Comparative efficacy and safety and dolutegravir and lamivudine in treatment naive HIV patients

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Objective: Compare the efficacy and safety of the 2-drug antiretroviral therapy regimen dolutegravir + lamivudine (DTG + 3TC) with traditional 3-drug regimens in treatment-naive patients with HIV-1.

Design: Data from double-blind, randomized controlled trials of at least 48 weeks' duration in treatment-naive patients with HIV-1 identified by systematic review were evaluated using a Bayesian network meta-analysis methodology.

Methods: The primary outcome was virologic suppression at Week 48 for 3-drug regimens versus DTG + 3TC (also analyzed in patient subgroup with baseline viral load >100 000 RNA copies/ml). Secondary outcomes included $CD4^+$ cell count change from baseline and safety (adverse events, serious adverse events, and drug-related adverse events) at Week 48.

Results: The network contains 14 unique regimens from 14 randomized controlled trials based on data from 10 043 patients. The proportional difference for viral suppression at 48 weeks for DTG + 3TC versus the other 13 regimens included in the network ranged from −2.7% (−11.0, 5.6%) versus DTG + tenofovir alafenamide/emtricitabine (FTC) to 7.3% (0.6, 13.8%) versus efavirenz + tenofovir disoproxil fumarate/FTC. DTG + 3TC was found to be significantly better than efavirenz + tenofovir disoproxil fumarate/FTC and similar to all other regimens analysed in terms of viral suppression at 48 weeks. With regard to other outcomes ($CD4^+$, adverse event, serious adverse event, drug-related adverse events) at 48 weeks, DTG+3TC was broadly similar to all regimens analysed.

Conclusion: This network meta-analysis demonstrates similar efficacy and safety outcomes over 48 weeks with DTG + 3TC compared with traditional 3-drug antiretroviral therapy regimens. Copyright © 2019 The Author(s). Published by Wolters Kluwer Health, Inc.

Introduction

Combination antiretroviral therapy (ART) is the standard of care for treatment–naive patients with HIV infection, allowing them to achieve and maintain long–term virologic suppression and achieve a life expectancy similar to that of the general population [1–3]. Despite their efficacy, many ART agents are associated with well established risks of long–term toxicities, including coronary disease, osteoporosis, renal failure or chronic kidney disease, and diabetes [4–8]. The high prevalence of comorbidities associated with HIV leads to poly-pharmacy, increasing the risk of drug–drug interactions and severe complications [9,10].

Combination ART traditionally comprises a 3-drug regimen of three active agents from two drug classes – two nucleoside/nucleotide reverse transcriptase

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inhibitors (NRTIs) and a non-NRTI core agent selected from one of the following drug classes: an integrase strand inhibitor (INSTI), a boosted protease inhibitor, or a non-nucleoside reverse transcriptase inhibitor (NNRTI) [1,2,11]. For treatment-naive patients with HIV, INSTIs are the preferred core agent according to the European AIDS Clinical Society (EACS) guidelines, a preferred option according to the US Department of Health and Human Services (DHHS) guidelines, and a regimen based on the INSTI dolutegravir (DTG) is recommended first line by the WHO [1,2,11].

Given the lifelong nature of HIV treatment and the potential toxicities associated with ART [5,12–15], 2-drug ART regimens that minimize cumulative drug exposure while maintaining the efficacy of 3-drug regimens are of interest [16,17]. In treatment-naive patients with HIV-1, the 2-drug regimen DTG + lamivudine (3TC) was investigated in two single-arm, pilot studies, and two large, multicenter, Phase III, randomized controlled trials (RCTs) – GEMINI-1 and GEMINI-2 [18–20]. In the GEMINI studies, DTG + 3TC was noninferior to DTG + tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) in terms of the proportions of treatment-naive patients achieving virologic suppression at Week 48 [91 versus 93%, respectively; treatment difference −1.7, 95% confidence intervals (CI): −4.4, 1.1], with a similar safety profile [20]. Based on these data, the 2018 guidelines from the US DHHS and EACS recommend the 2-drug regimen of DTG + 3TC as an alternative first-line regimen for treatment-naïve adults with HIV [1,2].

Given the clinical importance of the potential for reduced toxicity with 2-drug regimens over 3-drug regimens, signs of a paradigm shift from 3-drug to 2-drug regimens, and the inclusion of DTG + 3TC in the guidelines, it is important to determine the efficacy and safety of DTG + 3TC compared with traditional 3-drug ART regimens. Therefore, this network meta-analysis (NMA) was undertaken to compare the efficacy and safety of DTG + 3TC with traditional 3-drug regimens in treatment-naive patients with HIV-1, with the aim of providing clinically relevant data to support prescribing choices in this patient population.

Methods

Study identification
A systematic literature search was performed on 4 December 2018 using PubMed/MEDLINE, Embase, and Cochrane databases to update an original literature search conducted in 2013 [21]. The aim of the search was to identify Phase 3/4 RCTs evaluating the efficacy and/or safety of DTG + 3TC and/or guideline-recommended 3-drug regimens in treatment-naive

patients with HIV-1 (search terms can be found in Supplementary Table 1, http://links.lww.com/QAD/B492). In addition, the National Institute of Health clinical trial (NCT) registry database (www.clinicaltrials.gov), US Food and Drug Administration (FDA) approval summaries, European Medicines Agency, European Public Assessment Reports scientific discussions and package inserts of the treatments of interest were also systematically searched. Study selection was performed as previously described [21].

Eligible publications were Phase 3/4 RCTs of 48 or 96 weeks' duration, conducted in treatment-naive adults or adolescents (≥13 years of age) with HIV-1 infection, published in English, including a regimen of interest, and reporting at least one of the efficacy or safety endpoints of interest. Regimens of interest were those containing recommended core agents from the DHHS and EACS clinical guidelines (up to October 2018) [22,23] and the new INSTI bictegravir (BIC). Efavirenz (EFV) + TDF/FTC was also included to facilitate the formation of a connected network. The quality of the studies selected for inclusion in the NMA was assessed based on study design, confounders, blinding, data collection methods, withdrawals, and dropouts, using the Effective Public Health Practice Project Quality Assessment (EPHPP) tool [24].

