

Atazanavir / ritonavir versus Lopinavir / ritonavir-based combined antiretroviral therapy (cART) for HIV-1 infection: a systematic review and meta-analysis

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Abstract

Background: This systematic review and meta-analysis was conducted to evaluate the safety and effectiveness of Atazanavir/ritonavir over lopinavir/ritonavir in human immunodeficiency virus-1 (HIV-1) infection.

Methods: Clinical trials with a head-to-head comparison of atazanavir/ritonavir and lopinavir/ritonavir in HIV-1 were included. Electronic databases: PubMed/Medline CENTRAL, Embase, Scopus, and Web of Science were searched. Viral suppression below 50 copies/ml at the longest follow-up period was the primary outcome measure. Grade 2-4 treatment-related adverse drug events, lipid profile changes and grade 3-4 bilirubin elevations were used as secondary outcome measures.

Results: A total of nine articles from seven trials with 1938 HIV-1 patients were included in the current study. Atazanavir/ritonavir has 13% lower overall risk of failure to suppress the virus level < 50 copies/ml than lopinavir/ritonavir in fixed effect model (pooled RR: 0.87; CI: 0.78, 0.96; P=0.006). The overall risk of hyperbilirubinemia is very high for atazanavir/ritonavir than lopinavir/ritonavir in the random effects model (pooled RR: 45.03; CI: 16.03, 126.47; P< 0.0001).

Conclusion: Atazanavir/ritonavir has a better viral suppression at lower risk of lipid abnormality than lopinavir/ritonavir. The risk and development of hyperbilirubinemia from atazanavir-based regimens should be taken into consideration both at the time of prescribing and patient follow-up.

Keywords: Atazanavir, Atazanavir/ritonavir, lopinavir/ritonavir, viral suppression.

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Introduction

The introduction of combination antiretroviral therapy (cART) has led to a successful steep decline in mortality and improved quality of life among people living with HIV infection¹⁻³. This revolution transformed HIV infection to a chronic illness with life-long therapy. Currently, HIV/AIDS affects 37 million people worldwide⁴. The consolidated guideline published by WHO in 2016 is a great breakthrough to enhance access for all HIV infected people throughout the world⁴. This will increase patients eligible for cART from the current 28 million to all infected people. This guidance will definitely advance

efforts to succeed in the long-term goal to end the AIDS epidemic as a public health threat in 2030 .

First line cART treatment failure is a common phenomenon⁶⁻⁸. In sub-Saharan Africa alone, the number of patients on second-line cART is expected to reach up to 4.6 million in 2030⁹. Treatment failure has a strong link with drug resistance mutation and adherence which can be significantly reduced by careful selection of cART^{10,11}. The public health and clinical importance of incorporating an appropriate second-line cART in the national guidelines is undeniable. Generally, the low and middle-income countries use the WHO recommended regimens. The WHO recommends the inclusion of boosted protease inhibitors, ritonavir-boosted atazanavir (ATV/r) and ritonavir-boosted lopinavir (LPV/r), in second-line cART⁴. In our clinical experience, LPV/r is used more often than ATV/r although ATV/r is expected to have better oral bioavailability, low risk of lipid abnormality, and insulin sensitivity compared with other protease inhibitors¹².

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Two meta-analyses were conducted on the comparative efficacy of second-line antiretroviral therapy^{13,14}. However, the search was not comprehensive in the review by Menshaw and colleagues¹³. The review by Kanters and colleagues was not a head-to-head comparison of ATV/r and LPV/r based cART¹⁴. Therefore, we conducted this systematic review and meta-analysis to answer the question: what is the clinical significance of using ATV/r based regimen over LPV/r based regimen for adults with HIV-1 infection?

Methods

This systematic review was done based on PRISMA checklist¹⁵ and the protocol was registered at PROSPERO (registration number: CRD42017080737)

Search strategy

We had systematically searched Embase, PubMed/Medline CENTRAL, Scopus and Web of Science electronic databases from 2000 to October 2018 for human clinical trials. The keywords used were: atazanavir, atazanavir/ritonavir, ATV, ATV/r, lopinavir, lopinavir/ritonavir, LPV, LPV/r, HIV-1, human immune deficiency virus-1. The year of publication, study design, the English language and combined keywords “Atazanavir and lopinavir/ritonavir” and “atazanavir/ritonavir and lopinavir/ritonavir” were used to filter the result.

