South African National Essential Medicine List
Primary Healthcare and Adult Hospital Level of Care Medication Review Process
Component: HIV & AIDS

MEDICINE REVIEW:

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

DATE: 18 November 2021

Key findings

- We conducted a review of ritonavir-boosted atazanavir (ATV/r) compared with ritonavir-boosted lopinavir (LPV/r) in protease inhibitor naïve adult people living with HIV (PLHIV).
- We included 3 randomised controlled trials and conducted meta-analyses for important clinical outcomes.
- The proportion of patients with viral load <50 copies/mL at 48 and 96 weeks was slightly higher (about 10%) with ATV/r than LPV/r; 48 weeks: relative risk (RR) 1.11, 95% confidence interval (CI) 1.04 to 1.18 (3 studies, n=1105, moderate certainty evidence) and 96 weeks: RR 1.09, 95%CI 1.01 to 1.19 (2 studies, n=1045, moderate certainty evidence). Number needed to treat to achieve 1 additional viral load < 50: 12 (95% CI 8 to 30) and 16 (95% CI 9 to 190) at 48 and 96 weeks respectively.
- The proportion of patients who died by 48 and 96 weeks was not significantly different between ATV/r and LPV/r; 48 weeks: RR 1.01, 95% CI 0.25 to 4.00 (3 studies, n=942, moderate certainty evidence) and 96 weeks: RR 1.55, 95% CI 0.53 to 4.51 (2 studies, n=1045, moderate certainty evidence).
- The proportion of patients with grade 2 to 4 treatment related adverse events (AE) at 48 and 96 weeks was numerically lower with ATV/r than LPV/r, but this was not statistically significant; 48 weeks: RR 0.88, 95% CI 0.73 to 1.06 (3 studies, n=937, moderate certainty evidence) and 96 weeks: RR 0.88, 95% CI 0.73 to 1.06 (2 studies, n=1045, moderate certainty evidence).
- The proportion of patients with treatment discontinuations due to AEs at 48 and 96 weeks was numerically lower with ATV/r than LPV/r, but this was not statistically significant; 48 weeks: RR 0.65, 95%CI 0.37 to 1.15 (3 studies, n=1104, moderate certainty evidence) and 96 weeks: RR 0.54, 95%CI 0.29 to 1.00 (2 studies, n=1045, moderate certainty evidence).

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE 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: The PHC/Adult Hospital Level Committee suggests that ritonavir-boosted atazanavir be the preferred protease inhibitor for second-line therapy in all adult patients without concomitant TB. Ritonavir-boosted lopinavir must still be available for use with rifampicin-containing TB therapy.
Rationale: Ritonavir-boosted atazanavir is at least non-inferior to ritonavir-boosted lopinavir in terms of viral suppression, is associated with fewer gastrointestinal side-effects and lipid profile abnormalities than ritonavir-boosted lopinavir, and is dosed once-daily.
Level of Evidence: Low to moderate certainty evidence

NEMLC MEETING 9 DECEMBER 2021:
NEMLC Recommendation: The NEMLC accepted the proposed recommendation. It was furthermore noted that the global market is shifting from LPV/r to other protease inhibitors (i.e. DRV/r and ATV/r) and competition will likely push down the price of other protease inhibitors.

Monitoring and evaluation considerations

Research priorities

1. EXECUTIVE SUMMARY

Date: 18 November 2021
Medicine (INN): Atazanavir, boosted with ritonavir
Medicine (ATC): J05AR23
Indication (ICD10 code): B24
Patient population: PLHIV who are protease inhibitor-naive
Prevalence of condition: Adult population of PLHIV in South Africa, estimated at 14.0% (95% CI: 13.1–15.0).(1)
Level of Care: Primary and Adult Hospital Level
Prescriber Level: Nurse practitioner, Medical Doctor, Specialist
Current standard of Care: Lopinavir based PI therapy
Efficacy estimates: Viral suppression <50 copies/mL at 48 weeks: relative risk (RR) 1.11, 95% confidence interval (CI) 1.04 to 1.18. Number needed to treat to prevent 1 patient with viral load ≥50: 12 (95% CI 3 to 13).
Budget estimates: Refer to the evidence to decision framework.
Estimated annual cost of protease inhibitor consumption for PLHIV without co-morbid TB:

- Cost of LPV/r for one year: R 675 442 893
- Cost of ATV/r for one year: R 763 833 470

Motivator/reviewer name(s): Simba Takuva, Renee de Waal

2. REVIEWERS AND ACKNOWLEDGEMENTS

Reviewers: Simba Takuva, Renee de Waal.

Declaration of interests: ST (Perinatal HIV Research Unit, Faculty of Health Sciences, University of the Witwatersrand and School of Health Systems and Public Health, Faculty of Health Sciences, University of Pretoria and RdW (Centre for Infectious Disease Epidemiology and Research, University of Cape Town) have no interests to declare related to atazanavir/ritonavir or lopinavir/ritonavir.

Acknowledgements: T Leong (National Department of Health, Affordable Medicines Directorate, Essential Drugs Programme) assisted with the review and the costing, and the following assisted with the literature searches and screening of records: T Kredo (Cochrane South Africa, South African Medical Research Council, SA GRADE Network), J Oliver (Cochrane South Africa, South African Medical Research Council), A Brandt (Stellenbosch University, SA GRADE Network), VD Ngah (Stellenbosch University), E Pienaar (Cochrane South Africa, South African Medical Research Council).

3. INTRODUCTION/ BACKGROUND

Protease inhibitors (PI) are potent inhibitors of HIV-1 protease. In current South African National guidelines, lopinavir in combination with ritonavir (LPV/r) is the recommended PI for second-line antiretroviral therapy (ART) in adult PLHIV who received dolutegravir-based first-line regimens, and in those who received NNRTI-based first-line regimens who have a contraindication to dolutegravir. However, LPV/r is associated with high pill burden which may negatively impact adherence, poor gastrointestinal tolerability (diarrhoeal side effects are an established risk factor of treatment failure), adverse effects such as hyperlipidaemia, and the need to double dose during TB therapy.(2,3) Patients who experience adverse effects on LPV/r, may be switched to ATV/r.

ATV has a high genetic barrier to resistance, is generally better tolerated than LPV and can be taken once daily.(4,5) Several ATV/r fixed dose combinations are now registered locally. A pitfall of ATV is reduced

absorption with acid-lowering drugs like proton-pump inhibitors.(6) ATV causes a non-clinically significant unconjugated hyperbilirubinemia that manifests as jaundice in a small proportion of patients leading to a need to substitute the drug for cosmetic reasons.(7) Genetic variants of UGT1A1 have been found to predispose to more severe jaundice on ATV (8) and in a recent study, one third of people sampled in KwaZulu Natal had variant alleles in UGT1A1.(9)

The purpose of this review is to evaluate if ATV can be used as the preferred PI for PI-naïve adult PLHIV in South African national guidelines.

4. OBJECTIVE

Review question: Should atazanavir/ritonavir (ATV/r) be used as the preferred protease inhibitor in place of lopinavir/ritonavir for second-line antiretroviral therapy in HIV positive adults who are PI-naive.

