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Efficacy and safety of triple versus dolutegravir-based dual therapy in patients with HIV-1 infection: A meta-analysis of randomized controlled trials

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Abstract

A new strategy of simplification therapy shown the unique benefits in clinical treatment, by reducing pill burden and avoid drug exposure. To provide more evidence for the strategy, we compared the efficacy and safety of dolutegravir (DTG)-containing simplified dual combination antiretroviral therapy (cART) and traditional triple cART for people living with HIV/AIDS. The meta-analysis of randomized controlled trials compared DTG-containing dual therapy with triple cART. The primary outcome was virologic suppression. The secondary outcomes included CD4T cell recovery, lipids change from baseline, and adverse events (AEs). A total of 7 studies, 4852 patients were eligible, 2423 (49.9%) received DTG-based simplified dual cART, and 2429 (50.1%) received triple cART. The viral suppression rate was 94.7% at 24 weeks, 93.0% at 48 weeks, and 96.6% at 96 weeks in dual cART. The viral suppression rate of dual cART was non-inferior to triple cART at 24 weeks (risk difference [RD], –0.00; 95% confidence interval [CI] –0.02-0.01), at 48 weeks (RD, –0.01; 95% CI –0.02-0.01), and at 96 weeks (RD, –0.01; 95% CI –0.02-0.00). Sub-analysis results were consistent with the overall results. With regard to other outcomes (CD4T counts, lipids, any AEs, and AEs grade ≥ 3), there was no significant statistical difference between the two regimens. DTG-based simplified dual cART was non-inferior to triple cART in terms of efficacy and safety. This finding provides strong support for current consensus guidelines recommended the dual regimen as first-line treatment. (AIDS Rev. 2021;23:133-142)

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Key words

Dolutegravir. Dual therapy. Meta-analysis. Efficacy. Safety.

Introduction

Triple combination antiretroviral therapy (cART) recommended by WHO changed the progression of HIV infection, which has made HIV become a chronic manageable disease[1]. To a certain extent, it was the key of patients to reduce mortality and improve the quality of life for quite a long time. The addition of antiretrovirals to cART was no enhanced effectiveness[2]. In contrast, prolonged standard cART has significant challenges due to the drug-drug interactions, cumulative phytotoxicity, pill burden, resistance, and

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suboptimal adherence, which might result in treatment modification or interruption. To reduce pill burden and drug exposure, developing a more simplified strategy is necessary[3-5].

Dolutegravir (DTG) was one of the first fixed-dose, single-tablet dual therapy regimen approved by the FDA (USA). The dual therapy regimens composed DTG (50 mg) and plus rilpivirine (RPV, 25 mg) or lamivudine (3TC, 300 mg), which the official recommends, the evidence was mainly based on GEMINI-1/2[6,7] and SWORD-1/2[8,9]. Meanwhile, in real-world observational studies, switched to a two-drug regimen of DTG in cART-experienced patients have high rates of virological suppression[10-13]. These results support the dual regimens of DTG and plus RPV or 3TC[14,15], and both regimens indicated the same effect[16].

To evaluate the efficacy and safety of a simplified regimen, we compared the difference between DTG with PRV or 3TC and triple cART in treatment-naïve and treatment-experienced patients. Previous to this study, a meta-analysis showed that raltegravir (RAL)-based dual therapy, other integrase inhibitors (INIs), has demonstrated similar effects as the traditional three-drug regimen[17]. Therefore, we conducted a meta-analysis to provide more evidence supporting DTG-based simplified therapy.

Methods

Data sources and searches

Systematic searches included all of the literature regarding DTG of English, published in PubMed, Embase, Cochrane Library, and Web of Science databases (up to July 2020). To evaluate the efficacy and safety of dual therapy, we considered all randomized controlled trials (RCTs).

All database searches will be based on the combination of subject words and free words and will be adjusted according to the specific database. The following keywords were used: "DTG," "rilpivirine," "lamivudine," and "dual therapy."

Study selection and data extraction

RCTs compared dual cART with triple cART in treatment-naïve or treatment-experienced people living with HIV/AIDS (PLWHA) (age more than 18 years old) and evaluated at least one outcome of effective and/or safety. The dual cART included only DTG/RPV or DTG/3TC, because this dual cART was WHO recommended[18]. Studies with the following characteristics were excluded: (1) non-randomized studies, reviews, letters, observations studies, cohort studies, and retrospective studies; (2) *in vitro* model and animal test; (3) age younger than 18 years old; (4) pregnant; and (5) repetitive publish data. If the same study were overlapped in multiple publications, only the most complete or most recent literature was included in the present study.

The primary outcome from each trial was selected to undetectable HIV-RNA (plasma HIV-1 viral load [VL] < 50 copies/mL). Secondary outcomes of interest included CD4 T cell counts, lipids, and the measure of safety were any adverse events (AEs) and AEs ≥ grade 3 (3 = severe, 4 = potentially life-threatening, 5 = death).

