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Comparative effectiveness of tenofovir in HIV-infected treatment-experienced patients: systematic review and meta-analysis

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Background: Antiretroviral therapy (ART) regimens for HIV infection are frequently changed. We conducted a systematic review of randomized trials (RCTs) on the benefits and harms of switching to tenofovir disoproxil fumarate (TDF)-based regimens in ART-experienced patients.

Methods: We included RCTs in HIV-infected adults comparing switching to a TDF-containing regimen with maintaining or switching to another regimen. We searched MEDLINE, EMBASE, CENTRAL, LILACS, SCI, and the WHO Global Health Library. We assessed bias with the Cochrane tool and synthesized data using random-effects meta-analyses and Peto's approach. For further analyses, we added data from a previous systematic review in treatment-naïve patients.

Results: 17 RCTs with 2210 patients were included. All but one study had a high risk of bias. There was no significant association of switching to TDF-based regimens with mortality, fractures, CD4-cell count, body fat, virological failure, LDL-, and HDL-cholesterol. TDF-based regimens decreased total cholesterol (mean difference -12.05 mg/dL; 95% CI -20.76 to -3.34), triglycerides (-14.33 mg/dL; -23.73 to -4.93), and bone mineral density (BMD; hip: -2.46%; -3.9 to -1.03; lumbar spine -1.52%; -2.69 to -0.34). Effects on estimated glomerular filtration (eGFR) were inconsistent and depended on the measurement. Adding 22 RCTs from 8297 treatment-naïve patients gave consistent results with then significant reductions of LDL (-7.57 mg/dL; -10.37 to -4.78), HDL (-2.38 mg/dL; -3.83 to -0.93), and eGFR (-3.49 ml/min; -5.56 to -1.43).

Conclusions: Switching to TDF-based regimens is associated with reductions of BMD and lipid levels and possibly lowered kidney function. The evidence is limited by the high risk of bias.

Keywords: Tenofovir, HIV, Antiretroviral-experienced, Meta-analysis

Background

Tenofovir disoproxil fumarate (TDF) is a recommended first-line drug for antiretroviral therapy (ART) in HIV¹⁻³ and is frequently used as fixed dose co-formulation containing emtricitabine (TDF/FTC).

In around 40% of HIV-infected adults in Europe and North America, the first line ART regimen is modified within the first 28 months.⁴ Reasons include side effects, the wish for treatment simplification, patient's preferences, and virological, immunological, or clinical failure.^{1,4} Although TDF is widely used as second-line treatment, the randomized trial evidence on efficacy and safety in patients switching to TDF-based regimens has

not yet been systematically reviewed. Therefore, our primary objective was to provide a consistent overview of the available randomized trial evidence on benefits and harms of switching to TDF-based treatments. Our secondary goal was to evaluate if treatment effects of TDF differed when only the most commonly used fixed-dose regimens were compared (TDF/FTC and ABC/3TC). Finally, using data from a previous systematic review in ART-naïve patients,⁵ we aimed to explore if effects are different between ART-naïve and ART-experienced patients. By keeping a wide perspective with broad selection criteria, we aimed to analyze a large body of clinical trial evidence to assess the impact of diverse clinical settings, patient characteristics, or methodological factors on the comparative effectiveness of TDF treatment.⁶

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Methods

We applied widely identical methods as in our previous systematic review and meta-analysis in ART-naïve patients.⁵

Inclusion criteria

We included RCTs in HIV-infected adults who had received ART not containing TDF (i.e. ART-experienced, TDF-naïve patients). Eligible RCTs compared (1) switching to a TDF-containing regimen with (2) maintaining current or switching to another non-TDF-containing regimen. No other eligibility criteria were applied.

Identification of evidence

We systematically searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), LILACS, Science Citation Index, and the WHO Global Health Library with the support of an information specialist (last search 01/2015; see Webappendix for details). In addition, we screened clinicaltrials.gov (in 04/2013) and conference proceedings of major international HIV meetings.^{7–11} We checked clinicaltrials.gov entries and reference lists of included studies for further pertinent publications (in 06/2015). We applied no language restrictions. For all included studies, we systematically sought additional published information on clinicaltrials.gov and systematically contacted authors when analytical details were unclear or missing.

Two reviewers independently screened titles, abstracts, and trial registries. One reviewer screened conference proceedings and reference lists. We obtained any full text that either reviewer deemed to be a potentially eligible article, and two independent reviewers determined their eligibility. Discrepancies were resolved by discussion or with a third reviewer. Agreement between the first two reviewers was measured using a kappa statistic.¹²

Data extraction and study outcomes

We extracted information on characteristics of the study, patients, interventions, and on the predefined outcomes mortality, AIDS-defining events, virological failure, fractures, cardiovascular events, renal failure, rash, quality of life, CD4-cell count, HDL-, LDL-, total cholesterol, triglycerides, estimated glomerular filtration rate (eGFR), proteinuria, bone mineral density (BMD), and body fat change. For the outcomes death and clinical events, we extracted the latest time-point at which at least 80% of the randomized patients were analyzed to limit impact of attrition bias. For the outcomes CD4-cell count, lipids, eGFR, body fat, BMD, quality of life, and virological failure, we used 48-week results reflecting mid-term effects on outcomes reported as change from baseline.

