South African National Department of Health
HISTORICALLY ACCEPTED USE REVIEW OF DARUNAVIR
Committee: Third Line Antiretroviral Therapy (TLART) Committee

Executive Summary

Date: June 2025

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Declarations: MR and RL have no have no interests to declare on the topic.

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Medicine(s) (INN): Darunavir (DRV); darunavir/ritonavir (DRV/r) (Note – ritonavir must accompany darunavir)
Medicine(s) (ATC): J05AE10; J05AR26
Indication/s (ICD10 code/s): Human immunodeficiency virus (HIV) (B20)
Patient population/s: HIV-1 infected adults and children with virological failure and laboratory proven resistance to protease inhibitors (PI) and/or integrase-strand transfer inhibitors (INSTI)
Prevalence of condition/s: An estimated 8 million people were living with HIV in South Africa in 2024, representing 12.7% of the national population[1]. Of patients on TLD2 around 1 to 3% will develop resistance to dolutegravir[2], thus requiring Third Line Antiretroviral (TLART) management.
Level of Care: Hospital level, through specialist recommendation.
Prescriber Level: Doctor prescribed (Initiation by TLART Committee)
Current Standard(s) of Care: Third-line ART managed via an algorithm including darunavir/ritonavir (DRV/r) for the following indications:

- Patient is on 2nd line DTG regimen (i.e., ABC/3TC/DTG **OR** TLD **OR** AZT/3TC/DTG)**,** is PI naïve and has developed DTG resistance.*
- Patient is on 2nd line PI regimen (possibly previously on NNRTI-based regimen) and has developed LPV/r or ATV/r resistance (score ≥15) and DRV/r score 10-59 and no prior integrase inhibitor exposure.**
- Patient is on 2nd line DTG regimen, 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. */**

*Once daily DRV/r vs ** Twice Daily. If history suggests possible DRv/r cross resistance (prolonged non-suppression on ATV/r or LPV/r then increase dose to twice daily)

DRV/r is not indicated in any second line regimens.

Background:

Darunavir (combined with ritonavir) has been part of the third line ART regimens since October 2013[3], however it has never officially been reviewed/approved by the National Essential Medicines List Committee (NEMLC) for inclusion on the South African Essential Medicines List (EML); for use in HIV-1 infected adults and children with virological failure and laboratory proven resistance to protease inhibitors (PI) and/or integrase-strand transfer inhibitors (INSTI). To retain darunavir/ritonavir on the National Department of Health (NDoH) pharmaceutical tender for TLART use, it was recommended that a recommendation for inclusion on the EML be made by NEMLC.

A review of the use of DRV/r in second-line ART was conducted by NEMLC in 2021 and DRV/r was not recommended over LPV/r. The review found that DRV/r-containing ART regimens were associated with higher viral suppression rates and were better tolerated than LPV/r. However, at the time, DRV/r was considered unaffordable and there were additional concerns regarding the supply. The review also noted that DRV/r-containing regimens would not be suitable for patients on a PI-based regimen who require rifampicin-based tuberculosis treatment. DRV/r was recommended for inclusion on the therapeutic interchange database as an alternative to LPV/r and ATV/r for patients not on TB-rifampicin-based tuberculosis treatment. [4]

The TLART Committee ART algorithm is currently under review (as per discussions held with the TLART committee on the 26 and 28 August 2025) and will omit any reference to 2nd line treatment use. Decisions reached by the TLART committee were confirmed for named patient, restricted use only after a resistance test and not for 2nd line access.

Methods:

A search for World Health Organization (WHO) clinical practice guidelines outlining clinical evidence for optimising third-line antiretroviral therapy.

An AGREE II (Appraisal of Guidelines, for Research, and Evaluation)[5] assessment was conducted independently in duplicate (RL & MR) on the selected guideline to evaluate the process of guideline development and quality of reporting.

The AGREE II appraisal outcome is presented in Annexure 1. In summary the WHO Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach (July 2021) guideline can be considered a high-quality clinical practice guideline (AGREE II score of 84% overall and 83% for rigour of development) and was considered up-to-date and relevant to the committee's question.