After removal of duplicates, all studies identified in the search were screened by title and abstract by two independent reviewers (YS and XT), then full-texts were reviewed to determine eligibility. All the incongruity was resolved by group discussion arbitration. Data extracted included: (1) research characteristics (author, years of publication, study design, follow-up, and sample size); (2) patient demographics (age, sex, and ethnicity) and baseline characteristics (CD4T cell counts, VL, and lipids); and (3) results at the end of the study.

Risk of bias assessment

The risk of bias was evaluated by Cochrane Collaboration tool (Cochrane Handbook for Systematic Reviews of Intervention, version 5.1.0). Assessed risk of bias included six specific domains: sequence generation, allocation concealment, blinding, incomplete data, selection outcome reporting, and other possible biases. The risk of bias in each domain was judged as "low risk," "high risk," or "unclear risk," with the last category bias indicating either lack of information or uncertainty over the potential source of bias.

Data analysis

Triple cART was used as the control group in this meta-analysis. We assessed efficacy using the risk difference (RD) for dichotomous outcomes, mean difference (MD) for continuous outcomes, and 95% confidence interval (CI). By combined studies to obtain the difference of the overall estimate, if the difference was > 0 favored dual cART.

For those eligible trials that had monotherapy arm or dual therapy arm or triple therapy arm within the same

study, we only collect data of qualified arm. Considering some data were incomplete or not reported uniformly, the Mantel–Haenszel method may be less satisfactory in this context. Therefore, according to the clinical registration number in the articles, we searched the detailed results of the study in the clinical trial registry center. Due to the missing virological data caused by discontinued study (that is, loss of follow-up, treatment dropout, AEs, or death), which is a certain influence on the judgment of the results. So, if virologic data with more than 10% of missing data than the per-protocol population was used, the intention to treat exposed population was otherwise applied. Patients with no virological data will be excluded when analyzing the virological suppression effect of dual cART versus triple cART. Therefore, we included the analysis that may be slightly different from the results of the published articles.

To reduce heterogeneity, in studies with predefined subgroups, we performed subgroup analysis including female and male, age ≥ 50 years and < 50 years, different level CD4T cell counts, VL ≥ 100,000 copies per ml and < 100,000 copies per ml, treatment-experienced and treatment-naïve, and the class of the dual cART arm.

Statistical analysis of heterogeneity using Cochrane's Q test, depending on I^2 statistic and *P* value. If the test results were $P \geq 0.10$ and $I^2 \leq 50\%$, using the fixed-effect model for homogenous studies, in contrast, using the random-effect model for non-homogenous studies. To test whether the primary outcome may be influences, sensitivity analysis was conducted using the leave-one-out method, that is, iteratively removing one study each time and repeating the analysis. We also mutual transformation by the use of the fixed-models or random-effects models to test the stability of the primary result. Due to the insufficiency of studies or reported data, preliminary analysis of subgroup and sensitivity was not performed. Funnel plot was used for the primary endpoint analysis.

All data analyses were performed with Review Manager 5.4 (Cochrane Collaboration, London, UK).

Results

The flow chart summarized the detailed retrieval steps (Fig. 1). A total of 746 potentially relevant studies from four databases were selected by the initial screening. By screening titles, abstracts, and full texts, seven eligible studies were included in this systematic review[6,7,9,19-22].

Study characteristics

The main features of the included studies are summarized in table 1. Of 4852 patients who were randomized in the seven eligible studies (6 RCTs), 2423 participants were allocated to receive dual cART, and 2429 served as triple cART. Six studies combined DTG and 3TC[6,7,19-22], and one study combined DTG and RPV[9]. Meanwhile, five studies included treatment-experienced patients[9,19-22] and two studies included treatment -naïve patients[6,7].

All the studies were assessed at low risk of selection and reporting bias. Five articles were randomized and open-label trials[9,19-22], we judged as "high risk" of the performance bias, and the other two studies were randomized and double-blind trials[6,7]. Two studies only reported partial outcomes[20,22], we judged as "high risk" of the attrition bias, even if we visited the database of the clinical trial registry and viewed the original data, to incorporate these studies into other results analysis. Due to the baseline CD4, T cell counts were unequal in two groups of one study[22], we judged as "high risk" of the other bias from one study. Risk of bias graphs in Supplementary material (Figs. S1 and S2) summarized methodological quality items.

Primary outcome

Comparative virological suppression of dual versus triple cART

The results of the meta-analysis indicated dual cART (DTG plus RPV/3TC) versus triple cART have equal effects. At 24 weeks, 1621 patients in dual cART (95.0%) versus 1633 patients in triple cART (95.4%) has viral suppression at 6 studies (RD, −0.00; 95% CI −0.02-0.01)[7,9,19-22]. Data from 5 studies included 1561 (93.0%) patients in triple cART and 1577 (93.8%) in dual cART show same results at 48 weeks (RD, −0.01; 95% CI −0.02-0.01)[7,9,20-22]. Moreover, one study followed up to 96 weeks[6], the data indicated that the results were consistently in agreement (RD, −0.01; 95% CI −0.03-0.00) (Fig. 2).

A sensitivity analysis of the primary outcome was stable and reliable, which were not affected by the leave-one-out method, random-effects model, or fixed-effects model.

