South African National Essential Medicine List
Primary Healthcare and Adult Hospital Level Medication Review Process
Component: HIV and AIDs

MEDICINE REVIEW:

TITLE: DARUNAVIR/RITONAVIR vs LOPINAVIR/RITONAVIR FOR ADULT HIV PATIENTS

Date: 27 July 2021

Key findings

- We reviewed the evidence for darunavir/ritonavir versus lopinavir/ritonavir in patients; requiring a protease inhibitor-based regimen, who were treatment naïve to both drugs.
- We included two randomised controlled trials: the TITAN trial, for which published results were available for the 48- and 96- week period, and the ARTEMIS trial, for which 48-, 96-, and 192-week data were included. We also included a single systematic review and network meta-analysis, which did not include the TITAN or ARTEMIS trials, but included one additional randomised controlled trial.
- Darunavir/ritonavir (DRV/r)-based regimens are overall associated with a higher rate of **virological suppression** than lopinavir/ritonavir (LPV/r)-based regimens (moderate certainty of evidence). The absolute difference in rate of viral suppression to <50 copies/mL seen in the TITAN and ARTEMIS trials was 8.7% [95% CI 0.8-16.6] and 11.6% respectively [95% CI 4.4-18.8%]. This equates to a NNT of 9 and 13, respectively, for each additional patient with virological suppression).
- The rates of drug-associated **adverse events** are lower with DRV/r than LPV/r (absolute difference 3.9% and 7.8% in TITAN and ARTEMIS respectively, moderate certainty of evidence). This is partly driven by a significantly lower rate of gastrointestinal side-effects (~15% for LPV vs ~8% for DRV in both the TITAN and ARTEMIS trials)
- Patients on DRV/r-containing regimens may be less likely to develop **drug resistance-associated mutations** than those on LPV/r-containing regimens (9.3-15% for DRV/r vs 15.8-33% for PI-mutations, p <0.05) (low certainty of evidence due to limited and potentially biased sampling).
- Unlike LPV/r, DRV/r cannot be given with **rifampicin-based tuberculosis regimens**. Furthermore, a switch to DRV/r as the second-line protease inhibitor of choice may limit the third-line antiretroviral regimen options that are available to patients who require them.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE 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)**
Type of recommendation		X			

Recommendation: The Committee suggests that DRV/r not be used in preference to LPV/r.
Rationale: Despite DRV/r-containing ART regimens being associated with higher viral suppression rates and being better tolerated than LPV/r, at the current cost it is considered unaffordable, and there are concerns regarding the supply. It would also not be suitable for the minority of patients on a PI-based regimen who require rifampicin-based tuberculosis treatment. DRV/r is recommended for inclusion on the therapeutic interchange database as an alternative to LPV/r and ATV/r, for patients not on TB-rifampicin therapy.
Level of Evidence: Moderate certainty of evidence
Review indicators: Reduction in DRV/r price

NEMLC MEETING 29 JULY 2021:
The NEMLC accepted the proposed recommendation made by the PHC/Adult Hospital Level Committee above.

Monitoring and evaluation considerations

Research priorities

Executive summary:

Date: 26 July 2021
Medicine (INN): Darunavir/ritonavir (as a fixed dose combination)
Medicine (ATC): J05AR26
Indication (ICD10 code): B20
Patient population: HIV positive adults requiring a protease-inhibitor-based antiretroviral therapy regimen.
Prevalence of condition: 7.5 million South Africans living with HIV (2019 estimate)
Level of Care: Primary Healthcare and Adult Hospital Level of care
Prescriber Level: Primary health care nurses and doctors
Current standard of Care: Lopinavir/ritonavir
Efficacy estimates: (preferably NNT) For virological suppression, NNT = 9-13
Reviewer name(s): Jeremy Nel, Shelley McGee
PTC affiliation: JN: Helen Joseph Hospital PTC

Background

Protease inhibitors (PIs) are a class of agents that, as their name suggest, inhibit the protease enzyme of HIV. Protease's normal function is to cleave the translated polyproteins into HIV's final protein products, and inhibition of this step results in immature, non-infectious virions being produced instead.

There are three available protease inhibitor combinations available in South Africa: lopinavir (LPV), atazanavir (ATV) and darunavir (DRV), each given with low-dose ritonavir (r). The role of ritonavir is to act as a pharmacokinetic booster; by inhibiting CYP3A4, higher PI drug levels are achieved, permitting less frequent dosing.

PIs are generally used as second-line ART drugs, following first-line virological failure, or intolerance to first-line drugs. South Africa's move to a dolutegravir (DTG)-based first line regimen will likely reduce the number of patients requiring 2nd-line drugs, owing chiefly to a higher virological barrier to resistance compared to efavirenz (EFV). However, there will still be a need for PI-based therapy for some of those patients already on a PI-based regimen, for patients who fail first-line therapy, and for patients who are intolerant of certain 1st line drugs.

Historically, South Africa has utilised LPV/r as its PI-combination of choice, owing chiefly to its lower price. The current public sector price for DRV/r is more expensive than for LPV/r.

Boosted DRV is an important agent for use in treatment-experienced patients owing to a high barrier to resistance and darunavir's ability to maintain virologic activity despite multiple PI mutations.[1, 2]

Review Question:
For HIV-positive adults requiring protease inhibitor-based antiretroviral therapy (ART), how does darunavir/ritonavir-based therapy compare to lopinavir/ritonavir-based therapy?

Methods:

A rapid review of the evidence was conducted by searching selected electronic databases (PubMed, Epistemonikos and the Cochrane Library) on 14 June 2021. The search strategy is shown in Appendix 1. Retrieved records were screened against the eligibility criteria in the Covidence platform; the titles and abstracts were first screened in duplicate, followed by the screening of relevant full text papers in duplicate, with conflicts resolved by consensus. Data extraction from the included studies was done independently, with results reviewed and checked by a second reviewer. Table 1 lists the excluded studies and provides the rationale for exclusion.

Eligibility criteria

-P (patient/population): PLHIV who are darunavir and lopinavir naïve.
-I (intervention): Darunavir/ritonavir-based combination antiretroviral therapy.
-C (comparator): Lopinavir/ritonavir-based combination antiretroviral therapy.
-O (outcomes)*: mortality, viral suppression rates, adverse events, discontinuation rates, lipid profile, and development of resistance mutations.

** considered to be critical outcomes*

Only randomised control trials and systematic reviews of randomised control trials were included.

Results

Search

The search produced 663 studies; 135 were duplicates and were removed. Of the remaining 528 records, 501 were excluded in screening as they were not applicable to the PICO. The full test of the 27 remaining articles were assessed for eligibility. 21 of these were excluded, for reasons given in table 1. 6 studies were included in the qualitative analysis. The included studies are summarised in table 2.

