

Is less truly more? – reassessing antiretroviral efficacy – a safety analysis for HIV patients switching from triple to double regimens with integrase inhibitors

A systematic review and meta-analysis

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Abstract

Background: Antiretroviral therapy has marked a transformative advancement in the management of people living with human immunodeficiency virus type-1 (HIV-1) (PLWH), converting this disease into a manageable condition. Triple-drug regimens have long been considered the gold standard for treatment. However, recent developments have focused on 2-drug regimens to mitigate the toxicities associated with polypharmacy while maintaining viral suppression and improving patient outcomes. Although the efficacy of treatment simplification is established, the impact on adverse events (AEs) remains unclear.

Methods: To evaluate the relative risk (RR) of developing drug-related AEs (DRAEs), DRAEs leading to treatment discontinuation (DRAEs-LD), and serious AEs, a systematic review and meta-analysis of available phase 3 and 4 clinical trials lasting at least 48 weeks and assessing treatment simplification to oral INSTIs in virologically suppressed PLWH were conducted. The study also evaluated the effects of early (ES) and late (LS) treatment regimen switches.

Results: Participants who switched to 2DR exhibited a significantly increased RR of developing DRAEs (RR = 6.92; confidence interval [CI]: 3.02–15.86, $P < .001$) and DRAEs leading to discontinuation (DRAEs-LD) (RR = 4.41; 95% CI: 1.77–10.99; $P = .001$) compared to those who remained on 3DR/4DR, with no differences observed in the RR of developing serious AEs (RR = 1.06; 95% CI: 0.73–1.55; $P = .76$).

Conclusion: Our findings indicate that there is still limited evidence to confirm that treatment simplification to oral INSTIs improves safety and tolerability profiles in the short-mid term. Our analyses emphasize the importance of evaluating symptom burden when considering therapy regimen switches in clinical practice.

Abbreviations: 2DR = 2-drug regimen, 3DR = 3-drug regimen, 3TC = lamivudine, 4DR = 4-drug regimen, AEs = adverse events, AIDs = acquired immunodeficiency syndrome, ART = antiretroviral therapy, CD4+ = cluster of differentiation 4, CI = confidence interval, DRAEs = drug-related adverse events, DRAEs-LD = drug-related adverse events leading to discontinuation, DTG = dolutegravir, ES = early switch, GESIDA = Grupo de estudio del SIDA, HIV-1 = human immunodeficiency virus type 1, HSS = Health and Human Services, INSTI = integrase strand transfer inhibitor, LS = late switch, MeSH = medical subject headings, NICE = National Institute for Health and Care Excellence, NNRTIs = non-nucleoside reverse transcriptase inhibitors, NRTIs = nucleoside reverse transcriptase inhibitors, PI = protease inhibitor, PLWH = people living with HIV-1, PRISMA = preferred reporting items for systematic reviews and meta-analyses, Rob2 = Cochrane risk of bias tool, RPV = rilpivirine, RR = relative risk, SLR = systematic literature review.

Keywords: antiretroviral therapy simplification, benefits, safety, tolerability

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The datasets generated during and/or analyzed during the current study are publicly available.

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1. Introduction

Antiretroviral therapy (ART) has revolutionized the treatment of people living with human immunodeficiency virus type 1 (HIV-1), transforming the disease into a manageable chronic condition. By effectively suppressing viral loads, ART enhances immune function and significantly improves the overall quality of life for those affected.^[1] Triple-drug regimens (3DR) have long been the standard of care for treating HIV. These regimens typically combine a modern integrase strand transfer inhibitor (INSTI) with either non-nucleoside reverse transcriptase inhibitors or nucleoside reverse transcriptase inhibitors (NRTIs) as the backbone, effectively maintaining viral suppression and improving patient outcomes.^[2] 3DR-based therapies have demonstrated numerous benefits, including reducing morbidity and mortality associated with HIV-1, decreasing transmission rates and restoring baseline levels of cluster of differentiation 4 (CD4+) cell counts, with a lower incidence of complications.^[3]