Table 1. PICO framework of the technical review

Population	PLHIV who are PI-naive
Intervention/s and comparisons	Atazanavir/ritonavir (ATV/r) – based combination antiretroviral therapy Lopinavir/ritonavir (LPV/r) – based combination antiretroviral therapy
Outcomes	**Efficacy:** Viral suppression rates, Mortality, Development of resistance mutations **Safety:** Adverse events, Discontinuation rates, Lipid profile
Study designs	Systematic reviews of randomized controlled clinical trials in humans Randomized controlled clinical trials in humans (eligible trials not included in systematic reviews identified)

5. METHODS

PubMed, the Cochrane Database of Systematic Reviews, Epistemonikos databases were searched up to 25 July 2021 and references of systematic reviews were scanned. There was no restriction on date, language, or publication status. The search strategy is shown in Appendix A. Included were systematic reviews of randomized controlled clinical trials in humans and randomized controlled clinical trials. Excluded were none head-to-head comparison trials, observational studies, case reports, case series, case reports and narrative reviews. Trials of PI-treatment experienced patients were also excluded.

The search produced 440 studies; 334 were removed for either being duplicates, non-human, non RCTs or systematic reviews. The remaining 110 records were screened (abstracts and title) and 20 records were identified for full text review. Three systematic reviews, two network meta-analysis and 12 RCTs were identified. After full-text screening and review of the bibliography of systematic reviews, three of the seven RCTs included in the Tigabu et al systematic review(10) were eligible. The Prisma flow diagram for the search output including reasons for exclusion is shown below (Figure 1).

Risk of bias was assessed using the modified Cochrane Collaboration risk of bias tool (Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Cochrane, 2020. Available from www.training.cochrane.org/handbook. Outcomes from individual studies were pooled using the fixed-effects

model in Revman 5.3. Heterogeneity as evaluated by the i^2 statistic was low hence the fixed effects approach is appropriate. The summary of findings table was computed in GRADEPro.

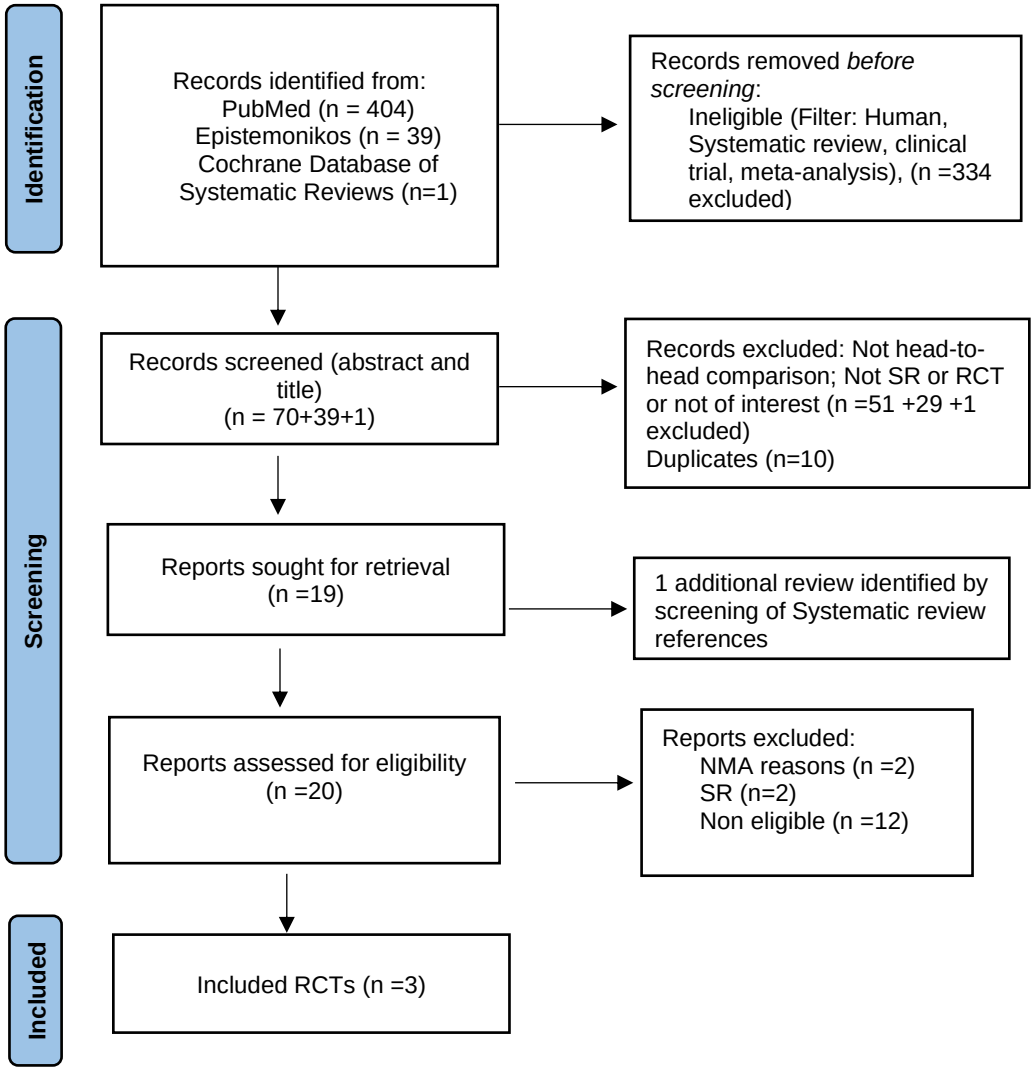

Figure 1. PRISMA flow-chart detailing study selection

6. RESULTS

The three included studies are summarised in Table 2, and the summary of findings is shown in Table 3, illustrating the effect sizes of the different outcomes evaluated. Table 3 shows the excluded studies from the Tigabu et al(10) systematic review and reasons for exclusion.

In the open label study by Andersson et al(11), 243 ART naïve HIV positive patients in 29 sites in Sweden and Norway were randomized to receive combination ART consisting of either EFV 600 mg once daily, ATV/r 300 mg/100 mg once daily or LPV/r 400 mg/100 mg twice daily. The primary endpoint was proportion with virologic suppression < 50 copies/ml at 48 and 144 weeks. This was a small under-powered study not designed to demonstrate non-inferiority or equivalence. NRTI backbone was heterogenous and not defined by the protocol and choice of NRTI may have confounded the findings. Genotypic resistance data was not available from this study.

The CASTLE study(12,13) was a 96 week open label non-inferiority trial that examined once-daily ATV/r and twice-daily LPV/r, both given in combination with once-daily, fixed dose tenofovir (TDF) and emtricitabine (FTC), in 883 treatment-naive HIV-1-infected patients from 134 centres in 29 countries. Primary endpoint was proportion of patients achieving virologic suppression of <50 copies/ml at 48 weeks. Outcomes at 96 weeks were also subsequently reported.

The Advanz-3 trial(14) was an open label multi-centre study that randomized 89 HIV positive ART naïve patients to receive either EFV 600 mg once daily, ATV/r 300 mg/100 mg once daily or LPV/R 400 mg/100 mg combined with FTC/TDF. Primary endpoint was median increase in CD4 cell count and secondary endpoints included patients achieving virologic suppression < 50 copies/ml at 48 weeks. This was a small study with insufficient power to detect differences in secondary outcomes across the three arms (including differences in virologic suppression).

