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Individual patient data meta-analysis of randomized controlled trials of dual therapy with a boosted PI plus lamivudine for maintenance of virological suppression: GeSIDA study 9717

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Background: Dual therapy (DT) with a ritonavir-boosted PI (PI/r) plus lamivudine has proven non-inferior (12% margin) to triple therapy (TT) with PI/r plus two nucleos(t)ide reverse transcriptase inhibitors [N(t)RTIs] in four clinical trials. It remains unclear whether DT is non-inferior based on the US FDA endpoint (virological failure with a margin of 4%) or in specific subgroups.

Methods: We performed a systematic search (January 1990 to March 2017) of randomized controlled trials that compared switching of maintenance ART from TT to DT. The principal investigators were contacted and agreed to share study databases. The primary endpoint was non-inferiority of DT to TT based on the current FDA endpoint (4% non-inferiority margin for virological failure at week 48). We also analysed whether efficacy was modified by gender, active HCV infection and type of PI. Effect estimates and 95% CIs were calculated using generalized estimating equation-based models.

Results: We found 881 references that yielded eight articles corresponding to four clinical trials (1051 patients). At week 48, 4% of patients on DT versus 3.04% on TT had experienced virological failure (difference 0.9%; 95% CI −1.2% to 3.1%), and 84.7% of patients on DT versus 83.2% on TT had <50 copies of HIV RNA/mL (FDA snapshot algorithm) (difference 1.4%; 95% CI −2.8% to 5.8%). Gender, active HCV infection and type of PI had no effect on differences in treatment efficacy between DT and TT.

Conclusions: DT was non-inferior to TT using both current and past FDA endpoints. The efficacy of DT was not influenced by gender, active HCV infection status, or type of PI.

Introduction

Since the mid-1990s, the standard of combination ART has been two nucleos(t)ide reverse transcriptase inhibitors [N(t)RTIs] with an anchor drug, namely, a ritonavir-boosted PI (PI/r), an NNRTI or an integrase inhibitor. The goal of ART is to suppress replication of HIV and thus improve the quality of life and life expectancy of infected patients. However, besides requiring strict adherence, lifelong ART is associated with a series of disadvantages in the form of adverse events, extensive exposure to drugs, and cost, all of which may affect the long-term effectiveness of treatment and its sustainability. Consequently, simplification strategies have been sought to improve the convenience of ART while maintaining effectiveness.

The combination of a boosted PI plus lamivudine (PI/r + 3TC) has the potential to suppress some of the long-term adverse events associated with some N(t)RTIs, preserve future treatment options and reduce the cost of ART. This strategy has proven to be efficacious and safe in several randomized clinical trials of

switching ART in stable patients (atazanavir boosted with ritonavir plus lamivudine,[1–3] lopinavir boosted with ritonavir plus lamivudine,[4] and darunavir boosted with ritonavir plus lamivudine[5]). Based on a non-inferiority margin of 12%, these trials showed the non-inferiority of dual therapy (DT) with PI/r + 3TC to triple therapy (TT) with the respective PI/r plus two N(t)RTIs, based on the percentage of participants with <50 copies of HIV RNA/mL of plasma at week 48. Nevertheless, it remains unclear whether DT is efficacious in specific subgroups, such as women and HIV/HCV-coinfected patients and whether PIs have same efficacy in the context of DT. The limited sample size of these trials (<150 patients per group) prevented the performance of such subgroup analyses.

In 2015, the US FDA updated its guideline for trials on switching ART.[6] The current guideline focuses on the rates of virological failure more than on the rates of treatment success, as was previously the case. This is because in switch trials patients start with HIV RNA levels that are already below the assay limit of quantification. Thus, the endpoint of major interest is the percentage of participants with suppressed HIV RNA at baseline who lose virological control after switching to a new drug or regimen. Since virological failure is typically in the range of 1% to 3% in this type of trial, a non-inferiority margin of 4% has been recommended and considered feasible from a drug development standpoint. With this new margin of 4%, it is unknown whether DT with PI/r + 3TC meets this non-inferiority criterion.

To overcome the limited sample size in prior trials, we performed an individual patient data (IPD) meta-analysis. Estimations made using this methodology result in more tightly defined and precise estimates of treatment differences. Classic meta-analysis is based on aggregate data extracted from publications or obtained from investigators. These aggregated data represent a summary of the individual participants for each study and may therefore potentially limit the spectrum of possible analyses and reduce power. In addition, results and conclusions apply to the groups studied but not to individual patients. The centralized collection of IPD is perhaps the most resource-intensive and time-consuming approach for systematic reviews. However, it has many advantages, such as the absence of reliance on aggregated data (published trials), more balanced interpretation of the results of the review, analysis based on the treatment allocated, the possibility of subgroup analysis (not feasible with aggregated data), and wider endorsement.[7] Given their considerable advantages, meta-analyses based on IPD have been called the 'gold standard' of systematic reviews.[8]

To our knowledge, this IPD meta-analysis is the first to be carried out through collaboration of academic investigators in the field of ART. We performed an IPD meta-analysis in order to obtain better estimates of the efficacy and advantages of DT based on PI/r + 3TC, to apply the new FDA criteria for non-inferiority in switch trials, and to analyse the effect of this simplification strategy on specific subgroups of patients.

Methods

Search strategy and selection criteria

We performed a systematic search for the period January 1990 to March 2017 to identify potentially eligible trials for an IPD meta-analysis. Details on review methods, including the search strategy, are described in the published protocol. This study is registered in PROSPERO with the identifier CRD42017058511.

