Lipid profiles in HIV-infected adults receiving atazanavir and atazanavir/ritonavir: systematic review and meta-analysis of randomized controlled trials

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Objectives: To compare lipid profiles in HIV-infected adults receiving atazanavir-based regimens.

Methods: We conducted a systematic review of randomized controlled trials (RCTs) comparing atazanavir or atazanavir/ritonavir with a comparator and evaluated lipids at 48 weeks. We searched MEDLINE, EMBASE, CENTRAL, LILACS, Current Controlled Trials, National Institutes of Health Clinical Trials Registry, trials at AIDSinfo and HIV conference proceedings to May 2009. Standardized mean difference (SMD) between study arms in change from baseline to week 48 in lipid parameters was determined weighted by study size and 95% confidence intervals (CI) were calculated.

Results: Nine eligible RCTs were identified (n=3346). SMDs (mmol/L) in four RCTs comparing atazanavir/ritonavir with a ritonavir-boosted protease inhibitor were: total cholesterol, 0.62 (95% CI 0.72, 0.51); low-density lipoprotein (LDL) cholesterol, 0.31 (95% CI 0.44, 0.17); high-density lipoprotein (HDL) cholesterol, 0.16 (95% CI 0.27, 0.06); non-HDL cholesterol, 0.58 (95% CI 0.69, 0.48); and triglycerides, 0.87 (95% CI 0.99, 0.76). Atazanavir compared with non-atazanavir (three RCTs) found lower total, LDL and non-HDL cholesterol, and triglycerides [SMD 0.87 mmol/L (95% CI 0.99, 0.76); 0.56 mmol/L (95% CI 0.69, 0.45); 0.88 mmol/L (95% CI 0.99, 0.76); and 0.56 mmol/L (95% CI 0.75, 0.36), respectively], but HDL cholesterol did not differ [−0.16 mmol/L (95% CI −0.49, 0.16)]. In the atazanavir/ritonavir versus atazanavir comparison (two RCTs), total [SMD 0.44 mmol/L (95% CI 0.23, 0.65)] and non-HDL cholesterol [SMD 0.44 mmol/L (95% CI 0.23, 0.65)] were higher, but HDL cholesterol, LDL cholesterol and triglycerides were not different.

Conclusions: At 48 weeks, plasma lipid concentrations were lower with atazanavir/ritonavir than with other ritonavir-boosted protease inhibitor regimens. Total and non-HDL cholesterol were higher with atazanavir/ritonavir than atazanavir alone.

Keywords: antiretroviral therapy, HDL, LDL

Introduction

Dyslipidaemia, characterized by raised triglyceride and low-density lipoprotein (LDL) cholesterol and reduced high-density lipoprotein (HDL) cholesterol levels, is common in HIV-infected individuals, and has been associated with HIV infection itself, antiretroviral therapy (ART) and antiretroviral-induced metabolic disturbances, such as impaired glucose tolerance with insulin resistance, visceral adiposity and peripheral lipodystrophy.1-6 These abnormalities are well-established markers of cardiovascular risk in the general population,7,8 raising concern about the impact of HIV infection and its treatment on the risk of future cardiovascular disease (CVD). Moreover, the similarities between lipid and metabolic alterations and metabolic syndrome, a multidimensional risk factor for atherosclerotic CVD,9,10 are problematic given the substantial progression to metabolic syndrome observed following ART initiation.11 Studies have suggested an increased risk of CVD associated with ART exposure over and above that conveyed by traditional cardiovascular risk factors.12,13 More recent analysis that was stratified by antiretroviral drug class found an increased risk of myocardial infarction due principally to on-therapy lipid changes.14 Both atazanavir and ritonavir-boosted atazanavir regimens have proven virological efficacy in antiretroviral-naïve15-18 and...
Materials and methods