Results:

A WHO meeting report (26 & 27 November 2023) on "Optimization of second-line and third-line antiretroviral therapy for people living with HIV" was identified[6]. A part objective of this working group was to discuss darunavir/ritonavir (DRV/r) as the preferred PI option in second-line and third-line ART for adults, pregnant women and children, based on updated evidence for DRV/r following a systematic review and meta-analysis commissioned by the WHO.

The WHO recommends that:

- Third-line regimens include new drugs with minimal risk of cross-resistance to previously used ART regimens, such as INSTIs and second-generation nonnucleoside reverse-transcriptase inhibitors (NNRTIs) and PIs.
- For individuals for whom a DTG-based first-line regimen and an ATV/r or LPV/r second-line regimen has failed, DRV/r in combination with two nucleoside reverse-transcriptase inhibitors (NRTIs) with the possible addition of DTG is a suitable third-line ART option.

WHO TLART recommendations for DRV/r include:

- Adults (including pregnant women)
- Adolescents,
- Paediatric patients over the age of 3 years

The Food and Drug Administration (FDA) does not recommend the use of DRV/r in children less than 3 years of age OR <10 kg.[7]

Summary of Evidence:

The following is a summary of the evidence cited in the WHO meeting report:

Systematic review and network meta-analysis on the use of DRV/r in second-line or first and second-line ART for adults and pregnant women (commissioned by WHO):

- No clear differences between DRV/r and ATV/r or LPV/r; limited comparative effectiveness data (2016 systematic review and network meta-analysis conducted).[8]
    - Estimated efficacy of ritonavir-boosted darunavir (800 mg/100mg once daily) was too imprecise to determine non-inferiority compared to than with both atazanavir and lopinavir plus two NRTIs
    - No significant differences between regimens with respect to
        - Continuations
        - AIDS-defining illnesses
        - WHO stage 3-4 disease
        - Mortality
- DRV/r use in TB: DRV/r interacts with rifampicin-based TB treatment.[6]

- A systematic review commissioned by WHO (See **Table 1** below extracted from the WHO meeting report (26 & 27 November 2023) showed that:
    - ATV/r and DRV/r tended to be more effective and tolerable than LPV/r, in second-line only studies and in combined first- and second-line studies
    - ATV/r had more favourable lipid outcomes than DRV/r in combined first- and second-line studies
    - DRV/r had better overall safety outcomes compared with other PIs in second-line only studies and in combined first- and second-line studies
- Pregnant Women *(based on observational data):*

- Higher risk of negative pregnancy outcomes, preterm births and small for- gestational-age births among women receiving LPV/r-based regimens (second line studies AND combined first and second line studies).
- Differences between ATV/r and DRV/r were less evident.
- Trend towards improved viral suppression for women on DRV/r-based regimens.
- DRV/r has good safety and viral efficacy in pregnancy, with some new comparative data suggesting superior viral efficacy of DRV/r (given in twice-daily dosing) compared to ATV/r.
- In later pregnancy, once-daily DRV/r is associated with a greater decrease in both total and unbound plasma concentrations of darunavir compared to twice-daily DRV/r.
- US FDA Administration recommends DRV/r 600/100 mg twice daily dosing.[9]
- European Medicines Agency recommends DRV/r 800/100 mg once-daily dosing in pregnancy.[10]
- International HIV clinical guidelines currently recommend DRV/r 600/100 mg twice-daily dosing for pregnant women, except if the woman becomes pregnant on DRV/r once-daily dosing and has suppressed viral loads. [11,12]

Table 1; Comparative efficacy and safety of regimens containing atazanavir/ritonavir, darunavir/ritonavir and lopinavir/ritonavir (Taken from *Optimization of second-line and third-line antiretroviral therapy for people living with HIV: meeting report, 27-28 November 2023*)

