



Dual treatment with atazanavir–ritonavir plus lamivudine versus triple treatment with atazanavir–ritonavir plus two nucleos(t)ides in virologically stable patients with HIV-1 (SALT): 48 week results from a randomised, open-label, non-inferiority trial

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Summary

Background Problems associated with lifelong antiretroviral therapy, such as need for strict adherence, drug-related toxic effects, difficulties with treatment schedules, and cost, mean that simplification strategies should be sought. We aimed to explore the efficacy and safety of dual treatment with atazanavir–ritonavir plus lamivudine as an option to switch to from standard combination antiretroviral therapy in patients with an HIV-1 infection who are virologically suppressed.

Methods In this randomised, open-label, non-inferiority trial, we recruited patients aged 18 years and older with chronic HIV-1 infection and no previous treatment failure or resistance, and with HIV-1 RNA of less than 50 copies per mL for at least 6 months, negative hepatitis B virus surface antigen, and good general health, from 30 hospitals in Spain. Exclusion criteria were switch in antiretroviral therapy during the previous 4 months, previous virological failure, pregnancy or breastfeeding, Gilbert's syndrome, use of contraindicated drugs, grade 4 laboratory abnormalities, and previous intolerance to any of the study drugs. We randomly assigned patients (1:1; stratified by active hepatitis C virus infection and previous treatment; computer-generated random number sequence) to dual treatment with oral atazanavir (300 mg once daily) and ritonavir (100 mg once daily) plus lamivudine (300 mg once daily) or triple treatment with oral atazanavir (300 mg once daily) and ritonavir (100 mg once daily) plus two nucleos(t)ide reverse transcriptase inhibitors at the discretion of the investigators. The primary endpoint was virological response, defined as HIV-1 RNA of less than 50 copies per mL at week 48, in the per-protocol population, with a non-inferiority margin of 12%. We included patients who received at least one dose of the study drug in the safety analysis. This study is registered at ClinicalTrials.gov, number NCT01307488.

Findings Between Sept 29, 2011, and May 2, 2013, we randomly assigned 286 patients (143 [50%] to each group). At week 48 in the per-protocol population, 112 (84%) of 133 patients had virological response in the dual-treatment group versus 105 (78%) of 135 in the triple-treatment group (difference 6% [95% CI –5 to 16%]), showing non-inferiority at the prespecified level. 14 (5%) patients developed severe adverse events (dual treatment six [4%]; triple treatment eight [6%]), none of which we deemed related to the study drug. Grade 3–4 adverse events were similar between groups (dual treatment 77 [55%] of 140; triple treatment 78 [55%] of 141). Treatment discontinuations were less frequent in the dual-treatment group (three [2%]) than in the triple-treatment group (ten [7%]; $p=0.047$).

Interpretation In our trial, dual treatment was effective, safe, and non-inferior to triple treatment in patients with an HIV-1 infection who are virologically suppressed who switch antiretroviral therapy because of toxic effects, intolerance, or simplification. This combination has the potential to suppress some of the long-term toxic effects associated with nucleos(t)ide reverse transcriptase inhibitors, preserve future treatment options, and reduce the cost of antiretroviral therapy.

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Introduction

The main objective of combination antiretroviral therapy (cART) is suppression of viral replication to improve the quality of life and life expectancy of patients with an HIV-1 infection. Combinations of two nucleoside reverse transcriptase inhibitors with a ritonavir-boosted protease inhibitor, a non-nucleoside reverse transcriptase inhibitor,

or an integrase inhibitor are the currently recommended standard approaches in first-line cART.^{1,2} Nevertheless, lifelong cART has drawbacks, such as the need for strict adherence, drug-related toxic effects, difficulties associated with treatment schedules, and cost, all of which can affect long-term treatment effectiveness. Therefore, simplification strategies for patients who are virologically

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Research in context

Evidence before this study

Before we started the SALT trial, only one study existed that described the effectiveness and safety of dual treatment based on a boosted protease inhibitor and lamivudine. The ATLAS study was a single-arm pilot study that switched 40 patients who were receiving atazanavir–ritonavir plus two nucleos(t)ide reverse transcriptase inhibitors to atazanavir–ritonavir plus lamivudine. Results at 48 weeks showed that only one patient discontinued because of virological failure. Increases in total, HDL, and LDL cholesterol occurred, and glomerular filtration rate improved. We did a systematic search of PubMed limited to articles published between Jan 1, 2000, and Nov 30, 2014, with no language restrictions. We did a secondary search by consulting the references of the articles included and the abstracts of the most important scientific meetings in the discipline of HIV infection (years 2013 and 2014). We only selected prospective studies. Search terms were (“nucleoside-sparing” OR “NRTI-sparing”) AND (“HIV” OR “AIDS”). We retrieved 189 articles and eight conference papers, from which we selected 15 (seven cohort studies and eight clinical trials). Dual combinations were based on raltegravir (plus etravirine, a boosted protease inhibitor, or maraviroc), a boosted protease inhibitor plus lamivudine, or unboosted atazanavir plus lamivudine. Overall safety and efficacy for these combinations was good in patients without previous virological failures. Nevertheless, for long-term experienced patients who received combinations based on raltegravir plus maraviroc or etravirine, virological failure was frequent (4–10%), with development of resistance mutations to raltegravir and changes in CCR5 tropism. Some combinations were inferior to standard treatment (boosted lopinavir plus efavirenz or boosted atazanavir plus raltegravir), whereas one of those with equivalent efficacy to standard cART was based on a non-marketed drug (GSK1265744) and another on a less convenient schedule

(boosted lopinavir plus nevirapine twice daily). The combination of boosted lopinavir plus lamivudine was examined in the OLE study, in which patients with an HIV-1 infection on triple treatment with lopinavir and ritonavir plus lamivudine or emtricitabine and a second nucleos(t)ide were randomly assigned to continue triple treatment or switch to dual treatment with lopinavir and ritonavir plus lamivudine. This trial has shown non-inferior efficacy and similar safety of this dual treatment to that of boosted lopinavir plus two nucleoside reverse transcriptase inhibitors. Additionally, in an interim analysis of the ATLAS-M study at 24 weeks, the combination of boosted atazanavir plus lamivudine showed non-inferiority to and the same safety profile as boosted atazanavir plus two nucleoside reverse transcriptase inhibitors.