Randomized controlled trials that evaluated switching TT based on PI/r plus two N(t)RTIs to DT based on PI/r + 3TC in patients with HIV-1 infection were eligible. The study population of interest included patients aged ≥18 years with HIV-1 infection, stable ART, viral suppression and hepatitis B surface antigen-negative status.

We made a systematic search of Medline, Embase, Web of Science, Lilacs and the Cochrane Central Register of Controlled Trials (CENTRAL) limited to articles published between 1 January 1990 and 31 March 2017, with no language restrictions. We made a secondary search by consulting the references of the articles included and the abstracts of the most important scientific meetings in the field of HIV infection (Conference on Retroviruses and Opportunistic Infections, International AIDS Society Conference on HIV, HIV Drug Therapy Glasgow, and European AIDS Clinical Society Congress). We used the search terms 'nucleoside-sparing', 'NRTI-sparing', 'dual therapy', 'HIV' and 'AIDS'. We used a methodological filter to focus only on randomized controlled trials. We examined ClinicalTrials.gov in order to identify unpublished trials.

Data extraction

We contacted the principal investigators of each trial identified to obtain anonymized raw data after signing agreement forms. Detailed definitions and diagnostic criteria of all study outcomes are provided in the study protocol. The data obtained included patients' demographic characteristics, virological data at baseline and throughout the follow-up to 48 weeks, blood lipid levels, CD4 cell count and renal function. Information about adverse events, treatment discontinuation, viral mutations after virological failure and change in concomitant medication were also obtained for all participants.

The primary endpoint of our IPD meta-analysis was to demonstrate the non-inferiority of DT to TT at 48 weeks, based on the proportion of patients with virological failure according to the FDA snapshot algorithm. Virological failure was defined as the proportion of patients with an HIV-1 viral load of ≥50 copies/mL at 48 weeks (including patients who discontinued the study drug or study before week 48 because of lack or loss of efficacy). The margin for non-inferiority was fixed at 4%. Missing patients, lack of virological data at 48 weeks, and changes in any study drug were not considered virological failures in this analysis. Based on the FDA snapshot algorithm, the secondary endpoint of the study was the proportion of patients with undetectable viral load (<50 copies/mL) at week 48. For this secondary endpoint patients without virological response were classified in the following categories: virological failure; missing patients; and changes in any study drug.

Data synthesis and validation

Data from the original trials were extracted by an investigator who was familiar with the data. The coordinating statistician verified the data to identify inconsistencies, outliers and invalid data. Any data clarification queries were forwarded to the investigators of the original trials. The primary analysis of the original trials was replicated before the IPD meta-analysis to ensure data robustness and consistency with original trial reports.

Assessment of risk of bias

Risk of bias was independently assessed by two investigators (J. A. P.-M. and C. C.) using five of the seven criteria of the Cochrane Risk of Bias tool. We did not consider the criterion 'Selective reporting', because any data needed for this analysis would have been requested from the authors regardless of whether or not they were reported in their publications. We did not use the criterion 'Other sources of bias' because we did not have any