However, the chronic nature of the disease and the associated comorbidities require prolonged exposure to multiple antiretroviral drugs, which can lead to cumulative toxicities^[4] These long-term effects include reductions in bone density and increased risks for renal, cardiovascular, and metabolic complications, such as diabetes.^[5] As a result, efforts are increasingly focused on minimizing these risks while maintaining virological suppression. Over the last decade, 2 drug-based regimens (2DR) have been approved to address these concerns by combining an INSTI with a single transcriptase inhibitor.^[6] For this reason, the U.S Department of Health and Human Services (HSS), the European Acquired Immunodeficiency Syndrome (AIDS) Clinical Society, the *Grupo de estudio del SIDA* (GESIDA), and the International Antiviral U.S. Society recommend the 2DR combination of dolutegravir (DTG) with lamivudine (3TC) as initial therapy or a switch option, or rilpivirine (RPV) as a switch option for virologically suppressed patients transitioning from 3DR or a 4-drug regimen (4DR).^[2,7–9]

These recommendations are based on findings from recent phase III GEMINI-1 and GEMINI-2 studies, which demonstrated that the combination of 3TC + DTG is non-inferior to 3DR regarding efficacy and safety in naïve patients.^[10,11] While recent clinical trials confirmed that switching strategy from 3DR or 4DR to 2DR is effective and safe,^[12–15] limited evidence has explored the potential impact of this simplification on adverse events (AEs). In this study, we conducted a systematic literature review (SLR) and meta-analysis of available phase III and IV clinical trials evaluating switching strategies from 3-drug (3DR) or 4DR to 2-drug regimens (2DR). We aimed to assess the rates of drug-related AEs (DRAEs), DRAEs leading to treatment discontinuation (DRAEs-LD), and serious AEs while also examining the impact of switching timing (early vs late) on these outcomes. Treatment simplification strategies are not guided by virological criteria but rather by the goal of reducing pharmacological load, improving tolerability, minimizing the associated long-term toxicity, and increasing cost-effectiveness. By compiling evidence, this study aimed to determine if there are benefits

of treatment simplification in terms of safety and tolerability to help in the decision-making in routine clinical practice and to provide the best therapeutic option for patients.

2. Methods

2.1. Systematic literature review

A systematic review phase III and phase IV trials from the last 10 years (2014–2024) reporting DRAEs in virologically suppressed PLWH who switch from 3DR or 4DR to 2DR was carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Cochrane recommendations.^[16,17]

2.2. Data sources and search strategy

The international databases PubMed/Medline, EMBASE, and the Cochrane library, were searched to identify relevant publications for review. Additionally, manual searches were performed to identify conference abstracts presented in the last 2 years (2022–2024) (Annex 1, Supplemental Digital Content, <https://links.lww.com/MD/Q301>), in the International AIDS Society (IAS/AIDS conferences), the European AIDS Clinical Society, the Conference on Retroviruses and Opportunistic Infections, the IDWeek, and the HIV Drug Therapy Glasgow. The different databases were searched using both MeSH (Medical Subject Headings) and free-text terms, combined with the Boolean connectors “OR” and “AND” (Annex 1, Supplemental Digital Content, <https://links.lww.com/MD/Q301>).

2.3. Study selection

Two independent reviewers performed a 2-level screening of the identified publications. Level 1 entailed a wide screen based on titles and/or abstracts, as available the title and abstract. At level 2, the reviewers independently assessed the full text of the articles, applying the inclusion/exclusion criteria. At both screening levels, discrepancies were resolved by consensus or by involving a third team member (Annex 1, Supplemental Digital Content, <https://links.lww.com/MD/Q301>).

