# Low-dose versus standard-dose ritonavir-boosted atazanavir in virologically suppressed Thai adults with HIV (LASA): a randomised, open-label, non-inferiority trial

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## Summary

**Background** **Thai patients with HIV have higher exposure to HIV protease inhibitors than do white people and dose reduction might be possible. We compared the efficacy of low-dose with standard-dose ritonavir-boosted atazanavir in virologically suppressed Thai patients with HIV.**

**Methods** **In this randomised, open-label, non-inferiority trial, we recruited patients aged 18 years or older who were receiving ritonavir-boosted protease-inhibitor-based antiretroviral therapy (ART) with HIV plasma viral loads of less than 50 copies per mL, an alanine aminotransferase concentration of less than 200 IU/L, and a creatinine clearance of at least 60 mL/min from 14 hospitals in Thailand. We excluded patients who had active AIDS-defining disease or opportunistic infections, had a history of an HIV viral load of 1000 copies per mL or more after 24 weeks of any ritonavir-boosted protease-inhibitor-based ART, used concomitant medications that could interact with the study drugs, were pregnant or lactating, had illnesses that might change the effect of the study drugs, or had a history of sensitivity to the study drugs. A biostatistician at the study coordinating centre randomly allocated patients (1:1) to switch the protease inhibitor for oral atazanavir 200 mg and ritonavir 100 mg or for atazanavir 300 mg and ritonavir 100 mg once daily, both with two nucleoside or nucleotide reverse transcriptase inhibitors at recommended doses. Randomisation was done with a minimisation schedule, stratified by recruiting centre, use of tenofovir, and use of indinavir as a component of the preswitch regimen. The primary endpoint was the proportion of patients with viral loads of less than 200 copies per mL at week 48, and we followed up patients every 12 weeks. Treatments were open label, the non-inferiority margin was –10%, and all patients who received at least one dose of study medication were analysed. This trial is registered with ClinicalTrials.gov, number NCT01159223.**

**Findings** **Between July 6, 2011, and Dec 23, 2013, we randomly assigned 559 patients: 279 to receive atazanavir 200 mg and ritonavir 100 mg (low dose) and 280 to atazanavir 300 mg and ritonavir 100 mg (standard dose). At week 48, 265 (97·1%) of 273 in the low-dose group and 267 (96·4%) of 277 in the standard-dose group had viral loads of less than 200 copies per mL (difference 0·68; 95% CI –2·29 to 3·65). Seven (3%) of 273 in the low-dose group and 21 (8%) of 277 in the standard-dose group discontinued their assigned treatment (p=0·01). 46 (17%) of 273 participants in the low-dose group and 97 (35%) of 277 in the standard-dose group had total bilirubin grade 3 or higher toxicity (≥3·12 mg/dL; p<0·0001).**

**Interpretation** **A switch to low-dose atazanavir should be recommended for Thai patients with well controlled HIV viraemia while on regimens based on boosted protease inhibitors.**

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## Introduction

WHO recommends a boosted protease inhibitor, with either lopinavir or atazanavir boosted with ritonavir, in combination with two nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) as preferred second-line antiretroviral therapy (ART).[1] Boosted lopinavir is associated with metabolic abnormalities that contribute to cardiovascular disease; atazanavir-based regimens have similar virological efficacy and fewer metabolic adverse effects, but are more costly.[2–4]

Ethnicity can influence the pharmacokinetics of ART. We have shown that concentrations of nevirapine,[5] indinavir,[6] saquinavir,[7] ritonavir-boosted lopinavir,[8] and ritonavir-boosted atazanavir are high in Thais[9,10] compared with those in white people when the same doses are taken. In a previous pharmacokinetic study,[9] we estimated that atazanavir exposure was 51% higher in Thais than in white people who use standard-dose atazanavir 300 mg boosted with ritonavir 100 mg.[10] In Thai patients with HIV using low-dose atazanavir 200 mg with ritonavir 100 mg pharmacokinetic exposure was similar to that in white people using standard dose.[9] Additionally, low-dose regimens had similar virological efficacy and a significantly decreased risk of hyperbilirubinaemia compared with

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## Research in context

### Evidence before this study

Dose reduction of antiretroviral drugs can sometimes be used to reduce adverse events and costs of treatment. We searched PubMed, with no language restrictions, for articles published up to March 14, 2016, with combinations of the search terms "protease inhibitors", "atazanavir/ritonavir", "dose optimization", "dose reduction", and "lower dose". Findings from the ENCORE1 study showed that regimens containing 400 mg of efavirenz were non-inferior in terms of virological efficacy to regimens with 600 mg of efavirenz in adults with HIV. Our group has shown higher exposure to several antiretrovirals (nevirapine, ritonavir-boosted lopinavir, and ritonavir-boosted atazanavir) in Thai patients with HIV than in white patients. In our pilot study, atazanavir exposure in Thai patients using atazanavir 200 mg and ritonavir 100 mg had similar atazanavir exposure to white patients using an atazanavir 300 mg regimen, and incidence of hyperbilirubinaemia was lower when taking the reduced-dose regimen. However, data on efficacy and safety of reduced-dose regimens are needed.

