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Review

Virologically suppressed HIV-infected patients on TDF-containing regimens significantly benefit from switching to TAF-containing regimens: A meta-analysis of randomized controlled trials

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ABSTRACT

Background: To investigate whether TDF-containing regimens significantly benefited efficacy, safety, and tolerability in TAF-containing regimens in virologically suppressed HIV-infected patients.
Methods: PubMed, Embase, Web of Science, and the Cochrane Trial Registry were systematically searched for eligible studies. We extracted and evaluated the pooled data from available randomized controlled trials (RCTs).
Results: Eight eligible RCTs were included. In the intention-to-treat (ITT) analysis, patients who switched to TAF-containing regimens had significantly better viral suppression than those continuing TDF-containing regimens at weeks 48 and 96 (RR, 1.02; 95CI, 1.00–1.03; $p < 0.05$), but no significant difference in the per-protocol (PP) analysis (RR, 1.00; 95CI, 0.99–1.01; $p > 0.05$). Compared with those receiving the TDF-containing regimens, virologically suppressed HIV-infected patients on the TAF-containing regimens had significant increases in CD4 cell counts (SMD, 0.12; 95CI, 0.08 to 0.17; $p < 0.05$), renal and bone parameters at the hip (RR, 2.86; 95CI, 2.24–3.64; $p < 0.05$) and the spine (RR, 2.43; 95 CI, 2.03–2.90; $p < 0.05$) between weeks 48 and 96.
Conclusions: Virologically suppressed HIV-infected patients on TDF-containing regimens significantly benefit from switching to TAF-containing regimens, resulting in better viral suppression, better immune reconstruction, and less bone and renal problems.

Contents

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Introduction

With the advent of potent antiretroviral therapy (ART), significant comorbidities have emerged, including osteoporosis and increased risk of fractures (McComsey et al., 2011). Tenofovir disoproxil fumarate (TDF) is a recommended first-line drug for ART in HIV, and although TDF is a potent and generally well-tolerated nucleotide analog, it has two substantial drawbacks (European AIDS Clinical Society, 2014; Panel on Antiretroviral Guidelines for Adults and Adolescents, 2014). First, it can cause nephrotoxicity, which can be manifested by decreased glomerular function or proximal tubulopathy. The wasting of phosphorus by damaged renal tubules can lead to osteomalacia over time (Gilead Sciences Ltd., 2019). Second, TDF-containing regimens have been noted to result in greater bone mineral density (BMD) reduction than other ART regiments, with 1–2% greater reductions, especially in the first 24 weeks of treatment (McComsey et al., 2011; Bolland et al., 2015; Bedimo et al., 2012; Gotham et al., 2017). Again, it seems to have no significant effect on the immune reconstitution system.

Tenofovir alafenamide (TAF) is a novel TFV prodrug that is associated with 90% lower plasma TFV levels compared with TDF, which leads to less adverse effects on bone and kidneys (Sax et al., 2015). Recent AIDS treatment guidelines have replaced TDF either with TAF or as part of the recommended initial treatment regimen. So far, findings of several clinical trials have demonstrated that patients switched to TAF-containing regimens were significantly benefited by continuing to use the TDF-containing regimens while remaining on the same third agent in maintaining viral suppression. This led to improvements in markers of bone and renal safety, which seems to have a minimum effect on bone density, if any (Sax et al., 2015; Mills et al., 2015).

To date, although TAF is widely used as an alternative treatment option to TDF, whether it is more reliable in efficacy and safety and more helpful to improve the immune reconstitution still deserves further study. The efficacy and safety of TAF-containing regimens have been mostly evaluated in the context of the coformulation of elvitegravir (E), cobicistat (C), emtricitabine (F), darunavir (D), rilpivirine (R), and TAF. Our primary objective was to investigate whether TDF-containing regimens significantly benefited efficacy, safety, and tolerability in TAF-containing regimens in virologically suppressed HIV-infected patients. Our secondary goal was to assess if the treatment effects of TAF are superior to TDF regarding renal function and BMD in fixed-dose regimens.

Methods

The meta-analysis was performed following the PRISMA statement and the recommendations of the Cochrane Collaboration. The protocol was registered on PROSPERO (registration number: CRD 42018089828).

Literature search strategy

We searched PubMed, Embase, Web of Science, and the Cochrane Trial Registry from January 2001 to July 2018, and limited to English publications. The search term used was as follows: "Tenofovir alafenamide (TAF) AND Tenofovir disoproxil fumarate (TDF) AND HIV." At the same time, if we found any related documents, we went back to its references for further searching.

Eligibility criteria and study selection

Two reviewers (XBT, YHZ) evaluated the included references by using this study search strategy to determine if the articles were potentially eligible for inclusion in this meta-analysis. The following inclusion criteria were used for this meta-analysis: (1) multicenter randomized, controlled trials (mRCTs); (2) HIV-1 infected patients who were experienced participants in antiretroviral regimens (aged $\geq$ 18 years); (3) experimental group was given the regimens containing TAF and control group was given the regimens containing TDF. The following types of studies were excluded: (1) non-randomized, observational, cohort, case-control and non-blinded clinical studies; (2) patients who were infected with hepatitis B virus (HBV) or hepatitis C virus (HCV) or tuberculosis (TB) or previously received antiviral therapy; (3) patients if they had a new AIDS-defining condition within 30 days of screening, or were pregnant; (4) studies not reporting any efficacy measures and safety measures; (5) experimental group did not involve the regimens containing TAF and control group did not involve the regimens containing TDF, synchronously.

Quality assessment and publication bias of studies

Quality assessment of included RCTs was undertaken using the Cochrane collaboration tool. This assessment included the evaluation of randomization, blinding of outcome assessment, and patient attrition (including the number of patients lost or excluded, along with reasons). The methodological domains were considered to perform as follows: sequence generation, allocation sequence concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting, and other potential threats to validity. We judged each of the domains as having low risk, high risk, or unclear risk of bias according to the Cochrane handbook. Unclear risks of bias were determined to be due to the lack of enough information or uncertainty factors over the potential for bias.

Table 1
General characteristics of studies included in the meta-analysis.