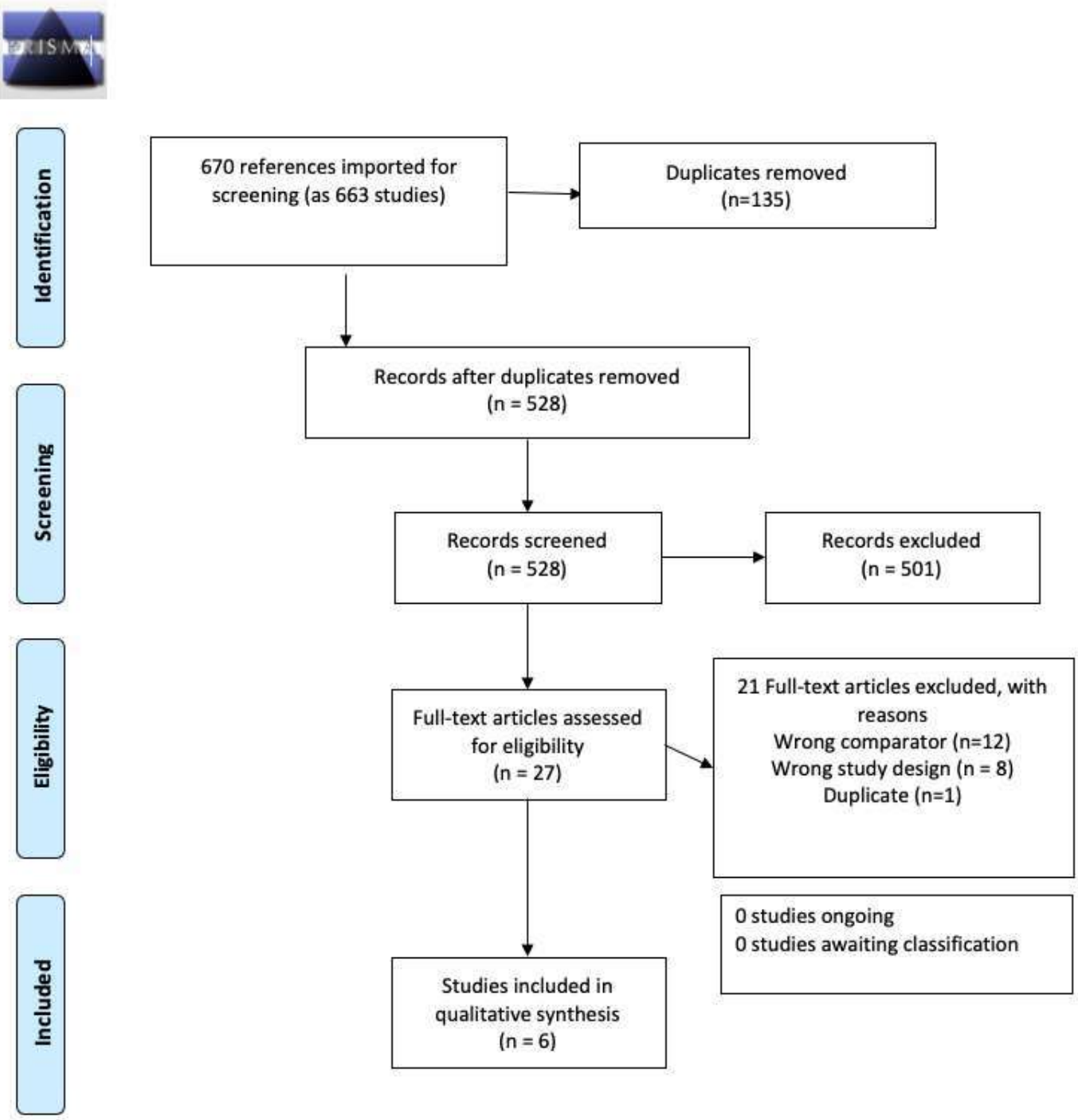
The TITAN study was a randomised, controlled, phase III trial to compare efficacy and safety of darunavir-ritonavir with that of lopinavir-ritonavir in treatment-experienced, lopinavir-naive patients. Patients received optimised background regimen plus non-blinded treatment with darunavir-ritonavir 600/100 mg twice daily or lopinavir-ritonavir 400/100 mg twice daily. For the TITAN study, both 48- and 96-week results were available in separate articles (by Madruga and Bánhegyi et al. respectively).[3, 4]

The ARTEMIS trial was a randomized, open-label phase III trial in treatment-naïve HIV-1-infected adults. Patients were stratified by baseline HIV-1 RNA and CD4 count, and randomized to once-daily DRV/r 800/100 mg or LPV/r 800/200 mg total daily dose (either once or twice daily) plus tenofovir/emtricitabine. Similarly, for the ARTEMIS trial, 48-, 96-, and 192- week data were available (Ortiz, Mills, and Orkin).[5-7]

So as to incorporate all data, all articles that included the two TITAN papers are discussed together as a group, as are the three ARTEMIS trial articles.

A single systematic review and network meta-analysis was also included that evaluated outcomes in treatment-experienced adults living with HIV who switched ART regimen after failure of a WHO-recommended first-line NNRTI-based regimen.[7] Only one study included in this meta-analysis was relevant to the review question. This was a 3-arm phase 3 open label randomised controlled trial of 454 patients of 48-week study duration, comparing tenofovir/emtricitabine + LPV/r (control group) to either abacavir + didanosine + LPV/r or tenofovir/emtricitabine + DRV/r regimens.[8]

Figure 1: Process for searching and selecting studies for inclusion



Results

Viral suppression rates

In the open label TITAN randomised control trial, treatment-experienced LPV- and DRV-naïve patients with HIV were randomised to either DRV/r or LPV/r, both in conjunction with an optimised background regimen consisting of 2 or more NRTIs and/or NNRTIs. At 48 weeks, more patients on DRV/r attained a viral load <400 copies in the intention to treat population: 77% vs 67% respectively (95% CI 2-17, p<0.0001). A similar gap in viral suppression was seen in the per protocol analysis (77% vs 68% respectively, 95% CI 2-16) and when a threshold of <50 copies/mL was used (71% vs 60% respectively).[3] After 96 weeks, a similar pattern was seen: more patients on DRV/r attained a viral load <400 copies/mL (66.8% vs 58.9%, difference 8.7% [95% CI 0.7-16.7), p=0.034) and a suppressed viral load (<50 copies/mL; non-virological failure censored population

80.0% vs 71.3%, difference 8.7% [95% CI 0.8-16.6, p=0.03]).[4] The TITAN trial was marked by a large discontinuation rate, but the main reason for discontinuation was due to adverse events (and thus is relevant), and the per protocol analyses were very similar to the intention-to-treat analyses in any case. Of note, when the efficacy results were analysed with reference to pre-existing PI resistance, DRV/r retained its efficacy even in the face of several major baseline PI mutations, whereas LPV/r did not.[1] The open label TITAN RCT was assessed as moderate certainty evidence due to imprecision (wide CIs) and a high rate of attrition.