Added value of this study

SALT is the first clinical trial to compare boosted atazanavir plus lamivudine with boosted atazanavir plus nucleoside reverse transcriptase inhibitors in a well-powered study that shows non-inferior efficacy and equivalent safety of dual treatment compared with standard cART. This finding is consistent with those of the OLE and ATLAS-M clinical trials, and some cohort studies.

Implications of all the available evidence

The combination of boosted atazanavir plus lamivudine has the potential to suppress some of the long-term toxic effects associated with nucleos(t)ide reverse transcriptase inhibitors, preserve future treatment options, and reduce the cost of cART. The results of the SALT and OLE trials suggest that dual treatment based on a boosted protease inhibitor plus lamivudine is a switch option that is effective, safe, and well tolerated for patients with virologically suppressed HIV-1 infections. They contrast with findings for other dual combinations, which cannot be deemed good options for simplification because of safety and efficacy issues.

suppressed have been sought to improve the convenience of cART without compromising its effectiveness.

Even though nucleoside reverse transcriptase inhibitors have been the backbone of cART since the advent of antiretroviral therapy, they induce substantial toxic effects in the form of peripheral neuropathy, pancreatitis, anaemia, lipoatrophy, hypersensitivity reactions, kidney and bone impairment, and lactic acidosis.³ Although old and toxic inhibitors (didanosine, stavudine, and zidovudine) have fallen into disuse, the newer drugs pose problems that remain unresolved. Tenofovir has been associated with proximal tubular dysfunction, nephrogenic diabetes insipidus, and nephrotic syndrome,^{4,5} and a decrease in bone mineral density and its consequent increased risk of osteoporotic fractures.^{6,7} Abacavir has been related to an increased risk of myocardial infarction and, even though this association is not consistent in all studies, it has generated some concern, especially in patients with high cardiovascular risk.^{8,9} Additionally, to

avoid severe hypersensitivity reactions, patients have to be screened for carriage of the *HLA-B*5701* allele.

Monotherapy with a ritonavir-boosted protease inhibitor is a potential alternative to nucleoside reverse transcriptase inhibitor-based regimens because it is less subject to the toxic effects than are nucleoside or non-nucleoside reverse transcriptase inhibitors, it has a high genetic barrier to resistance, it is free from some nucleoside reverse transcriptase inhibitor drug interactions, and it can reduce the number of tablets needed to be taken. Thus, future drug options are preserved and cost savings achieved. However, low-level viraemia is more frequent than with standard cART, protease inhibitor monotherapy is associated with a higher rate of virological failure, and the non-inferiority of this approach to standard cART has not been shown for all scenarios.^{10,11} Ritonavir-boosted protease inhibitor monotherapy is not widely accepted and should only be used in very selected patients (those with excellent adherence, no previous protease inhibitor resistance

mutations, and a nadir CD4 cell count of more than 100 cells per μL .¹²

Lamivudine is a potent nucleoside reverse transcriptase inhibitor with an excellent safety and tolerability profile.¹³ Its availability as a generic drug makes it attractive for cost containment. Thus, dual treatment based on a ritonavir-boosted protease inhibitor plus lamivudine could help clinicians overcome some of the disadvantages of monotherapy while maintaining the efficacy and convenience of robust cART. The advantage of dual treatment with ritonavir-boosted atazanavir plus lamivudine is that it can be given as three pills once daily. Additionally, atazanavir-ritonavir has a good tolerability profile and low effect on cardiovascular risk, long-term effectiveness in previously untreated patients, and ability to be switched.^{14–17} Data from a small single-arm pilot study of 40 patients who switched from standard cART with two nucleoside reverse transcriptase inhibitors plus atazanavir-ritonavir to dual treatment with atazanavir-ritonavir plus lamivudine showed promising efficacy and safety results at 48 weeks.¹⁸ Therefore, we set out to explore the efficacy and safety of dual treatment with atazanavir-ritonavir plus lamivudine as an option when switching from standard cART in patients who are virologically suppressed.

Methods

Study design and patients

In this randomised, open-label, non-inferiority trial, we recruited patients aged 18 years or older with chronic HIV-1 infection and no previous antiretroviral treatment failure, no resistance mutations to the study drug, HIV-1 RNA of less than 50 copies per mL for 6 months or longer, negative hepatitis B virus surface antigen, and good general health from 30 Spanish hospitals. Patients with no baseline resistance mutation study had to have HIV-1 RNA of less than 50 copies per mL during the previous 12 months as proof that treatment was fully suppressive. Exclusion criteria were switch in antiretroviral therapy during the previous 4 months (any reason), previous virological failure, pregnancy or breastfeeding, Gilbert's syndrome, use of contraindicated drugs, grade 4 laboratory abnormalities, and previous intolerance to atazanavir, ritonavir, or lamivudine.

We obtained ethics committee approval at all participating centres in accordance with the principles of the 2008 Declaration of Helsinki. All participants gave their written informed consent before undergoing any study procedure. Additional written informed consent was needed from patients participating in the neurocognitive substudy.

Randomisation and masking

We randomly allocated patients (1:1) to dual treatment with atazanavir-ritonavir plus lamivudine or triple treatment with atazanavir-ritonavir plus two nucleos(t)ide reverse transcriptase inhibitors using a centralised web-

based randomisation process (the random number sequence was computer-generated). We stratified randomisation by active hepatitis C virus (HCV) infection (positive HCV RNA) and previous treatment (non-nucleoside reverse transcriptase inhibitor, ritonavir-boosted protease inhibitor, CCR5 antagonist, or integrase inhibitor).

Procedures

Patients in the dual-treatment group received oral atazanavir 300 mg and ritonavir 100 mg plus lamivudine 300 mg given once daily, and those in the triple-treatment group received oral atazanavir 300 mg and ritonavir 100 mg given once daily plus two nucleos(t)ide reverse transcriptase inhibitors (selected at the discretion of the investigator).