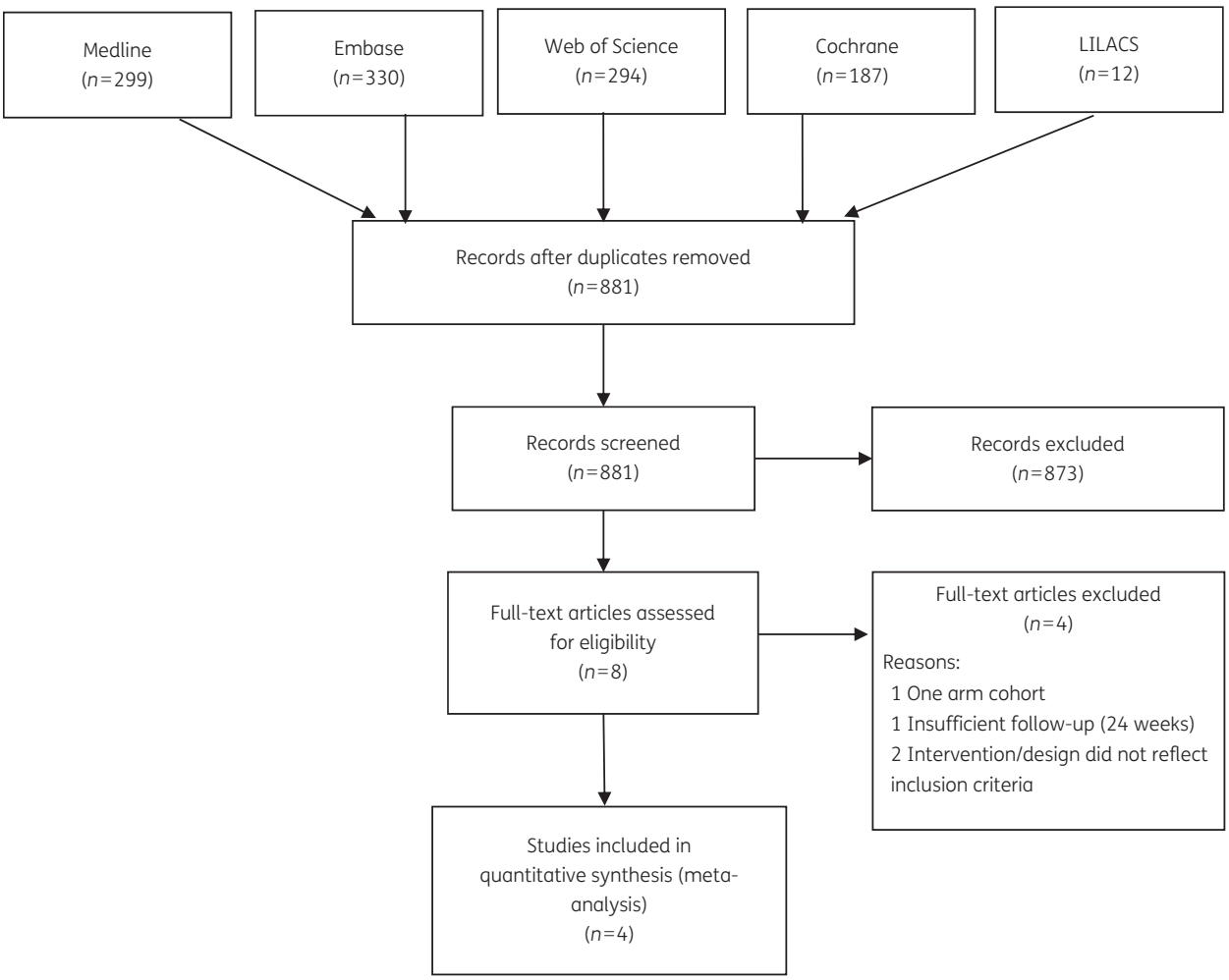

Figure 1. Flow diagram for selected studies.

major concern about bias that was not already included in the Cochrane Risk of Bias tool. The criteria were graded as low risk, high risk or unclear consensus. When the information was not available in the published paper, the trial's lead author was contacted to provide clarification or additional information.

Data analysis

Non-inferiority margins were established at 4% for the loss of efficacy outcome (virological failure) and at 12% for the undetectable viral load outcome. We used a generalized estimating equation (GEE) model in which the four studies were considered as clusters within the analysis. Non-inferiority of virological failure was considered demonstrated if the upper limit of the 95% CI of the difference between DT and TT was lower than the non-inferiority margin of 4%. Similarly, non-inferiority of undetectable viral load was considered demonstrated if the lower limit of the 95% CI of the difference between DT and TT was greater than the non-inferiority margin of 12%.

The effect of switching therapy on both outcomes was estimated using the absolute risk difference with its 95% CI. We assumed a binomial distribution of the response variable, an identity link function between the response variable and treatment, and an exchangeable correlation matrix. Interactions between treatment and gender, active HCV infection and type of PI were evaluated by including corresponding interaction terms in the GEE models.

Differences in CD4 cell count, blood lipid values and renal function between treatment groups were evaluated from baseline to 48 weeks using GEE models and assuming a Gaussian distribution for the response variable, an identity link function between the variable and the treatment, and an exchangeable correlation matrix.

We also analysed the total proportion of grade 3–4 adverse effects and the proportion of discontinuations due to adverse events caused by treatment in the dual and triple arms. Resistance mutations at virological failure were also described.

All statistical analyses were based on a significance level of $\alpha = 0.05$ and were performed with STATA 14 IC.

Results

The systematic search revealed 881 articles (Figure 1). After checking the title and abstract and eliminating duplicates, we ruled out 873 articles that did not meet our predefined criteria. After examining the full text of the remaining eight studies, we excluded four, as they involved a one-arm cohort, had insufficient follow-up (24 weeks), or the design/intervention did not reflect inclusion