Pre-specified subgroup analyses showed that the results did not vary considerably among baseline

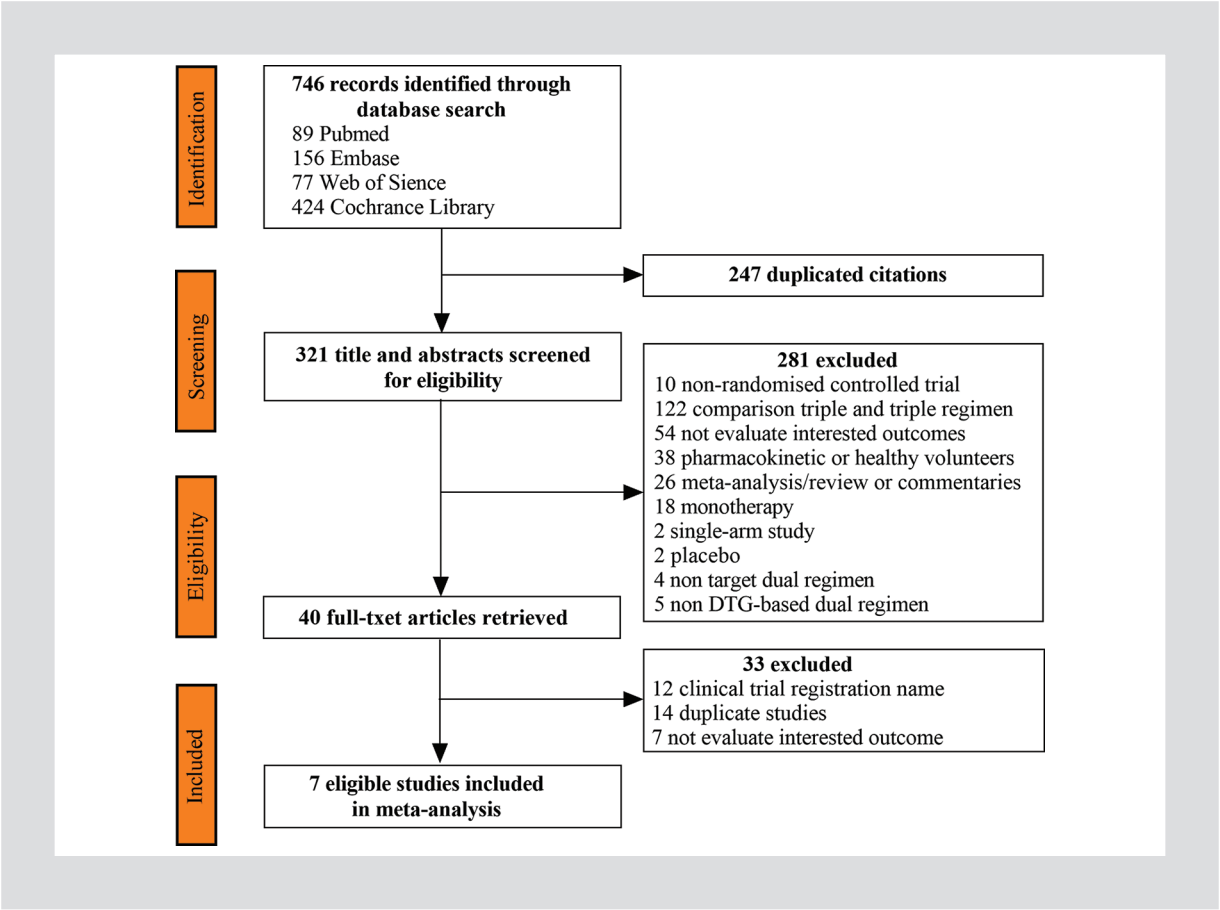

Figure 1. *Flow diagram: study screening process.*

characteristics (sex, age, ethnicity, CD4T cell counts, VL, treatment, and dual regimen) (Fig. 3).

Secondary outcomes

Comparative CD4T counts, lipids, and safety of dual versus triple cART

Only four studies contribute to the changes of CD4T cell counts analysis among these studies[7,9,20,21]. Two of four studies use the median to express the average CD4T cell counts[20,21]. To efficient merging, we have converted the median and IQR into mean and SD[23,24]. Dual cART was a significantly higher recovery of CD4T cell counts than triple cART at 48 weeks, but there was no significant statistical difference between the two regimens (MD, 10.49; 95% CI −0.30-21.27) (Fig. 4).

Four of the seven studies reported the changes from baseline in lipids[7,9,20,21]. Since some articles did not report detailed changes in lipid levels, we visited the database of the clinical trial registry by the registration number provided in the articles, and some studies data were transformed. We used the random-effect model because there was significant heterogeneity of lipids levels between the two regimens ($P \leq 0.001$, $I^2 \geq 85\%$). The results show that, compared to controls, total cholesterol (MD, 0.04; 95% CI −0.39-0.47), HDL cholesterol (MD, 0.03; 95% CI −0.05-0.10), LDL cholesterol (MD, 0.07; 95% CI −0.18-0.31), and triglycerides (MD, −0.10; 95% CI −0.28-0.09) were no significant different in dual cART (Fig. 5).