We extracted baseline HIV-RNA levels and reasons for switching treatment regimens. We assessed three different cutoffs for virological failure (HIV-RNA <50, <200 and <400 copies/mL) and used snapshot analyses if available, otherwise time-to-loss-of-virological-response analyses. Here, we accepted any approach for dealing with incomplete outcome data but for consistency we preferred analyses where missing data was counted as virological failure. We did not differentiate between virological and treatment failure (due to the highly inconsistent reporting). Rash was only evaluated in patients at low risk of developing allergic reactions, i.e. in studies in HLA-B*5701-negative patients or in studies not containing abacavir (ABC).^{1–3}

We used intention-to-treat (ITT) data including all randomized patients, where available, otherwise we used results from other reported approaches (e.g. “modified ITT”).^{13,14}

One reviewer extracted the data into pre-piloted electronic extraction forms and another double-checked them. Disagreements were resolved by consensus.

Risk of bias assessment

In teams of two reviewers, we independently used the Cochrane tool for bias assessment to assess the (1) randomization process; (2) blinding; (3) reporting bias (i.e. high risk for abstract publications; no exploration of other sources of reporting bias) and (4) attrition bias.¹²

Analysis

We combined the reported treatment effects in meta-analyses and calculated summary relative risks or mean differences (between the two groups compared) with 95% confidence intervals (CI).^{12,15} We used random-effects (DerSimonian and Laird method) to take between-study heterogeneity into account. If an outcome had an event rate of less than 1%, we used Peto’s approach which performs better when events are rare.¹² We used a continuity correction of 0.5 and assessed the between-study heterogeneity using the I^2 -metric.¹²

If the time-point of outcome assessment was not specified, we used the mean or median study follow-up.¹² If for continuous outcomes the number of patients analyzed at 48 weeks was unclear in a study, we imputed it by subtracting the median attrition reported for this outcome in other studies from the number of randomized patients. Where possible, we used the same outcome measures as in our previous meta-analysis,⁵ i.e. the absolute changes from baseline per group reported as mean with standard deviation (SD).¹² Missing means or SDs were converted or approximated from other given statistics or imputed from the remaining studies in the meta-analysis for this outcome.¹²

Table 1 Characteristics of included studies

Study	Centers Country	Recruitment period Follow-up	Number randomized (n)	Prior antiretroviral therapy	Experimental, Comparator	Age (years), Median (IQR)	Sex (% female)	Baseline CD4-cells/mm ³ , Median (IQR)	Baseline HIV-RNA (copies/mL)	Outcomes
<i>TDF/FTC vs. ABC/3TC</i>										
Calza 2009 ³⁹	n.r. Italy	01/2006 to 06/2007 48 weeks	E: 47, C: 42	PI-based ART including thymidine analog	E: TDF/FTC + ATV/r, C: ABC/3TC + ATV/r	E: 37.2 (13.9), C: 36.3 (13.1) ^a	E: 32, C: 29	E: 611 (209), C: 658 (272) ^a	<50	Rash, RF, CD4-cell count, LDL-cholesterol, HDL-cholesterol, TC, TG, HIV-RNA
ROCKET I ^{37,46}	Multicenter UK	03/2008 to 03/2009 12 weeks	E: 79, C: 80	ABC/3TC + EFV	E: TDF/FTC + EFV, C: ABC/3TC + EFV	E: 42 (36–48), C: 44 (40–50)	E: 23, C: 18	E: 459 (377–604), C: 450 (371–584)	<50 ^b	CVD, RF, TG
ROCKET II ³⁸	Multicenter Italy, Spain, Germany, Austria	09/2008 to 10/2009 12 weeks	E: 42, C: 43	ABC/3TC + LPV/r	E: TDF/FTC + LPV/r, C: ABC/3TC + LPV/r	E: 46.0 (38–51), C: 43.0 (38–48)	E: 17, C: 28	E: 507 (386–633), C: 525 (385–718)	<50	Rash, RF
SWIFT ³⁵	Multicenter USA	n.r. 48 weeks	E: 155, C: 156	3TC/ABC plus boosted PI	E: TDF/FTC + PI/r, C: ABC/3TC + PI/r	E: 46 (22–66), C: 46 (22–75) ^c	E: 17, C: 14	E: 532 (354–725), C: 532 (382–728)	<200	CVD, Rash, RF, mortality, fractures, CD4-cell count, LDL-cholesterol, HDL-cholesterol, TC, eGFR, HIV-RNA
<i>Other Regimens</i>										
2Lady ^{32,d}	Multicenter Cameroon, Burkina Faso, Senegal	01/2010 to 10/2012 48 weeks	E: 152, C: 145	n.r. (but naïve to TDF, ddi, ABC, DRV/r, LPV/r)	E: TDF/FTC + LPV/r, C: ABC + ddi + LPV/r	E: 38 (34–45), C: 38 (33–47)	E: 74, C: 72	E: 199 (92–318), C: 195 (100–288)	≥1000	AIDS, mortality, HIV-RNA
ACTG 5095 Substudy ^{45,e}	Multicenter USA	06/2003 to 02/2004 79 weeks	E: 85, C: 85	ZDV/3TC/ABC	E: ZDV/3TC/ABC + TDF, C: ZDV/3TC/ABC + EFV	E: 38 (33–43), C: 38 (32–44)	E: 21, C: 20	E: 446 (275–593), C: 457 (314–636)	<200	AIDS, CVD, Rash, mortality, HIV-RNA
GS-98–902 ^{30,f}	Multicenter USA	09/1998 to 03/2000 ^g 24 weeks	E: 56, C: 28	≤4 ART agents; Not specified	E: TDF 300 mg, C: Placebo	E: 41, C: 41 ^h	E: 6, C: 7	E: 381, C: 298	400 to 100000	RF, mortality
Loufy 2007 ¹⁶	Multicenter Canada	08/2002 to 02/2004 48 weeks	E: 50, C: 22	2 nucleoside analogs, 1 PI; NRTI naïve; tNRTI	E: TDF/3TC + LPV/r, C: current PI containing ART	E: 44.1 (38.7–49.9), C: 45.6 (38.2–56.1)	E: 2, C: 5	E: 487 (298–703), C: 598 (450–737)	<50	AIDS, mortality, CD4-cell count, TG, HIV-RNA
McComsey 2012 ⁴²	Single-center USA	05/2005 to 11/2007 48 weeks	E: 24, C: 26	ART, including tNRTI	E: ART + TDF, C: ART, including tNRTI + uridine	E: 48 (43–51), C: 48 (41–51)	E: 14, C: 14	E: 532 (334–858), C: 578 (439–781)	<400	Mortality, CD4-cell count, LDL-cholesterol, TG, BMD, BF, HIV-RNA
Milinkovic 2007 ^{31, j}	Single-center, n.r.	01/2004 to 05/2004 24 weeks	E: 17, C: 22	PI or non-NRTI, and d4T40	E: TDF, C: d4T40	E: 45 (42–48), C: 43 (36–49)	Total: 7	E: 529 (336–810), C: 569 (417–811)	<200	Fractures
PREPARE ^{43,44,k}	Multicenter Netherlands	06/2006 to 12/2007 48 weeks	E: 74, C: 68	ZDV/3TC + NNRTI or PI	E: TDF/FTC, C: ZDV/3TC	E: 47 (43.0–54.0), C: 45.0 (38.5–49.5), Total: 46.0	E: 7, C: 25	E: 490.0 (376.0–630.0), C: 485.5 (373.5–640.0)	<50	eGFR, BMD
RAVE ⁴¹	Multicenter UK	01/2003 to 10/2003 48 weeks	E: 52, C: 53	D4T or ZDV, PI	E: TDF, C: ABC	E: 42 (24–61), C: 43 (29–70)	E: 6, C: 13	Total: 579 (238) ^a , E: 486 (334–706), C: 521 (314–723) ^c	<50	Rash, CD4-cell count, LDL-cholesterol, HDL-cholesterol, TC, TG, BF, HIV-RNA