2.4. Eligibility criteria

Publications included Phase III and Phase IV clinical trials from the last 10 years (March 2014 to March 2024) and conference abstracts from the last 2 years (March 2022 to March 2024), published in English, reporting DRAEs, evaluating switch from 3DR or 4DR to oral INSTIs-based 2DR and with a minimum follow-up of 48 weeks for both arms. Publications were excluded if not reporting DRAEs, not published in English, focusing on specific subpopulations (e.g. pediatric), with follow-up periods < 48 weeks, switching to injectable or intramuscular INSTIs, switching to non-INSTIs treatments, or having an inappropriate study design (Phase IV hybrid trials,

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observational studies, narrative reviews, systematic reviews, meta-analysis, editorial articles, opinion articles or letters to the editor) (Annex 1, Supplemental Digital Content, <https://links.lww.com/MD/Q301>).

Both phase III and phase IV clinical trials were included in the SLR and meta-analysis to ensure comprehensive coverage of all available evidence on the topic. The included Phase IV trials were not observational, but conducted under controlled clinical conditions, maintaining methodological rigor comparable to Phase III studies. Inclusion of both designs also allowed for sufficient data to perform robust comparisons. Nevertheless, to assess the potential influence of trial phase on the findings, sensitivity analyses were performed excluding phase IV studies to verify the consistency and robustness of the results and conclusions derived from the full dataset.

2.5. Data extraction and quality assessment

Data extracted included study design, recruitment period, regimen and number of participants, sociodemographic characteristics (age, sex, race and ethnicity) clinical and treatment characteristics (CD4 + cell count, duration of ART before day 1, type of third agent class) and AE (DRAEs, DRAEs-LD, type of DRAEs and serious AEs). Two independent reviewers extracted all data employing a standardized data extraction form, and discrepancies were resolved by consensus. The quality of included publications was assessed using the quality appraisal checklist

recommended by the National Institute for Health and Care Excellence (NICE),^[18] with discrepancies being resolved by consensus. The SLR was not publicly registered. Ethical approval was not required for this study, as it is based solely on previously published data from clinical trials (Annex 1, Supplemental Digital Content, <https://links.lww.com/MD/Q301>).

2.6. Meta-analysis

A meta-analysis was performed to determine the relative risk (RR) of developing DRAEs in virologically suppressed PWH who switched from 3 or 4DR to 2DR with oral INSTIs. The RR of developing DRAEs leading to discontinuation and serious AEs were also assessed. Only comparable publications in design (Phase III and Phase IV studies), reported endpoints (comparable DRAEs), and follow-up times (48 weeks) were included in the meta-analysis. The risk of bias (RoB) from the selected studies was determined using the Cochrane RoB tool for randomized trials (RoB 2)^[19] (Annex 1, Supplemental Digital Content, <https://links.lww.com/MD/Q301>).

Heterogeneity among the studies was evaluated employing the heterogeneity index I² [low (I² < 25%), moderate (25% < I² < 50%), high (50% < I² < 75%), and very high (I² > 75%)], using STATA software v.14. A random-effects model was applied if heterogeneity was confirmed (I² > 50% and P < .05). Otherwise, a fixed-effects model was employed.^[20] Since a single Phase IV study (DOLAM) with a 48-week