In the ARTEMIS trial of first line PI-based therapies, a higher proportion of patients in the DRV/r arm obtained viral suppression at the 192-week mark (as they had at the 48 and 92 week marks in previous work). The rate of suppression at the 192-week mark was 68.8% in the DRV/r arm vs 57.2% in the LPV/r arm (difference 11.6%, 95% CI 4.4-18.8%, p=0.002). A similar sized difference was seen whether DRV was compared to a daily or 12-hourly LPV/r dosing schedule. At the 48- and 96-week marks, the suppression rates with DRV/r vs LPV/r were 84% vs 78% and 79% vs 71% respectively (p<0.001 in both instance). Thus the efficacy gap widened with time.

By contrast, the Kanter et al. fixed-effect network meta-analysis of second-line therapies in people with HIV with previous NNRTI-based ART failure, failed to find any significant difference in viral suppression rate with LPV/r + 2 NRTIs vs DRV/r + 2 NRTIs: OR 1.16 (95% CI 0.76 to 1.74) - , moderate certainty evidence due to imprecision. The network meta-analysis only reported on one RCT comparing LPV/r-containing regimen to DRV/r-containing regimen (neither the ARTEMIS nor TITAN trials were included), and did not include the DRV/r-containing regimen in the only league table described that allows for ranking of the interventions, comparing the relative effect between pairs of protease inhibitor interventions for the change from baseline in CD4 cell count.

Mortality

There were numerically fewer deaths in the DRV arm (2, 0.7%) than in the LPV arm (4, 1.3%) in the TITAN study by 96 weeks, although this difference was not statistically significant.

In the ARTEMIS trial, there were a lower proportion of deaths in the DRV arm at 192-weeks (1.2%) than the LPV/r arm (2.0%), but the absolute number of events was again very small (4 vs 7; total 11).

In the meta-analysis by Kanter et al., there was no significant mortality difference seen in those who, after failing first line therapy, switched to LPV/r with 2 NRTIs compared to DRV/r with 2 NRTIs: OR 0.53 (95% CI 0.11-3.13).

Adverse events, including lipid profiles

In the TITAN study's 96 week results, there were more grade 2-4 adverse events possibly related to the protease inhibitor in the LPV arm vs the DRV arm (44.8% vs 40.9%), and more serious adverse advents overall in the LPV arm vs the DRV arm (16.5% vs 13.8%). However, the rate of discontinuation due to adverse events was identical in each arm (8.1%). The total cholesterol and LDL were raised in similar percentage of cases between DRV and LPV. DRV was associated with a lower rate of grade 2-4 diarrhoea compared with LPV (8.1% versus 15.2%).

The ARTEMIS trial similarly suggested that DRV/r was better tolerated than LPV/r (in each case with TDF/FTC as a backbone). At 192-weeks, serious adverse events, regardless of causality, were less frequent in the DRV arm (16% vs 21%, p=0.116). Grade 2-4 adverse events related to the drug were similarly in the favour of DRV/r (28% vs 35.8%, p=0.028) as were adverse events of any grade (56.6% vs 74.9%, p<0.001). Those on

DRV/r were less likely to have an elevated total cholesterol (24.3% vs 32.7%, p=0.018), though the proportion with an elevated LDL were similar. Results were consistent at the 48-, 96-, and 192- week marks.

The Kanter et al. meta-analysis found a higher rate of serious adverse events in patients on LPV/r with 2 NRTIs vs those on DRV/r with 2 NRTIs. The OR calculated was 4.17, though the confidence interval narrowly crossed unity: 0.93-33.33.

Discontinuations

In the Kanter et al. meta-analysis, those on LPV/r-containing regimens were more likely to discontinue therapy (OR 1.26, 95% CI 0.49-3.71) and to discontinue therapy specifically due to adverse events (OR 2.56, 95% CI 0.24-100), although in both cases the confidence intervals around these point estimates were too wide for any firm conclusion to be drawn.

The ARTEMIS trial's data were more definitive. At 192-weeks, discontinuations due to adverse events had been significantly less frequent with DRV/r than they were with LPV/r (7.6% vs 14.5%, p=0.005).

In the TITAN trial, by 96 weeks, the rate of discontinuation overall was greater in the LPV/r arm (37.0%) than in the DRV/r arm (27.5%, p=0.01), although the rate of discontinuation due to adverse events was identical (8.1%). Similar results were seen at the 48-week mark - discontinuation due to adverse events was 7% in each arm (moderate certainty evidence).

Development of drug resistance mutations

In the TITAN study, fewer patients on DRV developed PI resistance (15% vs 33%) or NRTI mutations (8% vs 26%) at 96 weeks. This was statistically significant, with a p-value of <0.05.

In the ARTEMIS study, of those with paired baseline/endpoint genotypes, 9.3% in DRV/r arm vs 15.8% in LPV/r developed PI-resistance mutations (p=0.01). However, only ~15% of patients had paired baseline/endpoint genotypes done, putting this finding at high risk of bias.

Conclusion

The RCT evidence of follow-up > 48 weeks DRV/r-based antiretroviral regimens achieved higher rates of virological suppression than are LPV/r-base regimens. This absolute difference seen was clinically significant: 8.7% (95% CI 0.8-16.6) in the TITAN trial at 96 weeks, and 11.6% (95% CI 4.4-18.8%) in the ARTEMIS trial at 192 weeks, with a tendency for the differences to enlarge as the trials progressed. Whether this translates into fewer deaths is unclear, as relatively well patients were enrolled, and consequently the absolute differences in the small number of deaths were not statistically significant.

DRV/r-based antiretroviral regimens were better tolerated than LPV/r-based ones. This appears to be true of both severe adverse events and adverse events specifically thought to be related to the drugs. Some of this difference is driven by a consistently lower proportion of gastrointestinal events in the DRV/r-based arms, such as diarrhoea and vomiting. DRV/r-based therapy was also associated with a lower rate of therapy discontinuation due to adverse events in the ARTEMIS trial, but not in the TITAN trial.

There is some evidence that DRV/r-based therapy may be more virologically robust than LPV/r, with a lower rate of incident drug resistance-associated mutations. Furthermore, DRV maintains its virological activity better than LPV does in the face of baseline PI mutations.[1]

In evaluating DRV/r vs LPV/r, there are other programmatic considerations that are relevant to the South African context. Importantly, DRV/r cannot be co-administered with rifampicin-based tuberculosis treatment regimens. Furthermore, third line regimens in South Africa have traditionally been based on DRV/r and/or dolutegravir. The switch to dolutegravir in first line regimens, combined with a switch to DRV/r in second line regimens, could create challenges for the relatively small number of patients who would require third line therapy.