(Continued)

Table 1 (Continued)

Study	Centers	Country	Recruitment period Follow-up	Number randomized (n)	Prior antiretroviral therapy	Experimental, Comparator	Age (years), Median (IQR)	Sex (% female)	Baseline CD4-cells/mm ³ , Median (IQR)	Baseline HIV-RNA (copies/mL)	Outcomes
RECOMB ⁴⁶	Multicenter	Spain	05/2006 to 09/2008 72 weeks	E: 39, C: 41	HAART regimen containing ZDV+3TC plus NNRTI or PI	E: TDF/FTC + ATV/r, C: ZDV/3TC	E: 44 (10.6), C: 44 (7.4) ^a	E: 28, C: 10	E: 655 (505–789), C: 504 (363–756)	<50	CVD, RF, mortality; fractures, CD4-cell count, LDL-cholesterol, HDL-cholesterol, TC, TG, BF, HIV-RNA AIDS, mortality
STAR ¹⁷	Multicenter	Thailand	05/2008 to 11/2009 24 weeks ⁿ	E: 100, C: 100	PI-naive NNRTI (nevirapine, EFV) + 2 NRTIs ^o	E: TDF/3TC/LPV/r, C: mono-LPV/r	E: 38.2 (6.9), C: 36.8 (6.8) ^a	E: 52, C: 33	E: 211 (134), C: 194 (123) ^a	E: ≥1000	
Swap ^{47,48}	Single-center	Denmark	06 to 12/2008 48 weeks ^o	E: 20, C: 20	ZDV/3TC	E: TDF, C: ABC	E: 46 (8.7), C: 50 (11.9) ^a	E: 30, C: 45	E: 540 (206), C: 567 (256) ^a	E: <50 ^p	Rash, LDL-cholesterol, HDL-cholesterol, TC, TG, BMD
Sweet ^{33,34}	Multicenter	UK, Ireland	n.r. 48 weeks	E: 125, C: 125	ZDV/3TC + EFV	E: TDF/FTC+EFV, C: ZDV/3TC+EFV	E: 42 (8.8), C: 42 (9.1) ^a	E: 14, C: 18	n.r.	E: <400	QoL, RF, mortality, CD4-cell count, LDL-cholesterol, HDL-cholesterol, TC, TG, eGFR, HIV-RNA
Totem ⁴⁰	Multicenter	France	09/2005 to 04/2007 12 weeks ^s	E: 48, C: 49	ART (NRTI, NNRTI, PI) ^r	E: TDF/FTC, C: prior ART	E: 50 (42–58), C: 43 (39–50)	E: 17, C: 9	E: 463 (314–674), C: 559 (337–714)	E: <200 ^s	RF

Notes: /r: Ritonavir-boosted; 3TC: Lamivudine; ABC: Abacavir; ATV: Atazanavir; ART: antiretroviral therapy; BF: body fat; BMD: bone mineral density; C: Comparator group (not TDF-containing); CVD: Cardiovascular Disease; d4T: Stavudine; ddi: Didanosine-EC; DRV: Darunavir; DTG: Dolutegravir; E: Experimental group (TDF-containing regimen); EFV: Efavirenz; eGFR: estimated glomerular filtration rate; FTC: Emtricitabine; LPV: Lopinavir; MVC: Maraviroc; n.r.: Not Reported; NRTI: Nucleoside Reverse Transcriptase Inhibitor; NVP: Nevirapine; QoL: Quality of life; RAL: Raltegravir; RF: Renal failure; TC: Total cholesterol; TG: Triglycerides TDF: Tenofovir Disoproxil Fumarate; INRTI: thymidine Nucleoside Reverse Transcriptase Inhibitor; ZDV: Zidovudine. Reported are medians (with interquartile range) if not otherwise specified.