### Added value of this study

We compared the efficacy and safety of a switch from a protease inhibitor to atazanavir 200 mg and ritonavir 100 mg (low-dose group) or to atazanavir 300 mg and ritonavir 100 mg (standard-dose group) in virologically suppressed Thai patients with HIV who had been treated with boosted protease-inhibitor-based regimens. The low dose was non-inferior in terms of virological efficacy to the standard dose. When switches from randomised treatment were imputed as failures, the low-dose group was superior to the standard-dose group because the standard-dose group was associated with increased treatment discontinuation because of adverse events.

### Implications of all available evidence

Atazanavir 200 mg and ritonavir 100 mg-based regimens are safe and effective for virologically suppressed patients with well controlled HIV infection on boosted protease-inhibitor-based regimens. We feel that atazanavir 200 mg and ritonavir 100 mg can therefore be recommended as part of routine care for Thai adults who have well controlled HIV infection on a protease-inhibitor-based regimen.

standard-dose regimens.[9,11] We did a multicentre, randomised, open-label, non-inferiority trial to compare the efficacy and safety of a switch from boosted protease-inhibitor-based regimens to a regimen containing either atazanavir 200 mg and ritonavir 100 mg (low-dose group) or atazanavir 300 mg and ritonavir 100 mg-based regimen (standard-dose group) in Thai adults with HIV.

## Methods

### Study design and participants

The low-dose atazanavir–ritonavir versus standard-dose atazanavir–ritonavir (LASA) study is a randomised, open-label, non-inferiority trial. In 14 hospitals in Thailand, we recruited adults with HIV aged 18 years or older who had provided written informed consent, had received ritonavir-boosted protease-inhibitor-based ART for at least 3 months before the screening visit, had a history of HIV plasma viral load of less than 50 copies per mL within 12 months before the screening visit, had an alanine aminotransferase concentration of less than 200 IU/L, and had a creatinine clearance according to the Cockcroft-Gault equation of at least 60 mL/min. We excluded patients who had active AIDS-defining disease or opportunistic infections; had a history of a viral load of 1000 copies per mL or higher after 24 weeks of any ritonavir-boosted protease-inhibitor-based ART; used concomitant medications that could interact with the pharmacokinetics of the study drugs (rifampicin or proton pump inhibitors); were pregnant or lactating; had illnesses that might change the effects of the study drugs; or had a history of sensitivity to the study drugs. The protocol was approved by the Thai Ministry of Public Health and local ethics committees.

For the **study protocol** see http://www.hivnat.org/download/LASA_Protocol.pdf

### Randomisation and masking

Patients were randomly allocated (1:1) to receive low-dose or standard-dose ritonavir-boosted atazanavir, both taken together with two NRTIs. After randomisation, the NRTIs in the preswitch regimens remained unchanged if possible. Randomisation was stratified by recruiting centre, use of tenofovir, and use of indinavir as a component of the preswitch regimen at the screening visit, with use of a minimisation schedule. Randomisation was done by a biostatistician (TA), with use of a computer-generated random number sequence, at the study coordinating centre, the HIV Netherlands Australia Thailand Research Collaboration (HIV-NAT), Bangkok, Thailand. During the entire study, investigators and patients were masked to total bilirubin concentration results in an effort to reduce treatment changes prompted by an asymptomatic chemical abnormality.

### Procedures

Patients in the low-dose group received atazanavir 200 mg with ritonavir 100 mg as a soft gel capsule, whereas those in the standard-dose group received atazanavir 300 mg with ritonavir 100 mg as a soft gel capsule, both taken orally once daily and together with two NRTIs at recommended doses. We measured viral load at week 0, week 12, week 24, and week 48; tests were done with the Cobas Ampliprep/Cobas AMPLICOR HIV-1 ultrasensitive test, version 2.0 (Roche Molecular

Systems, Branchburg, NJ, USA), with a level of detection of 20 copies per mL. Patients with viral loads of 200 copies per mL or more at any visit were requested to come for an extra visit within 4 weeks to repeat the test. If the repeated measurement was less than 200 copies per mL, a viral blip or transient viraemia was indicated, therefore patients continued on the same therapy. Protocol-defined virological failure was a confirmed viral load of 200 copies per mL or higher. We did HIV genotype resistance testing only in patients with viral loads of 1000 copies per mL or higher.

