy (ART) programs in resource-limited settings develop third-line ART policies. South Africa developed a national third-line ART program for patients who have failed both first-line non-nucleoside reverse transcriptase inhibitor–based ART and second-line protease inhibitor (PI)-based ART. We report on this program.

Methods: Third-line ART in South Africa is accessed through a national committee that assesses eligibility and makes individual regimen recommendations. Criteria for third-line include the following: ≥1 year on PI-based ART with virologic failure, despite adherence optimization, and genotypic antiretroviral resistance test showing PI resistance. We describe baseline characteristics and resistance patterns of this cohort and present longitudinal data on virological suppression rates.

Results: Between August 2013 and July 2014, 144 patients were approved for third-line ART. Median age was 41 years [interquartile range (IQR): 19–47]; 60% were women (N = 85). Median CD4$^+$ count and viral load were 172 (IQR: 128–351) and 14,759 (IQR: 314–90,378), respectively. About 2.8% started PI-based ART before 2004; 11.1% from 2004 to 2007; 31.3% from 2008 to 2011; and 6.3% from 2012 to 2014 (48.6% unknown start date). Of the 144 patients, 97% and 98% had resistance to lopinavir and atazanavir, respectively; 57% had resistance to darunavir. All were initiated on a regimen containing darunavir, with raltegravir in 101, and etravirine in 33. Among those with at least 1 viral load at least 6 months after third-line approval (n = 118), a large proportion (83%, n = 98) suppressed to <1000 copies per milliliter, and 79% (n = 93) to <400 copies per milliliter.

Conclusion: A high proportion of third-line patients with follow-up viral loads are virologically suppressed.

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Presented at the meeting of the Conference of Retroviruses and Opportunistic

Mutation Scoring for Stanford database

Mutation Score	Significance
<0	Hypersusceptible
0-9	Susceptible
10-14	Potential low level Resistance
15-29	Low level Resistance
30-59	Intermediate Resistance
>60	High level Resistance

Principles of new 3rd line Algorithm for patients with PI resistance

- TLD in certain situations
- As long as there is a robust back up PI regimen
  - ie DRV/r

Drug Regimens - Rationale

1. If DRV fully susceptible (i.e. Stanford <10): Tenofovir/lamivudine/dolutegravir
2. If DRV score 10-59: Tenofovir/lamivudine/dolutegravir + darunavir/r 600mg/100mg bd
3. If DRV score 60 or above: Individualised regimen

New 3rd Line Algorithm

HIV DRUG RESISTANCE REGIMENS 2025

1. Treatment algorithm

1. Patient:
- **is on DTG regimen**
- **has developed DTG resistance**
- **is PI naïve**

a) TE + DRV/r dosed once daily

i. If not eligible for TDF*:
- Replace TE with TAF/FTC‡

ii. If not eligible for TAF‡:
- Replace TE with AL

2. Patient:
- **is on PI regimen**
- **has developed PI resistance**
- **is INSTI naïve, and:**

2.1. - **DRV score <10**

a) TLD¥

i. If not eligible for TDF*:
- Replace TLD with TAFED‡ or TAFLD‡

ii. If not eligible for TAF‡:
- Replace TLD with ALD / AL+DTG

2.2. - **DRV score 10-59**

a) TLD¥ + DRV/r dosed twice daily

i. If not eligible for TDF*:
- Replace TLD with TAFED‡ or TAFLD¥

ii. If not eligible for TAF‡:
- Replace TLD with ALD / AL+D

b) Discretion may be applied if there are adherence concerns ***and DRV/r score <30***: In these cases, the committee may consider using TLD alone or changing the twice daily DRV/r to once daily DRV/r. Both cases will require close VL monitoring. If VL rebound occurs, consult with ADReC.

2.3 - **DRV/r score ≥60**

a) Refer to ADReC for an individualised regimen based on genotype and clinical history.
b) Discretion may be applied. If there are adherence concerns, ADReC may consider using TLD alone.