We assessed patients at screening, day 1 (baseline), and weeks 4, 12, 24, 36, and 48. Further assessment will be at weeks 60, 72, 84, and 96, or at early termination. We put patients assigned to the dual-treatment group on triple treatment with atazanavir-ritonavir plus two nucleos(t)ide reverse transcriptase inhibitors (at the investigator's discretion) for 1 month before switching to dual treatment with atazanavir-ritonavir plus lamivudine. We used this transition phase to prevent possible induction of cytochrome P450 by efavirenz and nevirapine (non-nucleoside reverse transcriptase inhibitors that patients could be on before study entry), which could lower atazanavir plasma concentrations and jeopardise the efficacy of dual treatment. Patients assigned to the triple-treatment group received two nucleos(t)ide reverse transcriptase inhibitors chosen by the investigator depending on the reason for switching (intolerance, toxic effects, or convenience), which could be related to the two nucleos(t)ides or to the third drug of the triple antiretroviral treatment that patients had been taking before study entry. For these reasons, patients could change to another nucleos(t)ide or stay with the same one and only change the third drug. Participants who were going to start abacavir (one of the two nucleos(t)ides) for the first time underwent *HLA-B*5701* testing. We did a clinical assessment at each visit and included a physical examination and blood and urine analysis. We did a dual-energy x-ray absorptiometry scan where available at baseline and weeks 24, 48, and 96. We assessed safety up to 4 weeks after the study ended. We assessed adherence on the basis of tablet count (done when patients returned their drugs) and a simplified drug adherence questionnaire.¹⁹ We defined non-adherence as a proportion lower than 90% at any visit during the study period. We did all laboratory tests at the respective hospitals, including establishment of HIV-1 resistance mutations.

We did a neurocognitive substudy in which we assessed participants at baseline and weeks 48 and 96. The exclusion criteria for this substudy were active substance use or withdrawal syndrome (defined according to Diagnostic and Statistical Manual of Mental Disorders IV

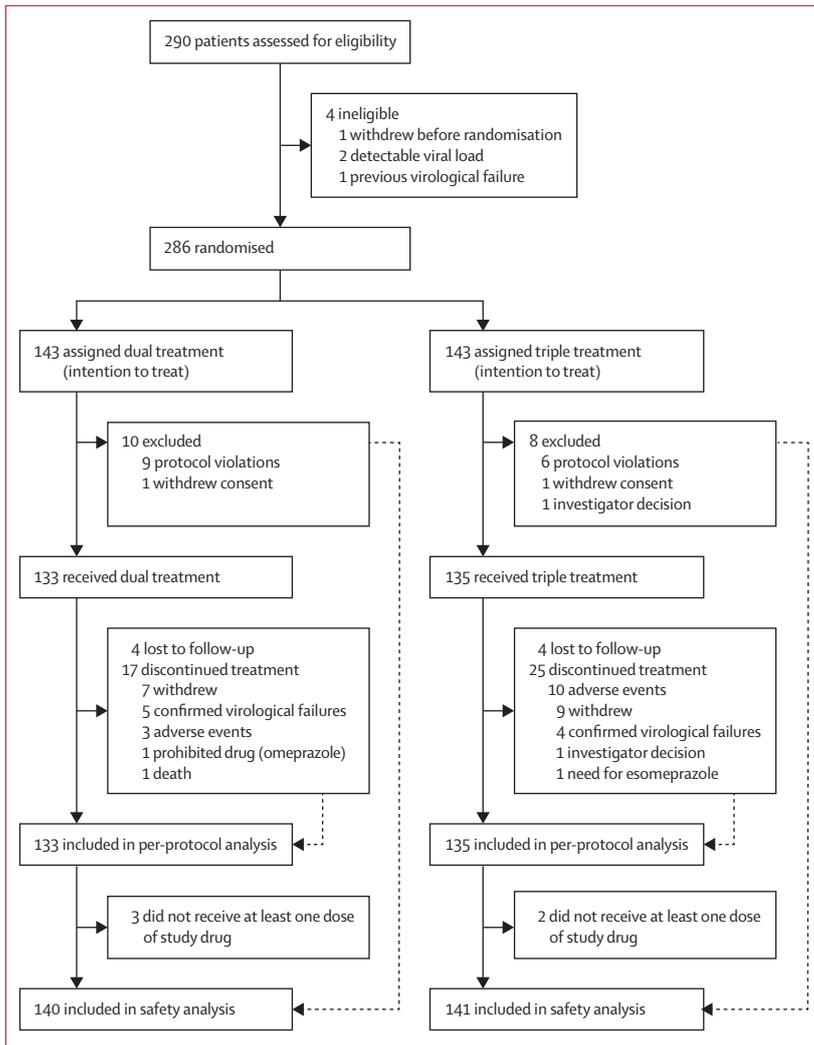


Figure 1: Trial profile

criteria²⁰), an active AIDS-defining disorder, decompensated cirrhosis, treatment with pegylated interferon, major psychiatric disorders (depression, psychosis, or bipolar disorder), previous diagnosis of dementia or mental retardation, and a score of 10 or higher on the Hospital Anxiety and Depression Scale.²¹ We did neurocognitive assessments with the American Association of Neurology 2007 criteria for diagnosis of HIV-1-associated neurocognitive disorders.²² The tests used to assess cognition were trail making A, trail making B, the digit symbol substitution test, and grooved pegboard test, with both the dominant and non-dominant hand (five neurocognitive domains; one test per domain). We converted raw test scores to demographically corrected standard scores using the best-available normative standards for the Spanish population. We estimated global neurocognitive performance using the global deficit score (GDS).²³

Outcomes

The primary endpoint was non-inferiority of the virological response between treatment groups, defined as the proportion of patients with an HIV-1 viral load of less than 50 copies per mL at week 48. We assessed virological efficacy using the time to loss of virological response (TLOVR) algorithm.²⁴ We defined virological failure as two consecutive viral loads (14 days or longer and not more than 30 days apart) greater than 50 copies per mL at any scheduled visit. We also deemed missing patients and changes in any study drug as failures. Secondary endpoints were safety, tolerability, changes in CD4 cell count, serum concentrations of 25(OH)-vitamin D, bone mineral density, body fat distribution, and proportion and type of resistance mutations after virological failure. We assessed changes in neurocognitive function (GDS for five domains) in the neurocognitive substudy.

Statistical analysis

We defined three populations for the analysis: the intention-to-treat population, which includes all randomly allocated patients; the per-protocol population, which consists of all randomly allocated patients except for those with major protocol violations and never-exposed patients; and the safety population, which consists of all participants who received at least one dose of the study drug. We used a non-inferiority margin of 12% to assess the primary outcome (ie, lower bound of the 95% CI of the difference between dual and triple treatment was no more than -12%). We chose this margin because it was the most consistently used for non-inferiority trials of cART at the time of the design of the study, and we used past evidence of sensitivity to drug effects.^{25,26} This analysis was done in the per-protocol population as generally recommended for randomised, non-inferiority trials. Pure intention-to-treat analysis often leads to smaller observed treatment effects than if all patients had adhered to treatment and often increases the risk of falsely claiming non-inferiority (type I error).²⁷ We did a sensitivity analysis using TLOVR to analyse the primary objective in the intention-to-treat population and the Food and Drug Administration snapshot algorithm²⁸ to analyse the primary objective in the per-protocol and intention-to-treat populations.