Viral suppression

Viral suppression (<50 copies/ml) was evaluated at 48 weeks (three studies)(11,12,14) or 96 weeks (two studies)(11,13). Where suppression rates were not available for the two time points, the longest follow-up period was evaluated. After 48 weeks of ART, there was a 11% statistically significant increased likelihood of achieving virological suppression in the ATV/r arm (453/551) compared to the LPV/r arm (410/554), pooled Relative Risk: 1.11; 95% CI 1.04 – 1.18 (fixed effects model). Similarly, when the studies reporting virological suppression over 96 weeks were pooled, there was a marginal higher chance of suppression while on an ATV/r regimen (374/521) compared to a LPV/r regimen (344/524), pooled RR 1.09; 95%CI 1.01 -1.19. Figure 2 illustrates the forest plots reproduced using the data from these studies.

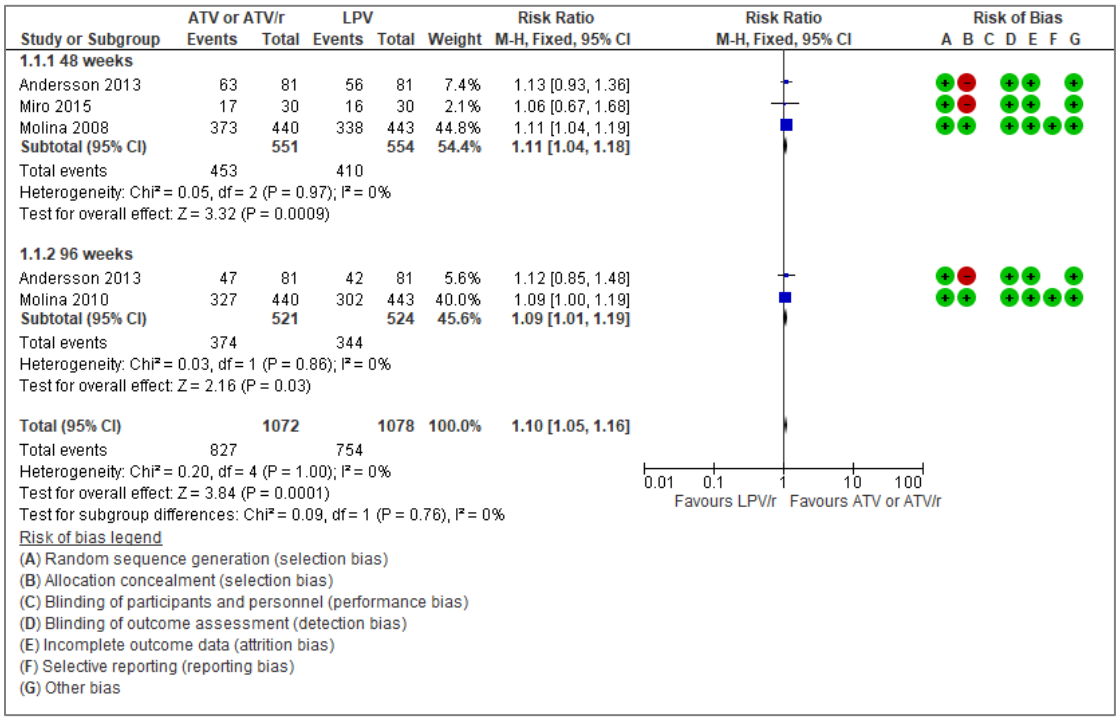

Figure 2. Forest plots for the comparison of ATV/r vs LPV/r for the treatment of PLHIV (virological failure <50 copies/ml)

Development of resistance mutations

In the CASTLE study(13) rates of development of resistance to PIs were low, with only a single patient in each treatment arm with virologic failure at 96 weeks developing phenotypic resistance to a study PI. The emergence of NRTI substitutions was also low, with 5 patients in each treatment group developing phenotypic resistance to emtricitabine and 2 patients on lopinavir/ritonavir with phenotypic resistance to tenofovir disoproxil fumarate. None of the other included studies conducted genotypic resistance testing.

Mortality

Mortality was generally low across the included studies. The proportion of patients who died by 48 and 96 weeks was not significantly different between ATV/r and LPV/r; 48 weeks: RR 1.01, 95% CI 0.25 to 4.00 (3 studies, n=942, moderate certainty evidence) and 96 weeks: RR 1.55, 95% CI 0.53 to 4.51 (2 studies, n=1045, moderate certainty evidence). None of the deaths were considered related to treatment (see Figure 3, below).

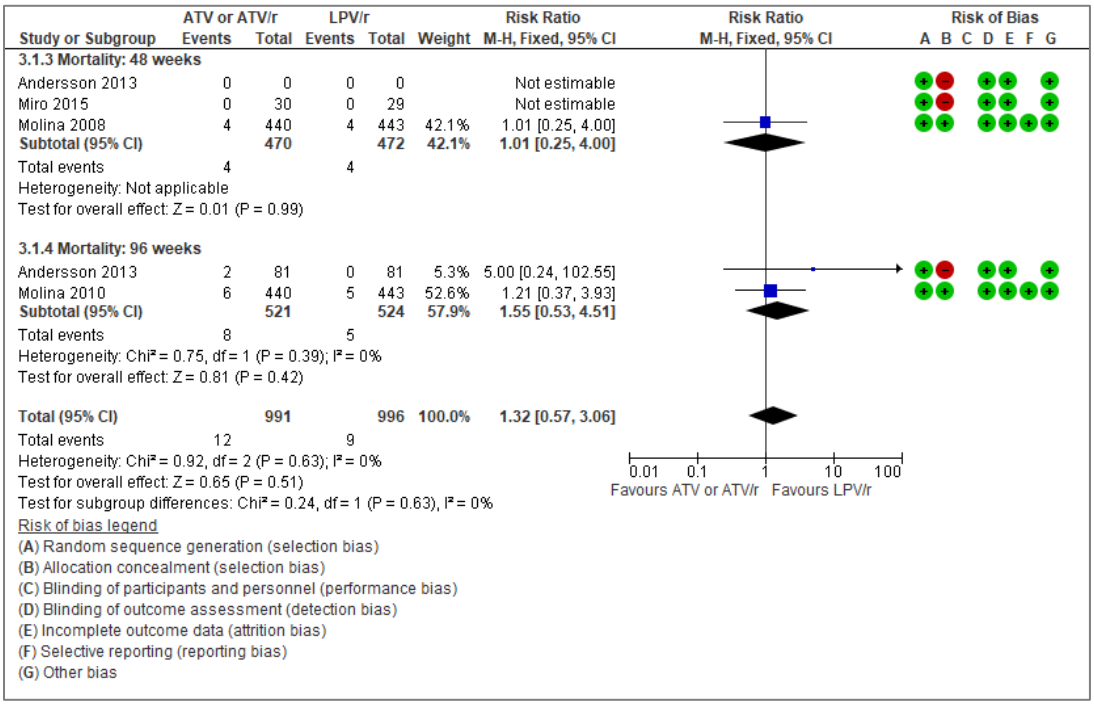

Figure 3. Forest plots for the comparison of ATV/r vs LPV/r for the treatment of PLHIV (Mortality)

Adverse events

Patients in the ATV/r arm had lower risk of occurrence of treatment related of grade 2-4 adverse events compared to those in the LPV/r arm, this was consistently seen across studies evaluated, pooled RR 0.88; 95% CI 0.77 – 1.00.(11–14) See Figure 4. Diarrhoeal events were much more common in the LPV/r arm vs. ATV/r arm and required use of anti-diarrhoeal events i.e., 24% vs. 12% in the CASTLE study.