Reference	Type	Study name	CTG	Phase	Treatment (week)	Experimental group	Control group	Masking	Patients	Age (years)	Men	Races	Countries	Analytic method
Mills et al. (2016)	mRCT	GS-US-292-0109	NCT01815736	3	48	E (150 mg)/C (150 mg)/F (200 mg)/ TAF (10 mg)	E (150 mg)/C (150 mg)/F (200 mg)/TDF (300 mg)	Open-label	1443	41	1283 (89%)	Native American, Asian, Black, Native Hawaiian, White	19 countries*	PP
Gallant et al. (2016)	mRCT	GS-US-311-1089	NCT02121795	3	48	F (200 mg)/TAF (10 mg or 25 mg)	F (200 mg)/TDF (200 mg or 300 mg)	Double-blind	663	49	561 (85%)	White, Black, Other	North America, Europe	ITT/PP
DeJesus et al. (2016)	mRCT	GS-US-292-0110	NCT01815736	3	96	E (150 mg)/C (150 mg) /F (200 mg)/ TAF (10 mg)	E (150 mg)/C (150 mg)/F (200 mg)/TDF (300 mg)	Open-label	1436	41	1283 (89%)	Black or African heritage	NA	ITT
Orkin et al. (2018)	mRCT	EMERALD	NCT02269917	3	48	D (800 mg)/C (150 mg)/F (200 mg)/ TAF (10 mg)	D (800 mg)C (150 mg)/F (200 mg)/ TDF (300 mg)	Open-label	1141	46	936 (82%)	White, Black or African American, Other	9 Countries*	ITT/PP
Orkin et al. (2017)	mRCT	GS-US-366-1216	NCT01815736	3b	48	R (25 mg)/F (200 mg)/TAF (25 mg)	R (25 mg)/F (200 mg)/ TDF (300 mg)	Double-blind	630	45	564 (90%)	White, Black, Asian	11 Countries*	ITT/PP
DeJesus et al. (2017)	mRCT	GS-US-366-1160	NCT02345226	3b	48	R (25 mg)/F (200 mg)/TAF (25 mg)	V (600 mg)/F (200 mg)/TDF (300 mg)	Double-blind	974	49	763 (78.3%)	Black or African heritage, Asian	NA	ITT/PP
Post et al. (2017)	mRCT	GS-US-311-1089	NCT02121795	3	48	F (200 mg)/TAF (25 mg or 10 mg)	F (200 mg)/TDF (300 mg)	Double-blind	663	49	564 (85%)	NA	USA	ITT
Raffi et al. (2017)	mRCT	GS-US-311-1089	NCT02121795	3	96	F (200 mg)/TAF (25 mg or 10 mg)	F (200 mg)/TDF (300 mg)	Double-blind	663	49	NA	NA	NA	ITT

Data are n (%) or mean/median (as available), unless stated otherwise. NA, not available; CTG, clinicals.gov identification number; mRCT, multicenter RCT; E, elvitegravir; C, cobicistat; F, emtricitabine; D, darunavir; R, rilpivirine; V, efavirenz; ITT, intention-to-treat; PP, per-protocal.
19 Countries*: North America, Europe, Latin America, Asia, and Australia.
9 Countries*: North America (Canada and USA) and Europe (Belgium, France, Poland, Spain, Sweden, Switzerland, and UK).
11 Countries*: North America (Canada and the USA) and Europe (Belgium, France, Germany, Italy, the Netherlands, Spain, Sweden, Switzerland, and the UK).

Subgroup analysis and investigation of heterogeneity

The subgroup analysis was also carried out according to the type of study design. I^2 test and p statistic values were used to investigate the heterogeneity of all included studies, according to the Cochrane review guidelines. High heterogeneity was defined as (I^2 test > 50% or p-value of < 0.1) among the studies; otherwise, it was considered that there was no heterogeneity (I^2 test < 50% or p-value of > 0.1). If there was a high heterogeneity, we conducted an appropriate method to investigate the potential covariates that might have substantial impacts on between-study heterogeneity.

Statistical analysis

Statistical analyses were conducted with Stata V.12.0 (Stata Corp, College Station, Texas, USA) software. The risk ratios (RRs) and standardized mean differences (SMDs) were used to compare dichotomous and continuous variables, respectively. The aggregated results and 95% CIs for effect size were calculated using inverse-variance weighted random-effects meta-analysis. Furthermore, SPSS 22 performed independent t-test to compare the continuous variables. All P-values were 2-tailed, and a probability level < 0.05 was considered statistically significant.

Results

Study characteristics

Our primary research identified 520 records. After removal of duplicates and initial screening, we independently reviewed 289 papers in full. Of these publications, by browsing the titles and abstracts of these articles, 202 papers did not involve relevant records; the 87 remaining full articles were assessed for eligibility. We then excluded 79 studies for other reasons, including no specific direction with the efficacy and safety switching from TDF-containing regimens to TAF-containing regimens for the treatment of HIV-1 infection (n = 68), or that they were reviews or meta-analyses and switching from TDF or TAF to other regimens (n = 5). Ultimately, eight independent RCTs met the inclusion criteria; they were randomized, actively controlled, multicenter, phase 3 trials included in our meta-analysis, which were published from 2016 to 2018, and altogether 7613 patients were recruited. Of these participants, 4434 were participants switching from TDF-containing regimens to TAF-containing regimens, and 3179 participants remain received TDF-containing regimens. The general characteristics of the included studies are summarized in Table 1. The study-recruited subjects came from different countries and races. Flow diagram of the study selection process for the meta-analysis is shown in Figure 1.

Risk of publication bias assessment

The risk-of-bias of the included studies is summarized in Figure 2 across studies utilizing the Cochrane Collaboration tool. All included studies achieved adequate random sequence generation as well as low risks of bias regarding allocation concealment. “Incomplete outcome data” and “selective reporting” domains were of low risk in all included studies (except for these studies (DeJesus et al., 2016; Post et al., 2017; Raffi et al., 2017), in which the authors did not report about the attrition bias domain). All studies were RCTs, thus “Allocation concealment,” “blinding of participants and personnel” and “blinding of outcome assessment” were deemed at low risks of bias in five included RCTs, except for these studies (DeJesus et al., 2016; Mills et al., 2016; Orkin et al., 2018), which were open-label studies.