Table 1. Characteristics of excluded studies

Excluded studies		Reasons
1	Johnson M, Grinsztejn B, Rodriguez C, Coco J, DeJesus E, Lazzarin A, Lichtenstein K, Wirtz V, Rightmire A, Odeshoo L, McLaren C. 96-week comparison of once-daily atazanavir/ritonavir and twice-daily lopinavir/ritonavir in patients with multiple virologic failures. AIDS. 2006 Mar 21;20(5):711-8. doi: 10.1097/01.aids.0000216371.76689.63. PMID: 16514301.	Atazanavir, not darunavir
2	Santos JR, Llibre JM, Bravo I, García-Rosado D, Cañadas MP, Pérez-Álvarez N, Paredes R, Clotet B, Moltó J. Short Communication: Efficacy and Safety of Treatment Simplification to Lopinavir/Ritonavir or Darunavir/Ritonavir Monotherapy: A Randomized Clinical Trial. AIDS Res Hum Retroviruses. 2016 May;32(5):452-5. doi: 10.1089/AID.2015.0248. Epub 2016 Feb 11. PMID: 26781004.	Monotherapy, not combination therapy.
3	Atazanavir Versus Lopinavir/Ritonavir (LPV/RTV) in Patients Who Have Not Had Success With Protease Inhibitor-Containing HAART Regimen(s). NCT00028301	Atazanavir, not darunavir
4	Sax PE. Meeting notes from the 2nd International AIDS Society Conference on HIV Pathogenesis and Treatment. Atazanavir in treatment-experienced patients. AIDS Clin Care. 2003 Sep;15(9):78. PMID: 14666914.	Atazanavir, not darunavir.
5	Venter WDF, Moorhouse M, Sokhela S, Serenata C, Akpomiemie G, Qavi A, Mashabane N, Arulappan N, Sim JW, Sinxadi PZ, Wiesner L, Maharaj E, Wallis C, Boyles T, Ripin D, Stacey S, Chitauri G, Hill A. Low-dose ritonavir-boosted darunavir once daily versus ritonavir-boosted lopinavir for participants with less than 50 HIV RNA copies per mL (WRHI 052): a randomised, open-label, phase 3, non-inferiority trial. Lancet HIV. 2019 Jul;6(7):e428-e437. doi: 10.1016/S2352-3018(19)30081-5. Epub 2019 Jun 12. PMID: 31202690.	Switch study in patients already suppressed and tolerating LPV/r. Patients not PI-naïve.
6	Brogan A, Mauskopf J, Talbird SE, Smets E. US cost effectiveness of darunavir/ritonavir 600/100 mg bid in treatment-experienced, HIV-infected adults with evidence of protease inhibitor resistance included in the TITAN Trial. Pharmacoeconomics. 2010;28 Suppl 1:129-46. doi: 10.2165/11587490-000000000-00000. PMID: 21182348.	Cost-effectiveness study.
7	Ferrer E, del Rio L, Martínez E, Curto J, Domingo P, Ribera E, Negredo E, Rosales J, Saumoy M, Ordóñez J, Gatell JM, Podzamczer D. Impact of switching from lopinavir/ritonavir to atazanavir/ritonavir on body fat redistribution in virologically suppressed HIV-infected adults. AIDS Res Hum Retroviruses. 2011 Oct;27(10):1061-5. doi: 10.1089/AID.2010.0254. Epub 2011 Jan 15. PMID: 21166602.	Atazanavir, not darunavir. Switch study, not PI naïve.
8	Randomised, multicentre, open clinical trial assessing the effectiveness and safety of simplification to atazanavir + ritonavir versus continuation of a stable antiretroviral regimen on lopinavir/ritonavir,Sponsor not yet defined (Spain)	Atazanavir, not darunavir
9	Johnson M, Grinsztejn B, Rodriguez C, Coco J, DeJesus E, Lazzarin A, Lichtenstein K, Rightmire A, Sankoh S, Wilber R. Atazanavir plus ritonavir or saquinavir, and lopinavir/ritonavir in patients experiencing multiple virological failures. AIDS. 2005 Apr 29;19(7):685-94. doi: 10.1097/01.aids.0000166091.39317.99. PMID: 15821394.	Atazanavir not darunavir
10	Ribera E, Azuaje C, Lopez RM, Diaz M, Feijoo M, Pou L, Crespo M, Curran A, Ocaña I, Pahissa A. Atazanavir and lopinavir/ritonavir: pharmacokinetics, safety and efficacy of a promising double-boosted protease inhibitor regimen. AIDS. 2006 May 12;20(8):1131-9. doi: 10.1097/01.aids.0000226953.56976.ad. PMID: 16691064.	Atazanavir not darunavir
11	A Multicentre Trial of Second-line Antiretroviral Treatment Strategies in African Adults Using Atazanavir or Lopinavir/Ritonavir," NCT01255371"	Duplicate
12	Efficacy and safety of switching suppressed patients with elevated triglycerides from lopinavir/ritonavir or fosamprenavir/ritonavir to atazanavir/ritonavir or darunavir/ritonavir based therapy: the LARD study," Skiest, DJ	Switch study of patients tolerating LPV/r and suppressed on it. Patients not PI naïve.
13	Hill A. Atazanavir/ritonavir versus lopinavir/ritonavir: equivalent or different efficacy profiles? AIDS. 2005 Nov 18;19(17):2054-5. doi: 10.1097/01.aids.0000194137.73876.d5. PMID: 16260922.	Atazanavir, not darunavir.
14	Johnson M. Response to "Atazanavir/ritonavir versus lopinavir/ritonavir: equivalent or different efficacy profiles?" by Hill. AIDS. 2006 Oct 3;20(15):1987. doi: 10.1097/01.aids.0000247125.42753.63. PMID: 16988525.	Atazanavir, not darunavir. Journal letter.
15	Study of HIV Patients With Undetectable Viral Load and Abnormal Lipids Switching to Atazanavir/Ritonavir. NCT00120393	Switch study, not PI naïve. Atazanavir, not darunavir.
16	Randomised and Prospective Clinical Study to Evaluate the Efficacy and Safety of Lopinavir/ritonavir Monotherapy Vs Darunavir/ritonavir Monotherapies as Simplification Switching Strategies of PI/NNRTI-triple Therapy Based-regimens," EUCTR2009-013287-39-ES,"	Monotherapy, not combination therapy
17	Cochrane Central Register of Controlled Trials. A 96 Week Phase IIIB Study Comparing the Antiviral Efficacy and Safety of Atazanavir/ritonavir ATV/RTV with Lopinavir/ritonavir LPV/RTV , Each in Combination with Fixed Dose Tenofovir-Emtricitabine in HIV-1 infected treatment naive	Atazanavir not darunavir