Hepatobiliary adverse events were significantly more in the ATV/r arm than the LPV/r arm. In the CASTLE study, three patients discontinued due to jaundice/ hyperbilirubinemia through week 48 with no additional discontinuations due to hyperbilirubinemia occurring between weeks 48 and 96. In pooled estimated across all included studies, RR 80.44; 95% CI 31.90 – 202.85. See Figure 5.

Serious adverse events (SAEs) were numerically higher in the ATV/r arm than the LPV arm across the three studies, overall, 78 in ATV/r arm vs. 57 in LPV/r am, pooled RR 1.24; 95%CI 0.97 – 1.57. Few of these serious adverse events were deemed related to the study treatment. See Figure 6.

Patients on the ATV/r regimen had significantly lower levels of total cholesterol and fasting triglycerides than those on LPV/r regimens after 48 weeks of treatment.(12–14) After 96 weeks of treatment and above, mean percentage changes in total cholesterol and triglycerides was significantly higher in LPV/r than ATV/r based regimens (all p<0.01).(11,13)

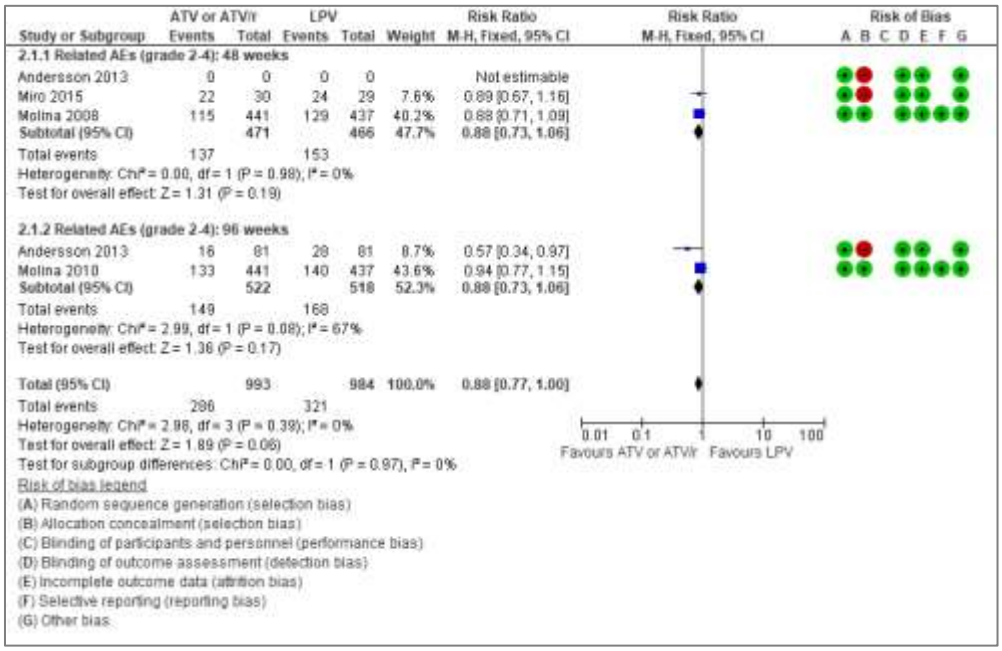

Figure 4. Forest plots for the comparison of ATV/r vs LPV/r for the treatment of PLHIV (treatment related adverse events)

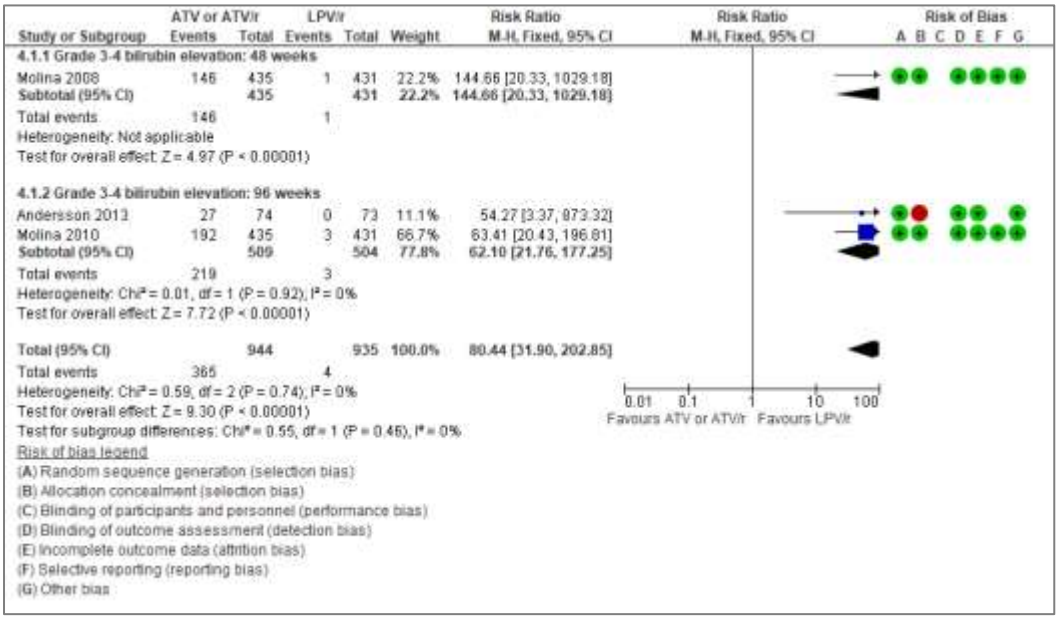

Figure 5. Forest plots for the comparison of ATV/r vs LPV/r for the treatment of PLHIV (Bilirubin levels)