Six articles contained the results of safety entered the meta-analysis[6,7,9,19-21]. According to model diagnostics, the random-effect model was used for safety outcomes of any AEs ($P = 0.004$, $I^2 = 74\%$), and the fixed-effect model was used for safety outcomes of AEs grade ≥ 3 ($P = 0.17$, $I^2 = 38\%$). There was no significant difference in any AEs (RD, 0.01; 95% CI −0.04-0.06) and AEs of grade ≥ 3 (RD, 0.00; 95% CI −0.01-0.02) between the two groups (Fig. 6).

Table 1. Characteristics of the included studies in the meta-analysis

Study name	Methods	Clinical characteristic	Interventions	Cases	Age (median, IQR, range, mean ± SD)	Male (%)	White (%)	Start ART duration (median, months)	Baseline CD4T (median, IQR, range, mean ± SD)
Llibre et al., 2018[9] NCT02429791 NCT02422797	Multicentre, randomized (1:1), open-label, phase 3	Stable suppression of HIV-RNA < 50 copies/mL for at least 6 months, age ≥ 18 years	DTG/RPV	513	43 (21, 79)	393 (76.6)	421 (82.1)	51	611 (3, 1774)
			Triple cART	511	43 (22, 76)	403 (78.9)	398 (77.9)	53	638 (9, 1671)
Taiwo et al., 2018[20] NCT02263326	Multicenter, randomized (1:1), open-label, phase 3	Stable suppression of HIV-RNA < 50 copies/mL within 48 weeks, age ≥ 18 years	DTG/3TC	44	46 (37, 56)	39 (88.6)	23 (52.3)	63.4	694 (533, 1034)
			Triple cART	45	50 (41, 53)	39 (86.7)	29 (64.4)	72.4	646 (380, 819)
van Wyk et al., 2020[21] NCT03446573	Multicenter, randomized (1:1), open-label, phase 3	Stable suppression of HIV-RNA < 50 copies/mL for at least 6 months, age ≥ 18 years	DTG/3TC	369	40 (20, 74)	344 (93.2)	297 (80.5)	33.8	682 (133, 1904)
			Triple cART	372	39 (18, 73)	339 (91.1)	289 (77.7)	35.1	720 (119, 1810)
Li et al. 2019[22]	Randomized (1:1), open-label	HIV-1 RNA < 50 copies/mL within 48 weeks, age ≥ 18 years	DTG/3TC	36	45.5	33 (91.7)	21 (58.3)	64.4	677
			Triple cART	36	50.5	31 (86.1)	26 (72.2)	72.5	637
Blanco et al., 2018[19] EudraCT: 201500027435	Multicentre, randomized (1:1), open-label, phase 3	Stable suppression of HIV-RNA < 50 copies/mL at least 12 months, age ≥ 18 years	DTG/3TC	29	44 ± 9	23 (79.3)	NA	NA	753 ± 214
			Triple cART	31	46 ± 12	27 (87.1)	NA	NA	675 ± 265
Cahn et al., 2019[7] NCT02831673 NCT02831764	Multicentre, randomized (1:1), double-blind, phase 3	HIV-RNA < 500000 copies/mL, age ≥ 18 years	DTG/3TC	716	32 (26, 40)	603 (84.2)	480 (67.0)	ART-naive	462 ± 219.2
			DTG/TDF/EMB	717	33 (26, 42)	619 (86.3)	497 (69.3)	ART-naive	461 ± 213.1
Cahn et al., 2020[6] NCT02831673 NCT02831764	Multicentre, randomized (1:1), double-blind, phase 3	HIV-RNA 1000 to 500000 copies/mL, age ≥ 18 years	DTG/3TC	716	32 (26, 40)	603 (84.2)	484 (67.6)	ART-naive	462 ± 219.2
			DTG/TDF/EMB	717	33 (26, 42)	619 (86.3)	497 (69.6)	ART-naive	461 ± 213.1