Although the primary endpoint was measured at 48 weeks, the study was powered to detect non-inferiority at 96 weeks, assuming a response of 81% in the control group. Thus, to show non-inferiority at a margin of 12% at week 96, with an α value of 5% and a power of 80%, we estimated the sample size at 365 assessable patients. The final study population consisted of 286 patients because of the low rate of recruitment during the last few months of the study. This decision to stop recruitment was taken by the sponsor and was independent of any efficacy analysis. We also implemented a stopping rule on the basis of an interim

analysis targeting early detection of a possible absence of effectiveness of dual treatment when a third of patients reached 24 weeks of follow-up. If the CI of 99·95% showed inferiority of dual treatment, the study was to be interrupted.²⁹ In that situation, patients randomly assigned to dual treatment would be offered the opportunity to restart triple treatment according to the investigator's decision.

We used an independent-samples *t* test to compare continuous variables and a Mann-Whitney test to compare non-normally distributed continuous variables. We assessed the association between categorical variables using the χ^2 test when samples were of sufficient size or with the Fisher's exact test when they were not. We assessed neurocognitive change (GDS at week 48 minus GDS at baseline) using analysis of covariance. We did all statistical analyses using SPSS version 17.

This study is registered with ClinicalTrials.gov, number NCT01307488.

Role of the funding source

The sponsor of the study managed the trial design, monitored the trial, collected and analysed data, and wrote the report. The funder of the study received the final draft of the manuscript for review and comments. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Sept 29, 2011, and May 2, 2013, we screened 290 patients, randomly allocating 286 (99%; 143 [50%] to each group; figure 1). The per-protocol population consisted of 268 patients (133 [50%] in the dual-treatment group and 135 [50%] in the triple-treatment group). We included 281 (98%) patients who received at least one dose of study drug in the safety population (140 [98%] in the dual-treatment group and 141 [99%] in the triple-treatment group). Baseline characteristics were balanced between groups (table 1).

At the baseline visit, 186 (65%) of 286 patients were taking a ritonavir-boosted protease inhibitor (dual treatment 92 [64%] vs triple treatment 94 [66%]; atazanavir-ritonavir 112 [39%]—63 [44%] vs 49 [34%]), and 93 (33%) were taking a non-nucleoside reverse transcriptase inhibitor (47 [33%] vs 46 [32%]; efavirenz 79 [28%]—40 [28%] vs 39 [27%]). Tenofovir plus emtricitabine was taken at baseline by 235 (82%—119 [83%] vs 116 [81%]) patients and abacavir plus lamivudine was taken by 44 (15%—dual and triple treatment 22 [15%] each). After randomisation, 102 (71%) of 143 patients in the triple-treatment group were prescribed tenofovir plus emtricitabine, 33 (23%) abacavir plus lamivudine, and one (1%) zidovudine plus lamivudine. For the patients that we excluded after randomisation, two (1%) did not start the study drug after randomisation, we had no information for five (3%), and one (1%) took tenofovir plus emtricitabine.

	Dual treatment (n=143)	Triple treatment (n=143)	Total (N=286)
Age (years)	45 (38–52)	42 (36–48)	43 (38–51)
Women	44 (31%)	32 (22%)	76 (27%)
Origin			
Native population	113 (79%)	114 (80%)	227 (79%)
Latin America	16 (11%)	20 (14%)	36 (13%)
Sub-Saharan Africa	8 (6%)	3 (2%)	11 (4%)
Other	6 (4%)	6 (4%)	12 (4%)
HIV-1 B subtype	69 (88%)*	66 (83%)†	135 (85%)
HCV RNA-positive	29 (20%)	29 (20%)	58 (20%)
Previous AIDS-defining illness	37 (26%)	35 (24%)	72 (25%)
Reason for switching			
Intolerance	4 (3%)	6 (4%)	10 (3%)
Toxic effects	32 (22%)	20 (14%)	52 (18%)
Simplification	105 (74%)‡	114 (80%)§	219 (77%)
Risk behaviour for HIV infection			
MSM	51 (36%)	59 (41%)	110 (38%)
Heterosexual relations	54 (38%)	49 (34%)	103 (36%)
IDU	32 (22%)	24 (17%)	56 (20%)
Other	6 (4%)	11 (8%)	17 (6%)
BMI (kg/m ²)	25 (22·5–28·0)	24·8 (22·9–28·0)	24·9 (22·8–28·0)
Known duration of HIV infection	6·4 (3·4–11·4)	5·7 (2·7–11·1)	5·9 (3·2–11·2)
Nadir CD4 count (cells per μ L)	211 (90–309)	215 (139–323)	212 (108–318)
Baseline CD4 count (cells per μ L)	579 (397–770)	614 (443–796)	582 (417–784)
Antiretroviral therapy before study entry (months)	39·4 (26·7–62·3)	40·5 (22·3–67·2)	39·8 (24·7–62·5)
Viral load <50 copies per mL before study entry (months)	27 (16–51)	29 (15–58)	28 (15–53)
Switched treatment including			
Non-nucleoside reverse transcriptase inhibitor	47 (33%)	46 (32%)	93 (33%)
Boosted protease inhibitor	92 (64%)	94 (66%)	186 (65%)
Tenofovir	119 (83%)	116 (81%)	235 (82%)

Data are median (IQR) or n (%). HCV=hepatitis C virus. MSM=men who have sex with men. IDU=intravenous drug user. BMI=body-mass index. *Data available for 78 patients. †Data available for 80 patients. ‡Data available for 141 patients. §Data available for 142 patients.