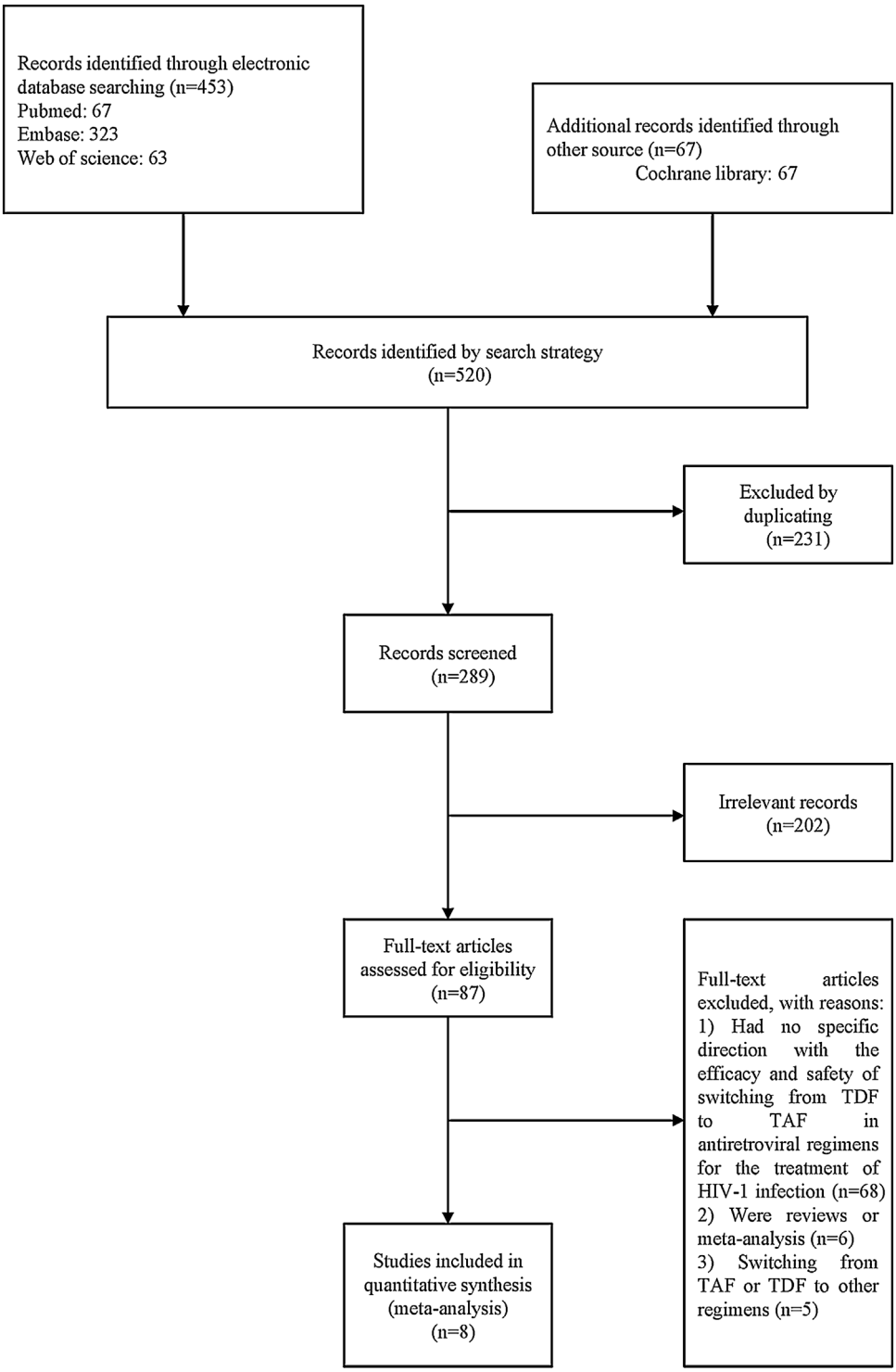

Figure 1. Flow diagram of the study selection process for the meta-analysis.

Efficacy analysis

Virologic response

At weeks 48 and 96, eight eligible RCTs (DeJesus et al., 2016, 2017; Post et al., 2017; Raffi et al., 2017; Mills et al., 2016; Orkin et al., 2017, 2018; Gallant et al., 2016) investigated the virologic suppression (defined as less than 50 copies of viral load per mL) in the ART-experienced patients, with a total of 8169 adult patients evaluated (six with 48 weeks of follow-up and two with 96 weeks of follow-up). In the intention-to-treat (ITT) analysis, the combined virologic response was achieved by 4473 (93.83%) of 4767 ART patients in the TAF-containing regimens. This achievement was significantly higher than those of the TDF-containing regimens involving 3134 (92.12%) of 3402 ART-experienced patients at weeks 48 and 96 (RR, 1.02; 95CI, 1.00–1.03; $p < 0.05$) (Figure 3, A). However, in the per-protocol (PP) analysis, for ART-experienced patients, the virologic response showed no significant difference between the two groups, including 2575 (98.47%) of 2615 ART-