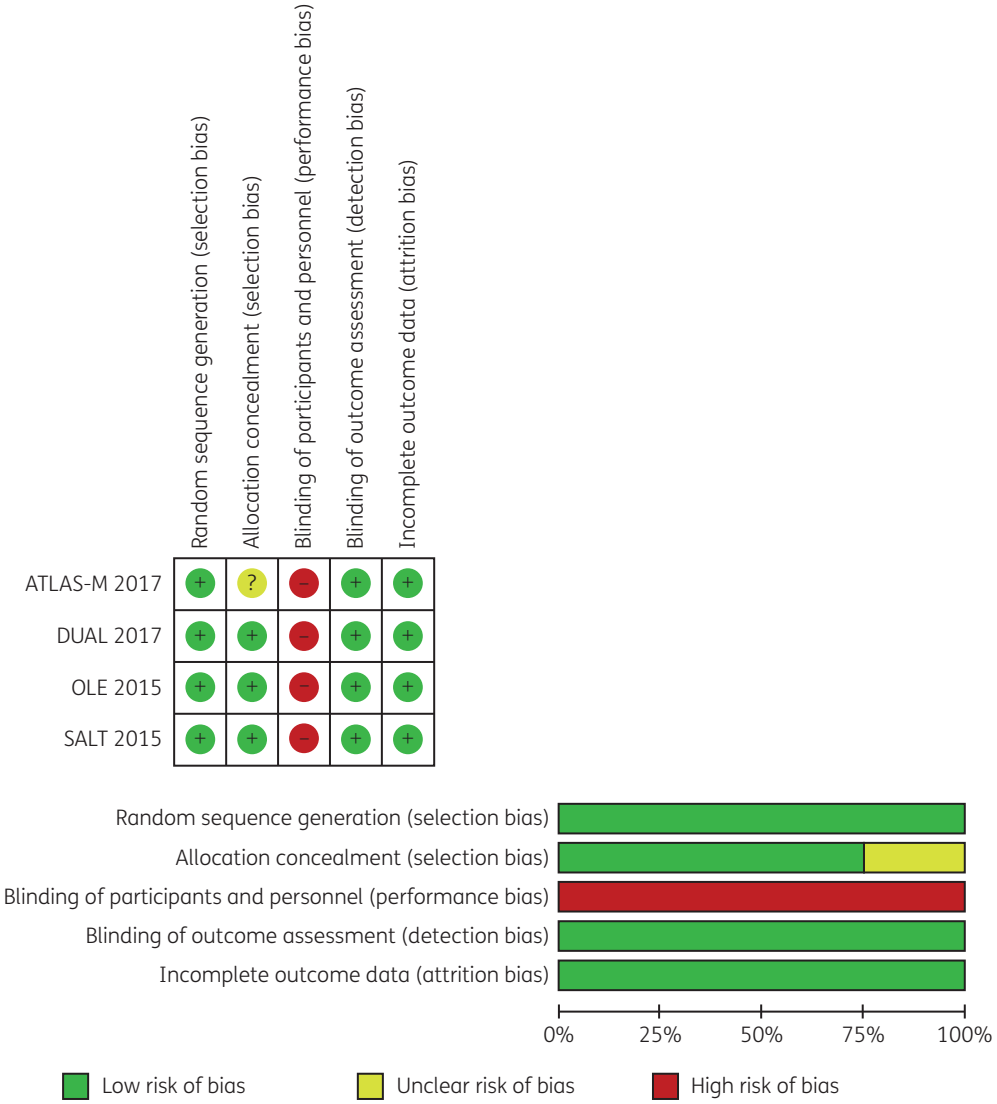

Figure 2. Assessment of the risk of bias. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

criteria. We finally selected four clinical trials[1,2,4,5] comprising data from 1051 patients for description and analysis. These four trials compared a strategy based on switching from a standard TT regimen based on PI/r plus two N(t)RTIs to a DT regimen based on PI/r + 3TC: in the ATLAS-M[1] and SALT[2] trials atazanavir boosted with ritonavir plus lamivudine was compared with atazanavir boosted with ritonavir plus two N(t)RTIs; in the OLE[4] trial lopinavir boosted with ritonavir plus lamivudine was compared with lopinavir boosted with ritonavir plus two N(t)RTIs; and in the DUAL[5] trial darunavir boosted with ritonavir plus lamivudine was compared with darunavir boosted with ritonavir plus two N(t)RTIs. All four studies analysed were open-label, randomized clinical trials. The risk of bias for the four studies was low overall, with the exception of the blinding of participants and personnel because of the open-label nature of their design (Figure 2).

The primary endpoint in these trials was non-inferiority of the virological response between treatment groups, defined as the proportion of patients with an HIV-1 viral load of <50 copies/mL at week 48, using a non-inferiority margin of 12% in accordance with the former recommendations of regulatory agencies. The population comprised mainly male adults in their forties, with a prevalence of HCV infection of 22%, and a median of 2.5 years of HIV-1 viral load of <50 copies/mL prior to study entry; 75% of the population were taking tenofovir disproxil fumarate and the median CD4 count of the population was 600 cells/mm^3 at baseline (Table 1).

At week 48, 21 patients on DT (4.0%) versus 16 patients on TT (3.04%) had ≥50 copies of HIV RNA/mL in the ITT population (FDA snapshot algorithm). Non-inferiority was shown at the current prespecified level of 4% for switch studies; the difference in the pooled proportion of virological failure between dual and triple regimens was 0.9% (95% CI −1.30 to 3.20) (Figure 3a). Subgroup analysis showed that the treatment difference between DT and TT was not affected by gender, HCV infection status or type of PI (Figure 3b). Non-inferiority was also demonstrated when it was

Table 1. Summary of the principal characteristics of patients included in the individual patient meta-analysis