We measured complete blood counts, CD4 cell counts, and alanine aminotransferase concentrations every 12 weeks, and fasting cholesterol, HDL, triglyceride, and glucose concentrations every 24 weeks. We collected plasma samples every 12 weeks for total bilirubin concentration testing, done centrally at HIV-NAT. Management of jaundice was based on clinical judgment. At week 12 and week 24, we collected serum samples from all participants for atazanavir trough concentration measurement. We retrospectively analysed trough concentrations at the end of the study at HIV-NAT. The target trough concentration of boosted atazanavir is 0·15 mg/L or higher.[9] At each study visit, we asked all participants to complete an adherence questionnaire for each antiretroviral with the modified Medication Adherence Self Report Inventory during the preceding 7 days.[12]

### Outcomes

The primary endpoint was the comparison of proportions of patients in each group with HIV plasma viral loads less than 200 copies per mL after 48 weeks. We followed up patients every 12 weeks until week 48. All viral load tests were done centrally at the College of American Pathologists-accredited HIV-NAT laboratory in Bangkok, Thailand. Secondary endpoints were the proportion of patients with viral loads of less than 50 copies per mL, CD4 cell count, tolerability, adverse events, trough concentration, treatment adherence, additional measures of HIV replication, quality of life, cardiovascular risk, and lipodystrophy. We assessed clinical jaundice during physical examination in all participants. We graded clinical events and clinically significant laboratory abnormalities according to the Division of AIDS Common Toxicity Grading Scale.[13]

### Statistical analysis

We calculated sample size under the assumption that 87% of patients taking atazanavir 300 mg and ritonavir 100 mg would have viral loads of less than 200 copies per mL at week 48.[3] We defined non-inferiority on the basis of the difference between groups in the proportion of patients with plasma viral loads of less than 200 copies per mL at 48 weeks; non-inferiority was defined with a margin of 10% for the lower bound of the 95% CI for the difference between groups. Assuming no difference in virological failure between treatment groups, 256 participants per arm were needed to have 90% power to show non-inferiority at a two-sided significance level of 5%. With a 10% adjustment for loss to follow-up and regimen swaps resulting from toxicity, the sample size increased to 280 patients per arm, 560 in total.

We assessed virological endpoints at week 48 in all randomly allocated participants who received at least one dose of study medication according to the treatment group that they were assigned to, irrespective of the treatment actually received; the per-protocol population, excluding data from patients from the point at which they ceased randomly assigned treatment for any reason or had protocol deviations that could potentially affect the primary endpoint; and the post-hoc non-completer as failure snapshot population, including all patients who received at least one dose of study medication, but with switches from randomised treatment also imputed as failures. We assessed thresholds of 200 copies per mL and 50 copies per mL in all of these groups. We did not consider changes to NRTI backbones as a change in randomised treatment. For the primary study endpoint, we imputed participants with missing data or who changed treatment because of virological failure as failures.

We summarise differences in proportions between randomised groups as percentage differences with 95% CIs and make a formal comparison with a Pearson's $\chi^2$-derived or Fisher's exact-derived p value. We used a *t* test to compare mean changes in variables from baseline to week 48 between randomised groups. We compared virological failure incidence and made formal comparisons with Cox regression. We assessed only the primary endpoint in terms of non-inferiority, with provision to test for superiority if non-inferiority criteria were met. All other comparisons were tests of superiority, with statistical significance at a two-sided p value of less than 0·05. One independent review was done by the data safety monitoring board, with prespecified terms of reference and stopping rules, when 50% of participants had reached study week 24. The board recommended that the study continue unchanged. We used Stata 13.1 for all analyses. This trial is registered with ClinicalTrials.gov, number NCT01159223.

### Role of the funding source

The Kirby Institute for Infection and Immunity in Society conceived and designed the study, collected, analysed, and interpreted data, prepared and reviewed the manuscript, and approved the paper for publication. TB, TA, and KR had full access to all the data in the study. KR had final responsibility for the decision to submit for publication.

