



Treating Health Seriously

3rd Line ART Regimens

Dr Leon Levin
Right to Care

Acknowledgements

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- Dr Ruth Lancaster – National 3rd Line Committee

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Previously



TEE



AZT/3TC/LPV/r



TLD+DRV/r

Now



TLD

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
- Low genetic barrier to resistance
- Twice daily dosing
- 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

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
- Stop your patient's ETR with expert guidance

Darunavir/ritonavir (DRV/r)


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


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

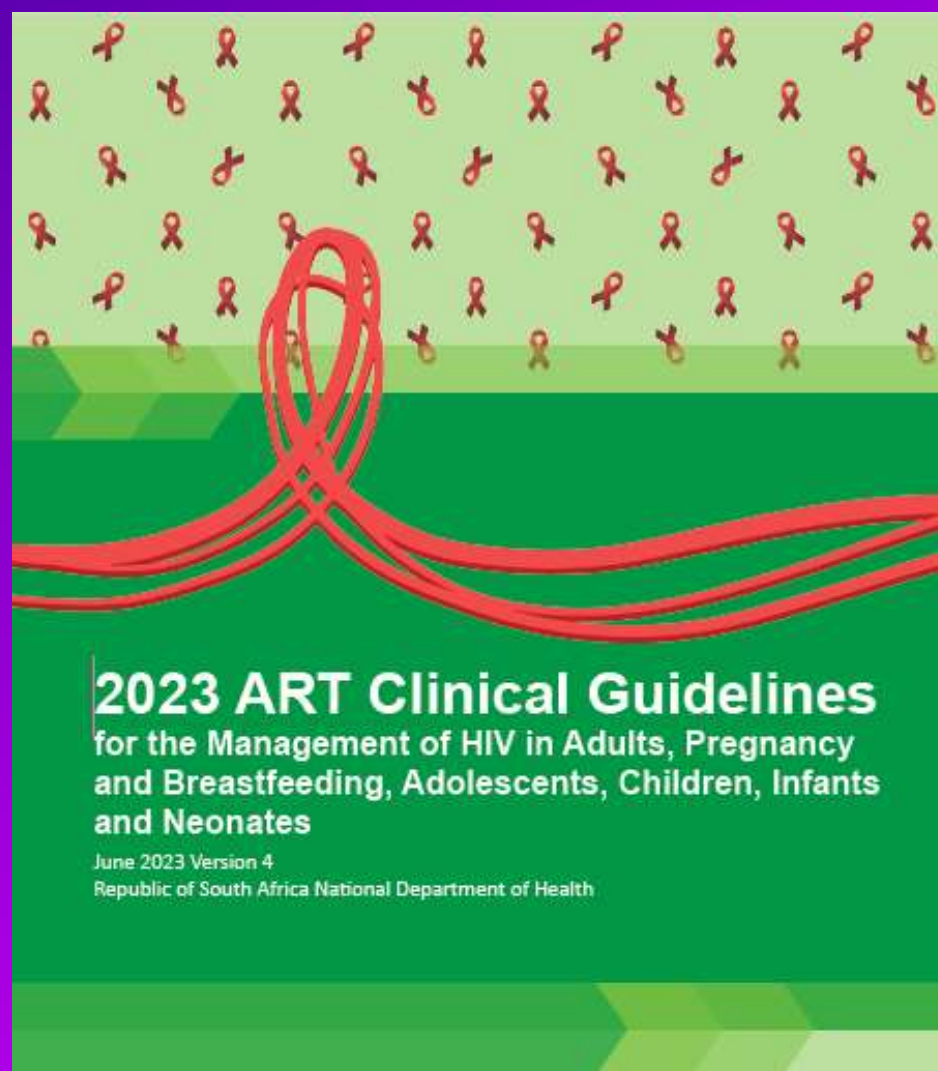
patient may switch from DRV / r 600 / 100 mg twice daily to DRV / r 800 / 100 mg once daily. The rest of the regimen should not be changed (see Figure 4). If the VL is detectable, manage further as appropriate according to current guidelines.