	DUAL ($n = 249$)		SALT ($n = 286$)		OLE ($n = 250$)		ATLAS-M ($n = 266$)		Pooled ($N = 1051$)	
Characteristic	DT ($n = 126$)	TT ($n = 123$)	DT ($n = 143$)	TT ($n = 143$)	DT ($n = 123$)	TT ($n = 127$)	DT ($n = 133$)	TT($n = 133$)	DT ($n = 525$)	TT ($n = 526$)
Age, years	44 (36–52)	43 (37–49)	46 (39–53)	45 (37–49)	44 (37–50)	47 (42–52)	43 (36–49)	44 (36–51)	44 (37–51)	45 (37–50)
Males, *n* (%)	107 (84.9)	100 (81.3)	99 (69.2)	111 (77.62)	90 (73.2)	81 (63.8)	112 (84.2)	100 (75.2)	408 (77.7)	392 (74.5)
Active HCV infection, *n* (%)	32 (25.4)	28 (22.8)	29 (20.3)	29 (20.3)	43 (35.0)	43 (33.9)	14 (10.5)	14 (10.5)	118 (22.5)	114 (21.7)
Time with VL <50 copies/mL (months)	20 (9–39)	28 (14–46)	27 (16–51)	29 (15–58)	43 (25–72)	52 (29–81)	23 (13–46)	21 (12–45)	29 (15–52)	32 (16–62)
CD4 count at baseline (cells/mm^3)	606 (397–790)	603 (470–791)	579 (398–770)	614 (443–796)	605 (410–778)	616 (459–796)	622 (473–777)	616 (486–781)	592 (419–778)	612 (464–792)
Patients taking TDF at baseline (%)	93 (74)	93 (76)	119 (83)	116 (81)	73 (62)	73 (60)	105 (79)	112 (84)	390 (74)	394 (75)
Cholesterol at baseline (mg/dL)	186 (163–208)	182 (157–204)	184 (162–213)	185 (163–210)	191 (164–223)	195 (175–228)	185 (161–221)	189 (162–219)	186 (163–215)	189 (164–213)
HDL (mg/dL)	45 (39–52)	44 (37–54)	47 (39–57)	44 (37–53)	50 (40–60)	53 (44–63)	43 (39–57)	44 (37–53)	46 (39–56)	47 (39–56)
LDL (mg/dL)	114 (95–131)	109 (88–126)	111 (90–134)	114 (88–131)	111 (91–136)	118 (92–137)	113 (91–139)	113 (92–136)	112 (91–134)	113 (90–133)
Triglycerides (mg/dL)	119 (85–166)	120 (84–170)	121 (88–183)	128 (88–180)	143 (106–200)	141 (198–195)	126 (85–168)	126 (95–172)	126 (90–179)	130 (90–176)
GFR at baseline (mL/min)	83.7 (64.6–107.7)	100 (73.0–109.8)	91.2 (66.1–108.4)	103.2 (69.0–112.6)	88.2 (65.8–111.10)	95.2 (68.3–107.2)	75.5 (64.8–108.9)	81.4 (66.1–105.5)	84.4 (65.3–108.6)	97.1 (68.6–110.0)

Continuous variables are expressed as median (IQR).
VL, viral load; TDF, tenofovir disoproxil fumarate; GFR, glomerular filtration rate.

analysed with the former endpoint (virological response) at a threshold of −12% (ITT population; FDA snapshot algorithm). At week 48, there were 445 patients on DT (84.7%) and 438 patients on TT (83.2%) who had <50 copies of HIV RNA/mL. The difference in the pooled proportions of virological success between dual and triple regimens was 1.47% (95% CI −2.9% to 5.8%) (Figure 4a). Similarly, the subgroup analysis for this endpoint did not demonstrate that the treatment difference between DT and TT was affected by gender, HCV infection status or type of PI (Figure 4b). The analysis of resistance mutations in patients with virological failure could be performed for 16 of them: 2 in the SALT trial (1 in the DT arm and 1 in the TT arm), 4 in the OLE trial (2 DT and 2 TT), 3 in the DUAL trial (2 DT and 1 TT) and 7 in the ATLAS-M trial (2 DT and 5 TT). Only three patients developed resistance mutations at failure. One patient belonging to the DT arm in the OLE trial (K103N + M184V), another in the TT arm of the SALT trial (M184V) and a third in the TT arm of the DUAL trial (L10I + A71T + L76W). Proportions of patients with resistance after virological failure were 0.19% (95% CI 0.004% to 1.0%) and 0.38% (95% CI 0.04% to 1.3%) in the DT and TT arms, respectively.

The total frequency of grade 3–4 adverse events was evenly distributed between the groups: 117 (22.3%) in the DT group versus 119 (22.6%) in the TT group ($P = 0.89$). The most common toxic effects were hyperbilirubinaemia [91 (77.7%) for DT versus 92 (77.3%) for TT; $P = 0.93$], impaired hepatic liver enzymes [5 (4.3%) for DT versus 1 (0.8%) for TT; $P = 0.094$], hypertriglyceridaemia [3 (2.6%) for DT versus 2 (1.7%) for TT; $P = 0.63$], respiratory diseases [e.g. tracheobronchitis, COPD, pulmonary hypertension or pneumonia, 3 (2.6%) for DT versus 3 (2.5%) for TT; $P = 0.98$], nephrolithiasis [2 (1.7%) for DT versus 3 (2.5%) for TT; $P = 0.66$], cardiovascular events [e.g. myocardial infarction and acute myocardial ischaemia, 0 (0%) for DT versus 3 (2.5%) for TT; $P = 0.084$], Hodgkin's lymphoma [2 (1.7%) for DT versus 1 (0.84%) for TT; $P = 0.55$] and renal toxicity [1 (0.85%) for DT versus 1 (0.84%) for TT; $P = 0.99$]. Only one patient died (DT group), secondarily to cardiac arrest.

Treatment discontinuation secondary to treatment-related adverse events was significantly less frequent in the DT group than in the TT group. Twenty-eight patients discontinued antiretrovirals overall: 7 (1.3%) on DT versus 21 (3.9%) on TT (difference −2.7%, 95% CI −4.5% to −0.72%; $P = 0.007$) (Figure 5). The reasons for discontinuation in the DT group were hyperbilirubinaemia (two patients), impairment of renal function, renal colic, possible distal tubulopathy (Fanconi syndrome), cutaneous rash and hyperlipidaemia. The reasons for discontinuation in the TT group were impairment of renal function (five patients), renal tubulopathy (one patient), renal colic (one patient), nephrolithiasis (one patient), kidney disease (one patient), osteopenia (one patient), osteoporosis or osteopenia (four patients), hyperbilirubinaemia (three patients), increased values in liver function tests (one patient), hypersensitivity reaction to abacavir (one patient), hypophosphataemia (one patient), diarrhoea (one patient) and Hodgkin's lymphoma (one patient).