Selection criteria and search strategy

We selected randomized controlled trials that included antiretroviral regimens containing either atazanavir or atazanavir/ritonavir compared with a comparator antiretroviral drug over ≥48 weeks that satisfied all of the following pre-specified eligibility criteria: (i) assessment of one of the following combination regimen comparisons—atazanavir or atazanavir/ritonavir plus backbone nucleoside analogues versus a regimen containing a comparator antiretroviral agent plus backbone nucleoside analogues (possible comparators included a non-nucleoside reverse transcriptase inhibitor, a boosted or unboosted protease inhibitor, or an integrase inhibitor); (ii) assessment of HIV-infected participants aged ≥16 years; and (iii) employed atazanavir at dosages recommended in current treatment guidelines (400 mg of atazanavir once daily; 300/100 mg of atazanavir/ritonavir once daily).24 We excluded studies if atazanavir and atazanavir/ritonavir data were not presented separately, the number of nucleoside analogues differed between arms, nucleoside analogue changes were permitted (except for treatment-limiting toxicity), or the comparator arm contained more than one protease inhibitor (apart from ritonavir at boosting dosages) or a protease inhibitor plus a non-nucleoside reverse transcriptase inhibitor. We excluded studies where the analysis included <90% of randomized participants or where the risk of bias was assessed as high.

Trials were identified by searching electronic databases and clinical trial registries, reviewing reference lists of published articles and conference abstracts, and drug company consultation. We did not limit our search by language or publication status. The following electronic databases were searched up to May 2009: MEDLINE (Ovid); EMBASE (Ovid); Cochrane Central Register of Controlled Trials (CENTRAL); and LILACS. Clinical trial registry and regulatory agency site searches included the National Institutes of Health Clinical Trials Registry, Current Controlled Trials in the metaRegister of controlled clinical trials, and clinical trials at AIDSInfo. The proceedings of the Conference on Retroviruses and Opportunistic Infections (CROI), and International AIDS Society (IAS) meetings from 2006 to May 2009 were searched for unpublished trials. Reference lists of published trials and clinical trials cited in treatment guidelines24 were handsearched for additional studies. Search terms included HIV infection, HIV infections, atazanavir, BMS-232632, anti-HIV agents and antiretroviral therapy, highly active.

Study selection and quality assessment

The title and abstract of records identified by search processes were screened initially by one reviewer (D. C.) and the full text of potentially relevant published studies extracted. Abstracts and/or presentations of potential unpublished studies were obtained from conference web sites, and investigators and/or sponsors were approached for missing information. Two additional reviewers (M. B. and K. P.) independently and in an unblinded manner assessed the full-text articles and conference presentations using the pre-determined eligibility criteria. To avoid double counting, substudies, roll-over studies or additional analyses of a primary study were excluded. Differences in extracted data were resolved after contact with the investigator or sponsor of the original study, or, where this was unsuccessful or not beneficial, by third-party adjudication.

The methodological quality of eligible studies was assessed at the study and outcome levels by the same two reviewers. Cochrane-based criteria were used and data on the following criteria collected: method of sequence generation; allocation concealment; blinding; incomplete data outcome; free of selective reporting; and adherence to intention-to-treat principle.25 The possibility of selective reporting bias was examined by comparing reported outcomes with those listed in the study protocol or, where this was not available, in the Methods section of the presentation/publication. Disagreements were resolved by third-party adjudication.

Data extraction

For each study, one reviewer (D. C.) abstracted study design characteristics plus group data on interventions, baseline participant characteristics and outcome measures into a database that contained pre-defined data fields. Study authors and/or sponsors were contacted, where necessary, for missing/unpublished data items. Data checking was performed according to standard operating procedures for clinical trial data management and consensus data were used in analyses.

Data analysis

Meta-analysis was performed according to a pre-specified analysis plan. Data from included studies were combined using random-effects methods and analyses were conducted on the basis of intention-to-treat on available data. The primary analysis utilized week 48 data and there were no imputations for missing data. Data were described using means (for continuous variables) and proportions (for categorical variables), with study group as the unit for analysis weighted by the number of participants per group. Where necessary, laboratory parameters were converted to SI units (mmol/L) and standard deviations calculated from standard errors.

The primary outcome for the meta-analysis was the standardized mean difference (SMD) [95% confidence interval (CI)] between study groups in change from baseline to week 48 in plasma levels of lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol, non-HDL cholesterol and triglycerides). Randomized treatment groups were compared as follows: atazanavir versus non-atazanavir; atazanavir versus atazanavir/ritonavir; and atazanavir/ritonavir versus protease inhibitor/ritonavir. Two-sided P values of <0.05 were considered statistically significant; no adjustments were made for multiple comparisons. A χ² test of heterogeneity and the I² measure of inconsistency were used to assess heterogeneity in the results of included studies.25 A funnel plot (1/standard error plotted against SMDs) was examined visually to estimate potential asymmetry due to selection bias or methodological flaws in smaller trials.26

