Amendment to the National HIV Clinical Management Guidelines for Adults and Adolescents
The chapter 12.3 Second line ART on page 62 to 64 of English version

Amendment to this chapter is based on the fact that :
1- Darunavir/ritonavir (DRV/r) has recently been recommended by WHO as second-line regimen for PLHIV for whom DTG-based first-line regimens are failing
2- DRV/r (400 mg/50 mg) has recently been prequalified by the WHO as a fixed-dose combination at a price of US $17.50/pack for use in LMICs.

Protease inhibitor in 2nd line ART regimen: Atazanavir /ritonavir

- Atazanavir / ritonavir is one of the 2 preferred protease inhibitors (with Darunavir /ritonavir) for use in the standard 2nd line ART. It is equivalent efficacy to LPV/r, has less metabolic side effects, and is taken just once daily.
- ATV/r 300mg/100mg is taken once daily with food in combination with 2NRTI drugs.
- ATV/r should not be used if the patient is taking rifampicin (In TB patients on rifampicin, double dose lopinavir/r should be used).
- Proton pump inhibitors and other gastric acid lowering drugs should be avoided as they decrease the absorption of ATV/r.
- Others major drug-interactions are described. The list of these drugs is available in: https://www.drugs.com/drug-interactions/atazanavir-index.html?filter=3
- ATV may increase the PR and QT intervals, so increasing risk of arrhythmia.
- The incidence of Chronic Kidney Diseases increased gradually with increasing exposure to ATV/r. DRV/r must be preferred for patients with chronic renal insufficiency.
- Potential side effects include:
    - Rash, which is usually self-limiting within 2 weeks, however ATV/r should be stopped if severe.
    - Icterus (jaundice) which if asymptomatic, and ALT/AST are N then is of no concern.
    - Headache, nausea, raised liver enzymes.
    - Long term metabolic complications: lypodystrophy, diabetes, hyperlipidemia
    - Osteopenia and osteoporosis
- See **Error! Reference source not found.**, *page 49 of the English version.*
- For information on the NRTI drugs see above sections on 1st line ARV agents.

Protease inhibitor in 2nd line ART regimen: Darunavir /ritonavir

- DRV/r is one of the 2 preferred protease inhibitors (with Atazanavir / ritonavir) for use in the standard 2nd line ART.
- DRV/r is superior to LPV/r, mainly because of a longer durability with fewer side effects and treatment discontinuation[1].
- DRV/r seems equivalent to ATV/r in terms of virological efficacy but superior for combined virologic efficacy and tolerability[2,3]. However, no RCT comparing the 2 drugs as part of second-line regimen is available.
- DRV/r has a high genetic barrier leading to a very low proportion of resistance associated mutations and lost phenotypic susceptibility in case of therapeutic failure[4,5]
- DRV/r 800mg/100mg is taken once daily with food in combination with 2NRTI drugs for patients failing a DTG-based first line, without previous exposure to protease inhibitors.

[1] C Orkin, HIV Med 2013 ; 2 Lennox JL, Ann Intern Med 2014; 3 Santos JR, HIV Med 2018; 4 Lathouwers E, J Med Virol 2021; 5 Lathouwers E, HIV Res Clin Prat 2020 ; 6 Ebrahim I, J Antimicrob Chem 2020 ; 7 Ryom L, Lancet HIV 2018; 8 Costagliola D, JID 2020 ; 9 Virginia A Triant, JID 2020

- DRV/r should not be used if the patient is taking rifampicin. Studies evaluating the strategy of doubling the dose of DRV/r to twice daily (to overcome reduced darunavir levels resulting from rifampicin-associated increased clearance) resulted in an unacceptable risk of hepatotoxicity[6]. (In TB patients on rifampicin, double dose lopinavir/r should be used.)
- Other major drug-interactions are described. The list of these drugs are available in: (https://www.drugs.com/drug-interactions/darunavir-index.html?filter=3).
- The cumulative use of DRV/r was associated with increasing risk of cardiovascular disease in the D.A.D study[7] while it was not reported in a French cohort[8]. The lower duration of exposure to DRV/r in the French cohort, 1 year, as compared to 2.5 years in the D.A.D study could explain this difference. Awaiting further data, ATV/r is preferred for patients with cardiovascular risk factors (family history of premature coronary artery disease, diabetes, hypertension, dyslipidemia, prior cardiovascular events, smokers) [9].
- Potential side effects include:
    - Rash, which is usually self-limiting within 2 weeks, however DRV/r should be stopped if severe.
    - Diarrhea, nausea
    - Elevated liver and pancreatic enzymes
    - Headache
    - Long term metabolic complications: diabetes, hyperlipidemia
    - Osteopenia and osteoporosis
- See **Error! Reference source not found.**, *page 49 of the English version.*
- For information on the NRTI drugs see above sections on 1st line ARV agents.

Table 20 Standard 2nd line ART regimens

1st Line Regimens Failure	Preferred 2nd Line Regimens
TDF (or ABC) + 3TC +DTG	AZT + 3TC + ATV/r OR AZT + 3TC + DRV/r
TDF (or ABC) + 3TC + (EFV or NVP)	AZT + 3TC +DTG
AZT + 3TC + EFV (or NVP)	TDF (or ABC) + 3TC +DTG
AZT + 3TC + DTG	TDF + 3TC + ATV/r OR TDF + 3TC + DRV/r
2 NRTI + any PIs*	Refer to NCHADS Technical Working Group on Care and Treatment for discussion

Note: if patient has HBsAg positive and the failure regimen contained TDF in 1st line it is recommended to keep it in the 2nd line regimen.
**If patients on PI contained regimen, the 2nd line ART regimen will be based on genotype testing and medical history. DTG and/or DRV/r-based regimen could represent an option.*

[1] C Orkin, HIV Med 2013 ; 2 Lennox JL, Ann Intern Med 2014; 3 Santos JR, HIV Med 2018; 4 Lathouwers E, J Med Virol 2021; 5 Lathouwers E, HIV Res Clin Prat 2020 ; 6 Ebrahim I, J Antimicrob Chem 2020 ; 7 Ryom L, Lancet HIV 2018; 8 Costagliola D, JID 2020 ; 9 Virginia A Triant, JID 2020

Conclusion

LPV/r must be removed from PI-based second-line option and reserved only for patients treated by rifampicin with double dose of LPV/r.
DRV/r and ATV/r must be the 2 preferred options for PI-based second-line regimen for PLHIV for whom DTG-based first-line regimens are failing and discussed case by case according to the tolerability in different population:

- Existence of cardiovascular risk factors: prefer ATV/r
- Chronic kidney disease: prefer DRV/r
- Chronic liver disease: prefer ATV/r

[1] C Orkin, HIV Med 2013 ; 2 Lennox JL, Ann Intern Med 2014; 3 Santos JR, HIV Med 2018; 4 Lathouwers E, J Med Virol 2021; 5 Lathouwers E, HIV Res Clin Prat 2020 ; 6 Ebrahim I, J Antimicrob Chem 2020 ; 7 Ryom L, Lancet HIV 2018; 8 Costagliola D, JID 2020 ; 9 Virginia A Triant, JID 2020