Eligibility criteria

Clinical trials done on adult HIV/AIDS patients on the head-to-head comparison of ATV (400 mg/day) or ATV/r (300 mg/100 mg/day) with LPV/r (400 mg/100 mg twice daily) and published in the English language from 2000 to 2018 were included. Viral suppression below 50 copies/ml at the longest follow-up was the primary outcome measure. Treatment-related adverse drug events, hyperbilirubinemia and lipid profile abnormalities were the safety outcome measures.

Study selection

Two independent reviewers screened the titles and abstracts of all records. Then, the full texts were selected based on the inclusion criteria by two reviewers independently. Discrepancies were settled by discussion and consensus including a third reviewer.

Data extraction

Two reviewers independently extracted the following information: first author name, year of publication, patient status, the mean or median age of participants, the total number of participants, the interventions given, viral suppression, treatment-related adverse drug events, and lipid profile abnormalities. Viral suppression at 48 or 96 weeks was recorded. However, if viral suppression at 48 or 96 weeks were not present, viral suppression at the longest follow-up was recorded. Grade 2-4 treatment-related adverse drug events, lipid profile changes and grade 3-4 bilirubin elevations were also recorded at the longest follow-up period.

Risk of bias assessment

The Cochrane risk of bias assessment tool was used to assess the bias in included studies¹⁶. Two reviewers did the assessment independently. The sequences generation, allocation concealment, incomplete outcome data, selective reporting, and other bias were assessed. The overall risk of bias was rated as low risk, unclear risk, or high risk for each trial. Low risk was defined as the low risk of bias in all domains. The unclear risk was defined as the indeterminate risk of bias in at least one domain with no high risk of bias domain. High risk was identified as high risk of bias in one or more domains. Publication bias was assessed by funnel plot techniques and Egger's test.

Statistical analysis

The pooled relative risk (RR) with 95% confidence intervals (CIs) was calculated. Statistical heterogeneity of the data was explored and quantified using the chi-square test and the I² test. Heterogeneity was predefined as P <0.1 with the chi-square test or an I² value >50%. The random-effects model was used if heterogeneity was observed; otherwise, the fixed effect model was used. Sensitivity analysis was conducted by excluding articles with different follow-up periods. P <0.05 was considered statistically significant. STATA 14 statistical software portable version (31/12/2015) was used to analyze the result.

Results

A total of 1117 records were identified from the database search. Nine articles from seven studies that fulfilled the inclusion criteria were selected (Figure 1). A total of 1938 adult HIV-1 patients were analyzed. The characteristics of the included studies were presented in Table 1.

Table 1. Characteristics of selected studies

Authors name	Year	Patients	Average /median age*	Follow-up*	Treatment arm (ATV/r or ATV)		Control arm (LPV/r)	
					Participants succeed < 50 copies/ml virus	Total number of participants	Participants succeed < 50 copies/ml virus	Total number of participants
Johnson, M. et al(17, 19)	2005	Adult patients who had failed two or more prior HAART regimens with baseline HIV RNA> 1000 copies/ml and CD4 cell count > 50 x 10 ⁶ cells/l	41-A 40-L	48 wks	62	120	66	123
	2006	Adult patients who had failed two or more prior HAART regimens with baseline HIV RNA> 1000 copies/ml and CD4 cell count > 50 x 10 ⁶ cells/l	41-A 40-L	96 wks	39	120	44	123
Molina, J. M. et al(18, 20)	2008	Adult naïve patients	34-A 36-L	48 wks	373	440	338	443
	2010	Adult naïve patients	34-A 36-L	96 wks	327	440	302	443
Soriano, V. et al(25)	2008	Patients on LPV/r based regimen with viral RNA < 50 copies/ml for longer than 24 weeks	42-A 40-L	48 wks	90	102	78	87
Mallolas, J. et al(23)	2009	Patients on LPV/r based regimen with viral RNA < 50 copies/ml for longer than 24 weeks	42-A 43-L	48 wks	115	121	118	127
				96 wks	110	121	115	127
Edén, A. et al(22)	2010	Adult naïve patients	39-A 38-L	28 day	4	64	8	67
Andersson, L. M. et al(21)	2013	Adult naïve patients	39-A 37-L	48 wks	63	81	56	81
				144 wks	47	81	42	81
Miro, J. M. et al(24)	2015	Adults patients with CD4 T-cell count < 100/mm ³	38.5-A 36.5-L	48 wks	17	30	16	30