The study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [25].

Outcomes
Efficacy
The primary efficacy outcome was the proportion of patients with virologic suppression at Week 48. In accordance with FDA guidance [26], virologic suppression was defined as (in order of preference): FDA Snapshot-50, time to loss of virologic response-50, confirmed virologic response-50, and HIV RNA less than 50 copies/ml. The secondary efficacy outcome was the mean increase in $CD4^+$ cell count from baseline to Week 48. Analysis of the primary outcome was also undertaken in the subgroup of patients with baseline viral load more than 100 000 RNA copies/ml.

Safety
Safety (secondary outcomes) were the proportions of patients with adverse events, serious adverse events, and drug-related adverse events by Week 48.

Data analysis
The NMA was conducted using a Bayesian analysis framework using WinBUGS software (version 1.4.3; MRC Biostatistics Unit, Cambridge, UK) to generate estimates of relative treatment outcomes [27,28]. Both fixed-effect and random-effect models were used to evaluate each outcome. The deviance information criterion, convergence criteria (based on 30 000 iterations on three chains, after a burn-in of 20 000), and total

residual deviations were used to determine the better fit between the fixed-effect and random-effect models.

A likelihood function was defined for each outcome measure, and treatment effects were modeled using a link function. The proportion of patients in each treatment group who achieved virologic suppression at Week 48 and change in $CD4^+$ cell count from baseline to Week 48 were analyzed as continuous outcomes using a normal distribution. The efficacy results are reported as the mean difference between the 3-drug regimens and DTG + 3TC for the proportion of patients achieving virologic suppression at Week 48 or the mean change in $CD4^+$ cell count (cells/μl) from baseline to Week 48, both with 95% credibility intervals (CrIs), representing the 95% probability that the parameter falls within the range. Safety outcomes (adverse events, serious adverse events, drug-related adverse events) at Week 48 were analyzed as binary outcomes using a binomial distribution. Results for the safety outcomes are expressed as odds ratios (ORs) and 95% CrI for 3-drug regimens relative to DTG + 3TC. Outcomes were considered significantly different if the 95% CrI did not include 1 for ORs, or 0 for mean difference or change from baseline. The Bayesian NMA methodology also allowed for estimates of the probability that one treatment is better than another to be calculated, for example, the probability that more patients will achieve virologic suppression at Week 48 with one regimen versus another.

Results

Studies included
The literature search identified 12 publications representing 14 distinct RCTs that were selected for inclusion in the NMA (Fig. 1a): AMBER [29], ECHO [30], FLAMINGO [31], GEMINI-1 and GEMINI-2 [20], GS-US-236-0102 [32], GS-US-292-0104 and GS-US-292-0111 [33], GS-US-380-1489 [34], GS-US-380-1490 [35], SINGLE [36], SPRING-2 [37], STaR [38], and STARTMRK [39]. Together, these publications included 10 043 treatment-naive patients with HIV-1. All studies included in the NMA were similar with respect to patient characteristics and inclusion/exclusion criteria. The NMA inputs can be found in Supplementary Table 2, http://links.lww.com/QAD/B492. All 14 studies reported virologic suppression, change in $CD4^+$ cell count, adverse event, and serious adverse events data [20,29–39]; 13 studies provided virologic suppression data in patients with viral load more than 100 000 RNA copies/ml [20,29–31,33–39], and 10 studies reported drug-related adverse event data [20,29–31,34–37,39]. All 14 studies included in the NMA had a global EPHPP rating of strong or moderate (Supplementary Table 3, http://links.lww.com/QAD/B492). The 3-drug regimens investigated in these studies ($n = 13$) and included

in the NMA network (Fig. 1b) were as follows: INSTIs + two NRTIs: BIC + tenofovir alafenamide (TAF)/FTC, DTG + abacavir (ABC)/3TC, DTG + TAF/FTC, DTG + TDF/FTC, cobicistat-boosted elvitegravir (EVG/c) + TAF/FTC, EVG/c + TDF/FTC, raltegravir (RAL) + ABC/3TC, and RAL + TDF/FTC; boosted protease inhibitors + two NRTIs: ritonavir-boosted darunavir (DRV/r) + ABC/3TC, DRV boosted with cobicistat or ritonavir (DRV/b) + TDF/FTC, and cobicistat-boosted DRV (DRV/c) + TAF/FTC; and NNRTIs + two NRTIs: EFV + TDF/FTC, and rilpivirine (RPV) + TDF/FTC. As each study did not report every outcome, networks for virologic suppression in the subgroups with baseline viral load more than 100 000 RNA copies/ml, and drug-related adverse events varied (data not shown).

Efficacy
Based on model diagnostics, the fixed-effect model was used for efficacy outcomes. In the overall population, efficacy endpoints were assessed for all 3-drug regimens investigated versus DTG + 3TC.

Virologic suppression at week 48
In the overall population, a significantly lower proportion of patients achieved virologic suppression at Week 48 with EFV + TDF/FTC compared with DTG + 3TC [mean difference: −7.3% (95% CrI: −13.8, −0.8)], with similar proportions for all other 3-drug regimens investigated versus DTG + 3TC (Fig. 2a). The probabilities of more patients in the overall population achieving virologic suppression at Week 48 with one treatment versus another are shown in Table 1. The probability of more patients achieving virologic suppression at Week 48 was greater with DTG + 3TC than all other 3-drug regimens (53.0–98.6%), except DTG + TDF/FTC (11.4%) and DTG + TAF/FTC (26.2%).