^aMean (SD).
^b96.2% (TDF) and 92.2% (control) had HIV-RNA levels below 50 copies/mL at baseline.
^cMedian (range).
^dAbstract /poster only; the study had three arms; we compared the arm TDF/FTC + LPV/r with the control ABC + ddi + LPV/r as both contain LPV/r. We did not analyze the arm TDF/FTC + DRV/r.
^eSubstudy; main trial was not eligible because patients were originally ART-naive.
^fThe study has four arms; we did not analyze two arms with TDF 75mg and TDF 150mg as these are uncommon doses; the placebo-arm crossed-over to TDF 300mg at 24 weeks – we used data only until week 24.
^gStudy period; recruitment period not reported.
^hMean.
ⁱPrior TDF in TDF-group 8% and in control-group 0%.
^jThe study has three arms; we did not analyze the arm with stavudine 30 mg as this is an uncommon dose.
^kSubstudy; a publication for the main trial could not be identified.
^lNot indicated whether mean or median; (range).
^mSystematic treatment switch at week 24 – we used data only until week 24.
ⁿOverall, 5% had prior TDF.
^oDiscontinuation after 48 weeks; reason not reported.
^pUndetectable" viral load.
^qSystematic treatment switch to TDF in week 12 – we used only data from before.
^rUnclear if patients had prior TDF. Authors list prior NRTIs, TDF could be among the item "other" with 4 and 9%.
^s98% of the participants had HIV-RNA levels below 200 copies/mL at baseline, 72% (TDF) and 76% (control) had HIV-RNA levels below 50 copies/mL at baseline.

If only a few patients of a study did not meet our inclusion criteria, we accepted this and we included two studies with less than 10% patients who had TDF-based ART before randomization^{16,17} (we excluded 7 studies with >20% patients being pre-treated with TDF^{18–29}). When studies compared more than two treatment arms, we included only two arms in the main analysis to avoid double-counting patients. This was the case in three studies: In the first two, we excluded the arms with uncommon doses (i.e. stavudine 30mg³⁰ and TDF 75 or 150mg³¹); in the third, we used the TDF-arm with a backbone treatment that was more similar to the control group³² (details in Table 1).

In secondary analyses, we assessed the comparison of the two fixed dose regimens TDF/FTC vs. ABC/3TC.

We conducted ancillary analyses that combined the studies on ART-experienced patients with studies in ART-naïve patients initiating a TDF containing regimen (reported in our previous meta-analysis⁵). This larger database improved the imputation of missing information and provided more precise overall estimates, allowed to explore if effects are different between ART-naïve and ART-experienced patients, and maximized statistical power to evaluate clinical outcomes. In these combined meta-analyses, we did not evaluate body fat (because studies in naïve patients reported mostly relative changes, studies in non-naïve patients mostly absolute changes) and virological failure (because clinical circumstances and

treatment objectives when initiating ART or when switching ART are both closely related to virological failure and clinically too heterogeneous to be reasonably combined in one analysis).

We used meta-regression analyses to test potentially different effects between ART-experienced and ART-naïve patients and to evaluate whether TDF effects are different when fixed-dose regimens are compared (TDF/FTC vs. ABC/3TC). In a *post hoc* analysis, we explored baseline lipid levels as modifier of TDF-effects on lipid levels. We conducted none of the pre-specified sensitivity/subgroup analyses on publication status, funding source, risk of bias, sex, pregnancy, breastfeeding, and renal disease because of too few studies per subset.

Stata 13.1 (Stata Corp, College Station, TX, USA) was used for all analyses; *p*-values are 2-tailed.

Results

We screened 5237 references of which we assessed 421 potentially relevant full texts to determine eligibility. Twenty-one publications were included which reported on 17 RCTs in treatment experienced patients (Fig. 1). The agreement between both reviewers was good (kappa = 0.64).

All RCTs were rather small, with the biggest trials including between 200 and 301 patients^{17,32–35} (Table 1). Study follow-up was between 12 and 79 weeks, with 13 of 17 RCTs reporting data observed at week 48 or