*A-ATV/r, L-LPV/r, wks-weeks

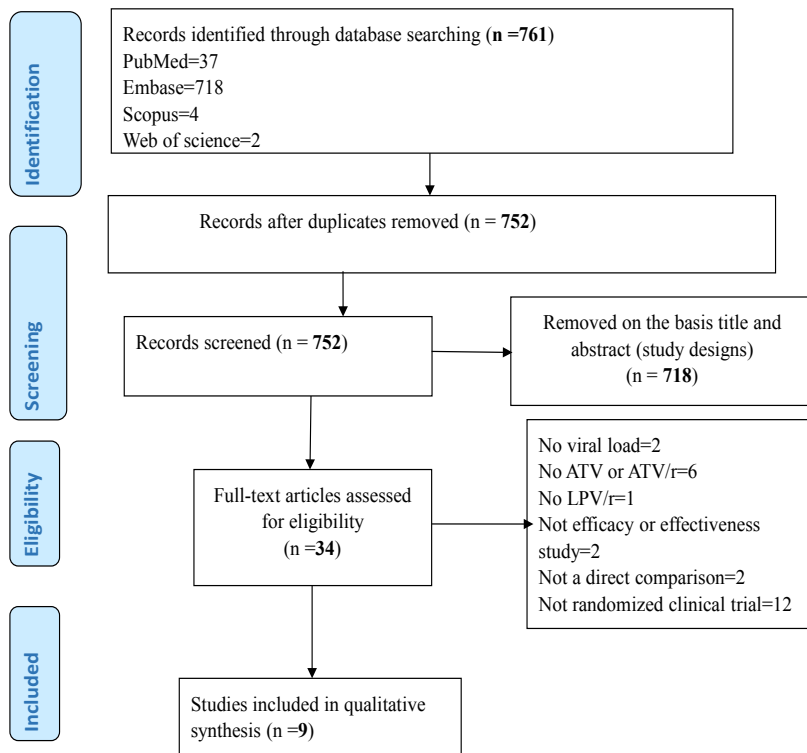


Figure 1. procedural flow diagram of article selection in accordance with PRISMA statement rule

Two of the reviewed articles^{17,18} were found to be part of the same trials with different follow-up periods^{19,20}. Therefore, the risk of bias assessment was done for only

seven articles. The overall risk of bias was high among all reviewed studies. The risk of bias in the included studies was shown in Table 2.

Table 2. Risk of bias assessment.

Studies	Sequence generation	Allocation concealment	Blinding of participants and researchers	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Overall risk of bias
Johnson, M. et al(19)	Low	High	High	High	Low	Unclear	Low	High
Molina, J. M.(20)	Low	High	High	High	Low	Unclear	Low	High
Soriano, V.(25)	Unclear	High	High	High	Low	Unclear	Low	High
Mallolas, J.(23)	Unclear	High	High	High	Low	Unclear	Low	High
Edén, A.(22)	Low	High	High	High	Low	Unclear	Low	High
Andersson, L. M.(21)	Low	High	High	High	Low	Unclear	Low	High
Miro, J. M.(24)	Low	High	High	High	Low	Unclear	Low	High

Sequence generation: Johnson, M et al used central randomization, Molina, J.M. et al, Andersson, L. M. et al and Miro, J. M. et al had used computer generated randomization, Edén, A. et al used randomization done by coordinating center and stratified by viral RNA level, and Soriano, V. et al, Mallolas, J. et al only mentioned the term randomization. Allocation concealment: all have not used appropriate allocation concealment. Blinding: all included studies are open label trials. Incomplete outcome: all mentioned the follow-up period and less than 5% drop out. Selective reporting: The protocols of the included studies were not assessed. Other bias: no other biases were not identified.

Viral suppression

The overall risk of failure to suppress the virus level < 50 copies/ml at the longest follow-up is 13% lower in ATV or

ATV/r based regimens than LPV/r based cART in fixed effect model (pooled RR: 0.87; CI:0.78, 0.96; P=0.006). The chi-square and the I2 tests revealed no statistically significant heterogeneity (P=0.049, I2=47.0%) (Figure 2).