	DRV/r + NRTIs versus LPV/r + NRTIs			ATV/r + NRTIs versus LPV/r + NRTIs			DRV/r + NRTIs versus ATV/r + NRTIs		
Comparison	Effect (95% CI)	Absolute effects	Overall quality of evidence	Effect (95% CI)	Absolute effects	Overall quality of evidence	Effect (95% CI)	Absolute effects	Overall quality of evidence
Viral suppression <50 copies/mL at 24 weeks	1.26 (0.85, 1.89)	49 per 1000 (–38 to 122)	⊕⊕⊕ Moderate	1.21 (0.97, 1.49)	40 per 1000 (–6 to 78)	⊕ Very low	1.11 (0.90, 1.37)	22 per 1000 (–22 to 63)	⊕⊕ Low
Viral suppression <50 copies/mL at 48 weeks	1.27 (0.95, 1.71)	48 per 1000 (–10 to 101)	⊕⊕⊕ Moderate	1.33 (1.08, 1.61)	55 per 1000 (16 to 87)	⊕ Very low	1.23 (1.00, 1.50)	41 per 1000 (1 to 75)	⊕ Very low
Viral suppression <50 copies/mL at 96 weeks	2.45 (1.65, 3.64)	150 per 1000 (92 to 195)	⊕⊕⊕ Moderate	1.37 (1.08, 1.76)	62 per 1000 (16 to 104)	⊕⊕ Low	1.49 (1.14, 1.96)	76 per 1000 (26 to 121)	⊕⊕⊕ Moderate
CD4 24-week change	–	36.02 cells/mL (–63.27, –8.83)	⊕⊕ Low	–	4.87 cells/mL (–23.07, 13.56)	⊕⊕ Low	–	12.46 cells/mL (–31.2, 6.24)	⊕⊕ Low
CD4 48-week change	–	17.71 cells/mL (–34.98, –0.62)	⊕⊕ Moderate	–	1.83 cells/mL (–13.37, 9.34)	⊕ Very low	–	16.23 cells/mL (–29.29, –3.42)	⊕⊕ Low
CD4 96-week change	–	17.3 cells/mL (–41.66, 8.82)	⊕⊕ Low	–	4.29 cells/mL (–24.9, 16.49)	⊕⊕ Low	–	17.3 cells/mL (–41.66, 8.82)	⊕⊕ Low
Discontinuations	0.56 (0.29, 1.05)	59 per 1000 (–101 to 7)	⊕⊕⊕ Moderate	0.70 (0.55, 0.89)	46 per 1000 (–72 to –16)	⊕⊕ Low	0.73 (0.57, 0.93)	42 per 1000 (–68 to –10)	⊕⊕ Low
Discontinuations due to adverse events	0.63 (0.18, 2.04)	14 per 1000 (–35 to 39)	⊕⊕ Low	0.63 (0.40, 1.00)	19 per 1000 (–32 to 0)	⊕⊕ Low	0.58 (0.38, 0.89)	21 per 1000 (–34 to –5)	⊕⊕⊕ Moderate
Overall adverse event (any grade)	0.74 (0.55, 0.99)	50 per 1000 (–108 to –2)	⊕⊕⊕ Moderate	0.91 (0.71, 1.16)	14 per 1000 (–56 to 21)	⊕⊕ Low	0.39 (0.27, 0.55)	182 per 1000 (–267 to –105)	⊕⊕⊕ Moderate