In the subgroups of patients with baseline viral load more than 100 000 RNA copies/ml, the proportion of patients achieving virologic suppression at Week 48 with DTG + 3TC was assessed relative to the same 3-drug regimens as virologic suppression at Week 48 in the overall population, except for EVG/c + TAF/FTC and EVG/c + TDF/FTC for which subgroup data were not available. A significantly higher proportion of patients with a baseline viral load more than 100 000 RNA copies/ml achieved virologic suppression at Week 48 with DTG + 3TC compared with RAL + TDF/FTC, DRV/r + ABC/3TC, DRV/b + TDF/FTC, EFV + TDF/FTC, and RPV + TDF/FTC, with similar proportions to all other 3-drug regimens analyzed (Fig. 2b).

$CD4^+$ cell count change from baseline at week 48
In the overall population, DTG + 3TC induced similar increases in $CD4^+$ cell count between baseline and Week 48 compared with all 3-drug regimens investigated, except for DTG + TAF/FTC, which was superior to
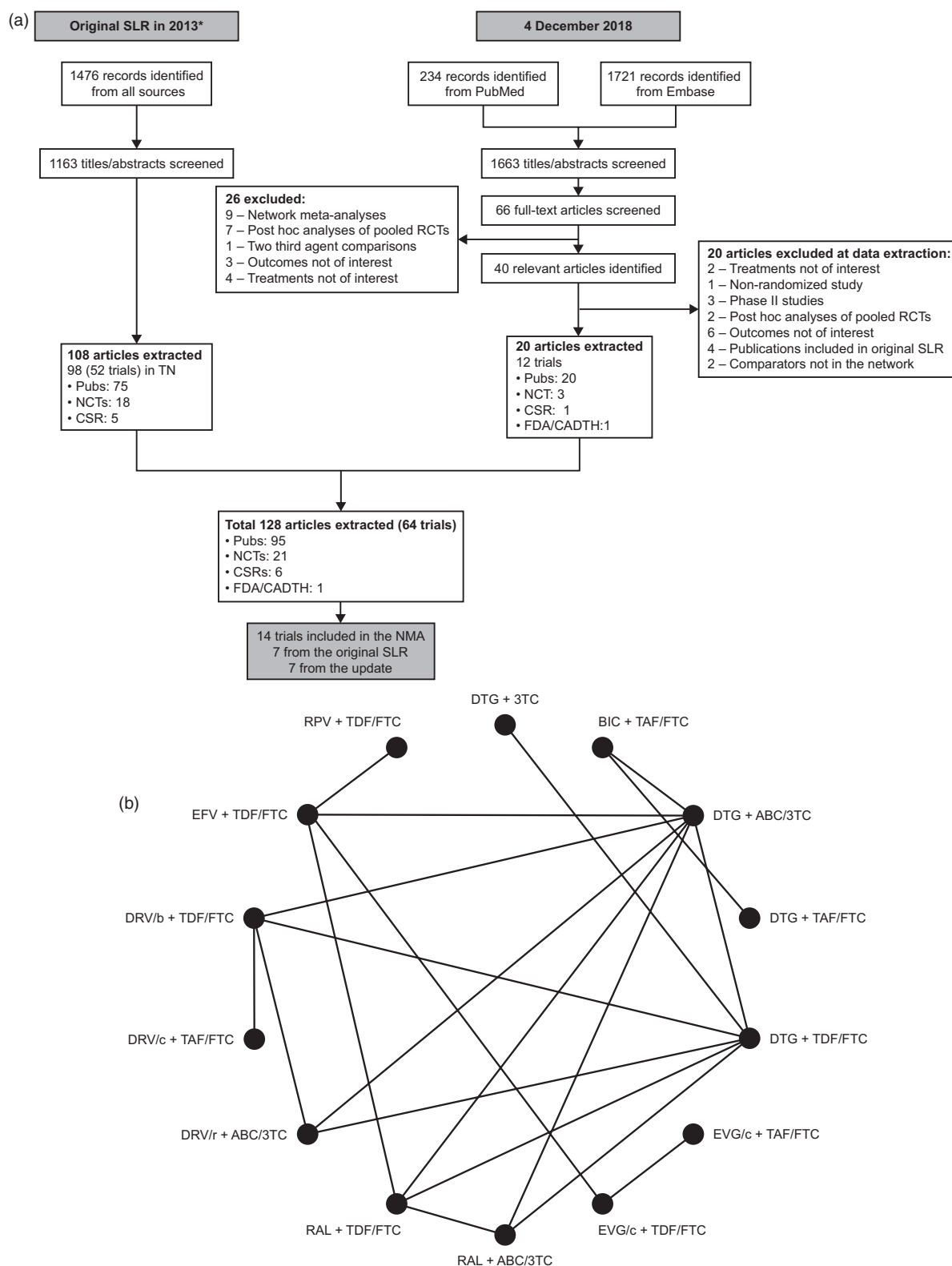
Fig. 1. (a) Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart; (b) network of treatment comparisons contained within the randomized controlled trials. (a) *A systematic literature review was undertaken in 2013 to inform an earlier meta-analysis [21]; the systematic search undertaken in December 2018 was used to update the original search and the results were combined; (b) network of treatment comparisons presented for the primary outcome of virologic suppression at Week 48, and the secondary outcomes of CD4$^+$ cell count change from baseline, adverse events, and serious adverse events at

DTG + 3TC (Fig. 3). Mean between-treatment differences for DTG + 3TC versus 3-drug regimens ranged from −44.49 cells/μl compared with DRV/r + ABC/3TC to 56.22 cells/μl compared with DTG + TAF/FTC (Fig. 3).

Safety (adverse events, serious adverse events, and drug-related adverse events) by week 48

Based on model diagnostics, the fixed-effect model was used for safety outcomes. Adverse events and serious adverse events at Week 48 were assessed for the same 3-drug regimens as the efficacy endpoints in the overall population at Week 48 relative to DTG + 3TC. Drug-related adverse events were assessed for the same regimens at Week 48 relative to DTG + 3TC, except EVG/c + TAF/FTC, and EVG/c + TDF/FTC for which data were not available.