Darunavir/ritonavir (DRV/r)

Dosing

- If No DRV/r mutations
 - Dosed at DRV 800mg and Ritonavir 100mg **ONCE** daily
- If DRV/r resistance
 - Dosed at DRV 600mg and ritonavir 100mg **TWICE** daily

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?

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

- **Dr Ruth Lancaster**
- **TLART@health.gov.za**
- **3rd line committee will only authorize 3rd line drugs where there is PI resistance, as per Earnest study and also 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)

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.

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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 $<1,000$ 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.

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

- 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 2024

For the management of protease inhibitor (PI) and dolutegravir (DTG) resistance

DTG resistance refers to INSTI resistance over 0 on the Stanford score

1.	Patient is on 1 st line DTG regimen and has developed DTG resistance
a)	TE + DRV/r dosed once daily (adults/>35 kg: 800 mg/100 mg once daily; <35 kg: refer to weight band dosing chart below).
b)	If not eligible for TDF (<10 years of age or <30 kg or inadequate renal function- see below – or prior TDF nephrotoxicity), replace TE with ABC/3TC
2.	Patient is on 2 nd line DTG regimen (i.e., AZT + 3TC + DTG or TLD), is PI naïve and has developed DTG resistance
a)	TE + DRV/r dosed once daily (adults/>35 kg: 800 mg/100 mg once daily; <35 kg: refer to weight band dosing chart below).
b)	If not eligible for TDF (<10 years of age or <30 kg or inadequate renal function- see below – or prior TDF nephrotoxicity), replace TE with ABC/3TC
3.	Patient is on 2 nd line PI regimen and has developed LPV/r or ATV/r resistance (score ≥15) but DRV/r score <10 and no prior integrase inhibitor exposure
a)	TLD
b)	If not eligible for TDF (<10 years of age or <30 kg or inadequate renal function- see below – or prior TDF nephrotoxicity), replace with ABC, or consider TAFED (>25kg, adequate renal function, if available)
c)	In children/adolescents/young adults with unknown prior PI exposure/ resistance: individualised regimen.
4.	Patient (possibly previously on NNRTI-based regimen) is on 2 nd line PI regimen and has developed LPV/r or ATV/r resistance (score ≥15) and DRV/r score 10-59 and no prior integrase inhibitor exposure
a)	TLD + DRV/r dosed twice daily (adults/>35 kg: 600 mg/100 mg twice daily, <35 kg: refer to weight band dosing chart below) See rationale below
b)	If not eligible for TDF (<10 years of age or <30 kg or inadequate renal function – see below – or prior TDF nephrotoxicity), replace TE with ABC/3TC
c)	Discretion may be applied if there are adherence concerns and DRV/r score <30. In these cases, can consider using TLD alone (after discussion with an expert/the TLART Committee).
5.	Patient is on 2 nd line PI regimen and has developed LPV/r or ATV/r resistance (score ≥15) and DRV/r score ≥60 and no prior integrase inhibitor exposure
a)	Discretion may be applied if there are adherence concerns can consider using TLD alone (after discussion with an expert/the TLART Committee).
b)	Individualised regimen based on genotype and clinical history; consider inclusion of etravirine (ETR) in regimen.
6.	Failing 3 rd line/treatment that includes DTG or DRV/r, or both DTG and DRV/r
a)	Individualised regimen based on genotype and clinical history; . (i.e., refer to DR HIV Committee).