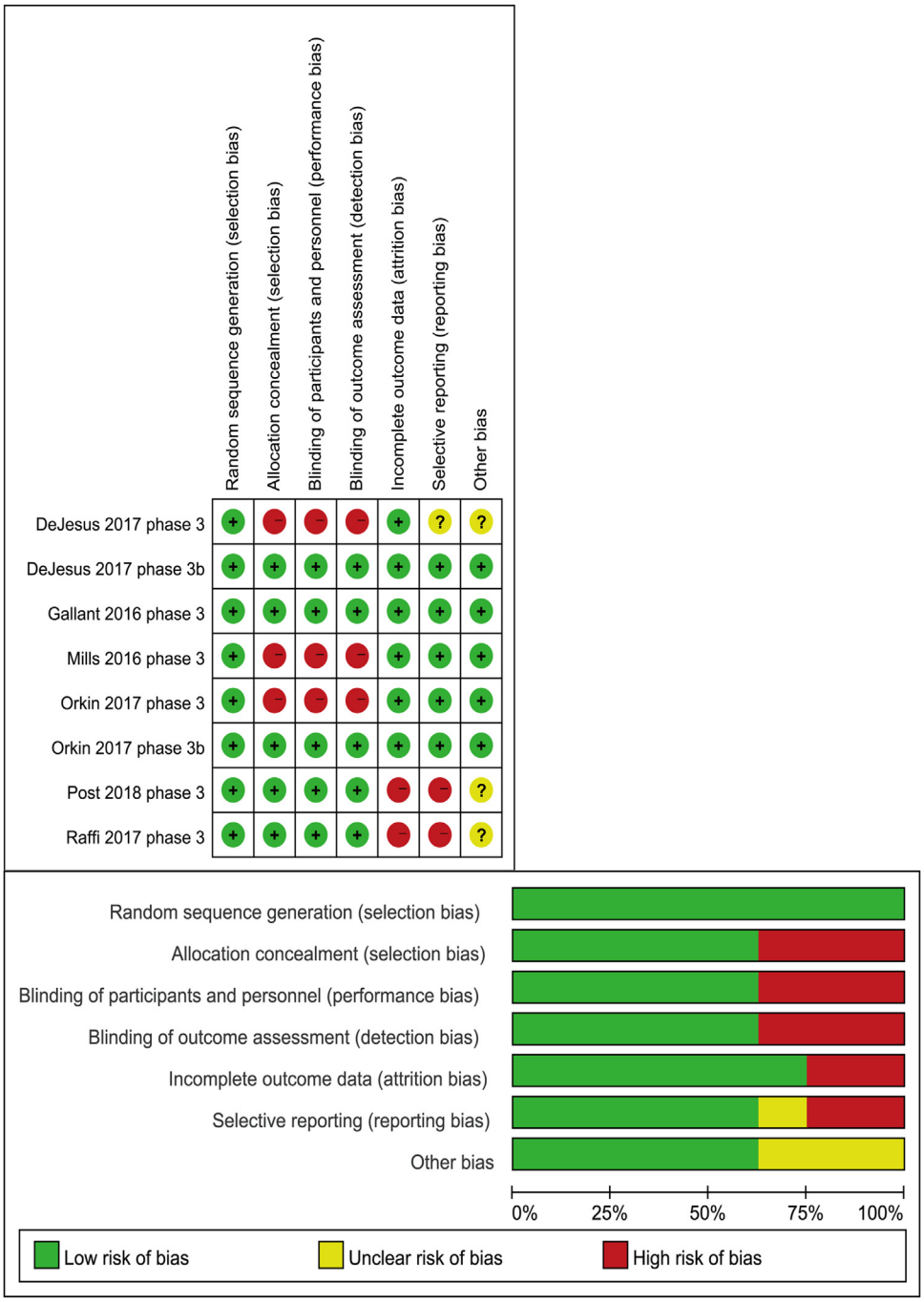

Figure 2. Risk-of-bias summary for the included studies.

experienced patients in the TAF-containing regimens versus 1754 (98.37%) of 1783 ART-experienced patients in the TDF-containing regimens at week 48 (RR, 1.00; 95% CI, 0.99–1.01; $p > 0.05$) (Figure 3, B).

$CD4^+$ cell counts

A total of eight RCTs (DeJesus et al., 2016, 2017; Post et al., 2017; Raffi et al., 2017; Mills et al., 2016; Orkin et al., 2017, 2018; Gallant et al., 2016), including 7507 patients, were enrolled in the assessment of CD4 cell counts at weeks 48 and 96. The combined standardized mean difference (SMD) showed a significant increase in $CD4^+$ cell counts by comparing the TAF-containing regimens with the TDF-containing regimens (SMD, 0.12; 95CI, 0.08 to 0.17; $p < 0.05$) (Figure 3, C).

Virologic failure

Fifty-five patients from seven RCTs (DeJesus et al., 2016, 2017; Raffi et al., 2017; Mills et al., 2016; Orkin et al., 2017, 2018; Gallant et al., 2016) had virologic failure after 48 and 96 weeks of treatment, 31 (0.84%) of 3671 patients who received the TAF-containing regimens had virologic failure with resistance. For the combined effect size of virologic failure, no significant difference was found in the ART-experienced patients between the two groups at week 48 (RR, 1.04; 95% CI, 0.44–2.47; $p > 0.05$) (Figure 3, D). In the subgroup analysis, the ART-experienced patients on the drug combination F/TAF regimen had significantly lower prevalence rate in virologic failure than that of F/TDF regimen at 48 weeks (RR, 0.09; 95CI, 0.01–0.7; $p < 0.05$) (Figure 3, D).

Safety analysis

Adverse events

Six RCTs (DeJesus et al., 2016, 2017; Mills et al., 2016; Orkin et al., 2017, 2018; Gallant et al., 2016), including 6181 patients, reported adverse events (AEs) during 48 and 96 weeks of therapy. The safety profiles of both TAF-containing regimens and TDF-containing regimens were similar, with 72.16% vs. 70.99% of patients reporting any treatment-emergent AEs. The combined incidence of AEs showed that there was no significant difference between the two groups (RR, 1.04; 95CI, 1.00–1.07; $p > 0.05$) (Figure 4, A). These main AEs include nausea, upper respiratory tract infection, sinusitis, insomnia, diarrhea, fatigue, bronchitis, nasopharyngitis, back pain, headache, and cough. In the subgroup analysis, comparing the TDF-containing regimens, we observed a significantly lower prevalence rate in sinusitis for the TAF-containing regimens than those of the TDF-containing regimens (RR, 0.60; 95CI, 0.36–0.98; $p < 0.05$) (Supplementary Figure S1 (continued)). However, the TAF-containing regimens showed higher prevalence rates in headaches (RR, 1.57; 95CI, 1.17–2.10; $p < 0.05$) and coughs (RR, 1.39; 95CI, 1.01–1.90; $p < 0.05$) (Supplementary Figure S1).

Discontinuation due to adverse events

The number of AEs leading to study drug discontinuation deemed related to study drugs was similar (DeJesus et al., 2016, 2017; Post et al., 2017; Raffi et al., 2017; Mills et al., 2016; Orkin et al., 2017, 2018; Gallant et al., 2016): sixty-six (1.49%) in the TAF-containing regimens and fifty (1.68%) in the TDF-containing regimens. The combined prevalence rate of discontinuations had no significant difference in both treatment groups between week 48 and week 96 (RR, 0.98; 95CI, 0.57–1.68; $p > 0.05$) (Figure 4, B). However, in the subgroup analysis, the ART-experienced patients on the drug combination E/C/F/TAF regimen had significantly lower prevalence rate than those of the E/C/F/TDF regimen between week 48 (RR, 0.37; 95CI, 0.16–0.88; $p < 0.05$) and week 96 (RR, 0.37; 95CI, 0.16–0.88; $p < 0.05$).

Grade 3 or 4 adverse events

After 48 and 96 weeks of therapy, 709 (18.82%) of 3767 participants in the TAF-containing regimens versus 452 (18.76%) of 2410 participants in the TDF-containing regimens had grade 3 or 4 laboratory abnormalities (DeJesus et al., 2016, 2017; Mills et al., 2016; Orkin et al., 2017, 2018; Gallant et al., 2016), which was similar between the two groups. The combined grade 3 or 4 AEs prevalence rate of ART-experienced patients with the use of TAF-containing regimens was not statistically different from those of TDF-containing regimens (RR, 0.92; 95CI, 0.80–1.06; $p > 0.05$) (Figure 4, C). However, those who received the E/C/F/TAF regimen had a significantly lower prevalence rate than those who previously received the E/C/F/TDF regimen for 48 weeks (RR, 0.81; 95CI, 0.68–0.98; $p < 0.05$) (Figure 4, C).