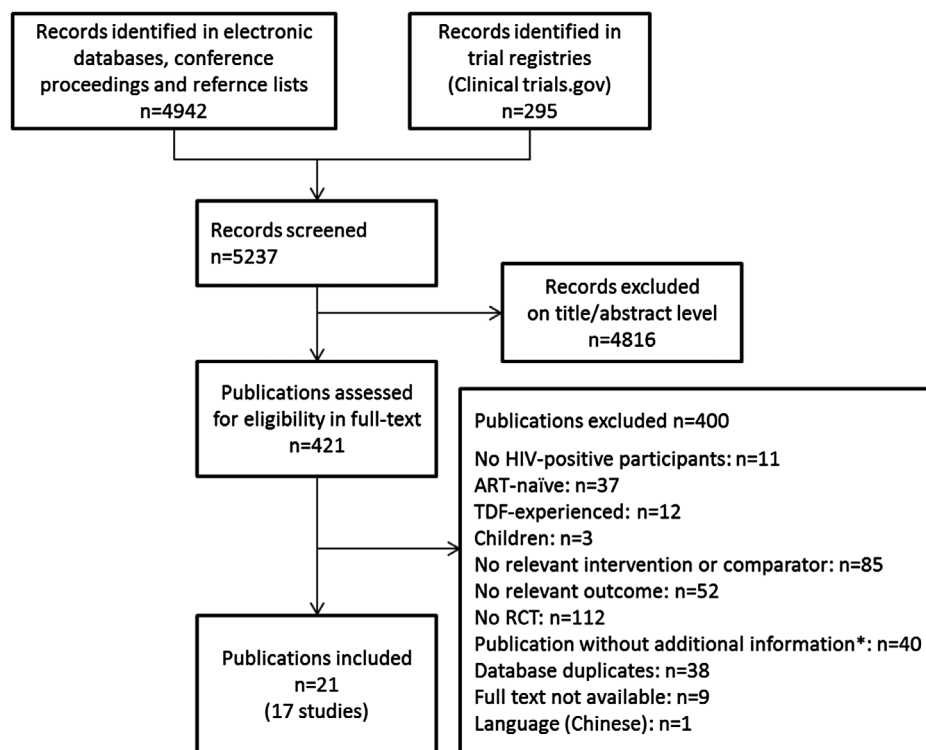


Figure 1 Study selection process

Note: “*” describes an included study not providing any additional pertinent data (i.e. beyond what the main publication(s) from which we extracted data already provided).

later. Four trials^{35–39} compared the fixed dose co-formulations TDF/FTC with ABC/3TC, the other studies used various other treatment regimens. Patients switched because of treatment failure in three trials (baseline HIV-RNA levels >1000 copies/mL^{17,32} or 400 to 100,000 copies/mL³⁰). In the other 14 studies, patients were virologically suppressed (baseline HIV-RNA levels < 50 copies/mL in 8 trials; <200 copies/mL in 4 trials; <400 copies/mL in 2 trials; see Table 1) and treatment was changed for other reasons. This included five trials where the indication of treatment switch was related to hyperlipidemia,³⁹ dyslipidemia,⁴⁰ lipoatrophy^{41,42}, or elevated total cholesterol.³⁸ None of the trials included pregnant women in their analyses.

Thirteen of 17 studies were supported by the pharmaceutical industry, 1 was governmentally funded, no details were reported in 3 (Webappendix). Most studies used ITT- or modified ITT-analysis (14/17), 1 used as treated analysis,⁴² 1 on treatment analysis,^{43,44} and 1 per protocol analysis.^{33,34}

Risk of bias assessment

All trials, with one exception,³⁰ had a high overall risk of bias due to an open study design which is associated with a high risk of performance and detection bias. The risk of bias in the other domains was mainly low or unclear for all studies (Webappendix).

Outcomes

Deaths

Nine trials^{16,17,30,32–35,42,45,46} were included in the analysis. In TDF-based regimens vs. other regimens, the relative risk (RR) for death was 0.69 (95% CI 0.20 to 2.37; median follow-up 48 weeks; range 24 to 79 weeks; Table 2).

Fractures

Three trials^{31,35,46} were included in the analysis. The RR for fractures was 0.65 (95% CI 0.08 to 5.18; median follow-up 72 weeks; Table 2).

CD4-cell count

Seven trials^{16,34,35,39,41,42,46} were included in the analysis. There was no indication that switching to TDF-based regimens had a different impact on CD4-cell count than maintaining or switching to other regimens (mean difference (MD) -13.76 cells/mm³; 95% CI -37.63 to 10.12 ; changes from baseline to week 48; Table 2).

Virological failure

Eight trials^{16,32,33,35,39,42,45,46} were included in the analysis. The RR for achieving HIV-1-RNA levels < 50 copies/mL was 1.02 (95% CI 0.98 to 1.07, Table 2) at 48 weeks.

Lipid levels

Overall, eight trials^{16,34,35,39,41,42,46,47} were included in the analyses for LDL-cholesterol, HDL-cholesterol, total-cholesterol, and triglycerides. All effect estimates indicated decreases of lipid levels (statistically significant for total cholesterol and triglycerides) in TDF-based regimens compared to other regimens (MD (95% CI): LDL-cholesterol -4.71 mg/dL (-9.80 to 0.37); HDL-cholesterol -2.04 mg/dL (-4.68 to 0.59); total cholesterol -12.05 mg/dL (-20.76 to -3.34); triglycerides -14.33 mg/dL (-23.73 to -4.93); changes from baseline to week 48; Table 2).

eGFR

Three trials^{34,35,44} were included in the analyses. Two trials reported results from the Modification of Diet in Renal Disease (MDRD) formula,^{34,35} all three trials used the Cockcroft-Gault formula; and in one trial, effects based on the Chronic Kidney Disease Epidemiology Collaboration formula were also reported.⁴⁴ There was no significant decrease when we used the MDRD-based effects where available and otherwise the Cockcroft-Gault estimate (MD -3.50 ml/min; 95% CI -7.35 to 0.36). Analyzing only the two MDRD-based effects yielded similar results (-3.04 ml/min/1.73 m²; -7.8 to 1.72). Renal function significantly decreased when assessed using Cockcroft-Gault formula estimates (-4.48 ml/min; -6.56 to -2.41) (changes from baseline to week 48; Table 2; Webappendix).