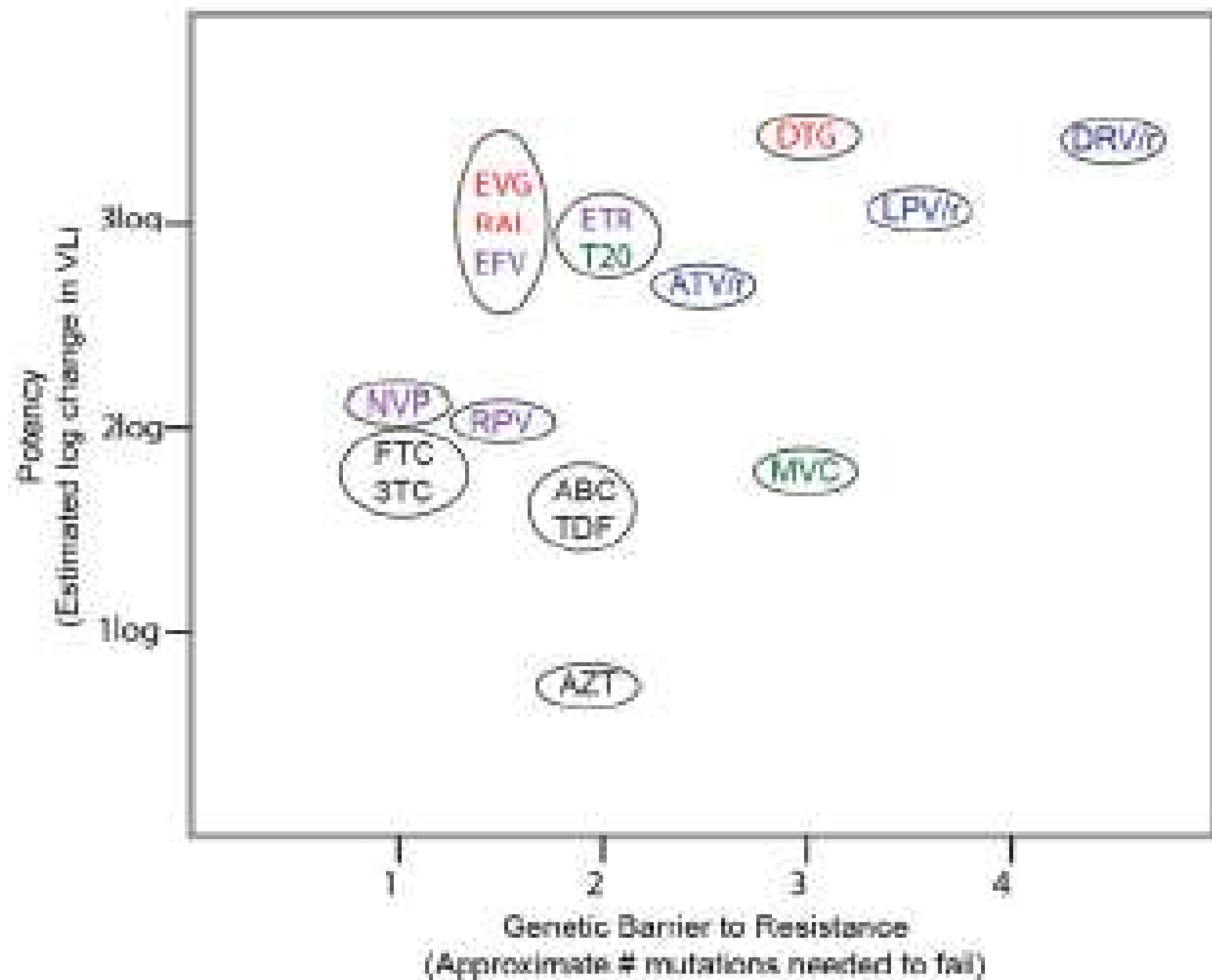
DTG Resistance

1.	Patient is on 1 st line DTG regimen and has developed DTG resistance
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2.	Patient is on 2 nd line DTG regimen (i.e., AZT + 3TC + DTG or TLD), is PI naïve and has developed DTG resistance
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- 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 ABC/3TC+ once daily DRV/r

- | |
|---|
| <p>a) TE + DRV/r dosed once daily (adults/>35 kg: 800 mg/100 mg once daily; <35 kg: refer to weight band dosing chart below).</p> <p>b) If not eligible for TDF (<10 years of age or <30 kg or inadequate renal function- see below – or prior TDF nephrotoxicity), replace TE with ABC/3TC</p> |
|---|



No INSTI exposure but PI resistance(score ≥ 15)

3)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 ALD or TAFED/TAFLD
 - Unknown PI exposure in children adolescents or young adults-individualised regimen