The odds of having an adverse event were similar in patients treated with all 3-drug regimens investigated and DTG + 3TC, except for DTG + TDF/FTC, EVG/c + TAF/FTC, and EFV + TDF/FTC for which the odds of having an adverse event were significantly higher (Fig. 4a). The odds of having a serious adverse event were similar with all 3-drug regimens investigated and DTG + 3TC (Fig. 4b). The odds of having a drug-related adverse event were significantly higher for most 3-drug regimens analyzed compared with DTG + 3TC, except BIC + TAF/FTC, DTG + TAF/FTC, and RAL + TDF/FTC, for which the odds were similar (Fig. 4c).

Discussion

The NMA was carried out to evaluate the efficacy and safety of the 2-drug regimen DTG + 3TC relative to traditional 3-drug regimens in treatment-naive patients with HIV-1. DTG + 3TC was similar to 3-drug regimens in terms of virologic suppression, change in CD4$^+$ cell count from baseline, and safety at Week 48 weeks. Results were consistent in the subgroup of difficult-to-treat patients with high baseline viral load (>100 000 RNA copies/ml). These findings support the use of the 2-drug ART regimen DTG + 3TC in treatment-naive patients with HIV.

The favorable efficacy and safety of the 2-drug regimen DTG + 3TC in treatment-naive patients with HIV-1 have been demonstrated in two single-arm, pilot studies [18,19]. Furthermore, two large, multicenter, Phase III, RCTs − GEMINI-1 and GEMINI-2 − demonstrated the noninferiority of DTG + 3TC relative to DTG + TDF/FTC with regard to virologic efficacy, with a similar safety profile [40]. However, conducting RCTs to directly compare 2-drug and 3-drug regimens in patients with HIV-1 infection is costly and time-consuming. Using robust methods such as NMA is therefore appropriate to compare the relative efficacy and safety of different regimens by indirect means [41], particularly in an evolving treatment landscape. Indeed, NMAs are used increasingly to support health technology assessment submissions and the development of treatment guidelines and are useful in informing prescribing choices in the clinical environment. For example, a 2016 systematic review and NMA evaluating ART regimens in treatment-naive patients with HIV-1 determined that the efficacy and safety of ART had improved substantially with the introduction of newer drug classes, specifically INSTIs and more specifically the INSTI DTG [42]. This NMA was used to inform WHO consolidated guidelines on the use of ART for the treatment and prevention of HIV infection [42]. Since then, new data have become available that have led to further changes in the guidelines, such as the US DHHS and EACS recommending the 2-drug regimen of DTG + 3TC as an alternative first-line treatment for treatment-naive adults with HIV [1,2]. In the absence of head-to-head trials comparing the 2-drug ART regimen DTG + 3TC with traditional 3-drug regimens, the current NMA provides valuable information on the comparative efficacy of these regimens in treatment-naive patients with HIV-1.

These data also add to the growing body of evidence demonstrating the noninferiority of 2-drug regimens compared with 3-drug regimens in patients with HIV. In treatment-experienced patients, two Phase III, RCTs, SWORD-1 and SWORD-2, were undertaken to evaluate the efficacy of the 2-drug regimen DTG + RPV compared with 3-drug regimens for the maintenance of virologic suppression in patients with HIV [43]. Plasma HIV RNA levels less than 50 copies/ml were maintained in 95% of patients in both the DTG + RPV and 3-drug regimen groups at Week 48, demonstrating the noninferiority of DTG + RPV compared with continuing their 3-drug

Week 48. (b) The network represents the connections between treatments of interest based on the studies included in the network meta-analysis. 3TC, lamivudine; ABC, abacavir; AEs, adverse events; BIC, bictegravir; CADTH, Canadian agency for Drugs and Technologies in Health; CSRs, clinical study reports; DRV/b, cobicistat-boosted or ritonavir-boosted darunavir; DRV/c, cobicistat-boosted darunavir; DRV/r, ritonavir-boosted darunavir; DTG, dolutegravir; EFV, efavirenz; EVG/c, cobicistat-boosted elvitegravir; FDA, Food and Drug Administration; FTC, emtricitabine; NCTs, National Institute of Health Clinical Trials results published on ClinicalTrials.gov; NMA, network meta-analysis; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; pubs, published articles; RAL, raltegravir; RCT, randomized controlled trial; RPV, rilpivirine; SAEs, serious adverse events; SLR, systematic literature review; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TN, treatment naïve; VS, virologic suppression.

(a)

Comparator	Mean difference (95% CrI) Comparator vs DTG + 3TC
BIC + TAF/FTC	−0.9 (−7.9, 6.1)
DTG + ABC/3TC	−0.2 (−5.8, 5.4)
DTG + TAF/FTC	2.7 (−5.6, 11.0)
DTG + TDF/FTC	1.7 (−1.0, 4.4)
EVG/c + TAF/FTC	−1.6 (−10.3, 7.2)
EVG/c + TDF/FTC	−3.5 (−11.8, 4.9)
RAL + ABC/3TC	−0.6 (−7.6, 6.4)
RAL + TDF/FTC	−2.7 (−8.8, 3.2)
DRV/r + ABC/3TC	−3.6 (−12.9, 5.7)
DRV/c + TAF/FTC	−4.0 (−13.0, 4.9)
DRV/b + TDF/FTC	−7.1 (−14.9, 0.8)
EFV + TDF/FTC	−7.3 (−13.8, −0.8)
RPV + TDF/FTC	−4.7 (−12.1, 3.0)

Mean (95% CrI) difference (%) in the proportion of patients achieving VS with 3-drug regimens compared with DTG + 3TC

(b)

Comparator	Mean difference (95% CrI) Comparator vs DTG + 3TC
BIC + TAF/FTC	−10.0 (−27.3, 7.1)
DTG + ABC/3TC	−6.7 (−18.7, 5.2)
DTG + TAF/FTC	−1.9 (−22.0, 18.0)
DTG + TDF/FTC	−3.4 (−9.5, 2.7)
RAL + ABC/3TC	−3.9 (−19.5, 11.6)
RAL + TDF/FTC	−12.9 (−25.5, −0.2)
DRV/r + ABC/3TC	−30.8 (−58.8, −2.6)
DRV/c + TAF/FTC	−16.3 (−35.8, 3.3)
DRV/b + TDF/FTC	−26.1 (−41.5, −10.6)
EFV + TDF/FTC	−14.9 (−28.1, −1.7)
RPV + TDF/FTC	−19.3 (−33.9, −4.7)