3. Patient has:
- **PI and INSTI resistance, or**
- **a history of multiple ARV class resistance**

a) Refer to ADReC for an individualised regimen based on genotype and clinical history.

4. Patient has
- **DTG resistance**
- **prior ATV/r or LPV/r exposure, but no resistance test was done at time of switch to DTG regimen**

a) TE + DRV/r dosed once daily

i. If not eligible for TDF*:
- Replace TE with TAF/FTC‡ or TAF/3TC¥

ii. If not eligible for TAF‡:
- Replace TE with AL

b) VL at 3 months': if not suppressed then repeat the genotyping.

DTG Resistance

1)Patient is on DTG Regimen, has developed DTG resistance and is PI naïve.

- No PI resistance
  - Once daily DRV/r is in order
  - Debate about other PIs-rather DRV/r
- Any NRTIs will work (EARNEST, NADIA)
- Therefore TDF/FTC +Once daily DRV/r
- If not eligible for TDF then use TAF/FTC or ABC/3TC+ once daily DRV/r

1. Patient: - is on DTG regimen - has developed DTG resistance - is PI naïve
a) TE + DRV/r dosed once daily i. If not eligible for TDF*: • Replace TE with TAF/FTC‡ ii. If not eligible for TAF‡: • Replace TE with AL

No INSTI exposure but PI resistance

2.1)No DRV/r resistance(score < 10)

- Can use once daily DRV/r as a backup regimen with 2 NRTIS in the future
- Therefore
  - **TLD**
  - If not eligible for TLD then TAFED/TAFLD or ALD

2.2)DRV/r resistance (score 10-59)

- Cant rely on DRV/r as a backup regimen with 2 NRTIS
- Cant use once daily DRV/r because of DRV/r resistance
- Therefore
  - **TLD + twice daily DRV/r** (600/100mg bd)
  - If not eligible for TLD then TAFED/TAFLD or ALD + bd DRV/r
  - If adherence concerns and **DRV/r score< 30 can** consider **TLD** alone or TLD+ once daily DRV/r 800/100 with ADReC advice

2. Patient:
- **is on PI regimen**
- **has developed PI resistance**
- **is INSTI naive, and:**

2.1. - **DRV score <10**

a) TLD*

i. If not eligible for TDF*:
- Replace TLD with TAFED‡ or TAFLD‡

ii. If not eligible for TAF‡:
- Replace TLD with ALD / AL+DTG

2.2. - **DRV score 10-59**

a) TLD* + DRV/r dosed twice daily

i. If not eligible for TDF*:
- Replace TLD with TAFED‡ or TAFLD*

ii. If not eligible for TAF‡:
- Replace TLD with ALD / AL+D

b) Discretion may be applied if there are adherence concerns *and DRV/r score <30*: In these cases, the committee may consider using TLD alone or changing the twice daily DRV/r to once daily DRV/r. Both cases will require close VL monitoring. If VL rebound occurs, consult with ADReC.

2.3) Patient with high level resistance to DRV/r (score > 60) but no INSTI exposure

- Discuss with the ADReC Committee
- TLD could possibly work but there is no backup regimen if it fails
- If Adherence concerns, then could try TLD
- Alternatively, an individualized regimen based on the resistance testing and clinical history

2. Patient: - **is on PI regimen** - **has developed PI resistance** - **is INSTI naive, and:**	
2.3	- **DRV/r score ≥60**
a) Refer to ADReC for an individualised regimen based on genotype and clinical history. b) Discretion may be applied. If there are adherence concerns, ADReC may consider using TLD alone.	

3).Patient has PI and INSTI resistance or a history of multiple ARV class resistance

- Consult with the ADReC
- Individualized regimen based on resistance testing and clinical history

3.	**Patient has:** - **PI and INSTI resistance, or** - **a history of multiple ARV class resistance**
a)	Refer to ADReC for an individualised regimen based on genotype and clinical history.