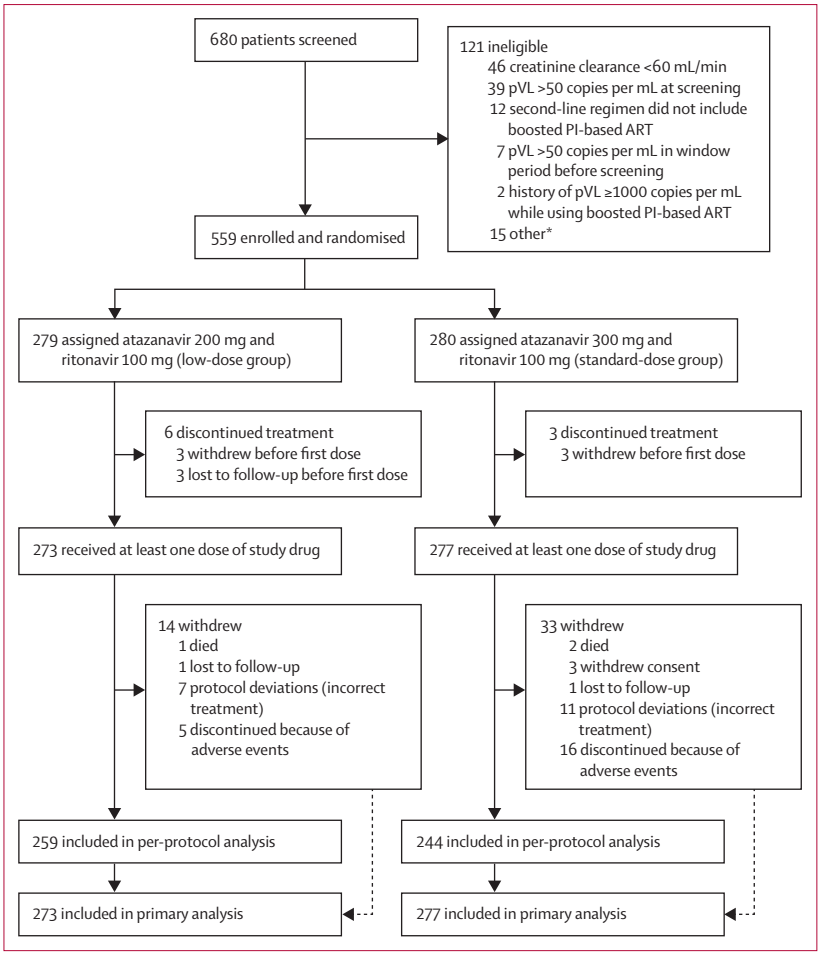


***Figure 1:*** **Trial profile**
ART=antiretroviral therapy. PI=protease inhibitor. pVL=plasma viral load. *For example, concurrent taking of drugs that would alter atazanavir metabolism and elevated alanine aminotransferase concentration.

| | Low-dose atazanavir (n=273) | Standard-dose atazanavir (n=277) | Total (n=550) |
|---|---|---|---|
| Age (years) | 42 (7·6) | 41 (7·4) | 42 (7·5) |
| Male sex | 129 (47%) | 145 (52%) | 274 (50%) |
| Bodyweight (kg) | 59 (11) | 60 (11) | 59 (11) |
| Height (cm) | 162 (8·4) | 163 (8·8) | 162 (8·6) |
| Body-mass index (kg/m²) | 22·7 (3·5) | 22·4 (3·4) | 22·5 (3·5) |
| CD4 nadir (cells per μL) | 120 (137) | 126 (133) | 123 (135) |
| History of ever used dual NRTIs | 35 (13%) | 39 (14%) | 74 (13%) |
| Duration of treatment with boosted protease-inhibitor-containing regimen before screening (years) | 5·2 (3·0) | 5·1 (3·1) | 5·2 (3·0) |
| Boosted protease inhibitor at screening (%) | | | |
| Lopinavir | 233 (85%) | 234 (84%) | 467 (85%) |
| Indinavir | 22 (8%) | 24 (9%) | 46 (8%) |
| Saquinavir | 18 (7%) | 19 (7%) | 37 (7%) |
| NRTIs at screening (%) | | | |
| Lamivudine | 223 (82%) | 222 (80%) | 445 (81%) |
| Tenofovir | 203 (74%) | 202 (73%) | 405 (74%) |
| Zidovudine | 108 (40%) | 124 (45%) | 232 (42%) |
| Didanosine | 16 (6%) | 14 (5%) | 30 (5%) |
| Stavudine | 10 (4%) | 12 (4%) | 22 (4%) |
| CD4 count (cells per μL) | 549 (256) | 528 (222) | 539 (240) |
| HIV RNA concentration <50 copies per mL | 263 (96%) | 266 (96%) | 529 (96%) |
| HIV RNA concentration <200 copies per mL | 271 (99%) | 277 (100%) | 548 (>99%) |
| Positive hepatitis B antigen | 23 (8%) | 14 (5%) | 37 (7%) |
| Positive hepatitis C antibody | 10 (4%) | 14 (5%) | 24 (4%) |
| ALT concentration (IU/L) | 29 (26·7) | 28 (24·9) | 29 (25·8) |
| Total bilirubin (mg/dL) | 0·9 (0·5) | 0·8 (0·3) | 0·8 (0·4) |
| Serum creatinine (mg/dL) | 0·8 (0·2) | 0·8 (0·2) | 0·8 (0·2) |
| Creatinine clearance with Cockroft-Gault formula (mL/min) | 94·5 (25·9) | 95·7 (25·8) | 95·1 (25·9) |

Data are mean (SD) or n (%). NRTI=nucleoside reverse transcriptase inhibitor. ALT=alanine aminotransferase.

***Table 1:*** **Baseline characteristics**

## Results

Between July 6, 2011, and Dec 23, 2013, we screened 680 patients, of whom 121 (18%) were not eligible (figure 1). 559 patients (82%) were randomly allocated, 279 to receive low-dose atazanavir 200 mg and ritonavir 100 mg and 280 to receive standard-dose atazanavir 300 mg and ritonavir 100 mg. The last 48 week study visit was completed on Nov 3, 2014. At baseline, the most common protease inhibitor was ritonavir-boosted lopinavir (table 1), and the two most common backbones were lamivudine and tenofovir. Other baseline characteristics were well matched between groups (table 1).