Mean (95% CrI) difference (%) in the proportion of patients achieving VS with 3-drug regimens compared with DTG + 3TC
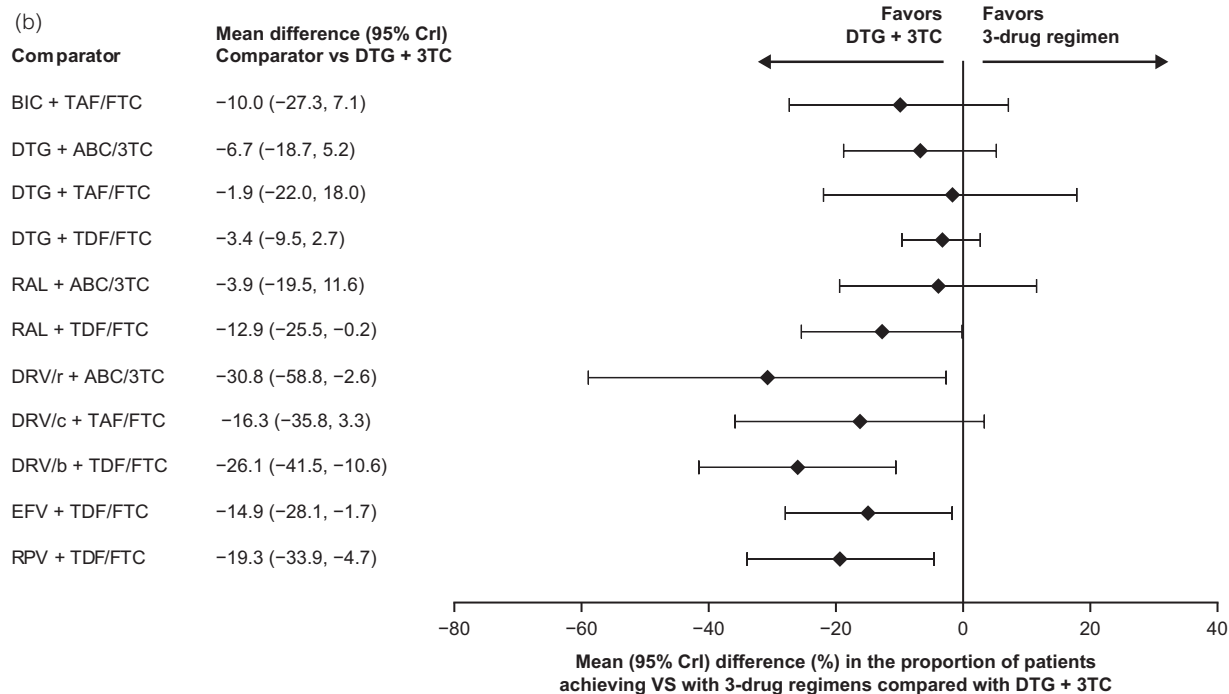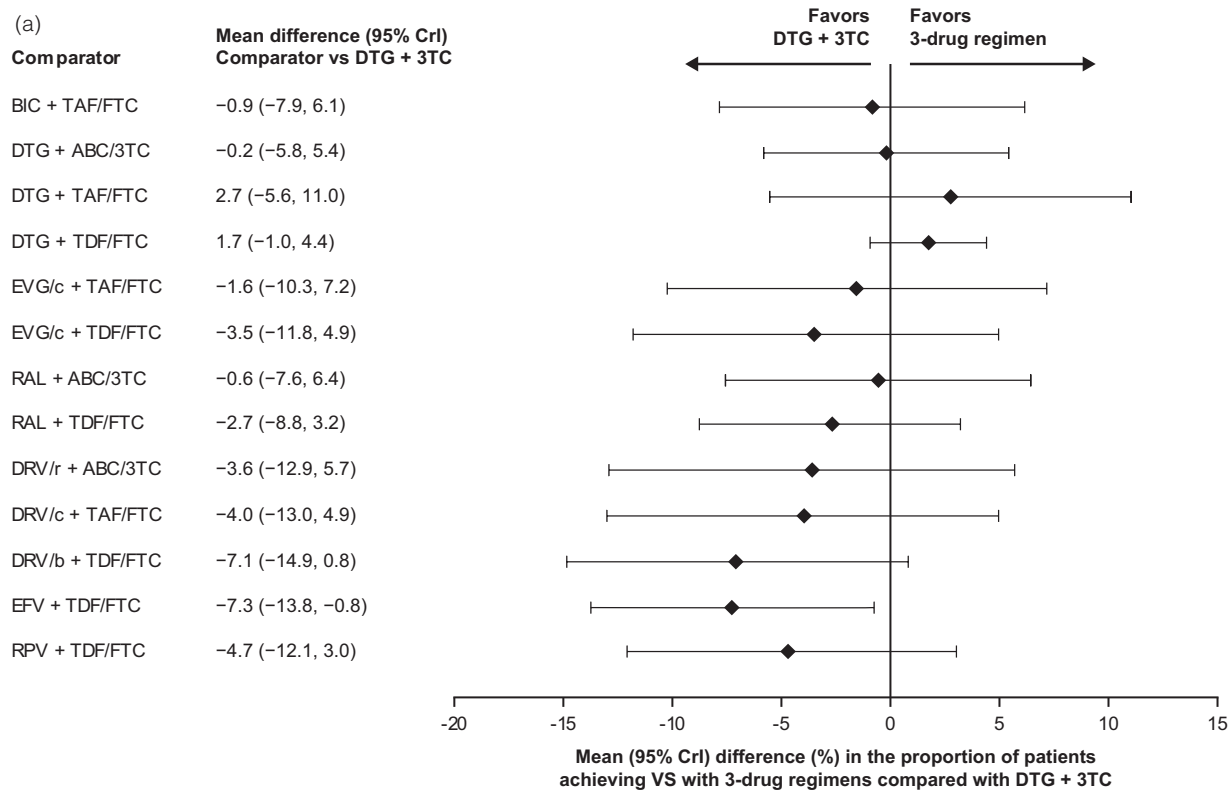