4)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 ALD + bd DRV/r
 - If adherence concerns and DRV/r score < 30 can consider **TLD** with expert advice

3.	Patient is on 2nd line PI regimen and has developed LPV/r or ATV/r resistance (score ≥ 15) but DRV/r score <10 and no prior integrase inhibitor exposure
	a) TLD
	b) If not eligible for TDF (<10 years of age or <30 kg or inadequate renal function- see below - or prior TDF nephrotoxicity), replace with ABC, or consider TAFED (>25 kg, adequate renal function, if available)
	c) In children/adolescents/young adults with unknown prior PI exposure/ resistance: individualised regimen.
4.	Patient (possibly previously on NNRTI-based regimen) is on 2nd line PI regimen and has developed LPV/r or ATV/r resistance (score ≥ 15) and DRV/r score 10-59 and no prior integrase inhibitor exposure
	a) TLD + DRV/r dosed twice daily (adults/ >35 kg: 600 mg/100 mg twice daily, <35 kg: refer to weight band dosing chart below) <i>See rationale below</i>
	b) If not eligible for TDF (<10 years of age or <30 kg or inadequate renal function – see below - or prior TDF nephrotoxicity), replace TE with ABC/3TC
	c) Discretion may be applied if there are adherence concerns and DRV/r score <30 . In these cases, can consider using TLD alone (after discussion with an expert/the TLART Committee).

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

- Discuss with the TLART 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

5.	Patient is on 2nd line PI regimen and has developed LPV/r or ATV/r resistance (score ≥15) and DRV/r score ≥60 and no prior integrase inhibitor exposure
a)	Discretion may be applied if there are adherence concerns can consider using TLD alone (after discussion with an expert/the TLART Committee).
b)	Individualised regimen based on genotype and clinical history; consider inclusion of etravirine (ETR) in regimen.

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

- May need to repeat resistance testing after a month of good adherence
- Consult with the third line committee
- Individualized regimen based on resistance testing and clinical history

6.	Failing 3rd line/treatment that includes DTG or DRV/r, or both DTG and DRV/r
a)	Individualised regimen based on genotype and clinical history; . (<i>i.e., refer to DR HIV Committee</i>).

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 DRV/r 800/100 once daily
 - plus 2 NRTIs (TDF/FTC)
- Do VL in 3 months and if VL not suppressed then repeat resistance testing after 1 month of good adherence
- If history suggests possible DRV/r resistance, could start with DRV/r twice daily (600/100mg bd)
- If not eligible for TDF then use ABC/3TC with DRV/r

- | | |
|----|--|
| 7. | Patient has developed DTG resistance and has 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 (adults/>35 kg: 800 mg/100 mg once daily; <35 kg: refer to weight band dosing chart below). <ul style="list-style-type: none">• If history suggests possible DRV/r cross-resistance (e.g. prolonged non-suppression whilst on ATV/r or LPV/r), then adjust dosing to DRV/r twice daily (adults/>35 kg: 600 mg/100 mg twice daily, <35 kg: refer to weight band dosing chart below).• Do a viral load in 3 months' time and another genotype if the patient is still not suppressed (<i>to pick up any possible DRV resistance</i>). |
| b) | If not eligible for TDF (<10 years of age or <30 kg or inadequate renal function- see below – or prior TDF nephrotoxicity), replace TE with ABC/3TC |

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 3rd line committee 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
- Maybe 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
 - Changing to TLD/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

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

6.	Failing 3 rd line/treatment that includes DTG or DRV/r, or both DTG and DRV/r
a)	Individualised regimen based on genotype and clinical history; . (i.e., refer to DR HIV Committee).

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

Right to Care HELPLINE

For nurses, doctors, pharmacists and other health care workers needing expert advice on all paediatric, adolescent and adult HIV and TB management.

**Call during office hours
"please call me", sms or whatsapps
may be sent and we can call you back.**

**HIV Helpline
(adult and paediatric)**

082 352 6642

**TB Helpline
063 698 6543**



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