In the primary analysis of patients who received at least one dose of study drug, non-inferiority of low-dose atazanavir regimens was shown. This finding was supported in per-protocol analysis and a post-hoc non-completer as failure analysis (figure 2). Non-inferiority of the low-dose regimen was also shown in analyses of patients achieving viral loads of 50 copies per mL or less. Superiority of the low-dose regimen was not shown in the primary analysis or per-protocol set. Although, a post-hoc non-completer as failure analysis of patients with viral loads of 50 copies per mL or less suggested superiority of the low-dose regimen (figure 2).

Seven (3%) patients in the low-dose group and three (1%) in the standard-dose group had genotypic resistance testing when their plasma viral load was 1000 copies per mL or more. Only one patient in the low-dose group developed major resistance to protease inhibitors (Ile50Leu, Val82Ala, and Leu90Met). This patient had HIV subtype B and a history of delayed dosing of atazanavir and ritonavir-based ART for more than an hour for about 20% of total doses before virological failure developed. The patient initiated ART with a dual NRTI regimen (zidovudine with lamivudine) before switching to stavudine, zalcitabine,

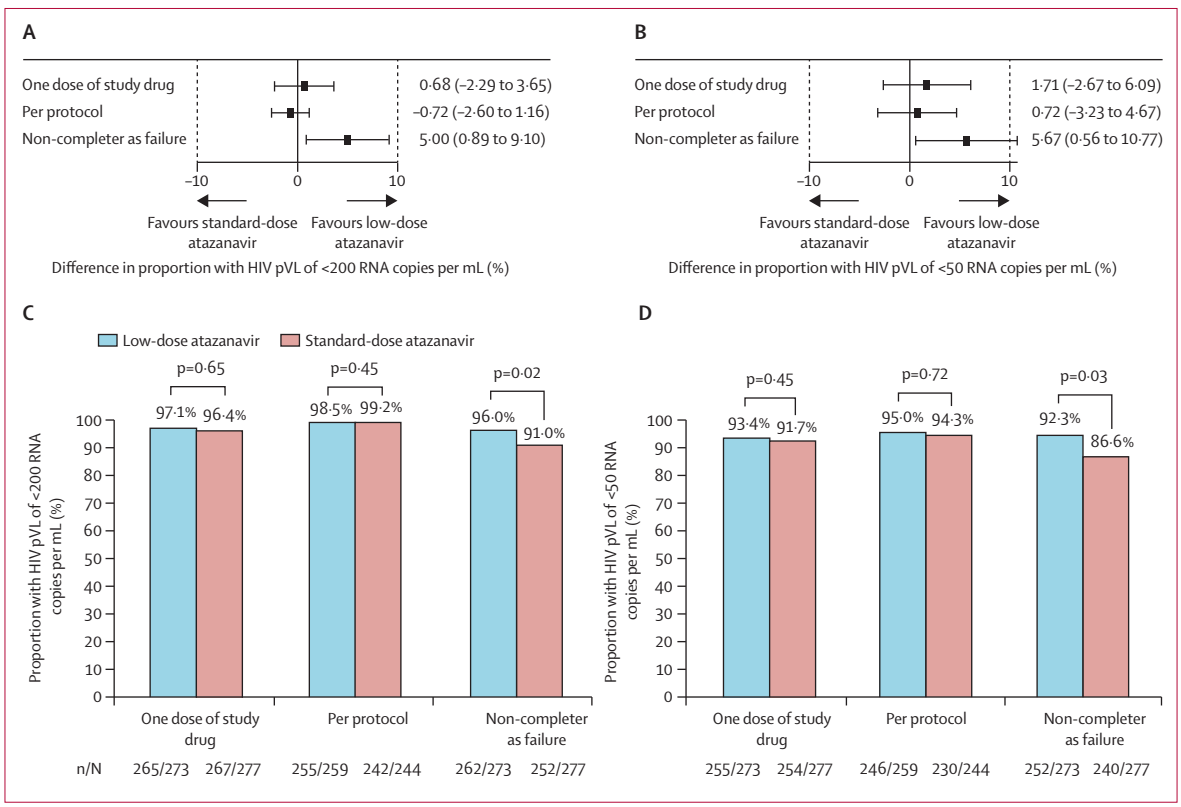


***Figure 2:*** **Plasma viral load at week 48**
Difference in proportion of participants with an HIV pVL of (A) less than 200 RNA copies per mL and (B) less than 50 RNA copies per mL at week 48; error bars are 95% CIs. Proportion of participants with an HIV pVL of (C) less than 200 RNA copies per mL and (D) less than 50 RNA copies per mL at week 48. pVL=plasma viral load.

and nelfinavir and then to tenofovir, lamivudine, and ritonavir-boosted lopinavir. The patient also had resistance to all nucleoside reverse transcriptase inhibitors. Other patients who had genotypic resistance testing had no major protease inhibitor resistance mutations. Seven (3%) of 273 patients in the low-dose group discontinued the study drug (figure 3): one death from oesophageal cancer, two virological failures, two rashes, one jaundice, and one pregnancy. 21 (8%) of 277 in the standard-dose group discontinued the study drug (figure 3): one death from oesophageal varices, one death from lymphoma, seven rashes, six jaundices, one pregnancy, and five others (one proximal tubular dysfunction, one elevated alanine aminotransferase concentration, one gastro-oesophageal reflux requiring omeprazole, one viral blip, and one patient's request). During the study, four patients changed their backbone NRTI. In the low-dose group, one patient changed from a zidovudine to a non-zidovudine backbone because of anaemia. In the standard-dose group, one patient also changed from a zidovudine to a non-zidovudine backbone due to anaemia and two changed from a tenofovir to a non-tenofovir backbone because of an elevated creatinine concentration.