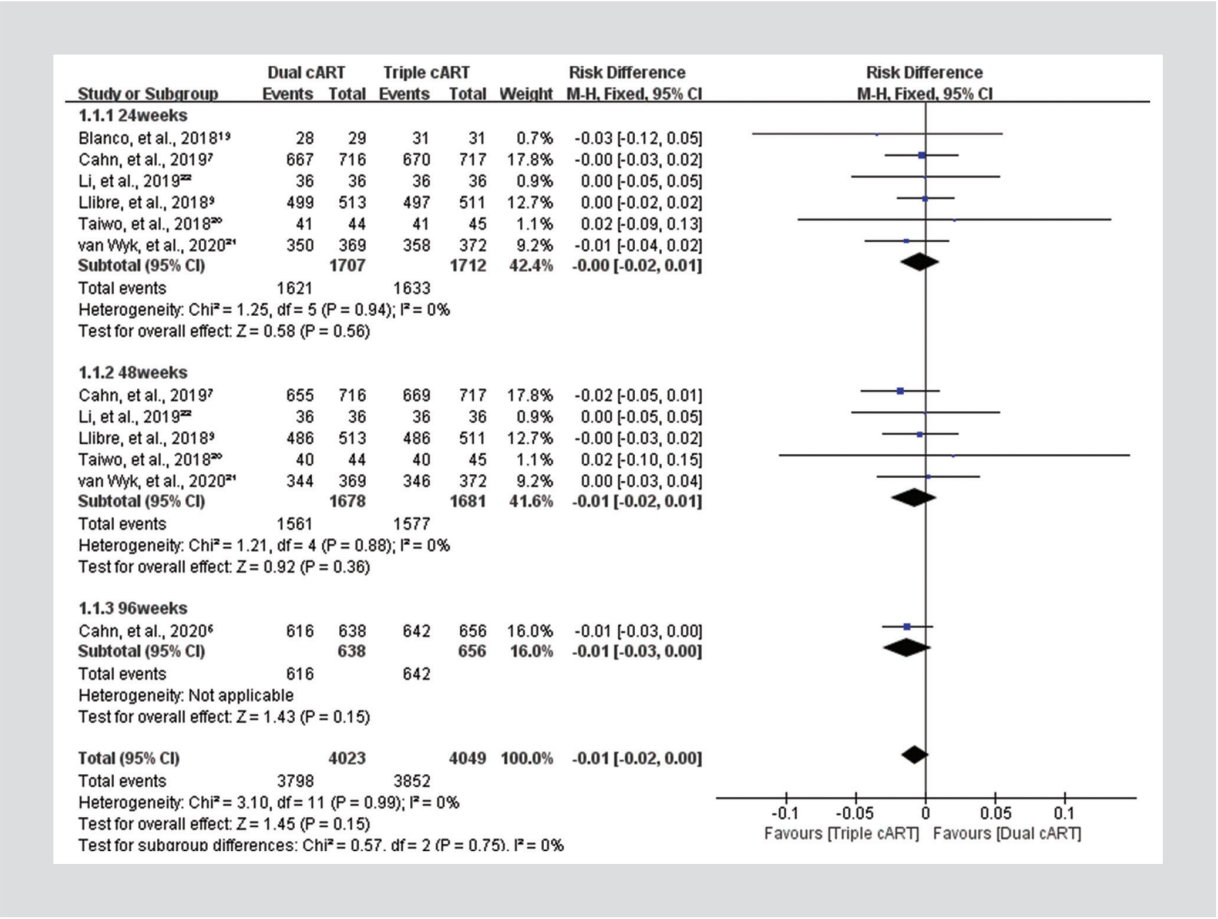

Figure 2. *Forest plot of compared viral suppression with the two regimens.*

Publication bias

Funnel plot was performed to evaluate the publication bias of the studies in this meta-analysis. The funnel plot of seven studies compared dual cART with triple cART shows symmetrical, which indicated a lower possibility of publication bias, and reliable (Supplementary material: Fig. S3). However, since the small number of studies, such bias could not be entirely ruled out.

Discussion

The major findings of this meta-analysis can be summarized as follows, DTG-based dual cART was non-inferior to triple cART in the efficacy of virological suppression. In subgroups, results were consistent between treatment-naïve, treatment-experienced, high baseline VL (VL ≥ 100,000 copies per ml), or low baseline CD4T cell counts (o 200 cells per μl). Moreover, the same result of CD4T cell counts recovery, changes in lipids from the baseline, and AEs in both regimens. These findings support the use of dual regimens, composed of DTG and RPV or 3TC, in treatment-naïve and treatment-experienced PLWHA.

The classical standard regimens, two nucleoside reverse-transcriptase inhibitors plus third core drug, are falling into the predicament, especially in patients with poor therapeutic outcomes. The addition of DTG made the antiretroviral regimen break away from the predicament and optimize treatment further. DTG-based triple cART versus the traditional regimens demonstrated non-inferior, more effective, or fewer discontinuations[25-27]. However, in fact, long-term use of multiple antiretrovirals so that they are unable to tolerate and overcome the pain of psychological and physical. To improve adherence and avoid drug exposure, clinicians have been constantly trying how to simplify the regimens. Dual cART and monotherapy containing DTG are emerged as the times required. However, the monotherapy showed that the major disadvantage of