Table 1: Baseline characteristics

111 (83%) of 133 patients in the per-protocol population had HIV-1 RNA of less than 50 copies per mL at week 48 in the dual-treatment group compared with 105 (78%) of 135 in the triple-treatment group. Six (5%) patients in the dual-treatment group had HIV-1 RNA of more than 50 copies per mL versus five (4%) in the triple-treatment group. The remaining patients discontinued treatment (figure 1). Non-inferiority was shown at the prespecified level of –12%—the difference in efficacy between dual and triple treatment was 6% (95% CI –5 to 16%). We also noted non-inferiority in the intention-to-treat population and the snapshot analysis for the per-protocol and intention-to-treat populations (figure 2). We recorded at least one viral load blip not leading to treatment interruption in 20 (15%) of 133 patients in the dual-treatment group and 23 (17%) of 135 patients in the triple-treatment group. We recorded two non-consecutive

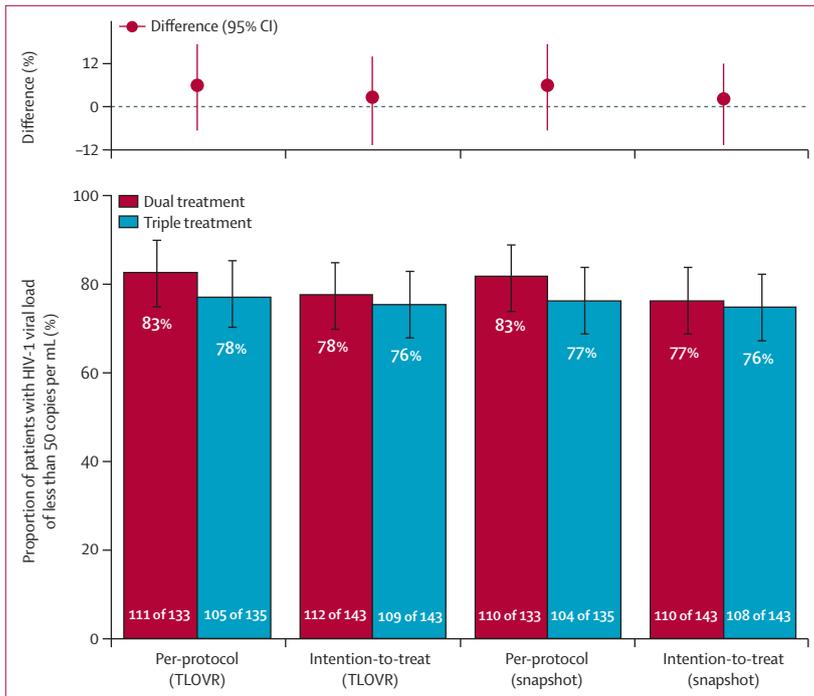


Figure 2: HIV RNA <50 copies per mL at week 48 for the per-protocol and intention-to-treat populations. Error bars are 95% CIs. TLOVR=time to loss of virological response.

See Online for appendix

	Dual treatment (n=140)	Triple treatment (n=141)
Toxic effect-related discontinuations		
Discontinuations due to any adverse event	3 (2%)	10 (7%)
Hyperbilirubinaemia or ocular icterus	2 (1%)	3 (2%)
Renal toxic effects	0	2 (1%)
Increased liver function test results	1 (1%)	1 (1%)
Nephrolithiasis	0	1 (1%)
Osteoporosis	0	1 (1%)
Hypersensitivity reaction to abacavir	0	1 (1%)
Hypophosphataemia	0	1 (1%)
Grade 3–4 AEs occurring in at least 1% of patients in either group		
Any adverse event	77 (55%)*	78 (55%)
Hyperbilirubinaemia	72 (51%)	71 (50%)
Icterus	0	2 (1%)
Increased liver function test results	2 (1%)	2 (1%)
Hyperlipidaemia	3 (2%)†	2 (1%)‡
Thrombocytopenia	2 (1%)	1 (1%)

Data are n (%). AE=adverse event. *Two patients had two grade 3–4 AEs. †Three hypertriglyceridaemias in three patients. ‡One hypertriglyceridaemia in one patient and one hypertriglyceridaemia plus hypercholesterolaemia in another patient.

Table 2: Adverse events

viral load blips in four (3%) of 133 patients in the dual-treatment group and five (4%) of 135 in the triple-treatment group. No patient had more than two viral load blips. The mean change in CD4 cell count from baseline was 11 cells per μL (SD 231) for dual treatment and

–11 cells per μL (SD 250) for triple treatment (difference 22 cells per μL [95% CI –35 to 80]; $p=0.45$).

At week 48, only ten (3%) patients in the intention-to-treat population had virological failure—six (4%) in the dual-treatment group and four (3%) in the triple-treatment group (nine [3%] in the per-protocol population—five [4%] in the dual-treatment group and four [3%] in the triple-treatment group; appendix). Eight samples could not be amplified because of low viral load. As for the remaining two patients, one belonging to the triple-treatment group developed resistance mutations (Met184Val) and the other did not. A further three patients had detectable viral load at the last follow-up visit (two in the dual-treatment group and one in the triple-treatment group) and were deemed treatment non-responders. Adherence to study drugs was good both for the dual-treatment (96%) and triple-treatment (93%) groups ($p=0.29$). Adherence was somewhat lower in patients with virological failure—(six [86%] good adherence patients of seven patients with failure) versus (254 [95%] good adherence patients of 268 patients without failure) in the intention-to-treat population (we recorded adherence for 275 patients), but the difference was not significant ($p=0.29$).

14 (5%) of 281 patients in the safety population developed severe adverse events (dual treatment six [4%] of 140; triple treatment eight [6%] of 141; appendix), none of which we deemed related to the study drug. The frequency of grade 3–4 toxic effects was evenly distributed between study groups—77 (55%) in the dual-treatment group versus 78 (55%) in the triple-treatment group (table 2). We recorded grade 3 hyperbilirubinaemia in 56 patients (40%) in the dual-treatment group and 59 (42%) in the triple-treatment group, and grade 4 hyperbilirubinaemia in 16 (11%) patients in the dual-treatment group and 12 (9%) in the triple-treatment group. Hyperbilirubinaemia led to treatment discontinuation in two (1%) patients (both grade 4) in the dual-treatment group and three (2%; two grade 3 and one grade 4) in the triple-treatment group. One (1%) patient discontinued dual treatment because of grade 4 toxic effects related to liver enzymes and another (1%) discontinued triple treatment because of grade 3 toxic effects. Treatment discontinuations were significantly less frequent in the dual-treatment group (three [2%]) than in the triple-treatment group (ten [7%]; $p=0.047$). Most of the discontinuations were because of hyperbilirubinaemia or toxic effects deemed secondary to nucleoside reverse transcriptase inhibitors: renal toxic effects, osteoporosis, hypersensitivity reaction to abacavir, and hypophosphataemia. Of the 143 patients who developed grade 3–4 hyperbilirubinaemia, 47 (33%) were taking atazanavir before study entry (dual treatment 25 [53%]; triple treatment 22 [47%]), whereas 96 (67%) were not (dual treatment 45 [47%]; triple treatment 51 [53%]).