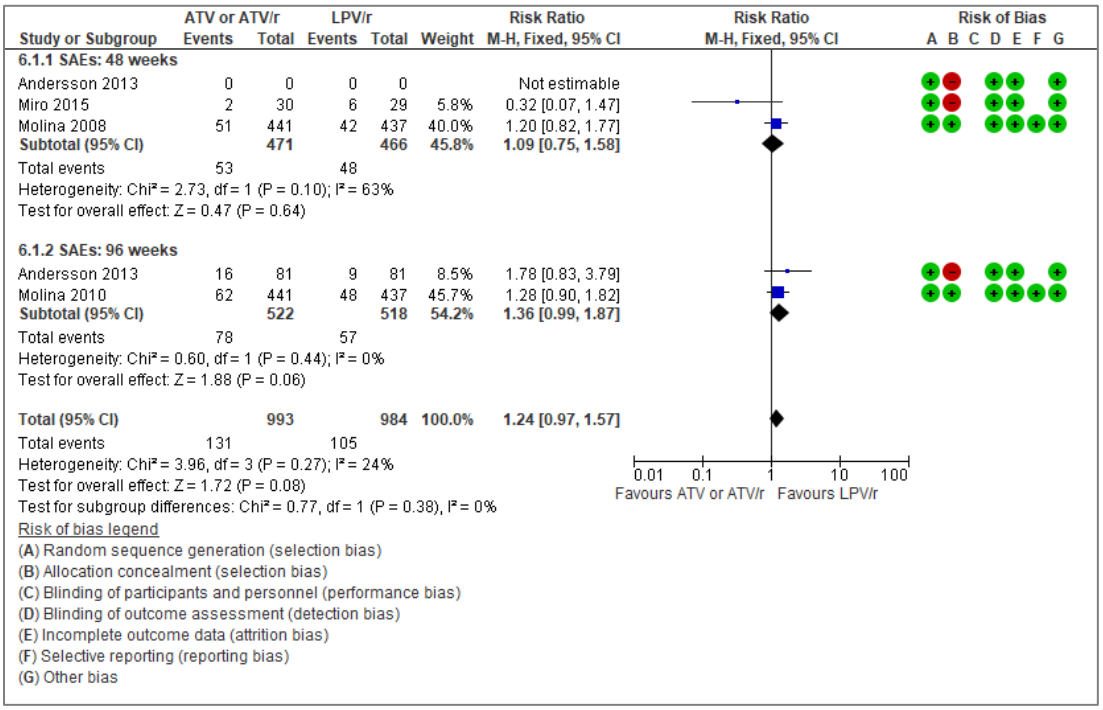

Figure 6. Forest plots for the comparison of ATV/r vs LPV/r for the treatment of PLHIV (Serious adverse events)

Discontinuation rates

Across the included studies, through 144 weeks, treatment discontinuation rates were significantly lower in the ATV/r arm (total 34) than the LPV/r arm (total 57), pooled RR 0.60; 95%CI 0.40 – 0.90. Gastrointestinal toxicities resulted in many discontinuations in the LPV/r arm. See Figure 7, below.

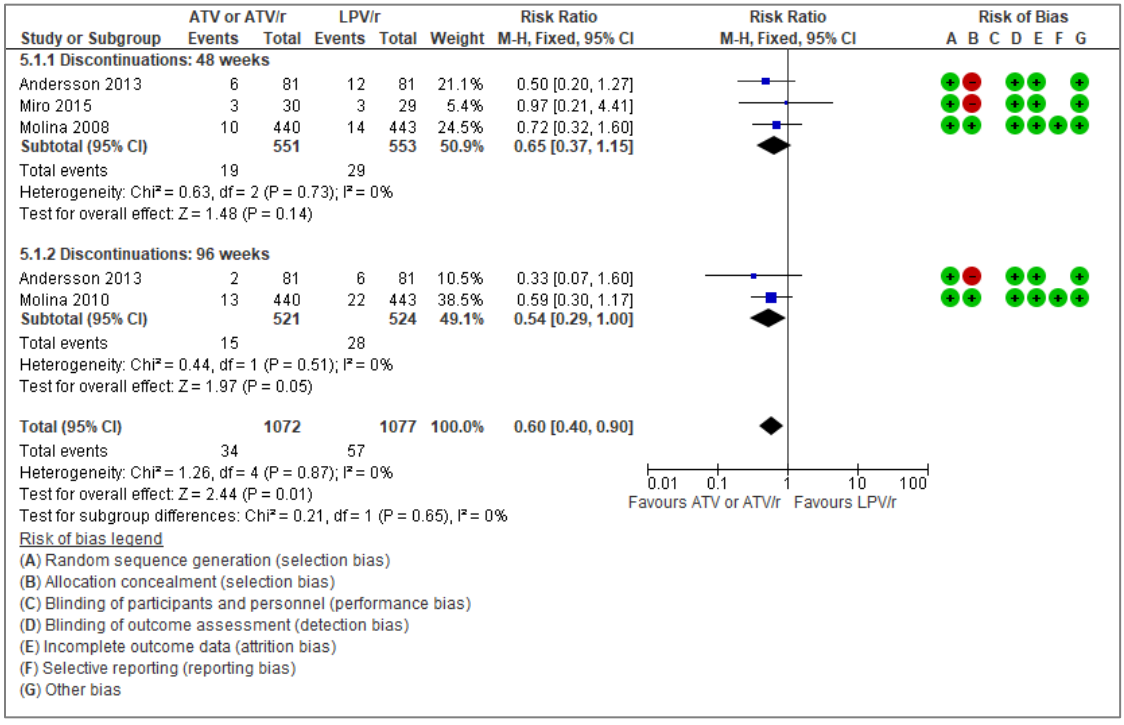

Figure 7. Forest plots for the comparison of ATV/r vs LPV/r for the treatment of PLHIV (discontinuations due to adverse events)

CONCLUSIONS

Overall, ATV/r is reported to be noninferior to LPV/r, but with improved tolerance in terms of gastrointestinal side-effects, once-daily administration, and importantly, a better lipid profile than LPV/r in treatment-naive patients. As a result of the lower incidence of diarrhoea and favourable lipid parameters among patients receiving ATV/r, significantly less use of concomitant medications such as either anti-diarrhoeal or lipid-lowering agents was observed in clinical studies.(11–14)

However, ATV/r has the following limitations, it cannot be used with rifampicin-based TB treatment and has important drug interactions leading to reduced absorption with acid-lowering drugs like proton-pump inhibitors; use also leads reversible indirect hyperbilirubinemia, with or without jaundice or scleral icterus, but without concomitant hepatic transaminase elevation. Discontinuations were reported in studies due to the negative cosmetic effects of the jaundice. Local data regarding the prevalence of hyperbilirubinemia associated with ATV/r is limited. However, Naidoo *et al.* extrapolated that about 1/3 of patients taking ATV/r would have a genetic polymorphism that may result in hyperbilirubinemia, but the proportion of patients that would develop cosmetically distressing hyperbilirubinaemia resulting in non-compliance is unknown.(16)

Based on the review, the balance of benefits vs harms favours ATV/r as an alternative PI to LPV/r.