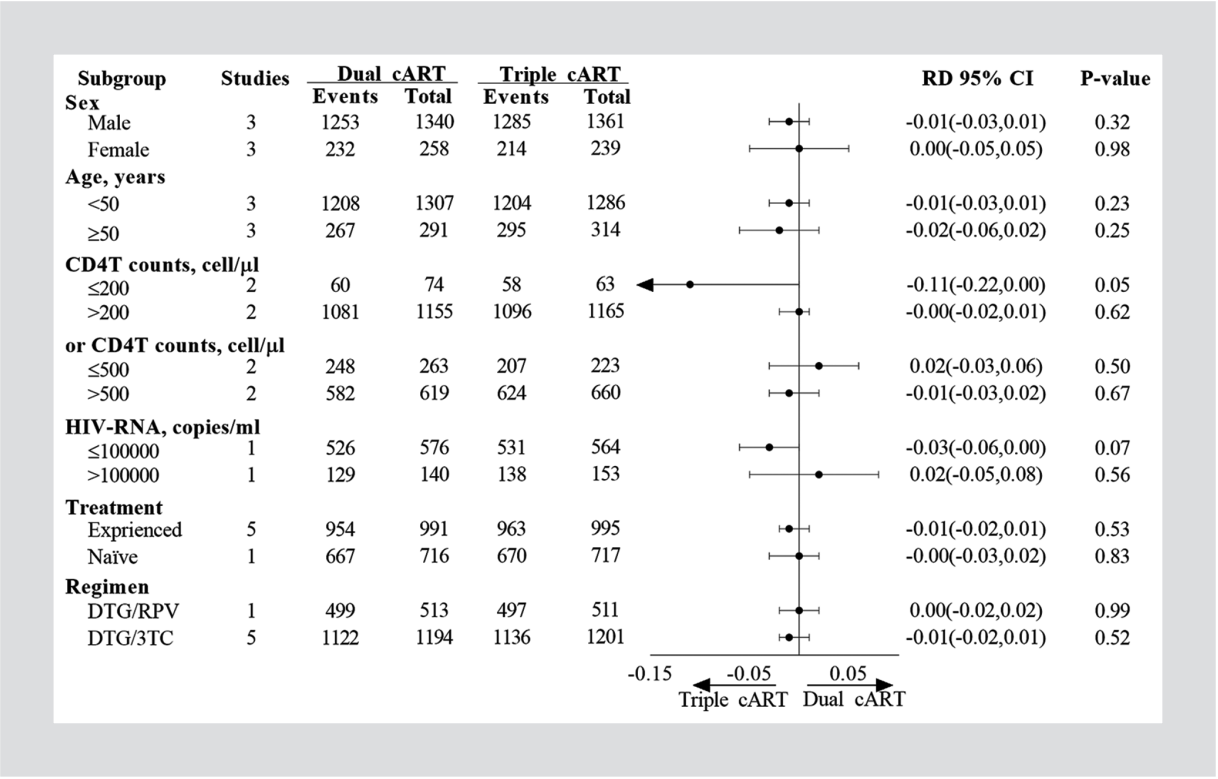

Figure 3. *Subgroup analysis according to baseline characteristics at 48 weeks.*

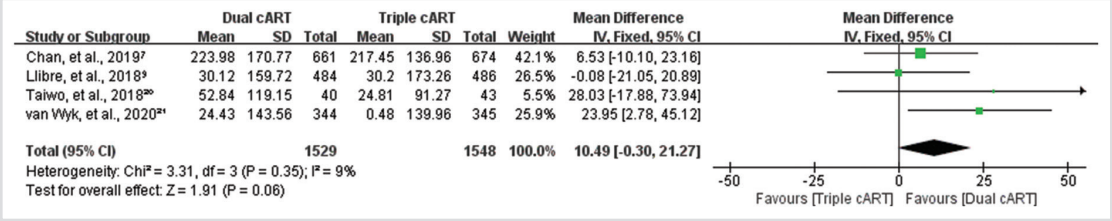

Figure 4. *Forest plot of compared CD4T cell counts recovery with the two regimens at 48 weeks.*

switching from treatment-experienced PLWHA[28-30]. It seems that dual cART has become a unique choice. A meta-analysis of dual cART contains PIs and RAL showed that the potential benefits included reduced toxicity, improved tolerability and adherence, and reduced cost[31]. An observational, retrospective study suggests that the comparable efficacy between RAL- and DTG-based dual cART[32], but DTG has a higher genetic barrier than RAL.

The meta-analysis showed that dual cART was no inferior virological suppression compared with triple cART at 24 weeks, 48 weeks, and 96 weeks. Whereas the RAL-based dual cART was superior to the triple cART at 24 weeks[17], of note, we registrant patients were 4 times of this study. Sub-analysis, in different conditions at baseline, showed the same as achieving virological suppression than triple cART, especially in high VLs and lower CD4T cell counts patients, these results support the overall findings. However, the participants with lower response and lower baseline CD4T cell counts in the dual cART should be interpreted with caution[7]. Besides, for the CD4T cell counts, dual cART