	subjects. – Castle. EUCTR2005-001895-11. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2005-001895-11-IT, 2006 | added to CENTRAL: 31 March 2019 | 2019 Issue 3	
18	Perry CM. Emtricitabine/tenofovir disoproxil fumarate: in combination with a protease inhibitor in HIV-1 infection. Drugs. 2009;69(7):843-57. doi: 10.2165/00003495-200969070-00005. PMID: 19441871.	Narrative review of tenofovir + lamotrigine + dolutegravir
19	Evaluation of inflammatory immune parameters predicting cardiovascular risk in HIV-1-infected antiretroviral therapy naive patients treated with atazanavir/ritonavir versus lopinavir/ritonavir based regimens. - CRISTAL," EUCTR2008-006644-19-IT,"	Atazanavir not darunavir
20	Simpson KN, Baran RW, Collomb D, Beck EJ, Van de Steen O, Dietz B. Economic and health-related quality-of-life (HRQoL) comparison of lopinavir/ritonavir (LPV/r) and atazanavir plus ritonavir (ATV+RTV) based regimens for antiretroviral therapy (ART)-naïve and -experienced United Kingdom patients in 2011. J Med Econ. 2012;15(4):796-806. doi: 10.3111/13696998.2012.691927. Epub 2012 Jun 7. PMID: 22563716.	Atazanavir vs LPV/r
21	De Meyer S, Hill A, Picchio G, DeMasi R, De Paepe E, dr Béthune, MP. Influence of Baseline Protease Inhibitor Resistance on the Efficacy of Darunavir/Ritonavir or Lopinavir/Ritonavir in the TITAN trial. J Acquir Immune Defic Syndr. 49(5):563-564	Discussion of TITAN outcomes relating to baseline resistance. Excluded as not an RCT or systematic review, but included in discussion.

Table 2. Included studies

Author, date	Type of study	Intervention	Population	Comparators	Primary outcome	Effect sizes	Comments
Bánhegyi D et al., 2012[4] (TITAN trial) – 96 week results	RCT	Darunavir/ritonavir 600/100mg 12-hourly, plus optimised background regimen.	Treatment experienced, LPV-and DRV-naïve, HIV-positive adults with HIV viral load >1000 copies/mL, who had been on ART for ≥12 weeks. Multicentre, across 27 countries. n=604.	Lopinavir/ritonavir 400/100mg 12-hourly, plus optimised background regimen	Proportion with HIV viral load <400 copies/mL at 96 weeks.	For VL <400 copies/mL, viral suppression (ITT population): 66.8% (DRV) vs 58.9% (LPV), difference 8.7% (CI 0.7-16.7), p=0.034 Per protocol: 67.5% vs 59.5%: difference 8.7%, p<0.001. Using VL <50 copies/mL as threshold, non-viral failure censored population had similar findings: 80% vs 71.3%; difference 8.7%, 95% CI 0.8-16.6, p=0.03	High rate of treatment discontinuation: 81/298 for DRV, and 110/297 for LPV/r. However, much of the discontinuation was due to drug side-effects, and thus relevant. Also per protocol analysis similar to ITT analysis for primary outcome. Open label study Some patients not PI-naïve, though all were LPV and DRV naïve. Baseline PI mutations could have exacerbated the difference between LPV and DRV.

Madruga et al.[3] (TITAN trial – 48 week results)	RCT, 48-week follow up – see Bánhegyi et al. for 96-week results	Darunavir/ritonavir 600/100mg 12-hourly, plus optimised background regimen.	Treatment experienced, LPV-and DRV-naïve, HIV-positive adults with HIV viral load >1000 copies/mL, who had been on ART for ≥12 weeks. Multicentre, across 27 countries. n=604.	Lopinavir/ritonavir 400/100mg 12-hourly, plus optimised background regimen	Proportion with HIV viral load <400 copies/mL at 96 weeks.	ITT population: 77% with VL <400 copies in DRV/r group vs 67% in LPV/r group (95% CI 2-17, p<0.0001). Per-protocol population: 77% (DRV) vs 68% (LPV), 95% CI 2-16.	48-week results from TITAN trial. See Bánhegyi et al. above for 96 week results. High rate of treatment discontinuation: 62/298 for DRV, and 86/297 for LPV/r. However, much of the discontinuation was due to drug side-effects, and thus relevant. Also per protocol analysis similar to ITT analysis for primary outcome. Open label study For VL<50 copies, similar pattern: 71% (DRV) vs 60% (LPV), with gap widening as trial progressed. Some patients not PI-naïve, though all were LPV and DRV naïve. Baseline PI mutations could have exacerbated the difference between LPV and DRV.
Kanters S et al., 2017[9]	Systematic review and network meta-analysis	Multiple comparisons between LPV/r, ATV/r and DRV/r, with or without other companion drugs.	HIV positive adults and adolescents who were failing first-line NNRTI-based therapy	[See intervention]	Viral suppression, mortality, AIDS-defining illnesses or WHO stage 3-4 disease, discontinuations, discontinuations due to adverse events, and serious adverse events.	Relating to LPV + 2 NRTIS vs DRV + 2 NRTIS – fixed-effect network meta-analysis: • Viral suppression at 48 weeks: OR 1.16 (95% CI 0.76-1.74, NS) • Mortality: OR 0.53 (95% CI 0.11-3.13, NS). • Discontinuations: OR 1.26 (0.49-3.71)	Multiple comparisons computed in the paper; LPV + 2 NRTIs vs DRV + 2 NRTIs extracted, since this is most representative of real-world clinical practice. GRADE evaluation for quality of evidence for this subset for 48-week viral suppression: MODERATE.

						• Discontinuations due to severe AE: OR 2.56 (0.24-100). • Serious AEs: OR 4.17 (0.93-33.33)	
Orkin C et al., 2012[6] (ARTEMIS trial – 192 week results)	RCT, phase 3.	DRV/r 800/100 daily with TDF/FTC.	HIV-positive adults, treatment-naïve with viral load ≥5000 copies. N=689.	LPV/r 800/200 (either daily or divided 12-hourly), with TDF/FTC	Viral suppression <50 copies/mL at week 192 in ITT population.	Viral suppression in 68.8% in DRV/r arm vs 57.2% in LPV/r arm; difference 11.6% (95% CI 4.4-18.8%), p=0.002. Resistance: Of those with paired baseline/endpoint genotypes, 9.3% in DRV/r arm vs 15.8% in LPV/r developed PI-resistance mutations. Discontinuation due to AE: Less frequent in DRV/r arm (7.6%) vs LPV/r arm (14.5%, p=0.005). Serious AEs (regardless of causality): 16% of DRV/r arm vs 21% in LPV/r arm. Grade 2-4 AEs (at least possibly related to drug): 28% DRV/r vs 35.8% LPV/r (p=0.028). Total cholesterol higher in DRV/r arm (p=0.018) but LDL difference not statistically significant.	Treatment naïve patients only. 2 different LPV/r regimens, but in subgroup analyses, DRV/r was superior to both daily and 12-hourly LPV/r re: virological suppression. Paired baseline/endpoint genotypes only available for a small minority of cases (risk of selection bias).