The mean increase in CD4 cell count from baseline to week 48 was 29 cells/mm^3 for the DT group and 13 cells/mm^3 for the TT group [difference 15 cells/mm^3 (95% CI −12 to 44); $P = 0.27$] (Table 2). We noted significant increases in the change from baseline for total cholesterol, LDL cholesterol and triglycerides in the DT group compared with the TT group, although we did not detect

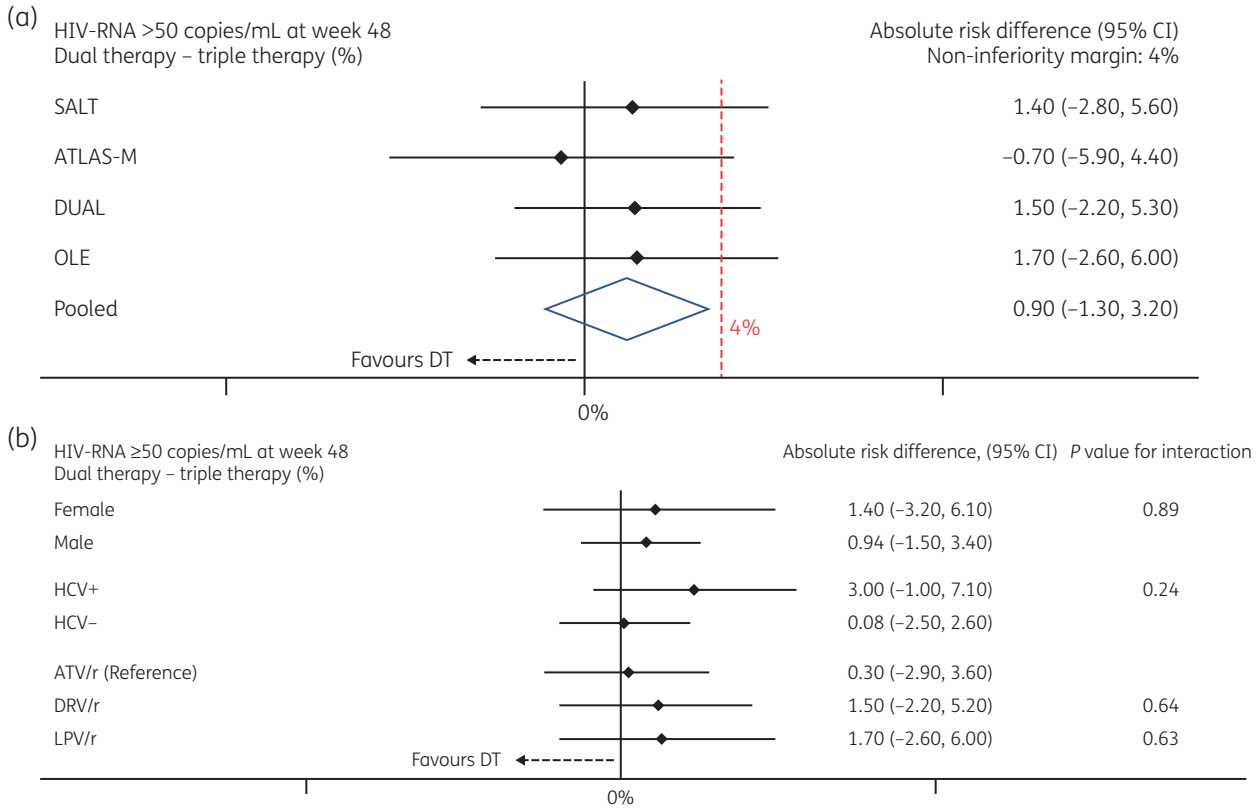

Figure 3. Primary endpoint. (a) Weighted estimation of the difference in the percentage of patients with HIV-1 viral load ≥50 copies/mL (DT versus TT). The red dashed line shows a margin of 4%. (b) Impact of sex, HCV infection status and PI on the percentage of patients with HIV-1 viral load ≥50 copies/mL. ATV/r, atazanavir boosted with ritonavir; DRV/r, darunavir boosted with ritonavir; LPV/r, lopinavir boosted with ritonavir. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

significant differences in HDL cholesterol or total cholesterol/HDL ratio (Table 2). The glomerular filtration rate improved significantly from baseline to week 48 in the DT group compared with the TT group (Table 2). When we only analysed the 784 (74.6%) patients who were receiving tenofovir disoproxil fumarate prior to study entry, the mean changes from baseline between DT and TT were comparable to those previously described for the whole population (Table 2). In this subgroup, only the difference in the total cholesterol/HDL ratio changed significantly in patients on DT versus TT compared with the whole population: 0.15 mg/dL (95% CI 0.01–0.29).

Discussion

In this IPD meta-analysis, we found that DT with a PI/r + 3TC was virologically non-inferior to TT with a PI/r and two N(t)RTIs for maintenance of HIV-1 viral suppression. We based our research on the virological failure endpoint with a 4% non-inferiority margin requested by the FDA for switch trials since 2015. This is the first time that non-inferiority of DT with PI/r + 3TC has been demonstrated using this strict FDA endpoint.