We noted no significant differences in change from baseline in renal function, bone mineral density, or fat gain or distribution between groups at week 48 (appendix). Use of tenofovir in the switched treatment

was not associated with a different effect on those characteristics. Similarly, concentrations of 25(OH)-vitamin D did not differ between study groups at week 48 (absolute change from baseline: dual treatment -1 ng/mL; triple treatment 0.9 ng/mL; $p=0.17$) and were not associated with previous use of efavirenz (previous efavirenz use -0.9 ng/mL; no efavirenz use 2.9 ng/mL; $p=0.10$).

Triglyceride concentration change from baseline did not differ between study groups (dual treatment median 0.2 [IQR -15.6 to 42.2]; triple treatment -4.3 [-25.4 to 34.5]; $p=0.10$), whereas total cholesterol (dual treatment 4.1 [-5.6 to 20.2]; triple treatment -6.5 [-12.3 to 5.4]; $p<0.0001$) and the total cholesterol to HDL index (dual treatment 1.3 [-9.4 to 17.7]; triple treatment -4.7 [-16.9 to 3.8]; $p=0.002$) improved slightly in the triple-treatment group compared with the dual-treatment group. Some of these changes were affected by previous use of tenofovir or ritonavir-boosted protease inhibitor—the percentage change in triglycerides was related to previous ritonavir-boosted protease inhibitor (-5.7%) versus no previous protease inhibitor (7.1% ; $p=0.04$). The percentage change in total cholesterol was associated with previous tenofovir (1.6%) versus no previous tenofovir (-5.6% ; $p=0.02$), and percentage change in the cholesterol to HDL index was related to previous ritonavir-boosted protease inhibitor (-4.5%) versus no previous ritonavir-boosted protease inhibitor (1.1% ; $p=0.04$).

76 (48%) patients in the dual-treatment group and 82 (52%) in the triple-treatment group participated in the neurocognitive substudy. 51 (67%) patients had neurocognitive impairment (NCI) at baseline in the dual-treatment group and 51 (62%) did in the triple-treatment group. The overall change in neurocognitive function from baseline (GDS score; five domains) did not differ between study groups: -0.26 (95% CI -0.40 to -0.07) for dual treatment versus -0.08 (-0.20 to 0.07) for triple treatment. We measured distribution of NCI at week 48 in 110 patients who had also been assessed at baseline (53 patients in the dual-treatment group and 57 in the triple-treatment group). Results were similar for both treatment groups: no NCI occurred in 13 (25%) patients in the dual-treatment group versus 15 (26%) in the triple-treatment group; NCI improved in ten (19%) versus seven (12%); new NCI occurred in three (6%) versus six (11%); and NCI remained unchanged in 27 (51%) versus 29 (51%).

Discussion

To our knowledge, the SALT study is the first randomised clinical trial to assess the efficacy and safety of treatment simplification to dual treatment in patients taking triple cART who needed to change treatment for reasons of toxic effects, intolerance, or convenience. This dual-treatment regimen was non-inferior to standard triple cART and had a good safety profile. The results from the

primary efficacy analysis were also consistent across several sensitivity analyses.

Switching from a triple to a dual atazanavir-based regimen is not associated with an increased risk of virological failure, which was low in both groups, with most patients with virological failure with HIV-1 RNA of less than 200 copies per mL. Although detectable low viral load counts could be transient and associated with factors not related to the antiretroviral regimen (eg, intercurrent infections, short-term poor adherence, and variability in HIV-1 RNA PCR assays),³⁰ we deemed these events treatment failures, patients stopped the study, and we gave rescue treatment to avoid emergence of resistance. Moreover, the frequency of blips throughout the 48 weeks was equivalent in each study group. Only one patient (triple-treatment group) developed resistance mutations (Met184Val). We detected no resistance mutations in the dual-treatment group. Similar findings have been reported in a study comparing ritonavir and lopinavir plus lamivudine dual treatment with ritonavir and lopinavir-based triple treatment.³¹ The good results obtained with strategies simplifying stable patients to lamivudine plus ritonavir-boosted protease inhibitor contrast with those obtained with lamivudine-sparing dual treatment in patients who are virologically suppressed and have resistance mutations.³²

Safety in the dual-treatment group was good and predictable. Few patients discontinued the study in the two groups because of toxic effects, with treatment interruptions being significantly more frequent in the triple-treatment group than in the dual-treatment group. The most common reasons were hyperbilirubinaemia and ocular icterus, which were more frequent in patients who were not taking atazanavir-ritonavir before study entry. Only one patient developed nephrolithiasis, which we deemed unrelated to the study drug, thus arguing against the theoretical risk of a high frequency of nephrolithiasis secondary to increased atazanavir concentrations in patients discontinuing tenofovir.²² In the remaining patients, toxic effects were mainly attributable to nucleoside reverse transcriptase inhibitors. Likewise, grade 3–4 adverse events almost exclusively resulted from hyperbilirubinaemia. We noted other severe adverse events, although they were not related to study drugs. Unsurprisingly, treatment interruptions because of toxic effects were more common than virological failures were because all patients were suppressed at study entry and most started drugs to which they had not been previously exposed.

As expected, hyperbilirubinaemia was the most common adverse event and the main reason for treatment interruption and withdrawal of informed consent. The frequency of hyperbilirubinaemia and icterus was not substantially different to findings from studies in which atazanavir was used in patients who were naive and switching.^{14,33–35} However, only 39% of patients were taking this drug before entering the study. In fact, 67% of

patients who developed grade 3–4 hyperbilirubinaemia were not taking atazanavir, whereas 33% were taking it before entering the study. The higher treatment discontinuation due to hyperbilirubinaemia in another study³⁶ could be related to the lower tolerance threshold of patients to adverse effects in view of the number of present treatment alternatives.

The absence of significant differences in changes from baseline in renal function, bone mineral density, and fat gain and distribution between groups might be attributable to the short duration that patients were studied for (48 weeks) and the low frequency of changes in body fat associated with new combination antiretroviral therapies.³⁷ Furthermore, frequent use of tenofovir in the triple-treatment group means that patients entered the study for reasons other than tenofovir-induced toxic effects. Unlike other studies, in which patients start a tenofovir-sparing regimen³⁶ or change from a specific antiretroviral regimen to a tenofovir-sparing one,^{18,31,38} participants in the SALT study changed either because of problems related to nucleos(t)ides, the third drug, or both; consequently, the effect of the changes is blurred. Changes in lipid variables were small, with slight percentage increases in total cholesterol and the cholesterol to HDL index in the dual-treatment group; however, these changes were significantly related to previous use of tenofovir or protease inhibitor. Thus, the percentage change in triglycerides was associated with previous ritonavir-boosted protease inhibitor, the percentage change in total cholesterol was associated with previous tenofovir, and the absolute change in the atherogenic index was associated with previous use of ritonavir-boosted protease inhibitor. In this sense, patients taking ritonavir-boosted protease inhibitor before study entry (specifically boosted lopinavir or fosamprenavir) were able to benefit from a switch to a protease inhibitor with a better lipid profile than that of the one they were taking. By contrast, patients that were no longer taking tenofovir lost the favourable lipid effect of this drug. A longer follow-up (up to 96 weeks) and a continuing subgroup analysis by drug received at baseline will clarify these issues.