Fig. 2. Mean difference (%) in the proportion of (a) all patients, and (b) patients with baseline viral load more than 100 000 RNA copies/ml achieving virologic suppression at Week 48 with 3-drug regimens (comparator) versus dolutegravir + lamivudine (fixed-effects model). 3TC, lamivudine; ABC, abacavir; BIC, bictegravir; CrI, credible interval; DRV/b, boosted darunavir (cobicistat or ritonavir); DRV/c, cobicistat-boosted darunavir; DRV/r, ritonavir-boosted darunavir; DTG, dolutegravir; EFV, efavirenz; EVG/c, cobicistat-boosted elvitegravir; FTC, emtricitabine; RAL, raltegravir; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; VL, viral load.

Table 1. Probability that one treatment is better than another for more patients achieving virologic suppression at Week 48 (row versus column; overall population; fixed effects model).

	DTG+ 3TC	DTG+ TDF/FTC	DTG+ ABC/3TC	RAL+ TDF/FTC	RAL+ ABC/3TC	BIC+ TAF/FTC	DTG+ TAF/FTC	EFV+ TDF/FTC	DRVb+ TDF/FTC	DRVr+ ABC/3TC	DRVc+ TAF/FTC	RPV+ TDF/FTC	EVGc+ TAF/FTC	EVGc+ TDF/FTC
DTG+3TC	–	0.114	0.530	0.817	0.563	0.596	0.262	0.986	0.962	0.778	0.811	0.886	0.635	0.793
DTG+TDF/FTC	0.886	–	0.775	0.949	0.754	0.782	0.399	0.999	0.990	0.879	0.905	0.961	0.771	0.899
DTG+ABC/3TC	0.470	0.225	–	0.841	0.541	0.623	0.173	0.999	0.956	0.763	0.796	0.934	0.637	0.828
RAL+TDF/FTC	0.183	0.051	0.159	–	0.260	0.282	0.087	0.967	0.839	0.566	0.604	0.725	0.377	0.578
RAL+ABC/3TC	0.438	0.246	0.460	0.740	–	0.530	0.239	0.966	0.912	0.714	0.745	0.833	0.580	0.739
BIC+TAF/FTC	0.404	0.218	0.378	0.718	0.470	–	0.057	0.982	0.916	0.703	0.732	0.852	0.563	0.742
DTG+TAF/FTC	0.738	0.601	0.827	0.913	0.761	0.943	–	0.996	0.974	0.868	0.887	0.958	0.811	0.910
EFV+TDF/FTC	0.014	0.001	0.001	0.033	0.034	0.018	0.005	–	0.476	0.234	0.254	0.084	0.027	0.073
DRVb+TDF/FTC	0.038	0.010	0.044	0.161	0.088	0.084	0.026	0.524	–	0.248	0.087	0.308	0.149	0.244
DRVr+ABC/3TC	0.222	0.121	0.237	0.434	0.286	0.298	0.132	0.766	0.752	–	0.530	0.575	0.361	0.491
DRVc+TAF/FTC	0.189	0.095	0.204	0.396	0.256	0.268	0.113	0.746	0.913	0.470	–	0.547	0.333	0.463
RPV+TDF/FTC	0.114	0.039	0.066	0.275	0.167	0.148	0.043	0.916	0.692	0.425	0.454	–	0.189	0.360
EVGc+TAF/FTC	0.365	0.229	0.363	0.623	0.420	0.437	0.189	0.973	0.851	0.639	0.668	0.811	–	0.917
EVGc+TDF/FTC	0.207	0.101	0.172	0.422	0.261	0.258	0.090	0.927	0.756	0.509	0.537	0.640	0.083	–

3TC, lamivudine; ABC, abacavir; BIC, bictegravir; CrI, credible interval; DRV/b, boosted darunavir (cobicistat or ritonavir); DRV/c, cobicistat-boosted darunavir; DRV/r, ritonavir-boosted darunavir; DTG, dolutegravir; EFV, efavirenz; EVG/c, cobicistat-boosted elvitegravir; FTC, emtricitabine; RAL, raltegravir; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; VS, virologic suppression.

ART regimen [43]. Furthermore, the safety profile of DTG + RPV was consistent with the safety profile of each individual component [43]. As a result of these data DTG + RPV is recommended in virologically suppressed patients with HIV by EACS and the DHHS [1,2].

Data from a systematic literature review and meta-analysis also demonstrated the noninferiority of 2-drug regimens and 3-drug regimens to reduce the risk of virologic failure at Week 48 in both treatment-naive and treatment-experienced patients (switch strategy) [44]. In a second meta-analysis, the estimated virologic failure rate was 0.7% (95% CI: 0.4, 1.3) at Week 48 with simplified DTG-based 2-drug regimens in treatment-experienced patients (i.e., switch strategy: DTG + 3TC, DTG + RPV, DTG + atazanavir, DTG + DRV) [45]. Furthermore, data from real-world clinical practice support the use of DTG-based 2-drug regimens in treatment-experienced patients, enabling them to achieve and maintain virologic suppression, while reducing cumulative ART exposure and the potential risk for toxicities [46–48].