BMD

Three trials^{42,43,48} were included in the analyses. They assessed both BMD of the hip and lumbar spine; one trial⁴³ also measured BMD of the femoral neck. Compared to other regimens, TDF-based regimens led to a loss of bone density at the hip (MD -2.46% ; 95% CI -3.9 to -1.03) and lumbar spine (-1.52% ; -2.69 to -0.34) (changes from baseline to week 48; Table 2, Webappendix).

Body fat

Three trials^{41,42,46} were included in the analyses. There was no significant difference of TDF-based vs. other treatments on the absolute changes of trunk fat (MD 218 g; 95% CI -255 to 692) and limb fat (271 g; -207 to 748) (changes from baseline to week 48; Webappendix).

Other outcomes

We did not pool results on AIDS-defining events, cardiovascular events, renal failure, proteinuria, rash, and quality of life as data was inconsistently reported or based on very heterogeneous definitions. Findings are described narratively in the Webappendix.

Secondary analyses in studies comparing only TDF/FTC-based vs. ABC/3TC-based regimens were in line with the

Table 2 Summary of results

Outcome ART-pretreatment	No. of studies	No. of patients	Effect estimate	95% CI	I ² (%)
<i>Mortality</i>					
Non-naïve	9	1598 (10 events)	RR 0.69	0.20 to 2.37	0
Naïve	18	7582 (106 events)	RR 0.88	0.60 to 1.30	0
Combined	27	9180 (116 events)	RR 0.86	0.60 to 1.25	0
<i>Fractures</i>					
Non-naïve	3	427 (3 events)	RR 0.65	0.08 to 5.18	0
Naïve	5	4007 (126 events)	RR 0.97	0.68 to 1.37	0
Combined	8	4434 (129 events)	RR 0.96	0.68 to 1.35	0
<i>CD4-cell count</i>					
Non-naïve	7	826	-13.76 cells/mm ³	-37.63 to 10.12	44.8
Naïve	14	5177	0.50 cells/mm ³	-15.35 to 16.34	72.2
Combined	21	6003	-2.40 cells/mm ³	-16.84 to 12.03	76.6
<i>Virological failure</i>					
<i>HIV-RNA threshold in copies/mL</i>					
Non-naïve					
<50	8	1300 (1027 events)	RR 1.02	0.98 to 1.07	12.6
<200	4	881 (739 events)	RR 1.02	0.98 to 1.07	0
<400	1	310 (244 events)	RR 1.03	0.92 to 1.16	-
Naïve					
<50	16	6244 (4980 events)	RR 1.03	0.99 to 1.07	50
<200	3	2489 (2349 events)	RR 1.02	1.00 to 1.04	30
<400	8	3422 (2776 events)	RR 1.03	0.97 to 1.09	59
<i>LDL-cholesterol</i>					
Non-naïve	7	786	-4.71 mg/dL	-9.80 to 0.37	42.7
Naïve	6	2214	-9.42 mg/dL	-12.16 to -6.78	17.5
Combined ^a	13	3000	-7.57 mg/dL	-10.37 to -4.78	42.2
<i>HDL-cholesterol</i>					
Non-naïve	6	759	-2.04 mg/dL	-4.68 to 0.59	67.1
Naïve	6	2294	-2.97 mg/dL	-2.97 to -1.57	40.1
Combined	12	3053	-2.38 mg/dL	-3.83 to -0.93	63.3
<i>Total cholesterol</i>					
Non-naïve	6	771	-12.05 mg/dL	-20.76 to -3.34	73.4
Naïve	8	2435	-18.35 mg/dL	-22.73 to -13.98	55.1
Combined	14	3206	-15.88 mg/dL	-20.18 to -11.59	67.8
<i>Triglycerides</i>					
Non-naïve	8	878	-14.33 mg/dL	-23.73 to -4.93	2.0
Naïve	8	2431	-29.84 mg/dL	-38.37 to -21.31	0
Combined	16	3309	-22.82 mg/dL	-29.35 to -16.30	4.5
<i>eGFR^b</i>					
Non-naïve					
MDRD	3	501	-3.50 ml/min	-7.35 to 0.36	33.2
MDRD	2	482	-3.04 ml/min/1.73 m ²	-7.80 to 1.72	65.4
C-G	3	501	-4.48 ml/min	-6.56 to -2.41	0
Naïve					
MDRD	8	3586	-3.55 ml/min	-5.99 to -1.11	76.0
MDRD	3	1856	-0.77 ml/min/1.73 m ²	-2.92 to 1.39	47.7
C-G	5	1742	-6.26 ml/min	-9.42 to -3.10	70.7
Combined	11	4087	-3.49 ml/min	-5.56 to -1.43	70.1
MDRD	5	2338	-1.55 ml/min/1.73 m ²	-3.67 to 0.56	58.2
C-G	8	2243	-5.62 ml/min	-7.62 to -3.62	53.5
<i>BMD</i>					
Non-naïve					
Hip	3	124	-2.46%	-3.9 to -1.03	51.5
Lumbar	3	125	-1.52%	-2.69 to -0.34	35.0
Naïve					
Hip	3	943	-1.38%	-1.81 to -0.95	0
Lumbar	3	961	-1.25%	-1.78 to -0.72	0
Combined					
Hip	6	1067	-1.64%	-2.15 to -1.13	25.3
Lumbar	6	1086	-1.32%	-1.78 to -0.85	0

Number of analyzed patients, summary effect estimates, and standard deviations reported here differ slightly from the separate analyses in naïve and non-naïve patients as the amount of studies used to impute missing data differed per meta-analysis. Results not using the additional imputation information are shown in our previous work⁶ and in the Webappendix.