At week 48, mean total bilirubin concentration was 1·9 mg/dL (SD 1·1) in the low-dose group versus 2·2 mg/dL (1·2) in the standard-dose group (p=0·0012);

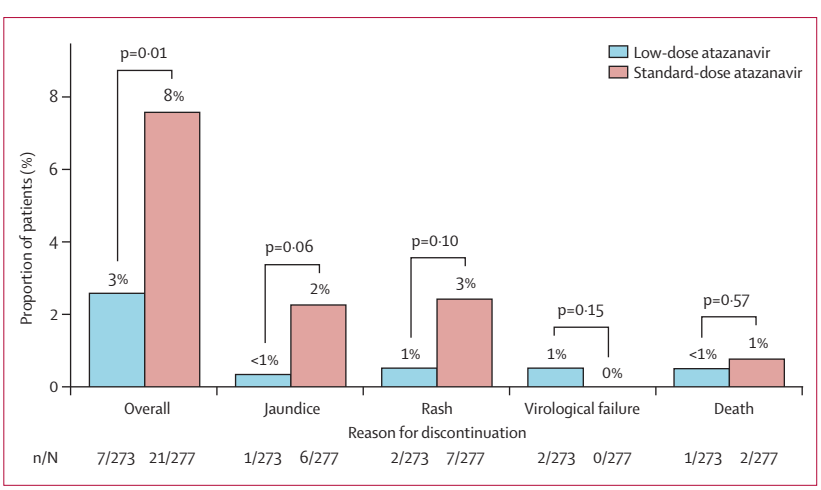


***Figure 3:*** **Reasons for discontinuation**

the number of patients with a total bilirubin concentration of at least grade 3 toxicity (≥3·12 mg/dL) was 46 (17%) of 273 in the low-dose group versus 97 (35%) of 277 in the standard-dose group (p<0·0001). Among the two patients in the low-dose group (1%) who developed rash, the duration from baseline to the first occurrence was 1 week in one patient and 14 weeks in another. Among seven patients in the standard-dose group (3%) who developed

| | Mean change | SD | p value within group |
|---|---|---|---|
| **Total bilirubin concentration (mg/dL)** | | | |
| Low-dose atazanavir | 1·05 | 1·19 | <0·0001 |
| Standard-dose atazanavir | 1·38 | 1·14 | <0·0001 |
| Difference (95% CI) | −0·33 (−0·50 to −0·10) | .. | .. |
| p value between groups | 0·0009 | .. | .. |
| **ALT concentration (IU/L)** | | | |
| Low-dose atazanavir | 10·49 | 33·36 | <0·0001 |
| Standard-dose atazanavir | 12·96 | 61·70 | <0·0001 |
| Difference (95% CI) | −2·47 (−10·85 to 5·89) | .. | .. |
| p value between groups | 0·56 | .. | .. |
| **Serum creatinine concentration (mg/dL)** | | | |
| Low-dose atazanavir | 0·01 | 0·13 | 0·50 |
| Standard-dose atazanavir | −0·01 | 0·13 | 0·17 |
| Difference (95% CI) | 0·02 (−0·01 to 0·04) | .. | .. |
| p value between groups | 0·15 | .. | .. |
| **Creatinine clearance with Cockcroft-Gault (mL/min per 1·73 m²)** | | | |
| Low-dose atazanavir | 1·40 | 15·38 | 0·17 |
| Standard-dose atazanavir | 3·14 | 16·62 | 0·002 |
| Difference (95% CI) | −1·74 (−4·45 to 0·96) | .. | .. |
| p value between groups | 0·21 | .. | .. |
| **Total cholesterol concentration (mg/dL)*** | | | |
| Low-dose atazanavir | −14·8 | 36·2 | <0·0001 |
| Standard-dose atazanavir | −20·2 | 33·2 | <0·0001 |
| Difference (95% CI) | 5·4 (−0·5 to 11·3) | .. | .. |
| p value between groups | 0·07 | .. | .. |
| **HDL cholesterol concentration (mg/dL)*** | | | |
| Low-dose atazanavir | 0·5 | 9·9 | 0·36 |
| Standard-dose atazanavir | 0·5 | 10·0 | 0·41 |
| Difference (95% CI) | 0·00 (−1·6 to 1·7) | .. | .. |
| p value between groups | 0·96 | .. | .. |
| **Triglyceride concentration (mg/dL)*** | | | |
| Low-dose atazanavir | −73·1 | 137·9 | <0·0001 |
| Standard-dose atazanavir | −59·5 | 147·9 | <0·0001 |
| Difference (95% CI) | −13·6 (−37·7 to 10·7) | .. | .. |
| p value between groups | 0·27 | .. | .. |
| **Fasting glucose concentration (mg/dL)*** | | | |
| Low-dose atazanavir | −0·4 | 37·8 | 0·86 |
| Standard-dose atazanavir | 1·1 | 22·8 | 0·43 |
| Difference (95% CI) | −1·5 (−6·8 to 3·8) | .. | .. |
| p value between groups | 0·57 | .. | .. |