The results of the current study provide further evidence to support the paradigm shift from 3-drug ART regimens to 2-drug regimens that is beginning to take place in real-world clinical practice. Thanks to the emergence of ART, the outcomes for patients with HIV have improved dramatically, making it a manageable chronic condition rather than a life-limiting disease [3]. However, as life expectancy among patients infected with HIV increases, they are exposed to ART for much longer than in previous decades [49,50]. Therefore, approaches to limit the potential for drug toxicities with cumulative exposure to ART regimens are of increasing clinical importance. In addition to similar efficacy and the potential for improved safety outcomes, 2-drug regimens are likely to be favored by patients, as demonstrated by a recent study in which the majority of patients living with HIV had concerns about the long-term effects of ART and would prefer to reduce their therapies if efficacy was not compromised [51]. Furthermore, 2-drug regimens may be associated with reduced costs compared with 3-drug regimens [52,53]. Given the potential for fewer pills with 2-drug regimens, it is also possible that patient adherence would improve, although further studies are required to confirm this.

Previous NMAs undertaken to investigate the comparative effectiveness of ART regimens in treatment-naive patients with HIV compared the effects of a non-NRTI core agent (or 'third agent') and controlled for the NRTIs used with the core agent [21,42]. As 2-drug regimens do not differentiate between a core agent and the NRTI backbone, it was necessary to modify this conventional approach to evaluate the 2-drug regimen DTG + 3TC versus 3-drug regimens. The full regimen comparison approach used here allowed a robust, broad investigation of DTG + 3TC against traditional 3-drug regimens in a large population of treatment-naive patients with HIV-1
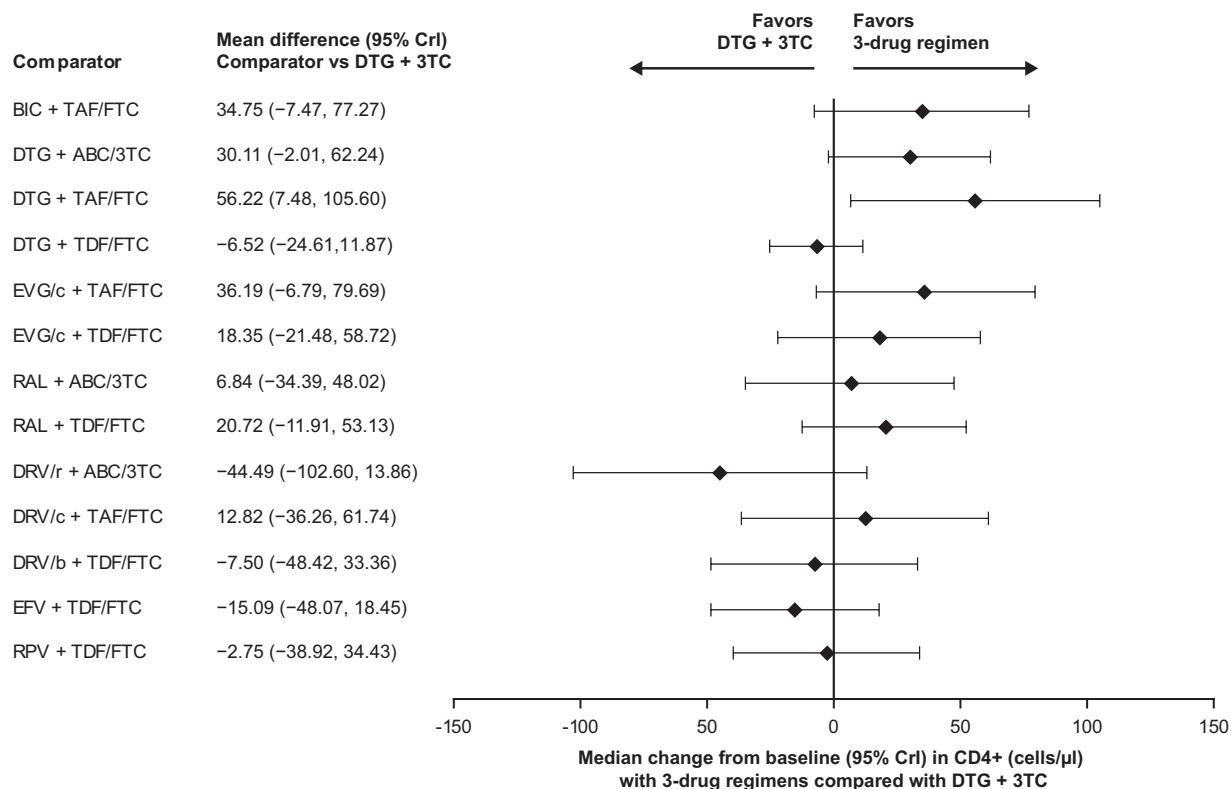
	Favors DTG + 3TC	Favors 3-drug regimen

Comparator	Mean difference (95% CrI) Comparator vs DTG + 3TC
BIC + TAF/FTC	34.75 (−7.47, 77.27)
DTG + ABC/3TC	30.11 (−2.01, 62.24)
DTG + TAF/FTC	56.22 (7.48, 105.60)
DTG + TDF/FTC	−6.52 (−24.61,11.87)
EVG/c + TAF/FTC	36.19 (−6.79, 79.69)
EVG/c + TDF/FTC	18.35 (−21.48, 58.72)
RAL + ABC/3TC	6.84 (−34.39, 48.02)
RAL + TDF/FTC	20.72 (−11.91, 53.13)
DRV/r + ABC/3TC	−44.49 (−102.60, 13.86)
DRV/c + TAF/FTC	12.82 (−36.26, 61.74)
DRV/b + TDF/FTC	−7.50 (−48.42, 33.36)
EFV + TDF/FTC	−15.09 (−48.07, 18.45)
RPV + TDF/FTC	−2.75 (−38.92, 34.43)