^aSignificantly stronger effects of TDF-regimens on LDL-cholesterol in ART-experienced patients in meta-regression analysis ($p = 0.028$). There was no interaction in the other outcomes.

^bCombined estimates using MDRD, where available, otherwise Cockcroft-Gault.

BMD: bone mineral density; C-G: Cockcroft-Gault; eGFR: estimated glomerular filtration rate; MDRD: modification of diet in renal disease.

primary findings (mortality: RR 0.50, 95% CI 0.05 to 5.49; fractures: RR 0.34, 0.01 to 8.17; CD4-cell count: MD -21.49 cells/mm³, -52.15 to 9.18; HIV-1-RNA levels <50 copies/mL: RR 1.00, 0.94 to 1.06; LDL-cholesterol: MD -7.98 mg/dL, -13.7 to -2.90; HDL-cholesterol: MD -0.63 mg/dL, -2.27 to 1.01; total cholesterol: MD -12.67 mg/dL, -25.20 to -0.14; for triglycerides -7.27 mg/dL, -22.03 to 7.49; eGFR Cockcroft-Gault: MD -3.99 ml/min, -6.38 to -1.59; eGFR MDRD: MD -5.3 ml/min/1.73m²; -8.83 to -1.77; Details and corresponding Forest plots are shown in the Webappendix). No study comparing TDF/FTC vs. ABC/3TC reported effects on BMD or body fat.

Heterogeneity and evaluation of effect-modifiers

Heterogeneity between studies in ART-experienced patients was low for mortality, fractures, virological failure, triglycerides, and Cockcroft-Gault eGFR ($P < 40\%$; Webappendix). It was moderate to high for the other outcomes ($P \geq 40\%$; Webappendix). Among these, estimated heterogeneity was 0% in the subset comparing only TDF/FTC vs. ABC/3TC for the outcomes CD4-cell count, LDL- and HDL-cholesterol explaining some of the statistical heterogeneity between studies as possibly resulting from heterogeneous comparators; it remained high for total cholesterol ($I^2 = 69.1\%$) and was not estimable for the other outcomes as there was either none or only one study per subset (Webappendix).

Type of regimen

We found no evidence that the effects of TDF in ART-experienced patients depended on the kind of regimen (i.e. fixed-dose TDF/FTC vs. ABC/3TC compared to other TDF-regimens vs. non-TDF-regimens), although the LDL-reductions were more pronounced with the fixed dose regimen (p for interaction 0.034; Details in Webappendix).

Baseline lipid levels

We detected no association of baseline lipid levels with lipid changes over 48 weeks in *post hoc* meta-regression analyses (data not shown).

HIV-RNA levels

The results on virological failure were similar in comparisons based on other cut-offs (i.e. 200 and 400 copies/mL), and in analyses excluding trials in patients with baseline HIV-RNA above 200 and 400 copies/mL (Webappendix).

Ancillary analyses of ART-naïve and ART-experienced patients

Combining the treatment effects reported in the 17 RCTs in 2210 ART-experienced patients switching to TDF-based

regimens with the effects from previously reviewed 22 RCTs in 8297 ART-naïve patients initiating TDF-based regimens as first-line treatment, yielded very similar effect estimates with smaller confidence intervals and statistical significant reductions of LDL and HDL-cholesterol and eGFR (Table 2). Between-study heterogeneity in the ancillary combined analyses was similar to the heterogeneity between studies in treatment-experienced patients (Table 2). We found no evidence that the effects of TDF depend on ART-experience, with the exception of triglycerides where greater reductions were seen in studies with ART-naïve patients (p for interaction 0.028).

Discussion

We analyzed the effects of switching to TDF-based regimens in 17 trials with 2210 ART-experienced HIV-patients. This switching was not associated with mortality, fractures, CD4-cell count, body fat, virological failure, LDL- and HDL-cholesterol. Switching to TDF-based regimens, however, decreased total cholesterol, triglycerides, and BMD. Effects on eGFR were inconsistent and depended on the measurement and effect estimates for indicated LDL- and HDL-cholesterol decreases but were not statistically significant. Findings were similar in trials on switching to fixed-dose TDF/FTC or ABC/3TC-based regimens.

The ancillary analyses in naïve and non-naïve patients using data from 39 RCTs involving over 10,000 patients provided more precise estimates, and in this large body of evidence, effects on eGFR, LDL-, and HDL-cholesterol were now statistically significant. The direction of effect estimates was consistent throughout all analyses (including the naïve, the non-naïve, or both populations combined). We found no evidence that effects of TDF differed between ART-naïve and ART-experienced patients or between fixed dose regimens (TDF/FTC and ABC/3TC) and non-fixed-dose regimens – with only two potential exceptions: Firstly, the lipid-lowering effect on triglycerides appeared to be stronger in treatment-naïve patients (-29.84 mg/dL vs. -14.33 mg/dL). One possible explanation could be that treatment-experienced patients have been exposed to first generation ART over longer periods with persistent adverse effects on lipid levels. We observed lower average baseline lipid levels in studies with naïve patient populations but *post hoc* meta-regression analyses revealed no association with TDF effects (although the analysis was based on aggregated data and we would need individual patient data to further explore this). Secondly, the difference between effects of TDF and other ART on LDL-reduction seemed to be greater in fixed dose regimens.