Table 2. Characteristics of included studies

Citation	Study design	Population	Intervention and Comparisons	Main findings (ATV/r versus LPV/r)
Molina, JM. et al(15) 48 weeks FU	RCT open label	Adults aged 18 years or older, naive to ART VL≥5000 copies/ml Up to 96 weeks follow up 134 sites in 29 countries (n=883)	ATV/r 300 mg/100 mg OD, or LPV/r 133/33·3 mg BD NRTI backbone: TDF/FTC 300/200 mg OD	**Efficacy**: VL Difference estimates, 1·7% (95%CI –3·8 to 7·1) **Mortality:** 4/440 ATV/r and 4/443 LPV/r **Adverse events:** Grade 2-4 related AEs: 115 (26%) ATV vs. 129 (30%) LPV/r **Grade 2/3-4 bilirubin**: 146/435 ATV/r vs. 1/431 LPV/r **SAEs:** 51 (12%) ATV vs. 42 (10%) **Lipids**: Total cholesterol (≥240 mg/dL) - 30/434 (7%) ATV/r vs. 77/428 (18%) LPV/r; Triglycerides (≥751 mg/dL) - 2/434 (<1%) ATV vs. 15/428 (4%) LPV/r **Discontinuations**: 10/440 (ATV/r) vs. 14/443 (LPV/r)
Molina, JM. et al(13) 96 weeks FU				**Efficacy**: VL Difference estimates, 1.8% (-2.6% to 6.3%) **Mortality** – 4/440 ATV/r and 4/443 LPV/r **Grade 2-4 related AEs**: 133 (30%) ATV vs. 140 (32%) LPV/r **Grade 2/3-4 bilirubin**: 146/435 ATV/r vs. 1/431 LPV/r **SAEs** – 62 (14%) ATV vs. 48 (11%) **Lipids**: Total cholesterol (≥240 mg/dL) - 47/434 (11%) ATV/r vs. 108/428 (25%) LPV/r; Triglycerides (≥751 mg/dL) - 3/434 (<1%) ATV vs. 18/428 (4%) LPV/r **Discontinuations**: 13/440 (ATV/r) vs. 22/443 (LPV/r)
Andersson, LM. Et al(11) 144 weeks FU	RCT open label	Antiretroviral-naïve adults 29 sites in Sweden and Norway (n=243)	EFV 600 mg OD, or ATV/r 300 mg/100 mg OD, or LPV/r 400 mg/100 mg twice OD	**Efficacy**: Week 48 HIV-1 RNA < 50 copies/ml – 86 (78–94)% EFV arm, 78 (69–87)% in ATV/r arm and, 69 (59–78)% in LPV/r arm Week 144 - 61 (50–72)% EFV arm, 58 (47–69)%, in ATV/r arm, and 51 (41–63)% in LPV/r arm **Mortality:** over 144 weeks - 0 in LPV/r vs. 2 in ATV/r (not related) **Grade 2-4 related AEs**: over 144 weeks – 16 ATV/r vs. 28 LPV/r **Grade 2/3-4 bilirubin**: over 144 weeks – 27/74 ATV/r vs. 0/73 LPV/r **SAEs**: over 144 weeks – 16 ATV/r vs. 9 LPV/r **Lipids**: over 144 weeks – median % change in fasting TC and TG from baseline through week 144 was higher in the LPV/r arm than the AZV/r arm (all p<0.05) **Discontinuations**: over 48 weeks – 6 ATV/r vs. 12 LPV/r and over 144 weeks – 2 ATV/r vs. 6 LPV/r
Miro, JM. et al(14) 48 weeks FU	RCT open label	Adults aged 18 years or older Antiretroviral naïve 5 sites in Spain (n=89)	EFV 600mg OD, ATV/r 300mg/100mg OD or LPV/r 400mg/100mg BD NRTI backbone	**Efficacy**: VL <50 copies/ml: 64.3% (45.8 to 79.3) EFV, 56.7% (39.2 to 72.6) ATV, 51.7% (34.4 to 68.6) LPV/r, p=0.63 **Mortality**: 0 **Grade 2-4 related AEs**: 13/28 EFV vs. 11/30 ATV/r vs. 14/29 LPV/r **Grade 2/3-4 bilirubin**: 0 EFV vs. 2/30 ATV vs. 0 **SAEs**: 2/28 EFV vs. 6/30 ATV vs. 6/29 LPV/r **Lipids**: Trend towards lower lipids for ATV arm than EFV arm

Citation	Study design	Population	Intervention and Comparisons	Main findings (ATV/r versus LPV/r)
				Discontinuations: 1/28 EFV vs. 3/30 ATV vs. 3/29

Table 3. Excluded reviews / RCTs: Reasons for exclusion

Excluded RCT studies		Reasons
1	Johnson M, Grinsztejn B, Rodriguez C, et al. 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.	Previous failure to PI
2	Kanters S, Socias ME, Paton NI, et al. Comparative efficacy and safety of second-line antiretroviral therapy for treatment of HIV/AIDS: a systematic review and network meta-analysis. Lancet HIV [Internet]. 2017;4(10):e433–41. Available from: http://dx.doi.org/10.1016/S2352-3018(17)30109-1	No ATV/r RCT was included. Study included was prospective observational study.
3	Atazanavir Versus Lopinavir/Ritonavir (LPV/RTV) in Patients Who Have Not Had Success With Protease Inhibitor-Containing HAART Regimen(s). NCT00028301	Previous failure to PI
4	Tigabu BM, Agide FD, Mohraz M, Nikfar S. Atazanavir / ritonavir versus lopinavir / ritonavir-based combined antiretroviral therapy (cART) for HIV-1 infection: A systematic review and meta-analysis. Afr Health Sci. 2020;20(1):91–101.	Three studies out of seven from this review were included.
7	Ferrer E, del Rio L, Martínez E, et al. 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.	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)	Switch study, not PI naïve
9	Johnson M, Grinsztejn B, Rodriguez C, et al. 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.	Not PI naïve
10	Ribera E, Azuaje C, Lopez RM, et al 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.	Not PI naive
11	Menshawy A, Ismail A, Abushouk AI, , et al. Efficacy and safety of atazanavir/ritonavir-based antiretroviral therapy for HIV-1 infected subjects: a systematic review and meta-analysis. Archives of Virology. 2017:1-10.	Three out of ten included studies in this review met eligibility for the current review
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	Edén A, Andersson LM, Andersson Ö, et al. Differential effects of efavirenz, lopinavir/r, and atazanavir/r on the initial viral decay rate in treatment naïve HIV-1-infected patients. AIDS Research and Human Retroviruses. 2010;26(5):533-40.	Very short 28 day study
14	Mallolas J, Podzamczer D, Milinkovic A, et al. Efficacy and safety of switching from boosted lopinavir to boosted atazanavir in patients with virological suppression receiving a LPV/r-containing HAART: the ATAZIP study. Journal of Acquired Immune Deficiency Syndromes (1999). 2009;51(1):29-36.	Switch study for patients stable on LPV/r
15	Study of HIV Patients With Undetectable Viral Load and Abnormal Lipids Switching to Atazanavir/Ritonavir. NCT00120393	Switch study, not PI naïve.
16	Soriano V, Garcia-Gasco P, Vispo E, et al. Efficacy and safety of replacing lopinavir with atazanavir in HIV-infected patients with undetectable plasma viraemia: final results of the SLOAT trial. The Journal of Antimicrobial Chemotherapy. 2008;61(1):200-5.	Switch study for patients stable on LPV/r

Table 3. Summary of Findings: ATV/r compared to LPV/r for treatment of HIV positive adults