Trial size-weighted random-effects metaregression analyses investigated baseline predictors of the difference between arms in change from baseline to week 48 in levels of total cholesterol, a well-established predictor of cardiovascular risk.7,27 Analyses were performed for comparisons of regimens comprising atazanavir versus non-atazanavir; atazanavir versus atazanavir/ritonavir; and atazanavir/ritonavir versus protease inhibitor/ritonavir. The following baseline variables and study characteristics were included: age; sex; prior AIDS-defining illness; plasma HIV-1 RNA; CD4 cell count; baseline lipid concentrations (total, LDL-, HDL- and non-HDL cholesterol, and triglycerides); publication status; and prior
antiretroviral exposure. All analyses were performed using STATA Release 10 (STATA Corporation, College Station, TX, USA).

Results

Of the 923 citations identified, 900 were excluded after screening of the title/abstract, as they failed to satisfy our eligibility criteria (Figure 1). Twenty-three full-text papers or presentations were retrieved for detailed review and of these 14 failed to satisfy the eligibility criteria. Seven published15–18,20,28,29 and two unpublished randomized trials21,30 that were either published or presented in English were selected for inclusion. Table 1 shows the characteristics of the included studies. Two studies contained a third ineligible treatment group (600 mg of atazanavir daily; atazanavir/saquinavir);15,28 hence, these data were excluded and analyses performed on the remaining 3346 participants. Of the nine studies, four compared regimens containing atazanavir/ritonavir with a ritonavir-boosted protease inhibitor,18,21,28,29 two compared atazanavir with atazanavir/ritonavir17,30 and three evaluated atazanavir with a non-atazanavir comparator (efavirenz, nevirapine and lapinavir/ritonavir).15,16,20 Nucleoside analogue backbones were varied. Four studies (n = 2165) were conducted in antiretroviral-naive individuals.15–18 Lipid outcomes were a primary endpoint in only one study.20 Seven studies had a primary efficacy endpoint with lipids as a secondary endpoint,15–18,20,21,28,30 and one had a body composition primary endpoint with secondary lipid endpoints.21 Lipid measurements were fasting in five studies,16,18,21,29,30 and LDL cholesterol and triglycerides were fasting in the remainder.15,17,20,28

We contacted study sponsors and gained protocol access for methodological and outcome information for eight studies.15–18,30,21,29,30 We requested and obtained additional baseline data from sponsors/investigators for six studies.15–17,21,29,30 Further outcome data were requested and obtained for all nine studies. Baseline characteristics of participants are shown in Table 2.

Assessment of risk of bias

The results of individual study quality assessments are detailed in Table 3. Generation of random sequence allocation and concealment of the allocation sequence were considered adequate for all but one study where these methods were not described adequately.29 Eight studies described in detail the numbers of and reasons for treatment discontinuation, withdrawal, and loss to follow-up.15–18,20,21,29,30 Methods of statistical analysis were well described in all studies and all but one18 reported the use of intention-to-treat analysis for participants who commenced treatment. All but one study utilized a last-value-carried-forward approach for participants lost to follow-up or discontinuing therapy for lipid analysis over time.28 Overall, the risk of bias in the nine studies was assessed as adequate.