Overall severe adverse events	0.82 (0.47, 1.42)	24 per 1000 (–74 to 51)	⊕⊕⊕ Moderate	1.07 (0.81, 1.41)	9 per 1000 (–24 to 48)	⊕⊕ Low	0.68 (0.41, 1.09)	41 per 1000 (–80 to 11)	⊕⊕ Low
Overall severe adverse events (treatment related)	1.15 (0.34, 4.25)	16 per 1000 (–81 to 257)	⊕⊕ Low	1.69 (0.33, 12.04)	70 per 1000 (–82 to 508)	⊕⊕ Low	0.59 (0.42, 0.82)	48 per 1000 (–71 to –21)	⊕⊕⊕ Moderate
Weight gain 48-week change	–	2.31 Kg (1.14, 3.52)	⊕⊕⊕ Moderate	–	2.02 Kg (1.17, 2.81)	⊕⊕⊕ Moderate	–	0.30 Kg (–1.09, 1.71)	⊕⊕ Low
Hypertension (any grade)	0.82 (0.36, 1.89)	4 per 1000 (–19 to 23)	⊕⊕⊕ Moderate	–	–	–	–	–	–
Total cholesterol 48-week change	–	1.13 mmol/L (–1.79, –0.46)	⊕⊕⊕ Moderate	–	0.51 mmol/L (–0.68, –0.34)	⊕⊕⊕ Moderate	–	0.56 mmol/L (–1.43, 0.17)	⊕ Very low
Fasting glucose 48-week change	–	0.12 mmol/L (–0.06, 0.29)	⊕⊕ Low	–	0.13 mmol/L (–0.01, 0.26)	⊕⊕ Low	–	0.12 mmol/L (–0.06, 0.29)	⊕⊕ Low
High-density lipoprotein 48-week change	–	0.28 mmol/L (–0.61, 0.06)	⊕⊕⊕ Moderate	–	0.07 mmol/L (–0.12, –0.01)	⊕⊕ Low	–	0.15 mmol/L (–0.38, 0.07)	⊕ Very low
Low-density lipoprotein 48-week change	–	0.46 mmol/L (–1.07, 0.17)	⊕⊕⊕ Moderate	–	0.36 mmol/L (–0.49, –0.23)	⊕⊕ Low	–	0 mmol/L (–0.01, 0.01)	⊕ Very low
Triglycerides 24-week change	–	0.04 mmol/L (–0.05, –0.02)	⊕⊕⊕ Moderate	–	0.85 mmol/L (–1.11, –0.58)	⊕⊕⊕ Moderate	–	0.04 mmol/L (–0.05, –0.02)	⊕⊕ Low
Triglycerides 48-week change	–	1.55 mmol/L (–2.4, –0.71)	⊕⊕⊕ Moderate	–	0.72 mmol/L (–0.94, –0.49)	⊕⊕⊕ Moderate	–	1.19 mmol/L (–2.81, 0.31)	⊕ Very low
Mortality	1.64 (0.43, 6.41)	22 per 1000 (–22 to 164)	⊕⊕⊕ Moderate	0.80 (0.35, 1.80)	6 per 1000 (–22 to 25)	⊕ Very low	0.87 (0.39, 1.88)	4 per 1000 (–20 to 28)	⊕ Very low

Second-Line Studies Only	Combined first- and second-line studies

Kanters et al[13] reviewed the estimated efficacy of ritonavir-boosted darunavir (800/100 mg once daily) was too imprecise to determine non-inferiority. Overall, regimens did not differ significantly with respect to continuations.

Limitation: Includes second-line only and combined first- and second-line studies. No studies of DRV/r as TLART included.

Table 2: Comparison of pharmacokinetic parameters of darunavir/ritonavir at different doses during late pregnancy (Taken from Optimization of second-line and third-line antiretroviral therapy for people living with HIV: meeting report, 27-28 November 2023)

DRV dosage	Area under the curve: total DRV	Area under the curve: unbound DRV	Trough: total DRV	Trough Unbound DRV	Trough level below: EC_{50} wild-type virus[a] EC_{50} resistant virus[b]	Viral load <50 copies/mL at delivery (pooled)	Mother-to-child transmission
DRV/r 600/100 mg twice daily *(14–16)*	17–26% ↓	7–8% ↓	11–28% ↓	11% ↓	0/40 (0%) 0/6 (0%)	26/44 (59%)	1/52 (2%)
DRV/r 800/100 mg four times daily *(15,16–18)*	31–39% ↓	20–24% ↓	42–57% ↓	24–38% ↓	3/99 (3%) 7/50 (14%)	81/100 (81%)	0/95 (0%)

DRV/r 800/100 mg twice daily (↑ dose) versus 600/100 mg twice daily postpartum *(19)*	36% ↓		53% ↓		80% (20/25)	0/24 (0%)
DRV/cobicistat 800/150 mg four times daily *(20,21)*	50–56% ↓	40% ↓	79–89% ↓	88%↓	86% (30/35)	

DRV = darunavir, DRV/r = darunavir/ritonavir, EC_{50} = half maximal effective concentration.
[a] EC_{50} wild-type virus = 0.055 ng/mL (55 mg/L). [b] EC_{50} resistant virus = 0.55 ng/mL (550 mg/L).