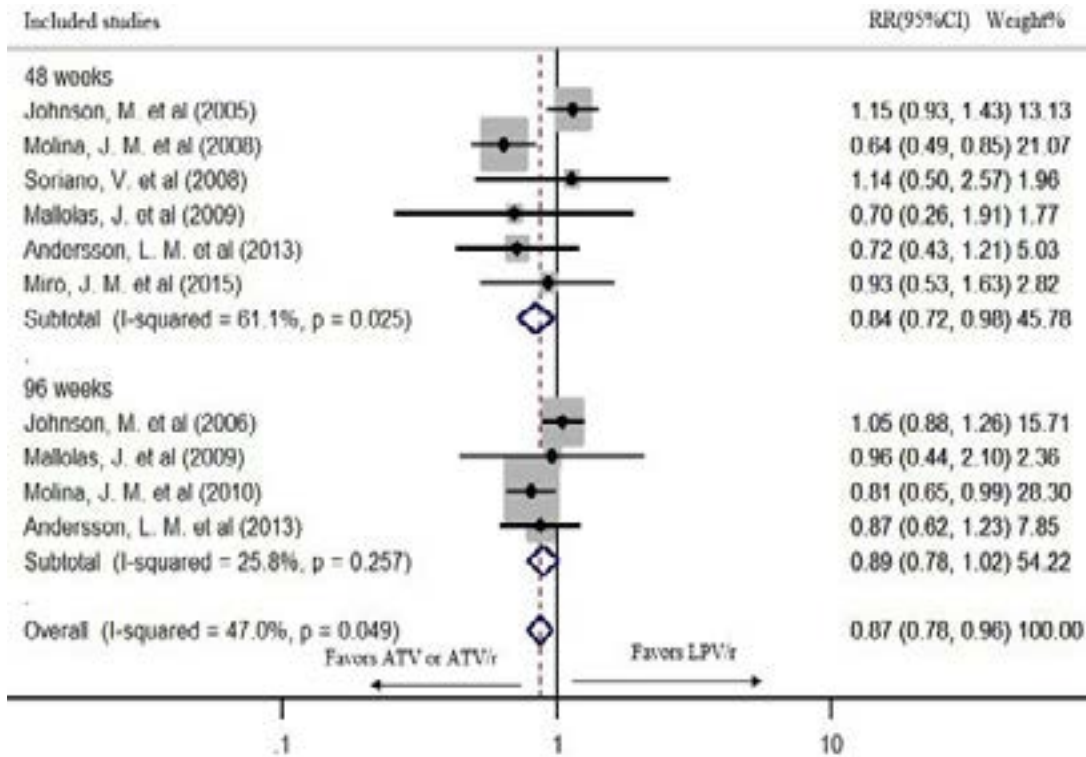


Figure 2. The risk of failure to suppress virus level < 50 copies/ml in fixed effect model

The Egger's test for small study effects (P=0.526) and the funnel plot showed no significant risk of bias (Figure 3).

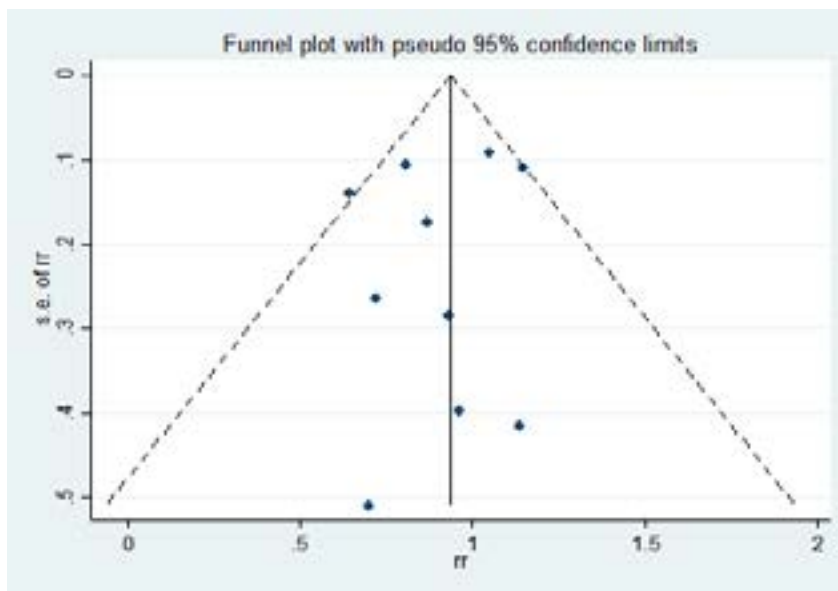


Figure 3. Funnel plot

Six studies had reported viral suppression < 50 copies/ml after 48 weeks of treatment. In the fixed effect model, ATV or ATV/r based regimen had a statistically significant lower risk of failure to suppress the virus < 50 copies/ml after 48 weeks of treatment (pooled RR: 0.84; CI: 0.72, 0.98; P=0.027). However, the chi-square and the I2

tests revealed heterogeneity (P= 0.025, I2=61.1%) (Figure 2). Therefore, the random effects model was used. In the random effects model, although it showed a tendency of lower risk of failure, the difference was not statistically significant (pooled RR: 0.86; CI: 0.64, 1.16; P=0.322) (Figure 4).