Meta-analysis

Four studies involving 1592 participants (atazanavir/ritonavir, n = 823; ritonavir-boosted protease inhibitor, n = 769) were included in the atazanavir/ritonavir versus protease inhibitor/ritonavir regimen comparison.18,21,28,29 At 48 weeks, total, LDL, HDL and non-HDL cholesterol, and triglycerides were significantly lower in atazanavir/ritonavir regimens than in ritonavir-boosted protease inhibitor regimens (SMD −0.62 mmol/L (95% CI −0.72, −0.51); −0.31 mmol/L (95% CI −0.44, −0.17); −0.16 mmol/L (95% CI −0.27, −0.06); −0.58 mmol/L (95% CI −0.69, −0.48); and −0.46 mmol/L (95% CI −0.58, −0.34), respectively) (Figure 2a). No significant heterogeneity was identified for any lipid parameter comparison.
<table>
<thead>
<tr>
<th>Trial</th>
<th>Country of recruitment</th>
<th>Antiretroviral status</th>
<th>Duration (weeks)</th>
<th>Randomized (n)</th>
<th>Commenced therapy (n)</th>
<th>Interventions</th>
<th>Regimen backbone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murphy et al., 2003</td>
<td>Multinational</td>
<td>Treatment-naive</td>
<td>48</td>
<td>467</td>
<td>464</td>
<td>(i) ATV 400 mg daily; (ii) NFV 1250 mg twice daily; (iii) ATV 600 mg daily</td>
<td>3TC + d4T</td>
</tr>
<tr>
<td>Squires et al., 2004</td>
<td>Multinational</td>
<td>Treatment-naive</td>
<td>48</td>
<td>810</td>
<td>805</td>
<td>(i) ATV 400 mg daily; (ii) EFV 600 mg daily</td>
<td>ZDV + 3TC</td>
</tr>
<tr>
<td>Cohen et al., 2005</td>
<td>Multinational</td>
<td>Treatment-experienced</td>
<td>48</td>
<td>300</td>
<td>290</td>
<td>(i) ATV 400 mg daily; (ii) LPV/r 400/100 mg twice daily</td>
<td>2 NRTIs</td>
</tr>
<tr>
<td>Johnson et al., 2005</td>
<td>Multinational</td>
<td>Treatment-experienced</td>
<td>96</td>
<td>358</td>
<td>347</td>
<td>(i) ATV/r 300/100 mg daily; (ii) LPV/r 400/100 mg twice daily; (iii) ATV/SQV 400/1200 mg daily</td>
<td>TDF + 1 NRTI</td>
</tr>
<tr>
<td>Malan et al., 2008</td>
<td>Multinational</td>
<td>Treatment-naive</td>
<td>48</td>
<td>200</td>
<td>199</td>
<td>(i) ATV 400 mg daily; (ii) ATV/r 300/100 mg daily</td>
<td>3TC + XR d4T</td>
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<td>Treatment-naive</td>
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<td>878</td>
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<td>TDF + FTC (FDC)</td>
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<td>Moyle et al., 2008</td>
<td>Multinational</td>
<td>Treatment-experienced</td>
<td>96</td>
<td>201</td>
<td>200</td>
<td>(i) ATV/r 300/100 mg daily; (ii) continue pre-study PI/r</td>
<td>Pre-study NRTIs</td>
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<tr>
<td>Delfraissy et al., 2008</td>
<td>Multinational</td>
<td>Treatment-experienced</td>
<td>48</td>
<td>172</td>
<td>172</td>
<td>(i) ATV 400 mg daily; (ii) ATV/r 300/100 mg daily</td>
<td>2 NRTIs</td>
</tr>
<tr>
<td>Mallolas et al., 2009</td>
<td>Spain (multicentre)</td>
<td>Treatment-experienced</td>
<td>96</td>
<td>265</td>
<td>248</td>
<td>(i) LPV/r 400/100 mg twice daily; (ii) ATV/r 300/100 mg daily</td>
<td>2 NRTIs</td>
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</table>

3TC, lamivudine; ATV, atazanavir; ATV/r, atazanavir/ritonavir; d4T, stavudine; EFV, efavirenz; FDC, fixed dose combination; FTC, emtricitabine; LPV/r, lopinavir/ritonavir; NFV, nelfinavir; NRTI, nucleoside analogue reverse transcriptase inhibitor; TDF, tenofovir; XR, extended release; ZDV, zidovudine; SQV, saquinavir; PI/r, protease inhibitor/ritonavir.
### Table 2. Baseline participant characteristics