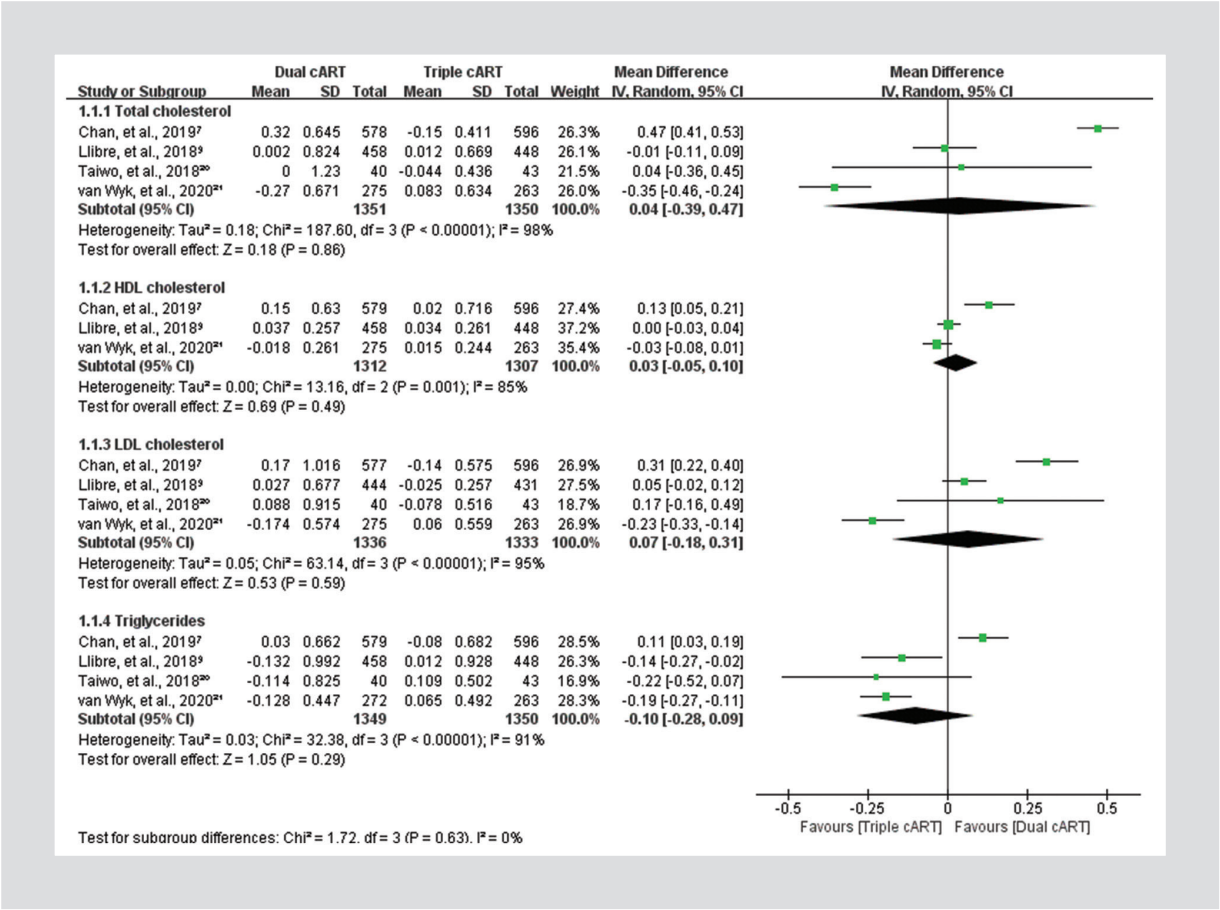

Figure 5. *Forest plot of compared lipid changes with the two regimens at 48 weeks.*

was more likely to promote the recovery than triple cART, unfortunately, but there were no significant statistical differences between the two regimens (MD, 10.49; 95% CI −0.30-21.27). Sensitivity analysis proved that the results were stable and reliable, the funnel plot was also fundamentally symmetric. These results supported the evidence which DTG-based dual cART was suitable for PLWHA.

PLWHA during DTG treatment has been reported to gain weight, especially in treatment-naïve[33]. Moreover, a significant role of tenofovir alafenamide (TAF) over tenofovir disoproxil fumarate (TDF) increased the weight[34]. The regimen containing DTG and FTA showed increased body weight more significantly than the standard-care regimen (TDF plus emtricitabine [FTE] plus efavirenz [EFV])[26]. Similar results were observed in dual cART[7]. We found the changes in lipids at week 48 were broadly favorable in two groups. Total cholesterol, LDL cholesterol, and HDL cholesterol increased from baseline to week 48 in the dual regimen, whereas triglycerides decreased from baseline. TDF and TAF were not included in our dual regimen (DTG plus RPV/3TC), but they were one of the most common skeletons in the triple cART. The favorable lipid impact was obtained by replacing ritonavir-boosted protease inhibitors (PI/r) and EFV with RPV and INIs[35], dual cART showed improved lipid profile[15], which explained why not the difference in this meta-analysis results we observed. It should be emphasized that when the drugs were administered after consumption of a moderate- or high-fat meal, the absorption of both DTG and RPV were increased, resulting in higher exposures[36].