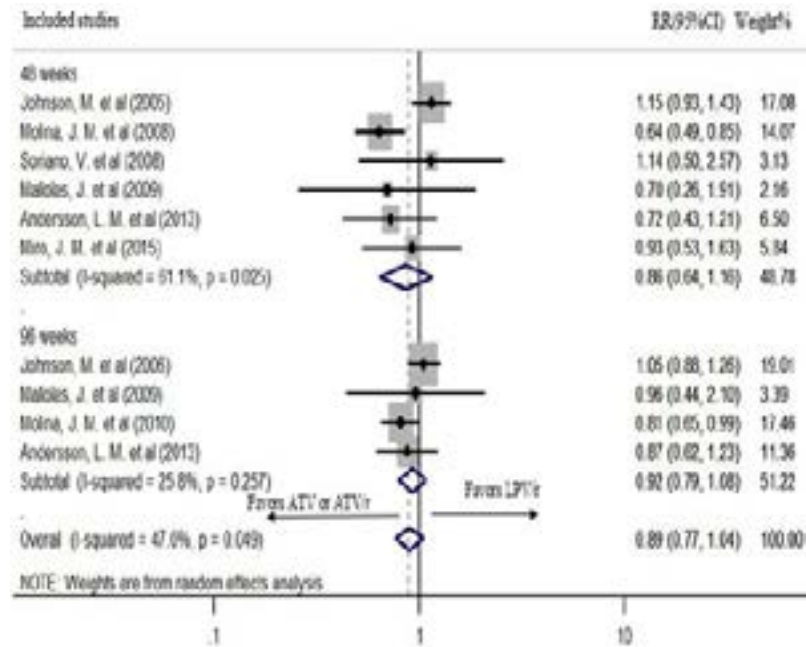


Figure 4. The risk of failure to suppress virus level < 50 copies/ml in the random effects model

Four studies reported viral suppression after 96 weeks of treatment. There was a statistically significant heterogeneity among the studies (P=0.257, I2=25.8%); hence, a random effects model was used for the analysis. Although a tendency of lower risk of failure was seen, ATV/r showed no statistically significant virus suppression

compared to LPV/r after 96 weeks of treatment (pooled RR: 0.92; CI: 0.79, 1.08; P=0.314) (Figure 4). The study by Andersson, L. M. et al.²¹ recorded the viral suppression for 144 weeks. Therefore, the sensitivity of the result was checked by excluding it from the analysis. The outcome was robust during sensitivity analysis (pooled RR: 0.93; CI: 0.74, 1.16; P=0.519) (Figure 5).

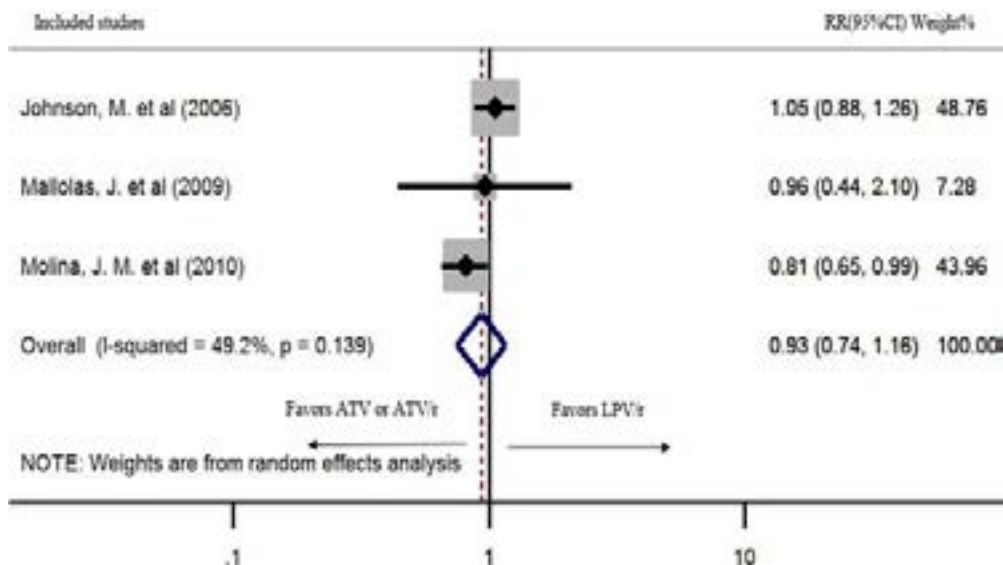


Figure 5. Sensitivity analysis for failure of viral suppression < 50 copies/ml after 96 weeks

The study by Edén, et al. reported viral suppression for one month only. Hence, it was not included in the meta-analysis. However, four (6%) of 64 patients on ATV/r regimen and eight (12%) of 67 patients on LPV/r regimen had a viral load < 50 copies/ml at day 28²².