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with LPV/r	Risk difference with ATV/r
Virological suppression (<50 copies/ml) - 48 weeks	1105 (3 RCTs)	⊕⊕⊕◯ MODERATE [a,b,c,d]	**RR 1.11** (1.04 TO 1.18)	740 per 1,000	**81 more per 1,000** (30 more to 133 more)
Virological suppression (<50 copies/ml) - 96 weeks	1045 (2 RCTs)	⊕⊕⊕◯ MODERATE [a,b,c,d]	**RR 1.09** (1.01 to 1.19)	656 per 1,000	**59 more per 1,000** (7 more to 125 more)
Related AEs (grade 2-4): 48 weeks	937 (3 RCTs)	⊕⊕⊕◯ MODERATE [a,b,c,d]	**RR 0.88** (0.73 to 1.06)	328 per 1,000	**39 fewer per 1,000** (89 fewer to 20 more)
Related AEs (grade 2-4): 96 weeks	1040 (2 RCTs)	⊕⊕⊕◯ MODERATE [a,b,c,d]	**RR 0.88** (0.73 to 1.06)	324 per 1,000	**39 fewer per 1,000** (88 fewer to 19 more)
Mortality: 48 weeks	942 (3 RCTs)	⊕⊕⊕◯ MODERATE [a,b,c,d]	**RR 1.01** (0.25 to 4.00)	8 per 1,000	**0 fewer per 1,000** (6 fewer to 25 more)
Mortality: 96 weeks	1045 (2 RCTs)	⊕⊕⊕◯ MODERATE [a,b,c,d]	**RR 1.55** (0.53 to 4.51)	10 per 1,000	**5 more per 1,000** (4 fewer to 33 more)
Grade 3-4 bilirubin elevation: 48 weeks	866 (1 RCT)	⊕⊕⊕◯ MODERATE [a,b,c,d]	**RR 144.66** (20.33 to 1029.18)	2 per 1,000	**333 more per 1,000** (45 more to 2,386 more)
Grade 3-4 bilirubin elevation: 96 weeks	1013 (2 RCTs)	⊕⊕⊕◯ MODERATE [a,b,c,d]	**RR 62.10** (21.76 to 177.25)	6 per 1,000	**364 more per 1,000** (124 more to 1,049 more)
Discontinuations: 48 weeks	1104 (3 RCTs)	⊕⊕⊕◯ MODERATE [a,b,c,d]	**RR 0.65** (0.37 to 1.15)	52 per 1,000	**18 fewer per 1,000** (33 fewer to 8 more)
Discontinuations: 96 weeks	1045 (2 RCTs)	⊕⊕◯◯ LOW [a,b,c,d]	**RR 0.54** (0.29 to 1.00)	53 per 1,000	**25 fewer per 1,000** (38 fewer to 0 fewer)
Serious adverse events: 48 weeks	937 (3 RCTs)	⊕⊕◯◯ LOW [a,b,c,d]	**RR 1.09** (0.75 to 1.58)	103 per 1,000	**9 more per 1,000** (26 fewer to 60 more)
Serious adverse events: 96 weeks	1040 (2 RCTs)	⊕⊕◯◯ LOW [a,b,c,d]	**RR 1.36** (0.99 to 1.87)	110 per 1,000	**40 more per 1,000** (1 fewer to 96 more)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. All included trials were open label studies with no blinding of participants and researchers. Open label studies are susceptible to numerous biases. However measurement bias is minimal for an outcome like virological suppression as this is a hardcore laboratory endpoint. While randomization methods and sequences were clearly described, allocation concealment is not clearly illustrated in Andersson and Miro (potential issues of selection and confounding bias). Attrition was good across all studies (<10%). Selective reporting was not assessed as there was no access to the study protocols. Overall Risk Of Bias classified as moderate as only one domain of risk was highlighted as serious bias resulting in downgrade.

b. Inconsistency across studies was negligible
c. Indirectness is assessed as not serious as the included studies were head-to-head comparisons of ATV/r versus LPV/r. However, none of the studies evaluated patients who had failed first-line therapy. The review question specifically seeks to inform use of ATV/r vs. LPV/r in patients who switch to second line therapy.
d. The sample size for two of the studies is quite small i.e. 81 per arm in the Andersson et al study and taking into consideration some of the small event occurrences this may have affected study power. The 95% CIs are quite wide in some of the studies. Two papers from the CASTLE study present larger sample size (about 440 per arm) and the precision is quite improved in these studies.

7. EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**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	**Overall certainty:** Low to moderate, due to open-label design, imprecision (as wide CIs) and modest sample sizes and event rate. The following outcomes were considered critical: ***Viral suppression rates***: moderate certainty evidence ***Mortality:*** moderate certainty evidence **Discontinuation rates**: moderate certainty evidence
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☐ Moderate ☒ Small ☐ None ☐	**ATV/r versus LPV/r (reference)** **Viral suppression rates**: 48 weeks – RR 1.11, 95%CI 1.04 – 1.18 and 96 weeks: RR 1.09, 95%CI 1.01 – 1.19 **Mortality**: 48 weeks -RR1.01, 95%CI 0.25 – 4.00 and 96 weeks: RR 1.55, 95%CI 0.53 – 4.51 **Treatment related grade 2-4 adverse events**: 48 weeks – 0.88, 95%CI 0.73 – 1.06 and RR 0.88, 95%CI 0.73 -1.06 **AE related discontinuations**: 48 weeks – RR 0.65, 95%CI 0.37 – 1.15 and 96 weeks: RR 0.54, 95%CI 0.29 – 1.00
QUALITY OF EVIDENCE OF HARM	**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	**Overall certainty:** moderate **Adverse events including laboratory abnormality AEs**: moderate certainty evidence **Serious adverse events**: moderate certainty evidence **Grade 3-4 bilirubin elevation**: moderate certainty evidence
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** **L**arge ☐ Moderate ☒ Small ☐ None ☐	Elevated bilirubin from the ATV/r group was observed in significantly higher rates, however this was deemed not harmful. Serious advents events were largely similar across the two arms. **ATV/r versus LPV/r (ref)** **Serious adverse events**: 48 weeks – RR 1.09, 95%CI 0.79 – 1.58 and 96 weeks: RR 1.36, RR 0.99 – 1.87 **Grade 3-4 bilirubin elevation**: 48 weeks – RR 144.66, 95%CI 20.33 – 1029.18 and 96 weeks: RR 62.10, 95%CI 21.76 – 177.25
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favour's intervention ☒ Favour's control ☐ Intervention = Control *or* Uncertain ☐	
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes ☒ No ☐	List the members of the group: DRV/r Specific exclusion from the group: n/a

<table>
<tr><th></th><th>JUDGEMENT</th><th>EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>FEASABILITY</td><td>Is implementation of this recommendation feasible?