<table>
<thead>
<tr>
<th>Trial</th>
<th>Age, (years)</th>
<th>Male (%)</th>
<th>Prior ADI (%)</th>
<th>HIV RNA (log copies/mL plasma)</th>
<th>CD4 count (cells/mm³)</th>
<th>Total cholesterol (mmol/L)</th>
<th>LDL cholesterol (mmol/L)</th>
<th>HDL cholesterol (mmol/L)</th>
<th>Non-HDL cholesterol (mmol/L)</th>
<th>Triglycerides (mmol/L)</th>
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<td>34.6</td>
<td>62</td>
<td>10</td>
<td>4.74</td>
<td>290</td>
<td>4.32</td>
<td>2.54</td>
<td>1.05</td>
<td>3.27</td>
<td>1.37</td>
</tr>
<tr>
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<td>33.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>65</td>
<td>5</td>
<td>4.89&lt;sup&gt;a&lt;/sup&gt;</td>
<td>283&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.23</td>
<td>2.54</td>
<td>1.00</td>
<td>3.23</td>
<td>1.51</td>
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<td>37.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>80</td>
<td>25</td>
<td>4.22&lt;sup&gt;a&lt;/sup&gt;</td>
<td>272&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.61</td>
<td>2.71</td>
<td>0.99</td>
<td>3.64</td>
<td>2.20</td>
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<td>40.5</td>
<td>79</td>
<td>5</td>
<td>4.46&lt;sup&gt;a&lt;/sup&gt;</td>
<td>300&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.78</td>
<td>2.74</td>
<td>1.00</td>
<td>3.74</td>
<td>2.32</td>
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<td>34.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>71</td>
<td>5</td>
<td>4.96&lt;sup&gt;a&lt;/sup&gt;</td>
<td>197&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.16</td>
<td>2.50</td>
<td>0.98</td>
<td>3.18</td>
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<td>35.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>69</td>
<td>4.5</td>
<td>4.98&lt;sup&gt;a&lt;/sup&gt;</td>
<td>205&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.81</td>
<td>2.36</td>
<td>0.92</td>
<td>2.85</td>
<td>1.24</td>
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<td>75</td>
<td>12</td>
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<td>459&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>1.23</td>
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<td>35.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>73</td>
<td>1</td>
<td>1.69&lt;sup&gt;a&lt;/sup&gt;</td>
<td>395&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.92</td>
<td>2.82</td>
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<td>79</td>
<td>49</td>
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<td>491&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>4.01&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.08&lt;sup&gt;a&lt;/sup&gt;</td>
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</tbody>
</table>

ADI, AIDS-defining illness; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Values are weighted mean/percentage (%) across study groups, unless specified.

<sup>a</sup>Weighted median across study groups.

<sup>b</sup>Percentage <400 copies/mL.

### Table 3. Assessment of study quality

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding</th>
<th>Incomplete outcome data addressed</th>
<th>Free of selective reporting</th>
<th>Free of other bias</th>
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<tbody>
<tr>
<td>Murphy et al., 2003&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes: ATV dose</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Squires et al., 2004&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes: ATV &amp; EFV</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cohen et al., 2005&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Johnson et al., 2005&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Malan et al., 2008&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<td>Molina et al., 2008&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Mayle et al., 2008&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes</td>
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<td>Delfraissy et al., 2008&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
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<td>Unclear (not stated)</td>
<td>Unclear (not stated)</td>
<td>No</td>
<td>No</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
</tbody>
</table>

ATV, atazanavir; EFV, efavirenz.
The atazanavir versus non-atazanavir regimen comparison comprised 1382 participants (atazanavir, \(n=736\); non-atazanavir, \(n=646\))\textsuperscript{15,16,20}. At 48 weeks, total, LDL and non-HDL cholesterol, and triglyceride levels were significantly lower in regimens containing unboosted atazanavir than in comparator regimens [SMD -0.87 mmol/L (95% CI -0.99, -0.76); -0.56 mmol/L (95% CI -0.67, -0.45); -0.88 mmol/L (95% CI -0.99, -0.76); and -0.56 mmol/L (95% CI -0.75, -0.36), respectively], but HDL cholesterol levels did not differ [-0.16 mmol/L (95% CI -0.49, 0.16)] (Figure 2b). Within this comparison, significant heterogeneity was identified for HDL cholesterol (\(I^2=87\%; \chi^2=14.91, \text{df}=2; P=0.001\)).

Two studies (\(n=372\)) compared unboosted with boosted atazanavir (atazanavir, \(n=192\); atazanavir/ritonavir, \(n=180\))\textsuperscript{17,30} (Figure 2c). Total cholesterol [SMD 0.44 mmol/L (95% CI 0.23, 0.65)], non-HDL cholesterol [SMD 0.44 mmol/L (95% CI 0.23, 0.65)], and triglyceride [SMD 0.56 mmol/L (95% CI 0.24, 0.87)] levels were significantly lower in regimens containing unboosted atazanavir than in comparator regimens [SMD -0.56 mmol/L (95% CI -0.75, -0.36); and -0.56 mmol/L (95% CI -0.75, -0.36), respectively].