The ART-experienced patients were at baseline mostly virologically suppressed with only 3 of 17 studies

including patients with previous treatment failure and baseline HIV-RNA levels of 1000 copies/mL and above. In our previous meta-analysis,⁵ the median baseline values were greater than 58,000 copies/mL HIV-RNA. However, there appears to be no difference between TDF-based regimens and other regimens in treatment-experienced and -naïve patients, irrespective of baseline viral load. Of note, as in our previous review, we found substantial incongruences across trial reports with regard to the definition of treatment failure (i.e. various cut-offs defining virological failure, different approaches for dealing with incomplete outcome data).

This is the first meta-analysis of RCTs exploring the effects of TDF in treatment-experienced patients. The ancillary analysis is, to our knowledge, the largest body of clinical trial evidence on treatment effects of TDF and the first meta-analysis evaluating influences of pretreatment and fixed-dose regime in ART-naïve and ART-experienced patients. Despite the clinically different treatment settings (with or without fixed-dose treatments, various comparators, previous ART or switching to alternative treatment choices) and diverse study populations, the overall findings were largely consistent. The broad perspective with wide selection criteria maximized the statistical power to assess clinical outcomes and the coverage of evidence supporting the clinical use of TDF.⁴⁹ The between-study heterogeneity introduced some imprecision in the random-effects models, but using all data allowed us to better deal with the problem of missing data which increased the precision of the treatment effect estimates as more data was available for imputation.

We used predefined endpoints relevant to patients and clinicians, used established methodology for meta-analysis throughout all processes and especially when addressing potential bias. Our highly sensitive literature search was developed in collaboration with research librarians to cover the entire evidence on TDF-based regimens.

Some limitations need to be discussed. First, none of the included studies considered mortality or the clinical outcomes as their primary endpoint but often reported them rather unsystematically alongside adverse events. We decided to not extract outcomes that were related to specific events (e.g. to the drug or to withdrawal) as this harbors potential for bias and subjectivity.^{12,50}

Second, for changes of outcome variables from baseline, we only extracted results at 48 weeks because this was the most consistently reported time-point. Still, some studies only reported data for diverse shorter or longer follow-up time-points.

Third, insufficient reporting led to (often unanswered) author queries and required numerous imputations for continuous outcomes. For example, authors rarely provided a measure of dispersion (e.g. 95% CI, standard

deviation), the number of analyzed patients, or the follow-up time-point; some results are only reported for all groups together or for one group but not the other. Another reporting issue was missing data. The majority of studies reported ITT or modified-ITT analyses; however, they often do not analyze all randomized or all treated patients. Often, a fair amount of missing patients (e.g. lost-to-follow-up, missing data points, discontinuation, withdrawal) were reported without a statement on how this missing data was dealt with, i.e. if and what kind of imputations were used, or which other methods were applied. For viral load, it was common to report an approach for missing data, e.g. “missing equals failure” but rarely authors reported how many patients were actually missing, so there is no way of knowing how many patients were observed to have a certain outcome event and how many were imputed or assumed to have an event. This lowers the reliability of the reported effects in the primary studies and ultimately limits the clinical interpretation.

Fourth, in some studies, it was not clear which backbone treatments (beyond randomization) were given at discretion of the treating physicians or if they were the same in both treatment groups. This information would have been particularly important in unblinded trials and because some co-administered drugs from different classes are known to influence the lipid profile.⁵¹

Fifth, all but one study had a high risk of bias due to lack of blinding. Due to the small number of studies with low risk of bias, we could not assess the impact of risk of bias.

Sixth, the statistical between-study heterogeneity in some analyses could not be explained with the data at hand despite various prespecified strategies to explore if publication status, funding source, sex, pregnancy, breastfeeding, or renal disease potentially modifies the reported effects of TDF. An individual patient-level meta-analysis might be warranted to further explore potential impact of patient-related factors.

We acknowledge these limitations and uncertainties and conclude that there is limited evidence from clinical trials – the majority being of relative short follow-up – indicating that TDF-based regimens have adverse effects on kidney function and bone mineral density but lower lipid levels irrespective of possible pretreatment with non-TDF-based ART. This is in line with current guidelines emphasizing favorable lipid effects of TDF and recommending alternative treatments (such as abacavir or the recently approved tenofovir alafenamide, an oral prodrug of tenofovir) in patients with chronic kidney disease or osteoporosis.²

However, the substantial reporting deficits in numerous trial reports and the high inconsistency of reporting of clinical events did not allow us to assess the effects on such patient-relevant clinical outcomes and increased the clinical uncertainty. This is a substantial waste of existing potentially useful evidence. Since the quality of reporting is

elementary for evidence-based decision-making, improved reporting can help closing important knowledge gaps and facilitate treatment decisions in HIV care.⁵²

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Disclaimer statement

Contributors

LGH and HCB conceived and designed the study; HE coordinated the review; all authors collected the data; HE and LGH analyzed the data; HE, LGH, and HCB interpreted the results; HE wrote the first draft and all authors made revisions on the manuscript and approved the final version of the paper. HE and LGH are the guarantors.

Declaration of competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf and declare: HCB has received in 36 months preceding the submission of this work travel grants, honoraria, and unrestricted research grants from Bristol-Myers-Squibb, Gilead, and ViiV Healthcare. The Basel Institute for Clinical Epidemiology & Biostatistics has received funding from Gilead for a previous project closely related to the current work. MS received travel grants, and is member of advisory boards of abbvie, Bristol-Myers-Squibb, Gilead, Janssen, Merck Sharp & Dohme, and ViiV. All other authors declare no competing interests.

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