Mills et al. 2009. (ARTEMIS trial – 96 week results)[5]	RCT, phase 3.	DRV/r 800/100 daily with TDF/FTC.	HIV-positive adults, treatment-naïve with viral load ≥5000 copies. N=689.	LPV/r 800/200 (either daily or divided 12-hourly), with TDF/FTC	Viral suppression <50 copies/mL at week 192 in ITT population.	Viral suppression in 79% (DRV) vs 71% (LPV). 95% CI for difference 1.9-14.8, p<0.001.	Treatment naïve patients. 2 different LPV/r regimens, but in subgroup analyses, DRV/r was superior to both daily and 12-hourly LPV/r re: virological suppression.
Ortiz et al. 2008. (ARTEMIS trial – 48 week results)[7]	RCT, phase 3.	DRV/r 800/100 daily with TDF/FTC.	HIV-positive adults, treatment-naïve with viral load ≥5000 copies. N=689.	LPV/r 800/200 (either daily or divided 12-hourly), with TDF/FTC	Viral suppression <50 copies/mL at week 192 in ITT population.	Viral suppression in 84% (DRV) vs 78% (LPV(. 95% CI for difference -0.1-11%, p<0.001.	Treatment naïve patients. 2 different LPV/r regimens, but in subgroup analyses, DRV/r was superior to both daily and 12-hourly LPV/r re: virological suppression.

Reviewers: JS Nel, S McGee
Declaration of interests: JN (Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand) has previously received lecture fees from Abbvie, and is a member of the HIV Clinicians' Society Adult ART Guidelines committee. SM (Ophathlmolgical Society of South Africa, which receives sponsorships, grants and support for CPD activities, conferences, meetings and registry activities from various companies including Genop, Bayer, Roche, Alcon, Zeiss, and Oculate).

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Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence? N/a** 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	The following critical outcomes were assessed: • ***Viral suppression rates***: moderate certainty evidence • ***Discontinuation rates:*** moderate certainty evidence Randomised controlled trials and systematic review, but downgraded to "moderate" certainty due to imprecision (wide CIs) and a high rate of attrition in TITAN trial.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☒ Moderate ☐ Small ☐ None ☐	***Viral suppression rates***: large – absolute difference in rate of viral suppression to <50 copies/mL seen in the TITAN and ARTEMIS trials was 8.7% (NNT=9) and 11.6% respectively (NNT= 13). ***Discontinuation rates***: large – absolute difference of 6.9% lower in ARTEMIS trial (at 192 weeks) with DRV/r; NNT=11 and 9.5% lower in TITAN trial (at 96 weeks); NNT=15
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence? n/a** 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	Moderate certainty evidence – randomised controlled trials and systematic review, but downgraded to "moderate" certainty due to imprecision and a high rate of attrition in TITAN trial.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes? n/a** Large ☐ Moderate ☐ Small ☐ None ☒	DRV/r is better tolerated. The rates of drug-associated adverse events are lower with DRV/r than LPV/r (absolute difference 3.9% and 7.8% in TITAN and ARTEMIS respectively), driven mostly by a difference in gastrointestinal side-effects, particularly drug-induced diarrhoea.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention ☒ Favours control ☐ Intervention = Control *or* Uncertain ☐	
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes ☒ No ☐	List the members of the group: Atazanavir/ritonavir List specific exclusion from the group: n/a
FEASABILITY	**Is implementation of this recommendation feasible?** Yes ☐ No ☐ Uncertain ☒	Single supplier – may pose supply chain challenges. Additional challenge for those on concurrent rifampicin for tuberculosis treatment as darunavir is contraindicated for use with rifampicin.

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
RESOURCE USE	**How large are the resource requirements?** More intensive [X] Less intensive [ ] Uncertain [ ]	**Price of medicines:** | Medicine	Price (ZAR) | |---|---| | LPV/r 200/50 mg, 112 tablets | 233.45* | | DRV/r 400/50 mg, 60 tablets | 647.62** | *Contract circular RT71-2019ARV **NDoH notice – reference 2020/11/03/EDP/01 – quotation price from Mylan **Estimated incremental budget impact for DRV/r-containing regimen:** *Assumptions:* • Utilisation data of LPV/r 200/50 mg formulation of 247 000 for 2020 comparable to 2021 [1] • Annual incidence of TB among people living with HIV 2506 per 100,000 (2.5%)[2] • 95.4% of TB cases are rifampicin-sensitive [3], and therefore can't be switched from LPV/r to DRV/r as rifampicin based therapy is required. *Model inputs:* *Estimated population:* • Number of patients on LPV/r estimated as 247 000/ annum. • Estimation of patients on LPV/r with HIV/TB co-morbidity per annum = 6175 • Estimation of patients on LPV/r who would require rifampicin-based therapy = 5891 • Estimation of patients on LPV/r with either no TB, or with rifampicin-resistant TB, who could switch to DRV/r = 241109 *Medicine price:* • Price of 30-day supply of LPV/r 200/50mg tablets (120) = R250.13 [4] • Price of 30-day supply of DRV/r 400/50mg tablets (60) = R647.62 [5] *Estimated annual cost of protease inhibitor consumption for PLHIV without co-morbid TB:* • Cost of LPV/r for one year: R 723 730 000 • Cost of DRV/r for one year: R 1 873 765 000 **Incremental budget impact for one year, using DRV/r = R 1 150 061 235** *Sensitivity analysis:* | Incidence of TB among patients on PI-based regimen	Incremental annual budget impact | |---|---| | 1% | R 1 166 921 000 | | 10% | R 1 065 764 000 | **References.** 1. NDoH data on file 2. UNAIDS 2019 report: https://www.unaids.org/sites/default/files/media_asset/2019-UNAIDS-data_en.pdf 3. Ismail NA, et al. Prevalence of drug-resistant tuberculosis and imputed burden in South Africa: a national and sub-national cross-sectional survey. Lancet Infect Dis. 2018 Jul;18(7):779-787. doi: 10.1016/S1473-3099(18)30222-6. doi: 10.1016/S1473-3099(18)30222-6 4. Contract circular RT71-2019ARV 5. NDoH notice – reference 2020/11/03/EDP/01 – quotation price from Mylan **Other resources:** n/a
VALUE	**Is there important uncertainty or variability about how much people value the options?**	No local survey data could be sourced but the Committee considered that that DRV/r would be acceptable to patients and healthcare workers

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
	Minor [x] Major [ ] Uncertain [ ] **Is the option acceptable to key stakeholders?** Yes [x] No [ ] Uncertain [ ]	as DRV/r would offer a better tolerated regimen compared to LPV/r, with better compliance of a once-daily regimen, compared to 12-hourly dosing for LPV/r-based regimens. However, DRV would not be able to be used with rifampicin-based TB treatment.
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [x] Uncertain [ ]	Would be more equitable, since patients in private care are more readily offered alterative, better-tolerated PIs other than LPV/r, such as ATV/r and DRV/r.

Version	Date	Reviewer(s)	Recommendation and Rationale
1.0	27 July 2021	JN, SM	DRV/r not be recommended for inclusion in the national EML, but be added as an alternative to LPV/r and ATV/r in ART-regimen in PLHIV not on concomitant rifampicin-containing TB therapy. Review indicator is DRV/r's price.