Grade 2-4 treatment-related adverse events

Five studies reported grade 2-4 treatment-related adverse

events. Four of the studies were included in meta-analyses. The two regimens did not demonstrate a statistically significant difference in grade 2-4 adverse events in a random effects model (pooled RR: 0.91; CI: 0.76, 1.09; P=0.322). The heterogeneity of the studies was significant (P=0.477; I²=0%) (Figure 6). The study by Anderson, L. M. et al. reported 12% and 20% serious adverse events in LPV/r and ATV/r based regimens after 144 weeks of treatment, respectively²¹.

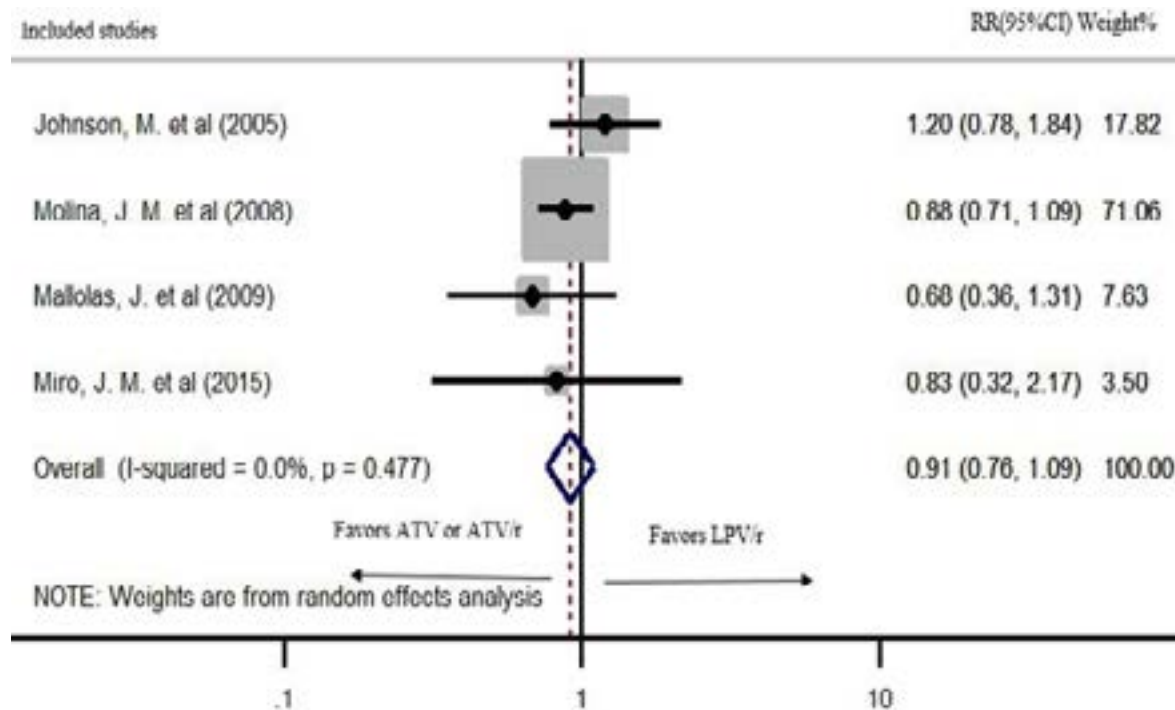


Figure 6. Grade 2-4 treatment-related adverse drug events at 48 weeks of treatment

Grade 3-4 bilirubin elevation

The prevalence of grade 3-4 bilirubin elevations was significant in ATV/r-based regimens while it was nonexistent or infrequent in LPV/r-based regimens in all studies that reported hyperbilirubinemia^{17-21,23,24}. The overall risk of hyperbilirubinemia is very high for ATV or ATV/r based regimens than LPV/r based cART in random ef-

fects model (pooled RR: 45.03; CI: 16.03, 126.47; P< 0.0001). The heterogeneity of the studies was significant (P=0.023, I²=61.6%). The RR of hyperbilirubinemia is very high for ATV or ATV/r based regimens than LPV/r based cART both after 48 weeks (pooled RR: 39.85; CI: 5.65, 281.14; I²=79%) and 96 weeks (pooled RR: 62.55; CI: 24.81, 157.68; I²=0%) of treatment in random effects model (Figure 7).