Fig. 3. CD4$^+$ change from baseline at Week 48 with dolutegravir + lamivudine versus 3-drug regimens (fixed-effects model). 3TC, lamivudine; ABC, abacavir; BIC, bictegravir; CrI, credible interval; DRV/b, boosted darunavir (cobicistat or ritonavir); DRV/c, cobicistat-boosted darunavir; DRV/r, ritonavir-boosted darunavir; DTG, dolutegravir; EFV, efavirenz; EVG/c, cobicistat-boosted elvitegravir; FTC, emtricitabine; RAL, raltegravir; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

infection. However, a number of limitations must be considered. These include common limitations of NMAs, such as the possibility that differences in the distributions of effect modifiers across the studies were large enough to invalidate the NMA (effect modifiers are rarely reported in publications), the fact that differences in how the networks were defined may induce different results, and that the power of the NMA is dependent on the number of studies included. Furthermore, not all of the studies included in the NMA reported all of the efficacy and safety outcomes of interest and/or data for the subgroup of interest, and not all commonly used regimens were included, due to the lack of available data. It was also necessary to split the arms of the SPRING-2 and FLAMINGO trials by treatment backbone, and to include EFV + TDF/FTC (which is no longer recommended as first-line treatment [1,2,11]), to facilitate the formation of a connected network. Finally, as only publications in English were considered, a small number of relevant publications may have been missed. Despite these limitations, this NMA provides valuable evidence of the comparative efficacy and safety of DTG + 3TC with traditional 3-drug regimens in treatment-naive individuals infected with HIV-1.

In conclusion, this NMA demonstrated similar efficacy and safety outcomes with DTG + 3TC and traditional

3-drug ART regimens, supporting the use of this simplified 2-drug regimen, which has the potential for lower prevalence of toxicities with cumulative drug exposure − a particularly important factor as the life expectancy of patients with HIV-1 continues to improve.
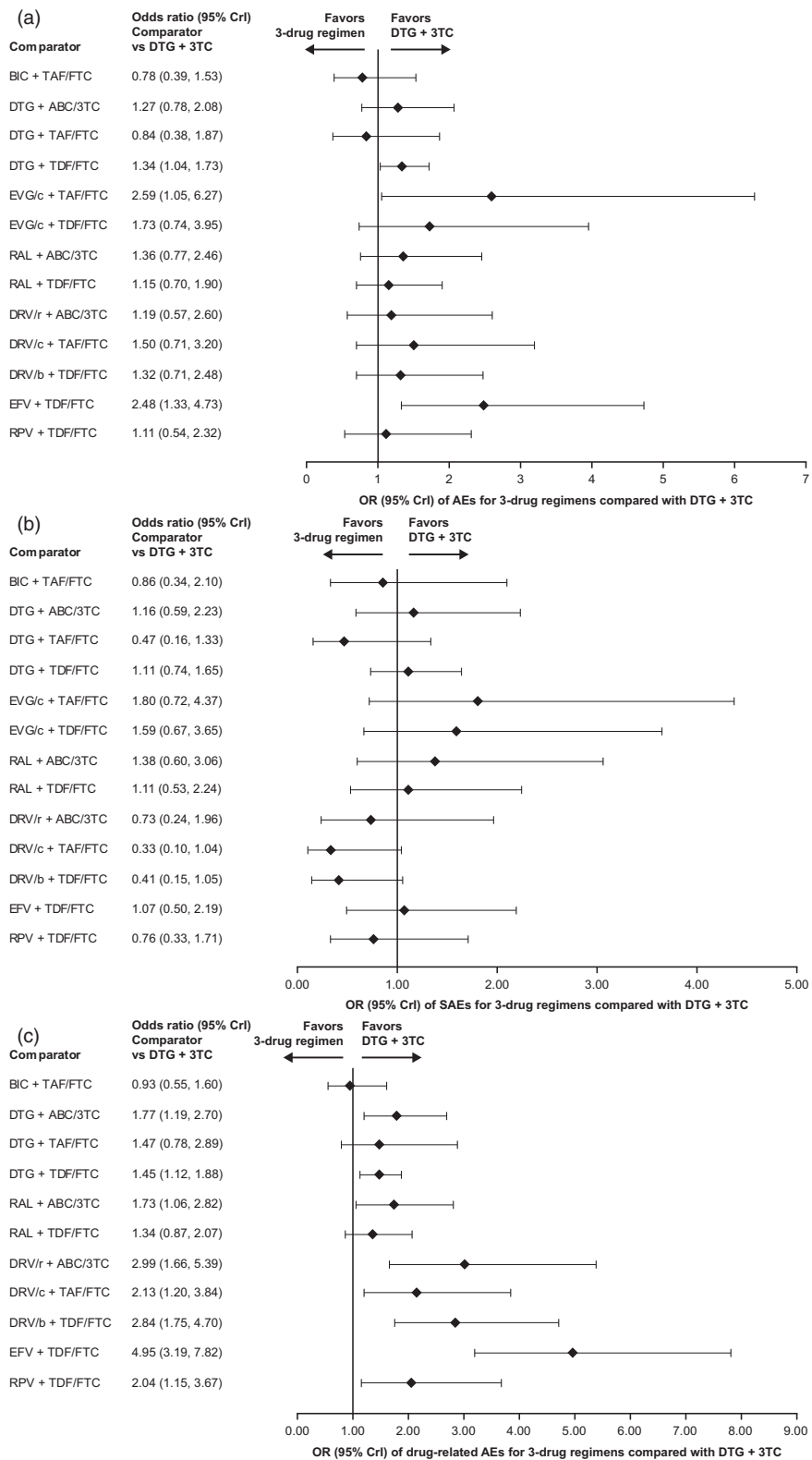
Acknowledgements

Fig. 4. (a) Adverse events, (b) serious adverse events, and (c) drug-related adverse events by Week 48 with 3-drug regimens versus dolutegravir + lamivudine (fixed effects model). 3TC, lamivudine; ABC, abacavir; AEs, adverse events; BIC, bictegravir; CrI, credible interval; DRV/b, boosted darunavir (cobicistat or ritonavir); DRV/c, cobicistat-boosted darunavir; DRV/r, ritonavir-boosted darunavir; DTG, dolutegravir; EFV, efavirenz; EVG/c, cobicistat-boosted elvitegravir; FTC, emtricitabine; OR, odds ratio; RAL, raltegravir; RPV, rilpivirine; SAEs, serious adverse events; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

D.C.P. and S.F. were involved in the data analysis and interpretation.

Conflicts of interest

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