** DRV/r 800/100mg twice daily in third trimester versus 600/100mg twice daily postpartum*

Systematic review of the safety of darunavir/ritonavir for children (3 to 18 years) and adolescents living with HIV[6]

- Total of 14 studies included comparing ATV/r, DRV/r, DTG and LPV/r.
  - 2 randomized clinical trials (CHAPAS-4 and SMILE)[14],[15]:
    - CHAPAS-4 (Child Antiretroviral Therapy in South Africa) - an open-label RCT that included > 900 children aged 3–15 years
    - 232 children were randomised to DRV/r containing second-line regimens and efficacy and safety outcomes compared to those randomised to LPV/r or ATV/r containing second-line regimens.
    - SMILE (**Strategy for Maintenance of HIV suppression with integrase inhibitor + darunavir/ritonavir in children)**, an open-label RCT included > 300 children aged 6–18 years comparing a switch to once-daily INSTI + DRV/r (158 children receiving DRV/r and INSTI) vs continuing standard NNRTI or PI-based regimens in virologically suppressed children virologically
  - 5 single-arm trials and,
  - 7 observational studies.
- DRV/r had the best efficacy and safety among the boosted PI options:
  - No deaths due to DRV/r.
  - Few drug-related severe adverse events.
  - Few discontinuations.
  - Small increases in total and LDL cholesterol.
  - Viral suppression (viral load <400 copies/mL) were satisfactory (**>85% suppression rates).** in both;
    - CHAPAS-4
      - At week-96, 88.3% of those randomised to DRV/r had VL <400 copies/mL
      - DRV/r-based regimens were reported to be as good as and trending towards being superior to ATV/r- and LPV/r-based regimens.
      - At week-96, 88.3% DRV/r, 84.3% ATV/r and 80.7% LPV/r had VL <400 copies/mL
    - SMILE
      - The study showed that switching to an INSTI plus DRV/r is highly efficacious and non-inferior virologically in maintaining virological suppression at 48 weeks.

- By 48 weeks, 8 INSTI + DRV/r vs. 12 current standard-of-care (SOC) triple ART (2NRTI + boosted PI/NNRTI) had confirmed HIV-RNA ≥50 copies/mL; difference (INSTI + DRV/r-SOC) −2.5% (95% CI: −7.6, 2.5%), showing non-inferiority[16].

In June 2024, Laurus Labs in conjunction with the Clinton Health Access Initiative (CHAI) and UNITAID for generic development filed for tentative USA FDA approval of film coated paediatric DRV/r (120/20 mg).[17]

The AGREE II appraisal outcome is presented in Annexure 1. In summary the WHO Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach (July 2021) guideline, which recommends DRV/R as TLART option, can be considered a high-quality clinical practice guideline (AGREE II score of 84% overall and 83% for rigour of development) and was considered up-to-date and relevant to the committee's question.

Conclusion and recommendations of WHO meeting report (26 & 27 November 2023):

- DRV/r should be the preferred boosted PI for third-line therapy.
- Concerns about the genetic barrier of resistance (higher for DRV/r than for ATV/r).
- Side-effects, drug–drug interactions and the need for research to address gaps in the guidelines.
- Concerns raised about the availability and cost of third-line therapies.
- Clarity required regarding the optimal dosing of DRV/r for pregnant women.
- Dosing and formulations need to be optimized for DRV/r in children.
- Recommended that ATV/r be an alternative.
- Recommended that LPV/r should be reserved for special circumstances (such as drug interactions and stock-outs) or phased out.