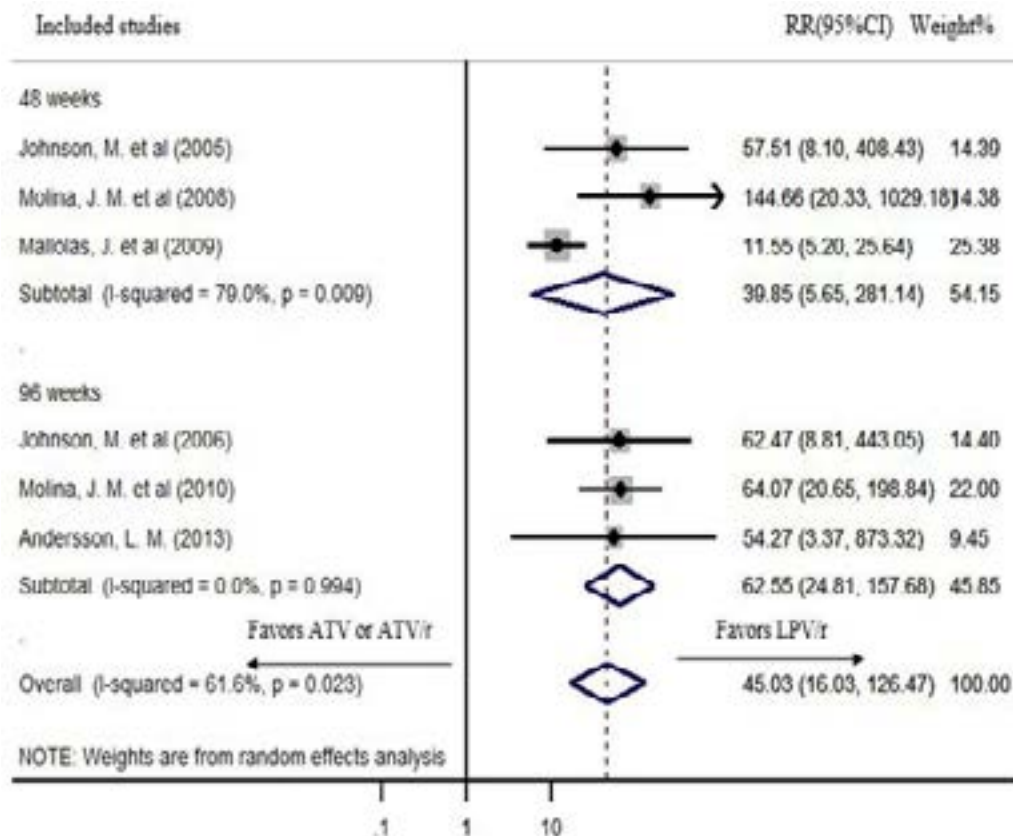


Figure 7. Hyperbilirubinemia in the random effects model

Lipid profile

In all of the eight studies that reported the lipid profile change, the ATV/r based regimen had a significantly lower level of total cholesterol and triglycerides than LPV/r based regimens. The studies by Johnson, et al., Molina, et al., Mallolas, et al., Soriano, et al. and Miro, et al. revealed a significant rise in total cholesterol and fasting triglycerides level in LPV/r arm than ATV or ATV/r arm after 48 weeks of treatment ($P < 0.005$, $P < 0.0001$, $P < 0.001$, $P < 0.001$ and $P = 0.03$ respectively)^{19,20,23-25}. Johnson, et al., and Molina, et al. reported a significant mean percentage change in total cholesterol and triglycerides after 96 weeks of treatment in LPV/r than ATV/r based regimens ($P < 0.0001$)^{17,18}. Andersson and colleagues had found a significant increase in total cholesterol ($P = 0.0064$) and triglycerides level ($P = 0.001$) after 144 weeks of treatment in LPV/r arm than ATV/r arm (21). Furthermore, the High-Density Lipoprotein Cholesterol (HDL-C) and Low-Density Lipoprotein Cholesterol (LDL-C) showed a significant difference between the two regimens^{19-21,23}.