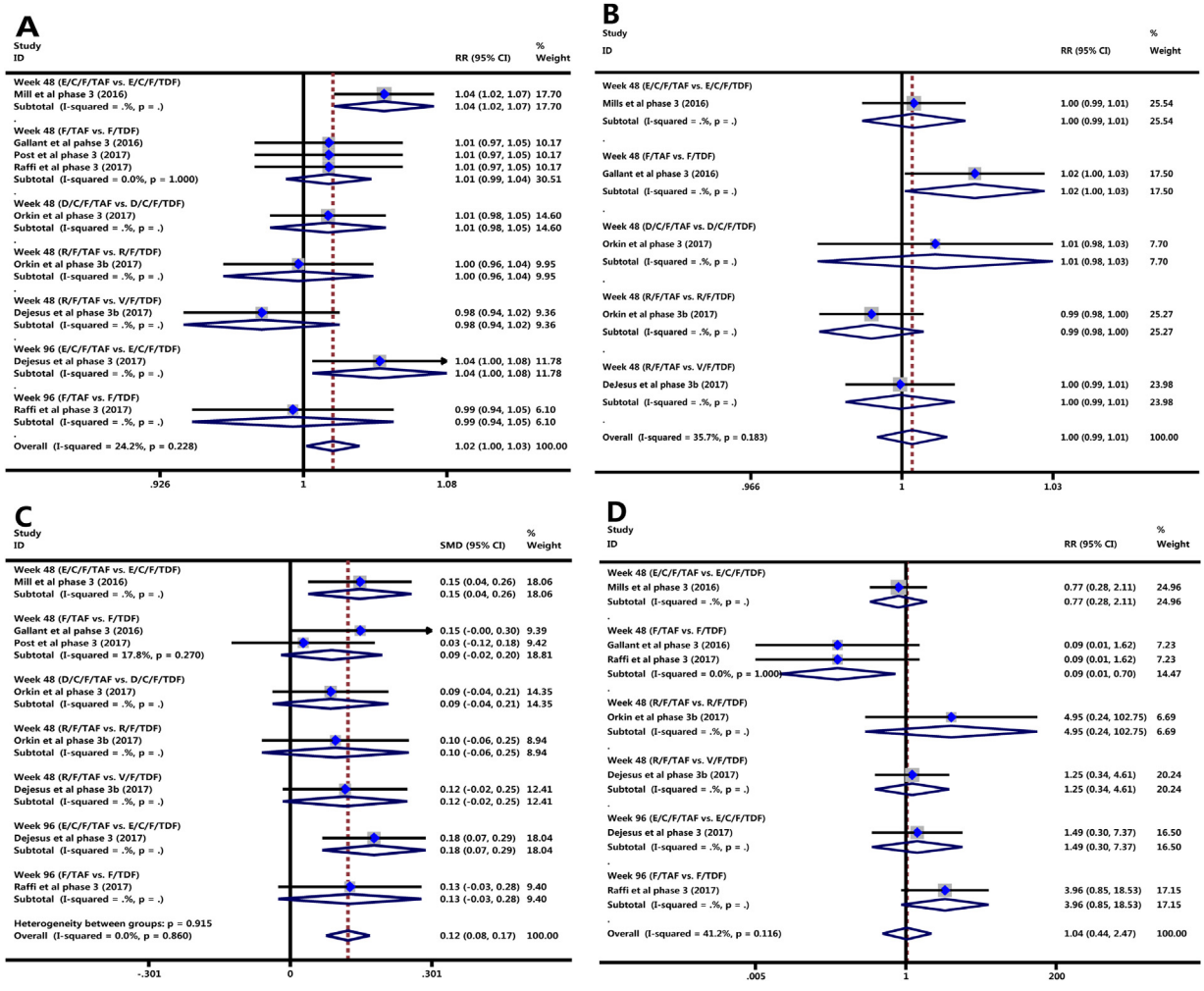

Figure 3. Meta-analysis of efficacy outcomes of 8 RCTs with the regimen switching from TAF-containing to TDF-containing in the treatment-experienced patients. (A) Virologic suppression under intention-to-treat analysis. (B) Virologic response under pre-protocol analysis. (C) CD4 cell counts. (D) Virologic failure.