Appendix 1 – search strategy details

Database: PubMed

Date: 9 June 2021

Search	Query	Results
#13	Search: #10 AND #12 Sort by: Most Recent	414
#12	Search: randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab] Sort by: Most Recent	5,094,658
#11	Search: #3 AND #6 AND #9 Filters: Systematic Review Sort by: Most Recent	11
#10	Search: #3 AND #6 AND #9 Sort by: Most Recent	521
#9	Search: #7 OR #8 Sort by: Most Recent	3,184
#8	Search: (lopinavir[mh] OR lopinavir[tiab]) AND (ritonavir[mh] OR ritonavir[tiab] OR norvir[tiab]) Sort by: Most Recent	3,128
#7	Search: "lopinavir-ritonavir drug combination" [Supplementary Concept] OR kaletra[tiab] OR lopimune[tiab] OR alluvia[tiab] Sort by: Most Recent	497
#6	Search: #4 OR #5 Sort by: Most Recent	1,861
#5	Search: (Atazanavir sulphate[mh] OR atazanavir[tiab] OR reyataz[tiab]) AND (ritonavir[mh] OR ritonavir[tiab] OR norvir[tiab]) Sort by: Most Recent	1,112
#4	Search: (Darunavir[mh] OR darunavir[tiab] OR prezista[tiab]) AND (ritonavir[mh] OR ritonavir[tiab] OR norvir[tiab]) Sort by: Most Recent	1,010
#3	Search: #1 AND #2 Sort by: Most Recent	127,157
#2	Search: antiretroviral therapy, highly active[MeSH] OR anti-retroviral agents[MeSH] OR antiviral agents[MeSH:NoExp] OR ((anti[tiab]) AND (hiv[tiab])) OR antiretroviral*[tiab] OR ((anti[tiab]) AND (retroviral*[tiab])) OR HAART[tiab] OR ((anti[tiab]) AND (acquired immunodeficiency[tiab])) OR ((anti[tiab]) AND (acquired immuno-deficiency[tiab])) OR ((anti[tiab]) AND (acquired immune-deficiency[tiab])) OR ((anti[tiab]) AND (acquired immun*[tiab]) AND (deficiency[tiab])) Sort by: Most Recent	206,302
#1	Search: HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tiab] OR hiv-1*[tiab] OR hiv-2*[tiab] OR hiv1[tiab] OR hiv2[tiab] OR hiv infect*[tiab] OR human immunodeficiency virus[tiab] OR human immunedeficiency virus[tiab] OR human immuno-deficiency virus[tiab] OR human immune-deficiency virus[tiab] OR ((human immun*[tiab]) AND (deficiency virus[tiab])) OR acquired immunodeficiency syndrome[tiab] OR acquired immunedeficiency syndrome[tiab] OR acquired immuno-deficiency syndrome[tiab] OR acquired immune-deficiency syndrome[tiab] OR ((acquired immun*[tiab]) AND (deficiency syndrome[tiab])) Sort by: Most Recent	420,176

Search	Query	Results
#9	Search: #6 AND #8 Sort by: Most Recent	180
#8	Search: randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab] Sort by: Most Recent	5,094,658
#7	Search: #3 AND #4 AND #5 Filters: Systematic Review Sort by: Most Recent	8
#6	Search: #3 AND #4 AND #5 Sort by: Most Recent	239
#5	Search: (Atazanavir sulphate[mh] OR atazanavir[tiab] OR reyataz[tiab]) AND (ritonavir[mh] OR ritonavir[tiab] OR norvir[tiab]) Sort by: Most Recent	1,112
#4	Search: (Darunavir[mh] OR darunavir[tiab] OR prezista[tiab]) AND (ritonavir[mh] OR ritonavir[tiab] OR norvir[tiab]) Sort by: Most Recent	1,010
#3	Search: #1 AND #2 Sort by: Most Recent	127,157
#2	Search: antiretroviral therapy, highly active[MeSH] OR anti-retroviral agents[MeSH] OR antiviral agents[MeSH:NoExp] OR ((anti[tiab]) AND (hiv[tiab])) OR antiretroviral*[tiab] OR ((anti[tiab]) AND (retroviral*[tiab])) OR HAART[tiab] OR ((anti[tiab]) AND (acquired immunodeficiency[tiab])) OR ((anti[tiab]) AND (acquired immuno-deficiency[tiab])) OR ((anti[tiab]) AND (acquired immune-deficiency[tiab])) OR ((anti[tiab]) AND (acquired immun*[tiab]) AND (deficiency[tiab])) Sort by: Most Recent	206,302
#1	Search: HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tiab] OR hiv-1*[tiab] OR hiv-2*[tiab] OR hiv1[tiab] OR hiv2[tiab] OR hiv infect*[tiab] OR human immunodeficiency virus[tiab] OR human immunedeficiency virus[tiab] OR human immuno-deficiency virus[tiab] OR human immune-deficiency virus[tiab] OR ((human immun*[tiab]) AND (deficiency virus[tiab])) OR acquired immunodeficiency syndrome[tiab] OR acquired immunedeficiency syndrome[tiab] OR acquired immuno-deficiency syndrome[tiab] OR acquired immune-deficiency syndrome[tiab] OR ((acquired immun*[tiab]) AND (deficiency syndrome[tiab])) Sort by: Most Recent	420,176

Database: EPISTEMONIKOS
Date: 14 June 2021
No. of records retrieved: 13
(darunavir AND atazanavir)

(title:(hiv* OR hiv-1 OR hiv-2 OR hiv1 OR hiv2 OR "human immunodeficiency virus" OR "human immuno-deficiency virus" OR "human immuno-deficiency virus" OR "human immunedeficiency virus" OR "human immune-deficiency virus" OR "human immune-deficiency virus" OR "acquired immunodeficiency syndrome" OR "acquired immuno deficiency syndrome" OR "acquired immuno-deficiency syndrome" OR "acquired immunedeficiency syndrome" OR "acquired immuno deficiency syndrome" OR "acquired immuno deficiency syndrome" OR "acquired immuno-deficiency syndrome") OR abstract:(hiv* OR hiv-1 OR hiv-2 OR hiv1 OR hiv2 OR "human immunodeficiency virus" OR "human immuno-deficiency virus" OR "human immuno-deficiency virus" OR "human immunedeficiency virus" OR "human immune-deficiency virus" OR "human immune-deficiency virus" OR "acquired immunodeficiency syndrome" OR "acquired immuno deficiency syndrome" OR "acquired immuno-deficiency syndrome" OR "acquired immunedeficiency syndrome" OR "acquired immuno deficiency syndrome" OR "acquired immuno deficiency syndrome" OR "acquired immuno-deficiency syndrome")) AND (title:((darunavir OR prezista) AND (ritonavir OR norvir)) OR abstract:((darunavir OR prezista) AND (ritonavir OR norvir))) AND (title:((atazanavir OR reyataz) AND (ritonavir OR norvir)) OR abstract:((atazanavir OR reyataz) AND (ritonavir OR norvir)))