Our IPD-based meta-analysis revealed two key secondary findings that were not reported in the individual clinical trials owing to their small sample size. First, the difference between DT and TT is not affected by gender, active HCV coinfection status or type of PI. Second, significantly more patients discontinued therapy owing to safety events in the TT arms than in the DT arms after 48 weeks of follow-up. The difference in discontinuation was mainly driven by excess renal and bone adverse events in patients receiving TT. Moreover, virological failure leading to development of drug resistance was very infrequent, with just three patients (one receiving DT and two receiving TT) who developed resistance mutations at failure. Taken together, the findings provided by our IPD meta-analysis strongly question the need to maintain a second N(t)RTI, other than lamivudine, in patients who are virologically suppressed while receiving a fully active PI/r and two N(t)RTIs.

Trials of PI/r monotherapy for maintenance of virological suppression have shown that individuals switched to PI/r monotherapy had a greater risk of losing suppression than those continuing TT. Indeed, a meta-analysis of 2303 patients has reported that the difference in suppression of plasma HIV-1 RNA in favour of TT is 8.3%.[9] Our meta-analysis shows that this difference in favour of TT disappears when lamivudine is maintained along with the PI/r. This result contrasts sharply with trials that could not demonstrate non-inferiority after comparing DT with PI/r and maraviroc[10,11] or atazanavir/r and raltegravir[12] with TT. Possible explanations for the better outcomes achieved with lamivudine include an increase in forgiveness of the regimen, given its long intracellular half-life, lack of any pharmacological interaction with PI/r and better penetration in tissues and reservoirs. At present, the only other dual ART strategy that has proven non-inferior to TT for maintenance of

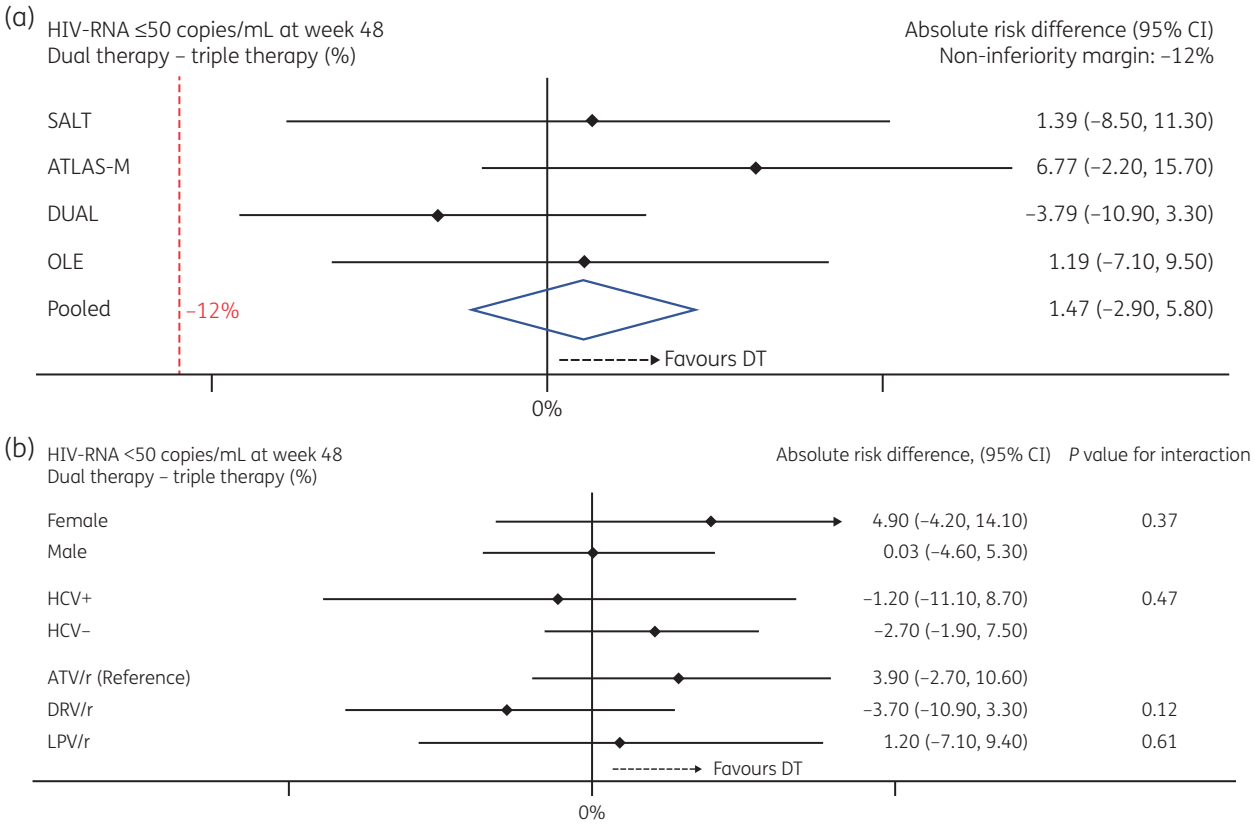

Figure 4. Secondary endpoint. (a) Weighted estimation of the difference in the percentage of patients with HIV-1 viral load <50 copies/mL (DT versus TT). The red dashed line shows a margin of −12%. (b) Impact of sex, HCV infection status and PI on the percentage of patients with HIV-1 viral load <50 copies/mL. ATV/r, atazanavir boosted with ritonavir; DRV/r, darunavir boosted with ritonavir; LPV/r: lopinavir boosted with ritonavir. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