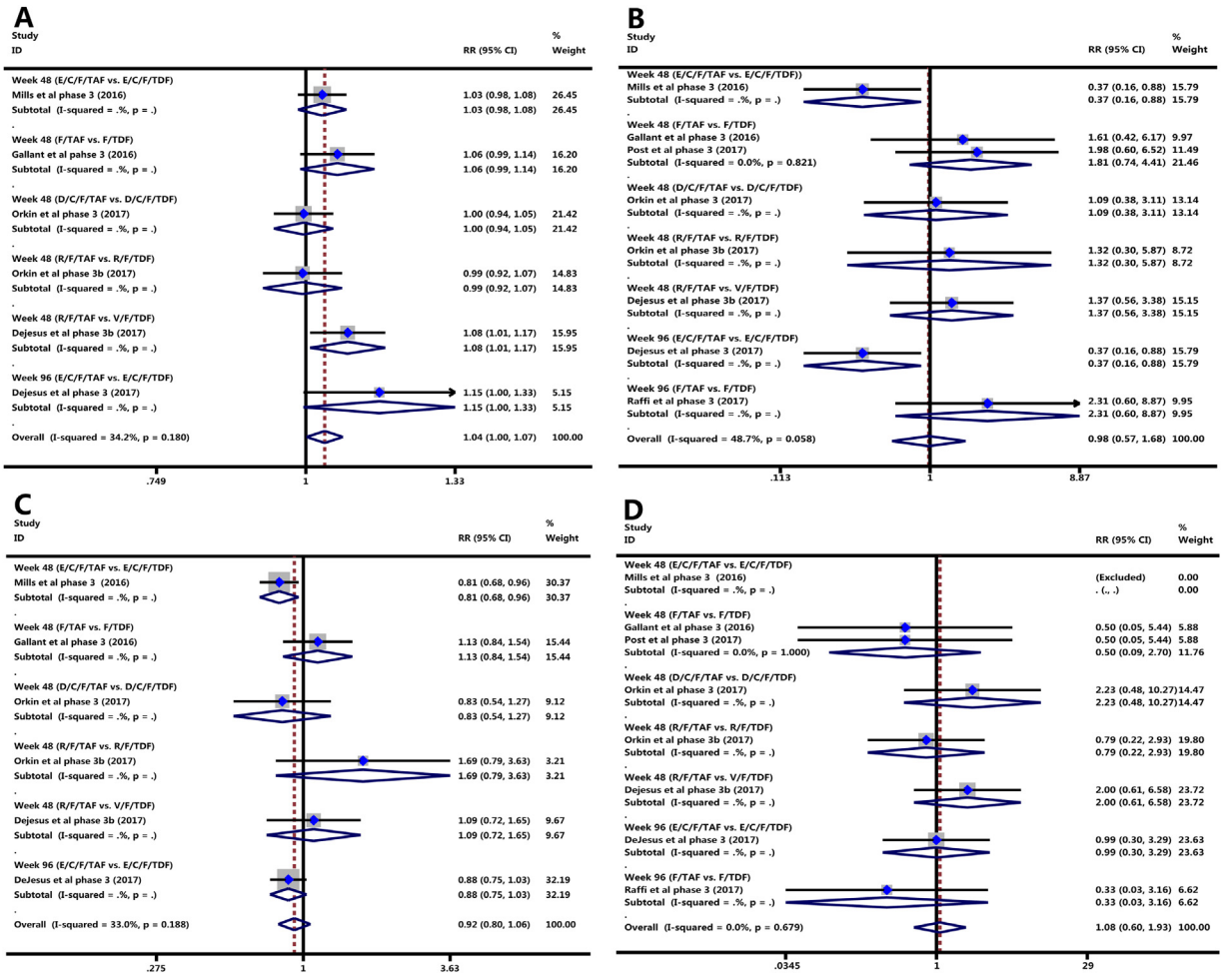

Figure 4. Meta-analysis of safety outcomes of 8 RCTs with the regimen switching fromTAF-containing to TDF-containing in the treatment-experienced patients. (A) Adverse events. (B) Discontinued due to adverse events. (C) Grade 3 or 4 adverse events. (D) Fractures.

Fractures

Fractures were uncommon in both treatment groups (thirty-two [0.72%] of 4434 patients in the TAF-containing regimens vs. twenty-two [0.72%] of 3073 patients in the TDF-containing regimens), which had no significant difference between the two groups (Post et al., 2017; Raffi et al., 2017; Mills et al., 2016; Orkin et al., 2017, 2018; Gallant et al., 2016; DeJesus et al., 2017; World Health Organization, 2016) (RR, 1.08; 95CI, 0.60–1.93; $p > 0.05$) (Figure 4, D). Therefore, we regarded all fractures as related to trauma and not to study drug, and none led to discontinuation of study drug.

Bone outcomes

Bone and renal measurements were performed in secondary endpoint analyses. We assessed the difference in percentage change from baseline for hip and spine BMD between the two groups. At weeks 24, 48, 72 and 96, no significant improvements in BMD were observed in the hip (RR, 1.00; 95CI, 0.98–1.01; $p > 0.05$) (Figure 5, A) and spine (RR, 1.11; 95CI, 0.98–1.01; $p > 0.05$) (Figure 5, B) among ART-experienced patients after switching to TAF-containing regimens compared with those continuing TDF-containing regimens. Although there was no significant difference in BMD in the hip and spine between the two groups from baseline to week 96, an absolute decrease was found with R/F/TDF regimen than R/F/TAF regimen during 24 weeks of treatment (Figure 5, A and B). Of note, however, more patients in the TAF-containing regimens group than in the TDF-containing regimens group had a significant increase of 3% or more in BMD at the hip (321 [23.09%] of 1390 patients vs. 72 [8.42%] of 855 patients) (RR, 2.86; 95CI, 2.24–3.64; $p < 0.05$) (Figure 5, C) and spine (485 [34.15%] of 1420 patients vs. 126 [14.43%] of 873 patients) (RR, 2.43; 95 CI, 2.03–2.90; $p < 0.05$) (Figure 5, D) from baseline to week 48 and 96. In the meta-analysis, we summarized the bone parameters changes in Supporting Table S1 and performed the comparisons of continuous data using independent *t*-test by SPSS between TAF-containing regimens and TDF-containing regimens. After 48 weeks of therapy, the mean percent BMD changes from baseline were significantly less decreased in the TAF-containing regimens at both the hip (1.385% vs. −0.205%, $p < 0.05$) and spine (1.501% vs. −0.201%, $p < 0.05$) as compared to the TDF-containing regimens in the treatment-experienced patients. Meanwhile, fewer changes in bone parameters in the TAF-containing regimens than in the TDF-containing regimens at both the hip (2.125% vs. –0.415%, $p < 0.05$) and spine (2.123% vs. −0.148%, $p < 0.05$) in the treatment-experienced patients further supported the BMD findings up to 96 weeks.

Renal outcomes

Renal AEs were reported from six RCTs (DeJesus et al., 2016; Post et al., 2017; Raffi et al., 2017; Mills et al., 2016; Orkin et al., 2018; Gallant et al., 2016), which occurred in 34 (0.92%) of 3680 participants in the TAF-containing regimens group vs. 32 (1.38%) of 2323 participants in the TDF-containing regimens group. Fewer patients had significant renal AEs in the TAF-containing