The CNS is one of the reservoirs in which replication of HIV-1 can have a substantial effect. The number of drugs included in an antiretroviral regimen to prevent HIV-1-associated neurocognitive disorders is the subject of debate. In this sense, whereas ritonavir-boosted protease inhibitor monotherapy has been related to a possible increase in the risk of viral escape in the cerebrospinal fluid,³⁹ triple treatment might increase the risk of cART-induced CNS toxic effects.⁴⁰ Data, however, do not suggest important differences in the pattern of neurocognitive profiles between patients receiving ritonavir-boosted protease inhibitor monotherapy and those on standard ritonavir-boosted protease inhibitor-based triple treatment.⁴¹ In the SALT study, change in neurocognitive function from baseline did not differ significantly

between study groups at 48 weeks. Dual treatment with atazanavir–ritonavir plus lamivudine could be an intermediate approach between triple cART and protease inhibitor monotherapy, with enough potency to prevent HIV-1-associated neurocognitive disorders and few CNS toxic effects.

Our study has strengths and limitations. Unlike other studies on a switch to a ritonavir-boosted protease inhibitor plus lamivudine,^{18,31} patients in the SALT study were previously receiving different combinations of drugs that did not always include atazanavir–ritonavir. In fact, only 39% of patients were on atazanavir–ritonavir-based treatment before entering the study. Moreover, the nucleoside reverse transcriptase inhibitors in the previous regimen could have differed from those that we gave patients after inclusion. Thus, all the toxic effects attributable to changes in cART could mean that failure penalises global efficacy in both groups. The fact that the trial was open-label—a weakness compared with a double-blind design—probably did not greatly affect comparative efficacy. Most discontinuations were attributable to atazanavir-induced toxic effects (present in both arms) or other objective causes, such as renal toxic effects, increased liver function test results, or hypophosphataemia. To consider switches for toxic effects to be equivalent to virological failures in efficacy analysis can be deemed a limitation of the study because we did not account for the virological outcome after treatment switching. Nevertheless, the rationale of the SALT study was to test a new drug-sparing strategy that maintained efficacy while protecting the patient from toxic effects, improving convenience, and potentially saving drug options for the future. Therefore, changes in the assigned drugs driven either by intolerance or toxic effects acquired the relevance of a virological failure. The frequency of blips noted in this study could have increased because one of the centres changed its viral load measurement technique in the first few months of the study. However, the effect of this change was transitory and evenly distributed between study groups. Finally, we chose the instruments used to assess neurocognitive performance because they were sufficiently sensitive to detect small changes in cognition between study groups more than to assess the prevalence of NCI. Such high sensitivity meant that abnormal neurocognitive results were more frequent than expected.

Contributors

JAP-M designed the study in consultation with RR and SM. The GESIDA-7011 Study Group enrolled patients into the study and acquired data. JAP-M, RR, and SM analysed data and clinically oversaw the study. JAP-M, RR, AR, JP, IS-L, MR, ME, JS, JS-M, JT, AM, AA, JN, and SM interpreted data. HE managed and coordinated the study. JAP-M drafted the report and RR and SM reviewed it. All authors provided input into the report and approved the final version.

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Declaration of interests

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References

- 1 European AIDS Clinical Society. Guidelines. Version 7.1. November 2014. Brussels: European AIDS Clinical Society, 2014.
- 2 Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Washington, DC: Department of Health and Human Services USA, 2014.
- 3 Carr A, Cooper DA. Adverse effects of antiretroviral therapy. *Lancet* 2000; **356**: 1423–30.
- 4 Calza L. Renal toxicity associated with antiretroviral therapy. *HIV Clin Trials* 2012; **13**: 189–211.
- 5 Mocroft A, Kirk O, Reiss P, et al. Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients. *AIDS* 2010; **24**: 1667–78.
- 6 McComsey GA, Kitch D, Daar ES, et al. Bone mineral density and fractures in antiretroviral-naïve persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: Aids Clinical Trials Group A5224s, a substudy of ACTG A5202. *J Infect Dis* 2011; **203**: 1791–801.
- 7 Bedimo R, Maalouf NM, Zhang S, Drechsler H, Tebas P. Osteoporotic fracture risk associated with cumulative exposure to tenofovir and other antiretroviral agents. *AIDS* 2012; **26**: 825–31.
- 8 Choi AI, Vittinghoff E, Deeks SG, Weekley CC, Li Y, Shlipak MG. Cardiovascular risks associated with abacavir and tenofovir exposure in HIV-infected persons. *AIDS* 2011; **25**: 1289–98.
- 9 Bavinger C, Bendavid E, Niehaus K, et al. Risk of cardiovascular disease from antiretroviral therapy for HIV: a systematic review. *PLoS One* 2013; **8**: e59551.
- 10 Bierman WF, van Aagtmael MA, Nijhuis M, Danner SA, Boucher CA. HIV monotherapy with ritonavir-boosted protease inhibitors: a systematic review. *AIDS* 2009; **23**: 279–91.
- 11 Pulido F, Serrano O, Rivero A, et al. Atazanavir/ritonavir monotherapy for maintenance of virologic suppression: 48-week primary analysis of the 96-week multicentre, open-label, single-arm, pilot OREY study. 12th European AIDS Conference; Cologne, Germany; Nov 11, 2009. Abstr PS4/6.
- 12 Mathis S, Khanlari B, Pulido F, et al. Effectiveness of protease inhibitor monotherapy versus combination antiretroviral maintenance therapy: a meta-analysis. *PLoS One* 2011; **6**: e22003.
- 13 Kumar PN, Patel P. Lamivudine for the treatment of HIV. *Expert Opin Drug Metab Toxicol* 2010; **6**: 105–14.
- 14 Gatell J, Salmon-Ceron D, Lazzarin A, et al. Efficacy and safety of atazanavir-based highly active antiretroviral therapy in patients with virologic suppression switched from a stable, boosted or unboosted protease inhibitor treatment regimen: the SWAN Study (A1424-097) 48-week results. *Clin Infect Dis* 2007; **44**: 1484–92.
- 15 Malan DR, Krantz E, David N, et al. Efficacy and safety of atazanavir, with or without ritonavir, as part of once-daily highly active antiretroviral therapy regimens in antiretroviral-naïve patients. *J Acquir Immune Defic Syndr* 2008; **47**: 161–67.
- 16 Molina JM, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/ritonavir compared with twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naïve HIV-1-infected patients: 96-week efficacy and safety results of the CASTLE study. *J Acquir Immune Defic Syndr* 2010; **53**: 323–32.
- 17 Jansen K, Sönnnerborg A, Brockmeyer N, et al. Long-term efficacy and safety of atazanavir/ritonavir treatment in a real-life cohort of treatment-experienced patients with HIV type 1 infection. *AIDS Res Hum Retroviruses* 2013; **29**: 564–73.