4)Patient with prior PI experience but no resistance testing done on the PI regimen. Now presents with DTG resistance

- May have PI resistance- we don't know
- Give TE + DRV/r 800/100 once daily
- If not eligible for TE then give TAF/FTC or ABC/3TC + DRV/r 800/100 once daily
- Do VL in 3 months and if VL not suppressed then repeat resistance testing (after 1 month of good adherence)

4.	**Patient has** - **DTG resistance**
	- **prior ATV/r or LPV/r exposure, but no resistance test was done at time of switch to DTG regimen**

a) <u>TE + DRV/r dosed once daily</u>

i. If not eligible for TDF*:

- Replace TE with TAF/FTC¥ or TAF/3TC¥

ii. If not eligible for TAF¥:

- Replace TE with AL

b) VL at 3 months': if not suppressed then repeat the genotyping.

Who should be using this algorithm?

- Members of all the different 3rd line committees
  - Maintain consistency
- Pharmacists with patients on 3rd line regimens
- Clinicians with patients with PI or DTG resistance before applying for 3rd line
  - Why?
  - What if the algorithm says to use TLD?
  - Can you change the patient to TLD without the ADReC authorizing it?

Can you change the patient to TLD without the 3rd line committee authorizing it?

- **Yes**, if the algorithm says to use TLD
- What are the advantages of this?
  - Shorten the waiting time to get the patient onto 3rd line ART
  - Prevent evolution of resistance
  - Give patients a convenient once a day regimen sooner
  - TLD is available at all facilities

Can you change the patient to TLD without the 3rd line committee authorizing it?

Do you still need to apply to the 3rd line committee?

- **Yes** the 3rd line committee needs to be aware of these patients
- The 3rd line committee may change the regimen in exceptional cases
- At some stage, these patients will need DRV/r- allows for planning

A word of caution

- These patients may be on **TLD** but they are 3rd line patients!
- It's very easy for them to be down referred and slip through the cracks
- You need to keep track of these patients
- Call them TLD3
- Make a note in their clinic file

What about patients already on 3rd line

What about patients on 3rd line regimens. Can we optimize their regimens as well?

- Definitely. There have been major advances in 3rd line regimens over the last few years (adults and paediatrics)
  - Moving away from Raltegravir(RAL) to DTG
  - Changing to once daily Darunavir/ritonavir regimens
  - Moving away from ETR regimens
  - Changing to TLD,TAFLD,TAFED,ALD regimens where possible
- Every patient on 3rd line needs to be reviewed towards optimizing their regimen
  - Especially if their viral load is suppressed
  - Use the new 3rd line algorithm
- Discuss with an expert

example

- Adult patient on 3rd line ART x 5 years
- VL always suppressed
- Regimen
  - AZT/3TC 1 tab bd
  - Raltegravir 400mg 1 tab bd
  - Darunavir 600mg 1 tab bd
  - Ritonavir 100mg 1 tab bd
- Cost approx R3200/month
- Based on 3rd line algorithm regimen was simplified to
  - **TLD** 1 tab nocte
- Cost approx R250/month

What about patients failing their 3rd line regimen

Failing 3rd line ART including DTG, DRV/r or both

- Consult with the ADReC
- Individualized regimen based on resistance testing and clinical history
- May need to repeat resistance testing after a month of good adherence
- May be some value to enroll in a clinical trial of new ARVs

3.	Patient has: - PI and INSTI resistance, or - a history of multiple ARV class resistance
	a) Refer to ADReC for an individualised regimen based on genotype and clinical history.

Summary

- 3rd line patients are complex
- Vast majority must have had adherence issues to get to 3rd line
- Traditionally 3rd line regimens have big pill burdens and are difficult to take making adherence worse
- Therefore, if we can simplify 3rd line regimens it will help improve our patients lives
- The new 3rd line algorithm does help simplify regimens, but it is only a guide
- Make use of expert advice

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