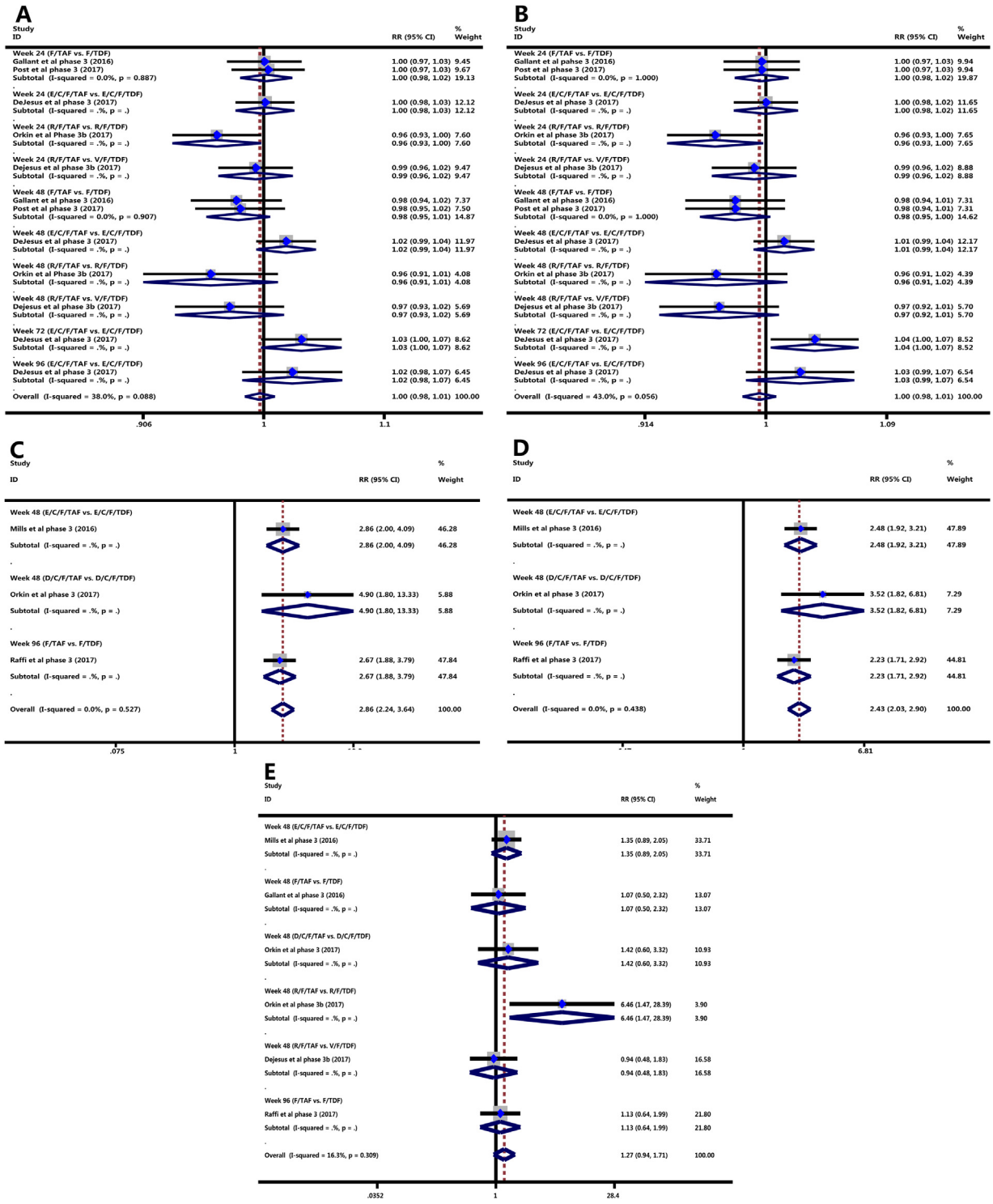

Figure 5. Bone and renal adverse events after switching from TAF-containing regimens to TDF-containing regimens in the hip and spine at weeks 24, 48, 72, and 96. (A) Changes in BMD in the hip. (B) Changes in BMD in the spine. (C) BMD increases of >3% or more from baseline at the hip. (D) BMD increases of >3% or more from baseline at the spine. (E) Renal events. (F) Initiation of lipid-lowering therapy.

regimens group than in the TDF-containing regimens group through 48 and 96 weeks (RR, 0.50; 95CI, 0.27–0.94; $p < 0.05$) (Figure 5, E). As shown in Supporting Table S2, renal parameters median changes in treatment-experienced patients were presented from baseline to week 48 and 96. The median decreases were significantly lower with TAF-containing regimens than TDF-containing regimens in urine protein/creatinine (UPCR) ratio [(−23.25% vs. −6.49% mL/min, $p < 0.05$) at week 48; −25.95% vs. 8.23% mL/min, $p < 0.05$) at week 96] and urine albumin/creatinine (UACR) ratio [(−10.715% vs. 10.293% mL/min, $p < 0.05$) at week 48; (−5.93 vs. 18.28 mL/min, $p > 0.05$) at week 96]. In addition, serum creatinine (Cr) and renal tubular proteinuria [retinol binding protein/Cr (RBP/Cr) and β-2-microglobulin/Cr (β-2M)] significantly decreased from baseline for both groups, but no statistically significant differences were observed after 48 and 96 weeks of therapy ($p > 0.05$ for all).

Lipid profile

The fasting lipid profile changes in the treatment-experienced patients were presented in Supporting Table S3. Eight RCTs (DeJesus et al., 2016, 2017; Post et al., 2017; Raffi et al., 2017; Mills et al., 2016; Orkin et al., 2017, 2018; Gallant et al., 2016) with 7613 adult participants were used to analyze the lipid profile from baseline to week 48 and 96. At week 48, there were significant differences in the median changes between the TAF-containing regimens and the TDF-containing regimens, which included total cholesterol (12.8 vs. 0.4 mg/dL, $p < 0.05$), low-density lipoprotein (LDL) cholesterol (9.62 vs. 0.98 mg/dL, $p < 0.05$), triglycerides (6.6 vs. −2.6 mg/dL, $p < 0.05$), and total cholesterol/HDL cholesterol ratio (0.13 vs. 0.04, $p < 0.05$), whereas high density lipoprotein (HDL) cholesterol remained unchanged (0.9 vs. −0.6 mg/dL, $p > 0.05$). However, at week 96, there were no significant differences in the median plasma lipid changes between the TAF-containing regimens and the TDF-containing regimens except LDL cholesterol (14 vs. 3 mg/dL, $p < 0.05$). Among these RCTs, 5.16% of all participants in the TAF-containing regimens and 3.84% of all participants in the TDF-containing regimens started lipid-lowering drugs, and no statistical differences were found between the two groups after 48 weeks and 96 weeks of treatment (RR, 1.27; 95%CI, 0.94–1.71; $p > 0.05$) (Figure 5, F).

Discussion

TDF was first approved in 2001 in the USA and 2002 in the European Union (EU), and TDF-based regimens are the preferred first-line treatment in international guidelines, such as the 2013 WHO consolidated guidelines (World Health Organization, 2016). TAF had been approved in the USA and EU, and it is considered that TAF is preferred over TDF as a nucleotide of choice in the preferred regimens (Saag et al., 2016). Although the safety profile of TDF-containing regimens is in general excellent, concerns have centered around renal and bone AEs (Campos et al., 2016). In addition to detrimental effects on BMD, TDF has known effects on renal function, with rates of acute kidney injury reported as affecting as much as 0.7–10% of patients and estimated glomerular filtration rate (eGFR) changes comparable with those seen in diabetic nephropathy (Campos et al., 2016). A disadvantage of TDF is the need for monitoring of renal function, which is not necessary with TAF. In low resource and decentralized HIV treatment settings, renal function tests and bone densitometry may be unavailable or expensive.