- 18 Di Giambenedetto S, Fabbiani M, Colafigli M, et al. Safety and feasibility of treatment simplification to atazanavir/ritonavir + lamivudine in HIV-infected patients on stable treatment with two nucleos(t)ide reverse transcriptase inhibitors + atazanavir/ritonavir with virological suppression (Atazanavir and Lamivudine for Treatment Simplification, ATLAS pilot study). *J Antimicrob Chemother* 2013; **68**: 1364–72.
- 19 Knobel H, Alonso J, Casado JL, et al. Validation of a simplified medication adherence questionnaire in a large cohort of HIV-infected patients: the GEEMA study. *AIDS* 2002; **16**: 605–13.
- 20 American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th edn (DSM-IV). Arlington: American Psychiatric Association, 2000.
- 21 Zigmund AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand* 1983; **67**: 361–70.
- 22 Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. *Neurology* 2007; **69**: 1789–99.
- 23 Carey CL, Woods SP, Gonzalez R, et al. Predictive validity of global deficit scores in detecting neuropsychological impairment in HIV infection. *J Clin Exp Neuropsychol* 2004; **26**: 307–19.
- 24 US Department of Health and Human Services. Guidance for industry. Antiretroviral drugs using plasma HIV RNA measurements—clinical considerations for accelerated and traditional approval. Washington, DC: US Department of Health and Human Services, 2002.
- 25 European Medicines Agency. Guideline on the choice of the non-inferiority margin. London: European Medicines Agency, 2005.
- 26 US Department of Health and Human Services. Guidance for industry. E 10 choice of control group and related issues in clinical trials. Washington, DC: US Department of Health and Human Services, 2001.
- 27 Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJ. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. *JAMA* 2006; **295**: 1152–60.
- 28 Smith F, Hammerstrom T, Soon G, Zhou S. A meta-analysis to assess the FDA DAVP's TLOVR algorithm in HIV submissions. *Drug Inf J* 2011; **45**: 291–300.
- 29 D'Agostino RB, Massaro JM, Sullivan LM. Non-inferiority trials: design concepts and issues—the encounters of academic consultants in statistics. *Stat Med* 2003; **22**: 169–86.
- 30 Brumme CJ, Swenson LC, Wynhoven B, et al. Technical and regulatory shortcomings of the TaqMan version 1 HIV viral load assay. *PLoS One* 2012; **7**: e43882.
- 31 Arribas JR, Girard P-M, Landman R. Dual treatment with lopinavir-ritonavir plus lamivudine versus triple treatment with lopinavir-ritonavir plus lamivudine or emtricitabine and a second nucleos(t)ide reverse transcriptase inhibitor for maintenance of HIV-1 viral suppression (OLE): a randomised, open-label, non-inferiority trial. *Lancet Infect Dis* 2015; published online June 1. [http://dx.doi.org/10.1016/S1473-3099\(15\)70129-5](http://dx.doi.org/10.1016/S1473-3099(15)70129-5).
- 32 van Lunzen J, Pozniak A, Gatell J, et al. HARNESST study: ritonavir-boosted atazanavir (ATV/r)+raltegravir (RAL) switch study in virologically suppressed, HIV-1-infected patients. 20th International AIDS Conference; Melbourne, Australia; July 20–25, 2014. Poster LBPE19.
- 33 Molina JM, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naïve HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. *Lancet* 2008; **372**: 646–55.
- 34 Mallolas J, Podzamczar 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. *J Acquir Immune Defic Syndr* 2009; **51**: 29–36.
- 35 Lennox JL, Ofotokun I, Kuritzkes DR, Benson CA, Rooney JF. Efficacy and tolerability of 3 nonnucleoside reverse transcriptase inhibitor-sparing antiretroviral regimens for treatment-naïve volunteers infected with HIV-1: a randomized, controlled equivalence trial. *Ann Intern Med* 2014; **161**: 461–71.
- 36 Stellbrink HJ, Orkin C, Arribas JR, et al. Comparison of changes in bone density and turnover with abacavir-lamivudine versus tenofovir-emtricitabine in HIV-infected adults: 48-week results from the ASSERT study. *Clin Infect Dis* 2010; **51**: 963–72.
- 37 Perez-Molina JA, Domingo P, Martínez E, Moreno S. The role of efavirenz compared with protease inhibitors in the body fat changes associated with highly active antiretroviral therapy. *J Antimicrob Chemother* 2008; **62**: 234–45.
- 38 Negro E, Domingo P, Alvarez NP. Multicenter randomized study to assess changes in HIV subjects with low bone mineral density after switching from tenofovir to abacavir: OsteoTDF study. 20th Conference on Retroviruses and Opportunistic Infections; Atlanta, Georgia, USA; March 3–6, 2013; abstr 824.
- 39 Pérez-Valero I, Bayón C, Cambron I, Gonzalez A, Arribas JR. Protease inhibitor monotherapy and the CNS: peace of mind? *J Antimicrob Chemother* 2011; **66**: 1954–62.
- 40 Robertson K, Liner J, Meeker RB. Antiretroviral neurotoxicity. *J Neurovirol* 2012; **18**: 388–99.
- 41 Pérez-Valero I, González-Baeza A, Estébanez M, et al. A prospective cohort study of neurocognitive function in aviremic HIV-infected patients treated with 1 or 3 antiretrovirals. *Clin Infect Dis* 2014; **59**: 1627–34.