ALT=alanine aminotransferase. *Results are for fasting blood.

*Table 2:* **Comparison of characteristics from baseline to week 48**

rash, the median duration from baseline to first occurrence of rash was 1 week (IQR 1–5). Overall, we found no difference in the proportion of patients between treatment groups who had adverse events (low-dose group 100 [37%] of 273; standard-dose group 106 [38%] of 277; p=0·69). Additionally, in a post-hoc analysis, we found no evidence of different proportions of adverse events by weight (<60 kg 116 [37%] of 314; ≥60 kg 90 [38%] of 236; p=0·94]).

We found no significant differences for other laboratory variables between treatment groups: mean CD4 count was 569 cells per µL (SD 259) in the low-dose group versus 552 cells per µL (213) in the standard-dose group (p=0·78); alanine aminotransferase concentration was 40 IU/L (37) versus 41 IU/L (63; p=0·56); creatinine clearance was 95·5 mL/min (26·2) versus 99·2 mL/min (26·8; p=0·21); total cholesterol concentration was 196 mg/dL (43·4) versus 187 mg/dL (38·8; p=0·07); and triglyceride concentration was 176 mg/dL (107·4) versus 182 mg/dL (120·1; p=0·27). We found no difference in mean change of CD4 count between week 48 and week 0 between the low-dose (21 cells per µL [154]) and standard-dose (24 cells per µL [SD 134]; p=0·77) groups. We also found no difference between treatment groups in total cholesterol concentration, triglyceride concentration, HDL cholesterol concentration, creatinine clearance, alanine aminotransferase concentration, serum creatinine concentration, and fasting glucose concentration (table 2). When compared within treatment groups, we found significant reductions of total cholesterol, triglyceride, total bilirubin, and alanine aminotransferase concentrations.

Median atazanavir trough concentration was 0·31 mg/L (IQR 0·19–0·47) in the low-dose group versus 0·46 mg/L (0·26–0·72) in the standard-dose group (p<0·0001). 51 (19%) of 272 patients in the low-dose group and 30 (11%) of 266 in the standard-dose group had atazanavir trough concentrations of less than 0·15 mg/L (p=0·015). Of patients with viral loads of 50 copies per mL or more, five (10%) of 51 and two (7%) of 30 achieved trough concentrations of less than 0·15 mg/L (p=0·63). According to a self-reported adherence questionnaire, median adherence to all antiretrovirals was 100% in both groups.

## Discussion

Atazanavir 200 mg and ritonavir 100 mg when combined with two NRTIs is non-inferior in terms of virological efficacy to atazanavir 300 mg and ritonavir 100 mg with two NRTIs in virologically suppressed Thai adults with HIV for use as second-line protease-inhibitor-based ART. We feel that atazanavir 200 mg and ritonavir 100 mg can therefore be recommended as part of routine care for Thai adults who have well controlled HIV infection on a protease-inhibitor-based regimen.

Few randomised controlled trials have compared antiretroviral doses.[14,15] Investigators of the ENCORE1 study[14] found that initial ART regimens containing efavirenz 400 mg were non-inferior in terms of virological efficacy to efavirenz 600 mg in ART-naive adults with HIV. The efficacy of low-dose atazanavair in our study is further evidence that important antiretroviral drugs are prescribed

at excessive unit doses. Dose reductions of atazanavir resulted in significantly fewer side-effects in our study, as was also seen with efavirenz dose reduction in ENCORE1.[14]

The recommended standard dose of atazanavir 300 mg and ritonavir 100 mg is associated with well recognised intolerability. Findings from a study of ART-naive US patients showed that a regimen based on standard-dose ritonavir-boosted atazanavir had similar virological efficacy to that of regimens based on raltegravir and ritonavir-boosted darunavir.[16] However, tolerability of the atazanavir regimen was inferior to that of raltegravir and darunavir regimens, with higher discontinuation.[16] As a result, US Department of Health and Human Services 2015 guidelines[17] moved regimens based on ritonavir-boosted atazanavir to the alternative regimen category for first-line treatment.