Yes [x] No [ ] Uncertain [ ]</td><td>Already included in the National essential medicine list.</td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?
More intensive [ ] Less intensive [x] Uncertain [ ]</td><td>
Price of medicines:
<table>
<tr><th>Medicine</th><th>Price (ZAR)</th></tr>
<tr><td>LPV/r 200/50 mg, 112 tablets</td><td>233.45*</td></tr>
<tr><td>ATV/r 300/100 mg, 30 tablets</td><td>264.00**</td></tr>
</table>
*Contract circular RT71-2019ARV
**NDoH notice, reference 2020/11/03/EDP/01, quotation price from Mylan/Emcure

<u>A: ESTIMATED INCREMENTAL BUDGET IMPACT FOR ATV/R-CONTAINING REGIMEN:</u>

<u>Assumptions:</u>
• 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 ATV/r as rifampicin based therapy is required.
<u>Model inputs:</u>
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 ATV/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 ATV/r 300/100mg tablets (60) = R264.00 [5]

<u>Estimated annual cost of protease inhibitor consumption for PLHIV without co-morbid TB:</u>
• Cost of LPV/r for one year: R 675 442 893
• Cost of ATV/r for one year: R 763 833 470

<u>Incremental budget impact for one year, using ATV/r = R 88 390 578</u>

<u>Sensitivity analysis:</u>
<table>
<tr><th>Incidence of TB among patients on PI-based regimen</th><th>Incremental annual budget impact</th></tr>
<tr><td>1%</td><td>R 89 686 351</td></tr>
<tr><td>10%</td><td>R 8 911 711</td></tr>
</table>
<u>B: NON-COMPLIANCE DUE TO HYPERBILIRUBINAEMIA WITH ATV/R:</u>
Assumption: Approximately 30% non-compliance on ATV/r-regimen due to hyperbilirubinaemia may occur after ±1 year.

<u>Amended estimated model inputs:</u>
• 30% non-compliant on ATV/r = 241109 x 30% = 72 333 patients and approximately 168 776 patients compliant on ATV/r)
</td></tr>
</table>

<table>
<tr><th></th><th>JUDGEMENT</th><th>EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td></td><td></td><td>
30% switching to LPV/r = 72 333 patients
<u>Estimated annual cost of protease inhibitor consumption for PLHIV factoring in non-compliance due to hyperbilirubinaemia:</u>
Cost of ATV/r for one year: R 534 683 318
Cost of LPV/r for one year: R 202 632 826
Total: R 737 316 144
<u>Incremental budget impact for one year, using ATV/r = R 61 873 392</u>
<u>Sensitivity analysis:</u>
<table>
<tr><th>Incidence of TB among patients on PI-based regimen</th><th>Incremental annual budget impact</th></tr>
<tr><td>15%</td><td>R 75 131 975</td></tr>
<tr><td>40%</td><td>R 53 034 336</td></tr>
</table>
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
6. Naidoo A, et al Hyperbilirubinemia in atazanavir-treated human immunodeficiency virus-infected patients: the impact of the UGT1A1*28 allele. Pharmgenomics Pers Med. 2017 Aug 23;10:233-234.
Other resources: LPV/r use requires monitoring of lipid profiles.
</td></tr>
<tr><td>VALUES, PREFERENCES, ACCEPTABILITY</td><td>
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 [ ]
</td><td>No local survey data could be sourced but the Committee considered that that ATV/r would be acceptable to patients and healthcare workers as ATV/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, ATV would not be able to be used with rifampicin-based TB treatment.</td></tr>
<tr><td>EQUITY</td><td>
Would there be an impact on health inequity?
Yes [ ] No [x] Uncertain [ ]
</td><td></td></tr>
</table>

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5. Kanters S, Socias ME, Paton NI, Vitoria M, Doherty M, Ayers D, et al. Comparative efficacy and safety of second-line antiretroviral therapy for treatment of HIV/AIDS: a systematic review and network meta-analysis. Lancet HIV [Internet]. 2017;4(10):e433–41. Available from: http://dx.doi.org/10.1016/S2352-3018(17)30109-1
6. Klein CE, Chiu Y-L, Cai Y, Beck K, King KR, Causemaker SJ, et al. Effects of acid-reducing agents on the pharmacokinetics of lopinavir/ritonavir and ritonavir-boosted atazanavir. J Clin Pharmacol. 2008 May;48(5):553–62.
7. McDonald C, Uy J, Hu W, Wirtz V, Juethner S, Butcher D, et al. Clinical significance of hyperbilirubinemia among HIV-1-infected patients treated with atazanavir/ritonavir through 96 weeks in the CASTLE study. AIDS Patient Care STDS. 2012 May;26(5):259–64.
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APPENDIX A: SEARCH STRATEGY

Database: PubMed

Date: 25 July 2021

Search	Query	Results
#1	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]))	422,178
#2	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])	207,971
#3	(Atazanavir sulphate[mh] OR Atazanavir sulfate[mh] OR atazanavir[tiab] OR reyataz[tiab])	1,923
#4	("lopinavir*"[mh] OR "abt 378"[tiab] OR "abt 378"[tiab] OR ("lopinavir"[mh] OR "lopinavir"[tiab] OR "abt378"[tiab])) AND ("ritonavir*"[tiab] OR ("ritonavir"[mh] OR "ritonavir"[tiab] OR "novir"[mh] OR "norvir"[tiab]))	3,187
#5	((coronavir* OR coronovirus* OR "corona virus" OR "virus corona" OR "corono virus" OR "virus corono" OR hcov* OR "covid-19" OR covid19* OR "covid 19" OR "2019-nCoV" OR cv19* OR "cv-19" OR "cv 19" OR "n-cov" OR ncov* OR "sars-cov-2" OR (wuhan* AND (virus OR viruses OR viral) OR coronav*) OR (covid* AND (virus OR viruses OR viral)) OR "sars-cov" OR "sars cov" OR "sars-coronavirus" OR "severe acute respiratory syndrome" OR "mers-cov" OR "mers cov" OR "middle east respiratory syndrome" OR "middle-east respiratory syndrome"))	183,992
#5	#1 AND (#2 AND #3 AND #4) NOT #5	404
#6	Filters: Clinical Trial, Meta-Analysis, Systematic Review, Humans Sort by: Most Recent	70

Database: Epistemonikos

Date: 25 July 2021

(Atazanavir sulphate[mh] OR Atazanavir sulfate[mh] OR atazanavir[tiab] OR reyataz[tiab]) AND ("lopinavir*"[mh] OR "abt 378"[tiab] OR "abt 378"[tiab] OR ("lopinavir"[mh] OR "lopinavir"[tiab] OR "abt378"[tiab])) AND ("ritonavir*"[tiab] OR ("ritonavir"[mh] OR "ritonavir"[tiab] OR "novir"[mh] OR "norvir"[tiab])) NOT ((coronavir* OR coronovirus* OR "corona virus" OR "virus corona" OR "corono virus" OR "virus corono" OR hcov* OR "covid-19" OR covid19* OR "covid 19" OR "2019-nCoV" OR cv19* OR "cv-19" OR "cv 19" OR "n-cov" OR ncov* OR "sars-cov-2" OR (wuhan* AND (virus OR viruses OR viral) OR coronav*) OR (covid* AND (virus OR viruses OR viral)) OR "sars-cov" OR "sars cov" OR "sars-coronavirus" OR "severe acute respiratory syndrome" OR "mers-cov" OR "mers cov" OR "middle east respiratory syndrome" OR "middle-east respiratory syndrome"))
No of records retrieved: 39

Database: Cochrane Library

Date: 25 July 2021

Atazanavir sulphate[mh] OR Atazanavir sulfate[mh] OR atazanavir[tiab] OR reyataz[tiab]

No of records retrieved: 1