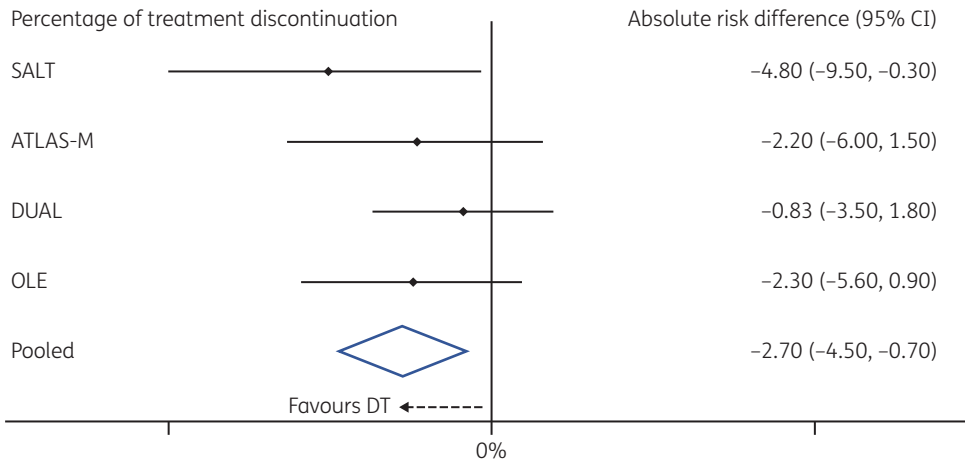

Figure 5. Weighted estimation of the difference in the percentage of treatment discontinuation secondary to treatment-related adverse events (DT versus TT). This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

virological suppression is the combination of dolutegravir and rilpivirine.[13] Given that dolutegravir also has a high barrier to resistance, we believe our data support ongoing clinical trials of DT with dolutegravir and lamivudine.

We collected IPD in order to bring together the largest sample to date in randomized trials of DT with a PI/r and lamivudine for maintenance of virological suppression. This increased sample size provided us with a considerably improved statistical power to

Table 2. Average difference in CD4 cell count, blood lipid levels and renal function from baseline to week 48

			Difference: DT minus TT (95% CI)	
Variable	DT group	TT group	all patients	TDF only
CD4 count (cells/mm^3)	29.6 (236.1)	13.8 (214.4)	15.8 (−12.7 to 44.3)	21.9 (−9.3 to 53.1)
Total cholesterol (mg/dL)	11.03 (34.4)	−1.66 (28.0)	12.6 (8.7–16.5)	18.4 (14.3–22.6)
LDL (mg/dL)	6.9 (28.2)	−1.01 (24.2)	7.8 (4.4–11.3)	10.3 (6.7–14.1)
HDL (mg/dL)	2.48 (17.6)	1.21 (19.2)	1.3 (−1.08 to 3.6)	1.8 (−1.2 to 4.8)
Triglycerides (mg/dL)	8.77 (98.9)	−4.7 (82.2)	13.5 (2.0–25.0)	22.4 (11.3–33.6)
Total cholesterol/HDL	0.017 (0.9)	−0.06 (0.9)	0.08 (−0.04 to 0.20)	0.15 (0.01–0.29)
GFR (mL/min)	3.32 (19.1)	−1.89 (17.9)	5.2 (2.9–7.5)	5.7 (3.0–8.5)

Variables are expressed as mean (SD).
TDF, tenofovir disoproxil fumarate; GFR, glomerular filtration rate.

precisely estimate treatment effects and test for interactions with relevant clinical characteristics. The performance of interaction tests in an IPD meta-analysis framework allows us to avoid the ecological bias inherent in the exploration of sources of heterogeneity via metaregression of aggregate data on study-level covariates.[14,15]

Our meta-analysis is limited by the open-label nature of the four trials included, which could have led to bias. However, the fact that the trials compare regimens with identical pill burdens reduces the likelihood of participant bias. Investigator bias with regard to discontinuations due to adverse events is also possible, but the most frequent adverse events leading to treatment discontinuation in the four individual trials (renal and bone adverse events) are less prone to subjective interpretation. Another limitation of these 48 week trials is that we did not demonstrate significant benefits in terms of specific safety endpoints. There was a statistically significant difference in estimated glomerular filtration rate in favour of the DT group and non-significant differences in lipids. It could be argued that the difference in estimated glomerular filtration rate between the groups is currently non-relevant because, with the advent of tenofovir alafenamide, changes in estimated glomerular filtration rate caused by a PI/r and tenofovir alafenamide/emtricitabine would be comparable to those caused by dual therapy with PI/r and lamivudine. Although triple therapy combinations including tenofovir alafenamide have demonstrated advantages in terms of bone and renal safety,[16–18] we believe that comparison of the safety of DT and TT combinations will not be definitively resolved until we have studies that evaluate safety endpoints after much longer periods of follow-up. It is also important to emphasize that our results do not apply to patients with prior virological failures, a history of resistance mutations, or chronic hepatitis B.

The main contribution of our meta-analysis is the highly precise estimate of the efficacy of DT with PI/r + 3TC compared with TT for maintenance of virological suppression. The sample size achieved in this IPD meta-analysis made it possible to evaluate potential interactions with gender, active HCV infection and type of PI, and we did not find any significant modifier effect for efficacy. DT is as efficacious as TT with a PI/r and two N(t)RTIs, even using the new strict non-inferiority margin set by the FDA. The high efficacy and improved safety of the DT combination gives clinicians a new choice of maintenance therapy for control of HIV infection.

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Transparency declarations

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