Only analyzed limited classes of AEs (any AEs and AEs grade ≥ 3), due to these studies did not clearly report the AEs types and inconsistent the evaluation criteria. Compared to controls, the occurrence of any AEs and AEs grade ≥ 3 in dual cART was no statistical significance. These results were similar to findings from RAL-based dual cART[17]. However, more patients discontinued treatment due to safety events in triple cART

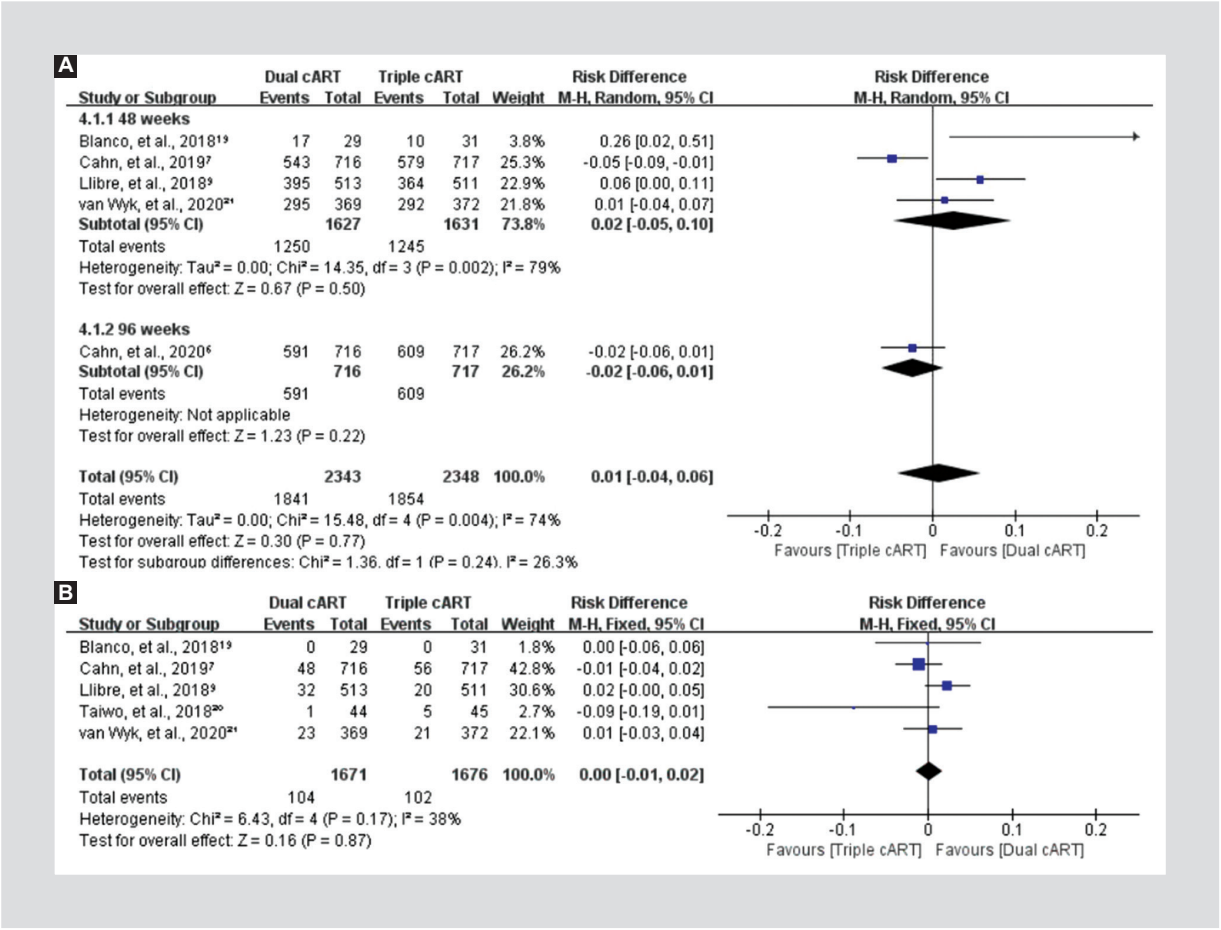

Figure 6. *Forest plot of compared AEs with the two regimens.* **A:** *any AEs;* **B:** *AEs grade ≥ 3.*

compared with PI/s-based dual cART at 48 weeks[37]. Unfortunately, these studies did not provide a reasonable solution strategy to this problem, the short- and long-term AEs from dual cART.

This study has some limitations. Although we conducted a meaningful subgroup analysis based on reported articles, without public disclosure, dual therapy applies is still unknown, such as opportunistic infection, potential interactions of DTG with other drugs. Only one study reported adherence, we did not discuss the differences in adherence at both regimens, but the adherence in dual cART was higher than triple cART[17]. Moreover, compared to atazanavir, darunavir, efavirenz, or RAL, the discontinuation rate was lowest for DTG[38]. Virologic non-inferiority is the main endpoint for simplification therapy, not the only endpoint, as virologic non-inferiority alone is not a benefit[39]. It was not currently recommended for switching to dual cART for all patients. Further supplementary data demonstrate that dual cART strategies provide adequate efficacy and safety in the long term.

Conclusion

In this review, the effects of dual cART appear to be non-inferiority to triple cART, in treatment-naïve or treatment-experienced adults with HIV-1 infection. This finding favors strong support for current consensus guidelines recommended DTG-containing dual cART as first-line treatment.

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no other relationship or activities that could appear to have influenced the submitted work.

Supplementary Data

Supplementary data are available at AIDS Reviews online (http://www.aidsreviews.com/). These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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