Discussion

The current study identified and measured the differenc-

es and similarities in the effectiveness and safety of the two WHO recommended protease inhibitors, ATV/r and LPV/r, based on head-to-head comparison clinical trials. The result of this study showed that ATV/r based regimen has 13% lower overall risk of failure to suppress the virus to < 50 copies/ml. The viral suppression after 48 weeks and 96 weeks of treatments are not statistically significant. However, the result revealed a tendency to be higher for ATV or ATV/r based regimens than LPV/r. Although the funnel plot and Egger's test did not show a significant publication bias and small study effects, the observed significant heterogeneity particularly to the 48 weeks' and 96 weeks' viral suppression warrants due consideration in the interpretation of this findings. Similarly, a trial which compared ATV or ATV/r with other PIs had demonstrated the superiority of ATV or ATV/r based cART to suppress the virus below 50 copies/ml²⁶. A multinational prospective observational study in high-income countries also reported a lower risk of hazard ratio for death, AIDS-defining illness and virological failure to ATV/r than LPV/r²⁷. Moreover, an economic evaluation from Sweden found the dominance of ATV/r based regimens over LPV/r²⁸. Nevertheless, a

number of studies reported no statistical significant viral suppression difference between the two boosted PIs²⁹⁻³¹. A study by Cohen C. et al.³² also showed the superiority of LPV/r over ATV. Generally, these two PIs are the preferred among the group. A study identified the use of PIs other than atazanavir or lopinavir as a predictor of second-line treatment failure within a short period of time³³. In this systematic review, the safety of the two boosted PIs showed no significant difference based on grade 2-4 treatment-related adverse events. However, hyperbilirubinemia and lipid abnormalities differ significantly. The risk hyperbilirubinemia is very high in ATV based regimens while the fasting total cholesterol and triglyceride elevations are significantly higher in LPV/r based cART. Similarly, randomized trials conducted to show the efficacy of atazanavir over other PIs also revealed a higher risk of hyperbilirubinemia, a lower risk of lipid abnormality and comparable treatment-related adverse events with ATV/r use^{26,30}. Moreover, all the reviewed studies homogeneously indicated the differences in the serum bilirubin and lipid abnormalities.

HIV protease has a crucial role for viral maturation through the cleavage of gag and gag-pol polyproteins and induction of its own release¹². Protease inhibitors block this maturation step. The multigene barrier for resistance and proven efficacy makes PIs a reliable group of antiretroviral³⁴. In the combination therapy, PIs demonstrated a lower risk of resistance than non-nucleoside reverse inhibitors and reduce the risk of resistance for the backbone nucleoside reverse inhibitors³⁵. However, the associated gastrointestinal and metabolic adverse effects, and lipohypertrophy decrease patient adherence with prolonged use. Although several guidelines recommend the use of PI-based cART as a reasonable initial therapy, the WHO reserves PIs for second-line treatment options^{4,35,36}

The main strengths of this review are precise research question on the clinical benefit of ATV/r and LPV/r based cART, the inclusion of head-to-head trials only, and the use of the safety profile as a secondary outcome measure. Furthermore, we used a comprehensive search in comparison with previously done reviews^{13,14} and Cochrane risk of bias assessment.

This review has several limitations. First, only nine articles from seven studies are included. Second, the follow-up period differs from 28-days to 144 weeks. Third, the study participants included in the original articles dif-

fer. Fourth, the backbones used in cART regimen was not considered. Fifth, the study by Soriano, et al.²⁵ used both ATV and ATV/r. Sixth, the overall risk of bias was high. Finally, the trials by Soriano, et al.²⁵ and Mallolas, et al.²³ are based on treatment switch from LPV/r to ATV/r. Finally, the publication bias and the small studies effect analysis was not reliable due to the small number of studies included in the review. We recommend large double-blinded clinical trials with a head-to-head comparison of ATV/r and LPV/r to be conducted on both treatment naïve and first-line treatment failure adult HIV-1 patients.

Conclusion

Boosted atazanavir has a better viral suppression at lower risk of lipid abnormality than boosted lopinavir. Based on these results, boosted atazanavir should be considered first whenever there is a need to include PIs in the regimen. The risk and development of hyperbilirubinemia from ATV based regimens should be taken to consideration both at the time of prescribing and patient follow-up.

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Authors' contributions

BMT and SN conceptualize the study, conducted the article review, do the analysis, interpreted the results, and drafted and finalized the manuscript. FDA and MM participated in the study designed, conducted the article review and revised the manuscript. BMT, SN, AK and MM revised the manuscript and approved the final manuscript.

Conflicts of interest

The authors declared that they have no conflict of interest.

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