In our meta-analysis, virologic effects were expressed as virologic suppression and virologic failure. In the ITT analysis for ART-experienced patients, the proportion of individuals concerning virologic suppression rate in the TAF-containing regimens was slightly higher than in the TDF-regimens between week 48 and week 96 (93.83% vs. 92.12%, $p < 0.05$) (Figure 3, A). However, in the PP analysis, after switching to TAF-containing regimens compared with those continuing TDF-containing regimens, our analysis results did not reveal statistically significant differences in virologic suppression for 48 weeks (98.47% vs. 98.37%, $p > 0.05$) (Figure 3, B). Also, our results indicated that the TAF-containing regimens could effectively improve the immunological outcome. After treatment of 48 weeks, we observed that $CD4^+$ counts maximally increased by 710 cells/mL from baseline, and the improvement of $CD4^+$ counts showed a significant increasing trend in all included RCTs for ART-experienced patients (Mills et al., 2016). Both treatment groups had similar rates of virologic failure at weeks 48 and 96, but more patients in the TDF-containing regimen group had a final viral load less than 50 copies per mL and discontinued study drug due to other reasons. Resistance to study treatment occupied a small proportion in the ART-experienced patients given the TAF-containing regimens and the TDF-containing regimens. In these two ART regimens, a small percentage of patients (<1% in both groups) did show drug resistance to some of the antiviral drugs, most commonly the nucleoside reverse transcriptase inhibitor mutations Met184Val, Val106lle/Leu, and Tyr188Leu selected by emtricitabine and rilpivirine (DeJesus et al., 2017).

For ART-experienced patients, the safety profile of TAF-containing regimens was similar to those of TDF-containing regimens after 48 and 96 weeks of treatment. The meta-analysis demonstrated that there was no significant difference in AEs, statistically significant superiority of TAF-containing regimens in bone and renal measures, and a statistically substantial lipid-increasing effect with TAF-containing regimens. Both treatments were generally safe and well tolerated, with most AEs reported as mild or moderate in severity. However, in the subgroup analysis, of note, the prevalence of AEs in the R/F/TAF combination regimen was significantly higher than in the V/F/TDF combination regimen (80.14% vs. 73.91%, $p < 0.05$) over 48 weeks (World Health Organization, 2016). Moreover, in the subgroup analysis, the discontinuations due to AEs and grade 3 or 4 AEs in the E/C/F/TAF group were significantly lower than those of the E/C/F/TDF group for the ART-experienced patients occurring between week 48 and week 96. The numerically higher frequency of AE reports for those switched to the TAF-containing regimens might be due to reporting bias in this double-blind study in conjunction with a selection bias for those who continued their previous treatment regimen and were already tolerant to it (Mills et al., 2016).

Previous data showed that HIV-1 infected patients who started ART had a reduction in BMD in the first 24 to 48 weeks, and the magnitude of this effect becomes higher with continued use of the TDF-containing regimens (Sax et al., 2015; World Health Organization, 2016). In our analysis, after switching to the TAF-containing regimens, for those patients who previously received TDF-containing regimens, improvements in BMD between the hip and spine was significant. Our results are consistent with prior findings of improved BMD when switching from TDF- to TAF-containing regimens; this switching strategy may be particularly beneficial for ART-experienced patients given anticipated decreases in BMD occurring in some high-risk patient groups (e.g., older adults). HIV-positive individuals had lower BMD and higher fracture rates than age-matched HIV-uninfected controls (Capeau, 2011). The decrease in BMD revealed an increased prevalence of osteopenia and osteoporosis in patients with HIV infection (Schafer et al., 2013). The cause is multifactorial, with both HIV disease-specific and treatment-specific effects observed. Although much remains unknown about the pathogenesis of low BMD in HIV-infected individuals, current research suggests that immune reconstitution was responsible for a significant proportion of the bone loss seen after ART initiation and that this effect can be mitigated by bisphosphonate therapy (Brown and Qaqish, 2006). However, in the meta-analysis, we noted that after switching TDF-containing regimens to TAF-containing regimens, both BMD and $CD4^+$ count increased significantly, which might be related to immune reconstitution. Renal events associated with TDF, such as proximal renal tubulopathy or renal failure, are rare in randomized clinical trials (Gallant et al., 2008, 2015; Wohl et al., 2014; Clumeck et al., 2014). Thus, the changes in renal parameters seem to favor TAF in several clinical trials for virologically suppressed patients. Similar findings were shown in patients with eGFRs of 30–50 mL per min, in whom TDF is generally avoided because of the risk of nephrotoxicity (Pozniak et al., 2016).

For TDF, the only renal safety signal seen in premarketing studies was a small decrease in eGFR with overt cases of nephrotoxicity reported after it became widely used (Wyatt and Baeten, 2015). However, cumulative data from all studies of

regimens containing TAF support an improved renal safety profile of this formulation, although this is based mainly on surrogate markers (eGFR and proteinuria changes) and absence of evidence of proximal tubulopathy in clinical trials. So far, only two studies reported the renal, bone, and lipid effects of TAF-containing regimens were available up to the 96-week time point. Data beyond 144 weeks of treatment are not yet reported. Thus, more studies are needed to clarify the long-term trend of these effects. The significant advantage of switching to TAF-based regimens would be removing the need for renal or BMD monitoring, as well as potentially avoiding more and more cases of renal impairment and osteoporosis.

Limitations

Limitations to this meta-analysis do exist. There were several open-label studies with inherent bias in patients switching from a treatment regimen due to tolerance, so it was challenging to interpret the consistency of adverse event-related discontinuations between different drug combinations in subjective safety reports. Moreover, the differences between treatment regimens and medication doses among included studies might affect the consistency of overall results. Furthermore, the safety of TAF-containing regimens in pregnancy, TB confection, and patients with low $CD4^+$ count is unknown. Consequently, in the meta-analysis, we only investigated the efficacy and safety of some of the clinical studies at the 48-week and 96-week follow-up periods. Therefore, longer-term follow-up is warranted to assess the clinical signs associated with the benefits, especially in terms of bone and renal safety after switching from a TDF-containing regimen to a TAF-containing regimen.

Conclusion

In conclusion, our findings lead us to argue that TAF would be an alternative substitute for TDF in the treatment of HIV infection. The meta-analysis indicated that switching from TDF-containing regimens to TAF-containing regimens significantly benefited ART-experienced patients in maintaining viral suppression and was well tolerated at weeks 48 and 96. Furthermore, compared with those receiving the TDF-containing regimens, ART-experienced patients on the TAF-containing regimens had significant advantages in improving immune function, renal and bone parameters. The evidence suggested that those virologically suppressed HIV-infected patients on TDF-containing regimens significantly benefit from switching to TAF-containing regimens, resulting in better viral suppression, better immune reconstruction, and less bone and renal problems. These findings support guidelines recommending TAF-based regimens as a part of universal antiretroviral regimens.

Author contributions

XBT and YKC wrote the main manuscript text, XBT and YHZ searched the library and reviewed all articles, XBT and YQL conducted all meta-analysis, YHZ and YQL prepared all figures, YC wrote part of the manuscript. All authors reviewed the manuscript.

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Ethical approval

Ethical approval was not required.

Conflict of interest

All authors declare there was no conflict of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2019.07.011.

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