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 1st 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 with ABC
2.	**Patient is on 2nd 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 with ABC or consider TAFED (25kg, adequate renal function, if available)
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 (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 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) ***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 with ABC or consider TAFED (25kg, adequate renal function, if available)
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 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.
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.e., refer to DR HIV Committee*).

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).
- 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 (*to pick up any possible DRV resistance*).

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

Adequate renal function:
- 10-<16 years of age: eGFR >80 mL/min using Counahan Barrett formula [(height (cm) x 40) / creatinine (umol/L)].
- ≥16 years of age: eGFR >50 mL/min using MDRD equation as provided by the laboratory.
- If pregnant: absolute creatinine level <85 umol/L

Drug Regimens - Rationale

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

Rationale: In patients who experience virological failure on a second line LPV/r or ATV/r regimen a switch to TLD is recommended provided DRV is reported as fully susceptible and there has been no prior DTG failure. TLD will be an effective regimen in most patients even if TDF + 3TC resistance is present, based on evidence from the NADIA, VISEND, D2EFT and ARTIST trials. For the minority of patients who will go on to fail this third line TLD regimen and develop DTG resistance then TDF + 3TC + DRV/r would be an appropriate and effective subsequent "rescue" regimen provided DRV is still fully active (based on NADIA findings).

Therefore, avoid switching to TLD alone after second-line ATV/r or LPV/r regimen failure if there is DRV cross-resistance reported on the resistance test. If DRV is reported as potential low level, low level or intermediate on this resistance test (i.e. Stanford score 10-59), switch to TLD plus DRV/r 600/100mg twice daily to provide a more robust regimen, because there is no fully active regimen with DRV available if the third-line regimen fails. Due to the higher pill burden with this DRV-based regimen, it is important to monitor adherence closely and address problems early.

The overarching rationale is that if there is not full susceptibility to DRV then DRV cannot be relied upon to ensure a "rescue" regimen for the minority of treatment-experienced patients who develop DTG resistance on TLD and therefore it should rather be used earlier in a regimen with TLD to provide a more robust regimen and prevent DTG resistance.

If patients in this scenario cannot take TDF (renal impairment or prior TDF nephrotoxicity) the regimen needs to be individualised.

Darunavir/ritonavir dosing chart

- DRV/r is not recommended in children <3 years of age OR <10 kg

Formulations available:

Darunavir (DRV):

1. 75 mg, 150 mg, 600 mg tablets (if not able to swallow whole, may be crushed or chewed).
2. FDC DRV/r 400/50 mg tablet must be swallowed whole.

Ritonavir (RTV):

1. Oral powder: 100 mg/packet (each 100 mg packet of RTV powder should be mixed with a small amount of water if administering the whole packet (100 mg), or 10 ml water if not administering the whole packet and administer the appropriate dose as per Table below or soft food and immediately ingested).
2. Tablets: 100 mg (must be swallowed whole, not crushed, or divided or chewed).

Weight band (kg)	**No DRV resistance-associated mutations on genotyping**	**DRV resistance-associated mutations on genotyping (V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V, L89V)**	**Weight band (kg)**
Dose of DRV (35 mg/kg, maximum 800 mg) and ritonavir (7 mg/kg, maximum 100 mg): once daily with food		**Dose of DRV (20 mg/kg, maximum 600 mg) and ritonavir (3 mg/kg, maximum 100 mg): twice daily with food**	
10 - <12	DRV 375 mg (2 x 150 mg + 1 x 75 mg tablets OR 5 x 75 mg tablets) + RTV 80 mg (100 mg oral powder (1 packet) in 10 ml water & administer 8 ml (80 mg))	DRV 225 mg (3 x 75 mg tablets or 1 X 150 mg + 1 X 75 mg), + RTV 40 mg (100 mg oral powder (1 packet) in 10 ml water & administer 4 ml (40 mg))	10 - <13
12 - <14	DRV 450 mg (3 x 150 mg tablets) + RTV 100 mg (100 mg oral powder (1 packet) in 10 ml water & administer 10 ml (100 mg))	DRV 300 mg (2 x 150 mg tablets) + 50 mg RTV (100 mg oral powder (1 packet) in 10 ml water & administer 5 ml (50 mg))	13 - <14
14 - <35	DRV 600 mg (1 x 600 mg tablet or 4 x 150 mg tablet) + RTV 100 mg (100 mg oral powder (1 packet) OR 100 mg tablet if able to swallow whole)	DRV 375 mg (2 x 150 mg + 1 x 75 mg tablets, OR 5 x 75 mg tablets) + RTV 100 mg (100 mg oral powder (1 packet) in 10 ml water OR 100 mg tablet if able to swallow whole). If patient able to swallow tablet whole, give DRV 400 mg+ RTV 50 mg (1 X DRV/RTV 400/50 mg tablet)	14 - <25
		DRV 400 mg + RTV 50 mg (1 x DRV/RTV 400/50 mg tablet if able to swallow whole). If patient unable to swallow whole 400/50 mg tabs, give DRV 450 mg (3 x 150 mg tabs or 6 x 75 mg tabs) + RTV 100 mg oral powder (1 packet) in 10 ml water	25 - <35
>35	DRV 800 mg + RTV 100 mg (2 x DRV/RTV 400/50 mg tablets)	DRV 600 mg (1 x 600 mg tablet) + RTV 100 mg (100 mg oral powder (1 packet) OR 100 mg tablet if able to swallow whole)	>35