Hyperbilirubinaemia is a common adverse event during treatment with atazanavir-based regimens and a major cause of intolerability. 34–50% of patients using standard-dose atazanavir had grade 3–4 hyperbilirubinaemia in previous studies.[16,18,19] In one trial,[16] 43% of patients had grade 3–4 hyperbilirubinaemia and 8% of those on taking boosted atazanavir regimens discontinued because of jaundice. In our study, we found that dose reduction of atazanavir significantly reduces the proportion of grade 3 or higher hyperbilirubinaemia; there was a non-significant suggestion that discontinuation due to jaundice might be less common in the low-dose group.

2–3% of patients using atazanavir 300 mg and ritonavir 100 mg plus two NRTIs developed rash in previous studies.[18,20] Occurrence of rash in our study was similar to in the standard-dose group; fewer patients in the low-dose group developed rash, but the difference was not statistically significant. Moreover, the numbers of discontinuations due to rash were not significantly different.

One patient in the low-dose group developed a major atazanavir-specific resistant associated mutation (Ile50Leu). This patient was initially given dual NRTIs, had a history of poor adherence by self-report, and on genotypic resistance testing, had virus that was resistant to all NRTIs. High numbers of active antiretrovirals in the boosted protease-inhibitor-based regimen are related to high proportions of virological suppression,[21] and the low number of active drugs in this case most probably resulted in virological failure.

We previously reported pharmacokinetic characteristics of atazanavir 200 mg and ritonavir 100 mg once daily plus two NRTIs in Thais similar to those in white people treated with standard-dose atazanavir 300 mg and ritonavir 100 mg once daily.[9] In this study, we found that more patients in the low-dose atazanavir group than in the standard-dose group had trough concentrations lower than the recommended therapeutic concentration of 0·15 mg/L. However, we found no difference in the proportion of patients with a trough concentration of less than 0·15 mg/L and plasma viral loads of 50 copies per mL or more.

Our study has important limitations. First, the applicability of our results to other ethnicities or populations with bodyweights greater than in our study is unknown. Second, our results are not generalisable to ART-naive patients or those not already suppressed. Coformulated atazanavir 200 mg and ritonavir 100 mg is not available, which could impede translation of our findings into routine clinical care. Long-term virological efficacy might also be a concern for extended use of low-dose atazanavir. We have, however, reported up to 4 years of virological efficacy in 127 Thai patients using atazanavir 200 mg and ritonavir 100 mg plus two NRTIs:[22] the proportion with plasma viral loads of less than 50 copies per mL was 82% in the intention-to-treat analysis and 91% in the on-treatment analysis.

In high-income countries, patients have access to new drug classes and improved formulations of existing drugs that can be given once daily. The costs of these new drugs are prohibitive in low-income countries. Use of the low dose of atazanavir, with less toxicity than the standard dose, would benefit both patients and health-care systems in these settings. The price of atazanavir 200 mg (US$135 per month) is substantially cheaper than that of 300 mg ($220 per month) on the basis of price at the Thai Red Cross AIDS Research Center, Bangkok, Thailand, as of December, 2014. Thailand has about 20 000 patients in the National Treatment Program taking second-line ART (Bhakeecheep S, unpublished). If all of these patients were switched to atazanavir 200 mg instead of 300 mg, the cost saving for Thailand would be about $102 million over 5 years.

**Contributors**

TB and AA designed the study, collected data, wrote the initial manuscript, and reviewed the final draft of the manuscript before submission. SK, PC, MT, NL, PK, CB, SBa, VK, SM, SN, SJ, WP, WM, SBh, and SC designed the study, collected data, and reviewed the final draft of the manuscript before submission. PP and DAC designed the study and reviewed the final draft of the manuscript before submission. TA did the randomisation, prepared the data safety monitoring board reports, drafted the statistical analysis plan, did the statistical analysis for the study, and assisted in drafting the manuscript and subsequent revisions. SJK drafted the statistical design and analysis sections of the protocol, supervised the statistical analysis, and assisted in drafting the manuscript and subsequent revisions. SE and KR designed the study, wrote the initial manuscript, and reviewed the final draft of the manuscript before submission. All authors approved the manuscript for submission.

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#### Declaration of interests

PC has received speaker honoraria or educational grants from Abbott, Bristol-Myers Squibb, Janssen-Cilag, GlaxoSmithKline, Merck Sharp & Dohme, Al Ittihad Drug Store, and Roche. SK has received speaker honoraria or educational grants from Bristol-Myers Squibb, Janssen-Cilag, GlaxoSmithKline, Merck Sharp & Dohme, and Gilead Li & Fung Asia. SE has received research grant support from ViiV, Pfizer, and Merck Sharp & Dohme in the last 5 years. KR has received a Senior Research Scholar Award from the Thailand Research Fund, honoraria or consultation fees from Merck Sharp & Dohme, Roche, Jensen-Cilag, Tibotec, Myland, and The Governmental Pharmaceutical Organization. He has also participated in a company-sponsored speaker's bureau from Abbott, Gilead, Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, Jensen-Cilag, GlaxoSmithKline, and The Governmental Pharmaceutical Organization. All other authors declare no competing interests.

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