Historically accepted use Criteria

SECTION A		
	Criteria	**Comment**
1	The medicine is included in the World Health Organization (WHO) Model Essential Medicines List, either as a core or complementary item, for the indication requested.	YES: X / NO: ***https://list.essentialmeds.org/?query=darunavir**
2	The medicine is currently registered by South African Health Products Regulatory Authority (SAHPRA).	YES: X / NO:
3	A documented rapid literature review identified no new safety concerns or new evidence of lack of efficacy.	YES: X / NO: *See above: Summary of Evidence*
4	The anticipated costs and usage are not likely to result in a substantial impact on the budget.	YES: X / NO: *Comment: small population*

SECTION B		
1	There is evidence prior to 2007* of safety and efficacy for the recognised indication (a systematic review/meta-analysis, or at least one critically appraised controlled trial.) *Information after 2007 would need to be subject to standard review processes for a new inclusion.*	YES: X / NO: *See above: Summary of Evidence*
OR		
2	It is included as part of standard of care in a critically appraised clinical practice guideline (CPG) of adequate quality, for the particular indication. Refer to Annexure 1 AGREE II assessment of the "Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, 2021 update". Geneva: World Health Organization; 2021	YES: X / NO: *See above: CPG recommendations*
AND		
3	It is currently used in practice for this indication.	YES: X / NO: *Comment: Part of the third line antiretroviral therapy treatment bundle since October 2013.*[3]

Modified Evidence to Decision Framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large [ ] Moderate [ ] Small [x] None [ ]	***Systematic review and network meta-analysis on the use of darunavir/ritonavir for adults and pregnant women (commissioned by the WHO):*** *A systematic review commissioned for the WHO meeting report (26 & 27 November 2023) showed that:* ○ *DRV/r had better overall safety outcomes compared with other PIs* ***Pregnant Women (based on observational data):*** • *Trend towards improved viral suppression for women on DRV/r-based regimens.* • *DRV/r has good safety and viral efficacy in pregnancy, with some new comparative data suggesting superior viral efficacy of DRV/r (given in twice-daily dosing) compared to ATV/r.* ***Systematic review of the safety of darunavir/ritonavir for children (3 to 18 years) and adolescents living with HIV*** • *DRV/r had the best efficacy and safety among the boosted PI options:* ○ *No deaths due to DRV/r* ○ *Few drug-related severe adverse events* ○ *Few discontinuations.*

		○ *Small increases in total and LDL cholesterol* ○ *Viral suppression (viral load <400 copies/mL) were satisfactory in both CHAPAS-4 and SMILE (>85% suppression rates).* ○ *In CHAPAS-4, DRV/r-based regimens were reported to be as good as and trending towards being superior to ATV/r- and LPV/r-based regimens* *Lower certainty evidence*
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large ☐ Moderate ☐ Small ☒ None ☐	***Systematic review and network meta-analysis on the use of darunavir/ritonavir for adults and pregnant women (commissioned by the WHO):*** *A systematic review commissioned for the WHO meeting report (26 & 27 November 2023) showed that:* ○ *DRV/r had better overall safety outcomes compared with other PIs* ***Pregnant Women (based on observational data):*** • *DRV/r has good safety and viral efficacy in pregnancy* ***Systematic review of the safety of darunavir/ritonavir for children (3 to 18 years) and adolescents living with HIV*** • *DRV/r had the best safety among the boosted PI options:* ○ *No deaths due to DRV/r* ○ *Few drug-related severe adverse events* ○ *Few discontinuations.* ○ *Small increases in total and LDL cholesterol*
QUALITY OF EVIDENCE	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☐ Very low ☐ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect **Very low to moderate**	*Very Low to Moderate – see Table 1 above*
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention ☒ Favours control ☐ Intervention = Control *or* Uncertain ☐	*See Table 1 above*

THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes [ ] No [X]	*There is no alternative.* *DRV/r is used when there is resistance to other PIs such as ATV and LPV.*
FEASIBILITY	**Is implementation of this recommendation feasible?** Yes [x] No [ ] Uncertain [ ]	*Darunavir is already part of the third line ART regimens in South Africa since October 2013 and recommended by the WHO as part of the TLART.* *However, lack of a readily available DRV/r paediatric formulation in South Africa and drug-drug interactions with DRV/r and rifampicin-based TB therapy will limit feasibility of implementation.*
RESOURCE USE	**How large are the resource requirements?** More intensive [ ] Less intensive [X] Uncertain [ ]	*Medicines Health Product List (MHPL -June 2025)* Darunavir, Ritonavir; 400mg, 50mg; Tablet; 56 Tablets — R397.40 Darunavir; 150mg; Tablet; 240 Tablets — R816.44 Darunavir; 600mg; Tablet; 56 Tablets — R862.08 Darunavir; 75mg; Tablet; 480 Tablets — R910.05 Ritonavir; 100mg; Tablet; 56 Tablets — 91.81 Ritonavir; 100mg; Suspension; 30 Sachets — 62.31
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [X] Major [ ] Uncertain [ ] **Is the option acceptable to key stakeholders?** Yes [X] No [ ] Uncertain [ ]	*The are challenges of administering DRV/r to people with tuberculosis (TB) considering interactions with rifampicin-based TB treatment.* *Paediatric formulations are registered and available in the country: 150mg and 75mg.*
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [X] Uncertain [ ]	

RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
				X	

Recommendation: It is suggested that darunavir/ritonavir be included on the Essential Medicines List for adults and children as a special access item; as recommended by the TLART committee, following a genotype resistance test, for use on a named patient basis as per TLART treatment algorithm. *Rationale: A systematic review commissioned by the WHO showed that: DRV/r had better overall safety outcomes compared with other PIs in adults (very low to moderate level of evidence). In pregnant women (based on observational data) DRV/r has good safety and viral efficacy in pregnancy. Finally, a WHO commissioned systematic review of the safety of darunavir/ritonavir for children (3 to 18 years) and adolescents living with HIV showed that DRV/r had the best safety among the boosted PI options.* **Level of Evidence: Very Low ((Uncertain)** **Review indicator: Change in resistance, safety and efficacy?**
NEMLC RECOMMENDATION (16 October 2025): NEMLC accepted the ERC suggestion and recommended that darunavir/ritonavir be included on the Essential Medicines List for adults and children as a special access item; as recommended by the TLART committee, following a genotype resistance test, for use on a named patient basis as per TLART treatment algorithm.
Monitoring and evaluation considerations: Patientoutcomes as well as patterns of resistance
Research priorities: Monitor response in TLART named patients

Annexures

Annexure 1: Duplicate AGREE II Appraisal

AGREE II assessment scores																							
Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach																							
Scoring the guidelines																							
	Scope and purpose			Stakeholder involvement			Rigour of development								Clarity of presentation			Applicability				Editorial independence		Overall assessment
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1	7	7	7	7	4	7	6	7	7	7	7	7	7	4	7	7	7	4	5	4	2	3	7	6
Appraiser 2	7	4	7	7	6	7	6	6	5	6	7	7	6	1	6	6	6	6	7	7	6	6	7	6
Item Total	14	11	14	14	10	14	12	13	12	13	14	14	13	5	13	13	13	10	12	11	8	9	14	12
Domain Total	39			38			96								39			41				23		276
Minimum possible score	6			6			16								6			8				4		46
Maximum possible score	42			42			112								42			56				28		322
Domain score	**92%**			**89%**			**83%**								**92%**			**69%**				**79%**		**84%**

Overall assessment: The Guideline is recommened for use in this context

Score: (e.g. domain 1)

Maximum possible score = 7 (highest score) x no. of items x no. of appraisers

Minimum possible score = 1 (lowest score) x no. of items x no. of appraisers

Score for each domain

$$\frac{\text{Obtained score - minimum possible score}}{\text{Maximum possible score - minimum possible score}} \times 100$$

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