### Figure 2

Standardized mean difference (95% CI) between study arms in change from baseline to week 48 in lipid parameters for (a) atazanavir/ritonavir versus protease inhibitor/ritonavir, (b) atazanavir versus non-atazanavir and (c) atazanavir versus atazanavir/ritonavir. SMD, standardized mean difference; CI, confidence interval; df, degrees of freedom.
and triglycerides [SMD 0.56 mmol/L (95% CI 0.35, 0.78)] were significantly higher in atazanavir/ritonavir arms at week 48, but HDL and LDL cholesterol levels were not different [SMD 0.05 mmol/L (95% CI -0.15, 0.26) and SMD 0.12 mmol/L (95% CI -0.09, 0.33), respectively], with no evidence of heterogeneity ($I^2 = 0\%$).

Metaregression analyses to investigate predictors of the difference between arms in change in total cholesterol were performed separately for the atazanavir/ritonavir versus ritonavir-boosted protease inhibitor comparison ($n=4$) and atazanavir versus non-atazanavir ($n=3$). Owing to the small study number, trials that compared atazanavir with atazanavir/ritonavir ($n=2$) were excluded. No baseline participant characteristic or variable of interest was associated with SMD between arms in change from baseline to week 48 in total cholesterol levels for either comparison (data not shown).

### Risk of bias across studies

Access to eight study protocols enabled investigation of selective reporting of outcomes (Table 3). For the remaining study, reported outcomes were compared with those detailed in the Methods section of the publication. Risk of bias assessment across studies was difficult, owing to the small study number. A funnel plot of difference in total cholesterol mean change (x-axis) and 1/standard error (y-axis) for atazanavir/ritonavir versus ritonavir-boosted protease inhibitor studies was symmetrical when examined visually (data not shown).
Discussion

This systematic review of the literature identified nine randomized controlled trials that compared antiretroviral regimens containing atazanavir, atazanavir/ritonavir or a non-atazanavir comparator in HIV-infected adults. Subsequent meta-analysis identified a number of significant between-group differences in plasma lipid profiles. At 48 weeks, all lipid levels were lower with atazanavir/ritonavir compared with other boosted protease inhibitors. Ritonavir co-administration resulted in higher total cholesterol, non-HDL cholesterol and triglyceride concentrations compared with unboosted atazanavir. Lipids, apart from HDL cholesterol, were higher in non-atazanavir comparator regimens than in those that contained atazanavir. No predictor of a difference between arms in change from baseline to week 48 in total cholesterol levels was identified.

Treatment guidelines recommend regimens that contain either a non-nucleoside reverse transcriptase inhibitor or a boosted protease inhibitor as initial therapy.\textsuperscript{24,31} In contrast to non-nucleoside reverse transcriptase inhibitors, boosted protease inhibitors provide a high genetic barrier to resistance, but have been associated with metabolic abnormalities, including dyslipidaemia.\textsuperscript{4,5} Since dyslipidaemia accounts for \(\approx 50\%\) of the protease inhibitor risk for myocardial infarction,\textsuperscript{14} our finding that lipids were lower at 48 weeks with boosted atazanavir than with other boosted protease inhibitors is of clinical importance and further supports assigning boosted atazanavir to preferred protease inhibitor status.\textsuperscript{24}
In the atazanavir versus non-atazanavir comparison, lipids, apart from HDL cholesterol, were higher in non-atazanavir regimens at 48 weeks. Non-atazanavir comparators included the protease inhibitors nelfinavir and lopinavir/ritonavir, and efavirenz, a non-nucleoside reverse transcriptase inhibitor. Within this comparison we detected considerable heterogeneity for HDL cholesterol change ($P=0.001; I^2=87\%$). We believe this heterogeneity is of clinical origin, driven principally by the comparator efavirenz, and is perhaps not surprising given that clinical trial data have demonstrated greater increases in HDL cholesterol with non-nucleoside reverse transcriptase inhibitor-based regimens compared with those that are protease inhibitor-based. This beneficial class effect has been demonstrated in longitudinal and cross-sectional cohort data.

We found that total cholesterol, non-HDL cholesterol and triglyceride levels were higher with boosted than with unboosted atazanavir. Our findings highlight those of previous studies in both patients and healthy volunteers, where the pharmacokinetic benefits of low-dose ritonavir were counterbalanced by an increased risk of dyslipidaemia. Although this comparison comprised only two studies, pooled estimates across all lipid parameters were consistent, as demonstrated by the lack of heterogeneity, and so we believe these data are of clinical relevance. Although boosted atazanavir is used more frequently, unboosted atazanavir offers an acceptable protease inhibitor-based regimen component for treatment-naive individuals with pre-existing risk factors where ritonavir-associated hyperlipidaemia would be undesirable.