Database: EPISTEMONIKOS
Date: 14 June 2021
No. of records retrieved: 38
(darunavir OR atazanavir)

(title:(hiv* OR hiv-1 OR hiv-2 OR hiv1 OR hiv2 OR "human immunodeficiency virus" OR "human immuno-deficiency virus" OR "human immuno-deficiency virus" OR "human immunedeficiency virus" OR "human immune-deficiency virus" OR "human immune-deficiency virus" OR "acquired immunodeficiency syndrome" OR "acquired immuno deficiency syndrome" OR "acquired immuno-deficiency syndrome" OR "acquired immunedeficiency syndrome" OR "acquired immuno deficiency syndrome" OR "acquired immuno deficiency syndrome" OR "acquired immuno-deficiency syndrome") OR abstract:(hiv* OR hiv-1 OR hiv-2 OR hiv1 OR hiv2 OR "human immunodeficiency virus" OR "human immuno-deficiency virus" OR "human immuno-deficiency virus" OR "human immunedeficiency virus" OR "human immune-deficiency virus" OR "human immune-deficiency virus" OR "acquired immunodeficiency syndrome" OR "acquired immuno deficiency syndrome" OR "acquired immuno-deficiency syndrome" OR "acquired immunedeficiency syndrome" OR "acquired immuno deficiency syndrome" OR "acquired immuno deficiency syndrome" OR "acquired immuno-deficiency syndrome")) AND (title:((lopinavir OR kaletra OR lopimune OR alluvia) AND (ritonavir OR norvir)) OR abstract:((lopinavir OR kaletra OR lopimune OR alluvia) AND (ritonavir OR norvir))) AND (title:(((darunavir OR prezista) AND (ritonavir OR norvir)) OR ((atazanavir OR reyataz) AND (ritonavir OR norvir))) OR abstract:(((darunavir OR prezista) AND (ritonavir OR norvir)) OR ((atazanavir OR reyataz) AND (ritonavir OR norvir))))

Database: CLIB, Issue 6 of 12, June 2021
Date: 14 June 2021
(darunavir OR atazanavir)

ID	Search	Hits
#1	MeSH descriptor: [HIV Infections] explode all trees	12861
#2	MeSH descriptor: [HIV] explode all trees	3134
#3	hiv* or hiv-1 or hiv-2 or hiv1 or hiv2 or (hiv near infect*) or (human immunodeficiency virus) or (human immunedeficiency virus) or (human immune-deficiency virus) or (human immuno-deficiency virus) or (human immune deficiency virus) or (human immuno deficiency virus) or (acquired immunodeficiency syndrome) or (acquired immunedeficiency syndrome) or (acquired immuno-deficiency syndrome) or (acquired immune-deficiency syndrome) or (acquired immun* next deficiency syndrome) (Word variations have been searched)	30926
#4	MeSH descriptor: [Lymphoma, AIDS-Related] this term only	22
#5	MeSH descriptor: [Sexually Transmitted Diseases, Viral] this term only	29
#6	#1 or #2 or #3 or #4 or #5	30868
#7	MeSH descriptor: [Antiretroviral Therapy, Highly Active] this term only	1230
#8	MeSH descriptor: [Anti-HIV Agents] explode all trees	3576
#9	MeSH descriptor: [Antiviral Agents] this term only	4033
#10	MeSH descriptor: [AIDS Vaccines] this term only	444
#11	(anti hiv) or antiretroviral* or (anti near retroviral*) or (aids near vaccin*) (Word variations have been searched)	13008
#12	#7 or #8 or #9 or #10 or #11	17035
#13	#6 and #12 (Word variations have been searched)	13485
#14	([mh Darunavir] or darunavir:ti,ab,kw or prezista:ti,ab,kw) and ([mh ritonavir] or ritonavir:ti,ab,kw or norvir:ti,ab,kw) (Word variations have been searched)	563
#15	([mh "Atazanavir sulphate"] or atazanavir:ti,ab,kw or reyataz:ti,ab,kw) and ([mh ritonavir] or ritonavir:ti,ab,kw or norvir:ti,ab,kw) (Word variations have been searched)	651
#16	#14 or #15	1056
#17	([mh lopinavir] or lopinavir:ti,ab,kw or kaletra:ti,ab,kw or lopimune:ti,ab,kw or alluvia:ti,ab,kw) and ([mh ritonavir] or ritonavir:ti,ab,kw or norvir:ti,ab,kw) (Word variations have been searched)	1305
#18	#13 and #16 and #17 in Cochrane Reviews	1

#19	#13 and #16 and #17 in Trials	204

Database: CLIB, Issue 6 of 12, June 2021
Date: 14 June 2021
(darunavir AND atazanavir)

ID	Search	Hits
#1	MeSH descriptor: [HIV Infections] explode all trees	12861
#2	MeSH descriptor: [HIV] explode all trees	3134
#3	hiv* or hiv-1 or hiv-2 or hiv1 or hiv2 or (hiv near infect*) or (human immunodeficiency virus) or (human immunedeficiency virus) or (human immune-deficiency virus) or (human immuno-deficiency virus) or (human immune deficiency virus) or (human immuno deficiency virus) or (acquired immunodeficiency syndrome) or (acquired immunedeficiency syndrome) or (acquired immuno-deficiency syndrome) or (acquired immune-deficiency syndrome) or (acquired immun* next deficiency syndrome) (Word variations have been searched)	30926
#4	MeSH descriptor: [Lymphoma, AIDS-Related] this term only	22
#5	MeSH descriptor: [Sexually Transmitted Diseases, Viral] this term only	29
#6	#1 or #2 or #3 or #4 or #5	30868
#7	MeSH descriptor: [Antiretroviral Therapy, Highly Active] this term only	1230
#8	MeSH descriptor: [Anti-HIV Agents] explode all trees	3576
#9	MeSH descriptor: [Antiviral Agents] this term only	4033
#10	MeSH descriptor: [AIDS Vaccines] this term only	444
#11	(anti hiv) or antiretroviral* or (anti near retroviral*) or (aids near vaccin*) (Word variations have been searched)	13008
#12	#7 or #8 or #9 or #10 or #11	17035
#13	#6 and #12 (Word variations have been searched)	13485
#14	([mh Darunavir] or darunavir:ti,ab,kw or prezista:ti,ab,kw) and ([mh ritonavir] or ritonavir:ti,ab,kw or norvir:ti,ab,kw) (Word variations have been searched)	563
#15	([mh "Atazanavir sulphate"] or atazanavir:ti,ab,kw or reyataz:ti,ab,kw) and ([mh ritonavir] or ritonavir:ti,ab,kw or norvir:ti,ab,kw) (Word variations have been searched)	651
#16	#13 and #14 and #15 in Cochrane Reviews	0
#17	#13 and #14 and #15 in Trials	125

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