Nucleoside reverse transcriptase inhibitors have been associated with dyslipidaemia. Therefore, to ensure the nucleoside backbone did not confound lipid values, we excluded any study where nucleosides were not common across study arms or where on-study nucleoside changes, other than for treatment-limiting toxicity, were permitted. As a result, our pooled estimates more closely reflect actual differences in lipid levels between atazanavir, atazanavir/ritonavir and comparator. With metaregression analyses to determine possible predictors of total cholesterol change over 48 weeks. No baseline demographic or HIV-related participant characteristic, or publication status predicted a difference between arms in change from baseline for total cholesterol for either the boosted atazanavir versus boosted protease inhibitor or atazanavir versus non-atazanavir comparison. This lack of effect may represent the small number of studies available for analysis.

The strengths of this study include its broad scope, which included treatment-naive and -experienced HIV-infected adults recruited in multiple geographical locations plus the variety of antiretroviral regimens; thereby maximizing both the power of the analysis and the generalizability of our findings. Our literature search was extensive in order to retrieve all relevant eligible randomized trials of atazanavir, both published and unpublished. Eligibility criteria for the systematic review were strict, and most studies utilized an intention-to-treat analysis so as to minimize bias and ensure high-quality evidence. As a result, we identified only nine eligible studies. Access to most trial protocols enabled full assessment of methodological quality, including selective reporting of outcomes, a common source of bias in randomized trials.

Our analysis has limitations. The small number of studies that could be combined statistically may mean meta-analysis comparisons, especially atazanavir versus atazanavir/ritonavir, may be underpowered. However, sample sizes for the other comparisons were substantial and provided adequate power to detect important clinical differences given the lack of heterogeneity and inconsistency, and the relatively narrow confidence intervals of point estimates. We were unable to perform planned sensitivity analysis due to the small study number. Included studies were not blinded by author or journal. We believed that with reviewers’ knowledge of the literature, complete secrecy would have been extremely difficult to achieve; therefore, we relied on Cochrane-based criteria to assess methodological quality. We also used aggregate rather than individual patient data, such that groups not individuals were the unit of study. Four studies collected only fasting LDL cholesterol and triglycerides, but as current guidelines advise that total, HDL and non-HDL cholesterol can be non-fasting measurements, we do not see this as a study limitation. We were unable to include total cholesterol/HDL cholesterol ratios, as these data were absent in the original studies. We included only lipid outcomes of the various interventions. Had our review assessed primary outcome/s of the original studies, then morbidity, mortality and adverse event/toxicity outcomes would have been important elements in the interpretation of results, but as we focused on secondary endpoints their inclusion was deemed unnecessary.

We found that in adults receiving unboosted atazanavir the addition of low-dose ritonavir increased total cholesterol, non-HDL cholesterol and triglyceride levels, but lipid increases were less than those of other boosted protease inhibitors at 48 weeks. As HIV-infected individuals survive to older ages, strategies to manage antiretroviral-associated dyslipidaemia and metabolic disturbances are vital to reduce the higher prevalence of age-related cardiovascular risk compared with the general population. Moreover, cross-sectional data suggesting the risk of cognitive impairment in HIV-infected men receiving ART is associated more with cardiovascular and metabolic co-morbidities than with HIV positivity underscore the importance of optimal risk management in order to minimize the potential for subsequent cognitive decline. Inter- and intradrug class differences in lipid profiles have been well described and are essential considerations in drug selection, given that responses to hypolipidaemic agents are less favourable and adverse event rates higher in HIV-infected individuals than in the general population.

This review highlights the need for new, non-toxic, lipid-friendly agents able to inhibit both cytochrome P450 isoenzymes in the gastrointestinal tract and liver as well as drug transporters, as such compounds could potentially replace low-dose ritonavir as a pharmacokinetic enhancer. However, considerable laboratory and clinical research would be required prior to their availability. In the meantime, a more comprehensive approach to managing cardiovascular and metabolic risks, with a focus on modifiable lifestyle factors, particularly smoking cessation, and the judicious selection of lipid-friendly antiretroviral agents is of utmost importance.

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