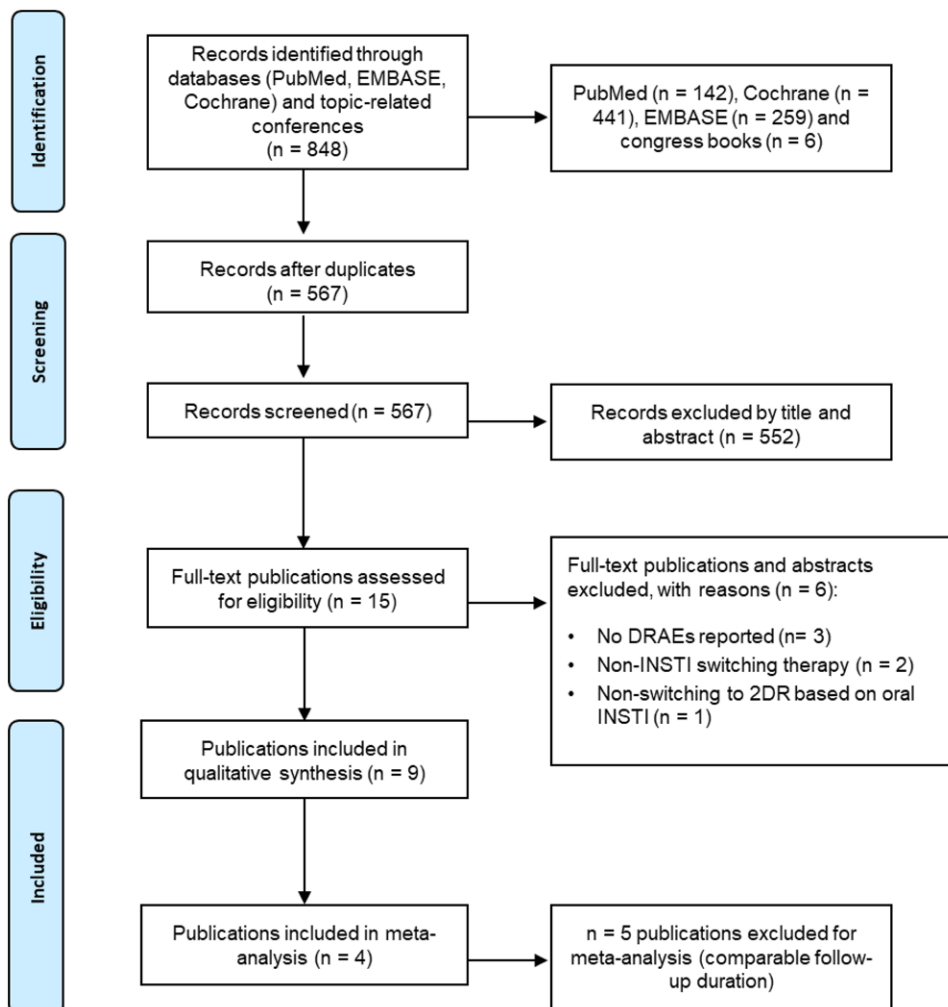


Figure 1. PRISMA flow chart of included publications. PRISMA flow chart illustrating the publications included in the systematic literature review and the meta-analysis. 2DR = 2-drug regimen, DRAE = drug-related adverse event, INSTI = integrase strand transfer inhibitor.

Table 1
Characteristics of the publications included in the systematic literature review and the meta-analysis.

| Study- follow-up weeks, study design | Recruitment | Regimen number of participants | Age, median years (range) | Sex (female), n (%) | Race, n (%) | Ethnicity, n (%) | CD4 + cell count mean, n (%) [cells/mm ³] | Duration of ART before day 1, median of months (range) |
|---|--------------------------------|--------------------------------|---------------------------|---------------------|--|---|---|--|
| TANGO-48, Phase III, randomized, open-label, non-inferiority study | January 18, 2018– May 18, 2018 | 3DR or 4DR, TAF-BR, 372 | 39 (18–73) | 33 (8.9) | 58 (15.6) African American/ African heritage; 13 (3.5) Asian; 289 (77.7) White; 12 (3.2) other | 66 (17.7) Hispanic or Latino; 306 (82.3) not Hispanic or Latino | 720; 74 (19.9) [<500]; 298 (80.1) [≥ 500] | 35.1 (7.0–160.8) |
| TANGO-96, Phase III, randomized, open-label, non-inferiority study | 18th Jan 2018–18th May 2018 | 3DR or 4DR, TAF-BR, 372 | 39 (18–73) | 33 (8.9) | 58 (15.6) African American/ African heritage; 13 (3.5) Asian; 289 (77.7) White; 12 (3.2) other | 66 (17.7) Hispanic or Latino; 306 (82.3) not Hispanic or Latino | 720; 30 (8) [<350]; 342 (92) [≥ 350] | 35.1 (7.0–160.8) |
| TANGO-144, Phase III, randomized, open-label, non-inferiority study | 18th Jan 2018–18th May 2018 | 3DR or 4DR, TAF-BR, 372 | 39 (18–73) | 33 (8.9) | 58 (15.6) African American/ African heritage; 13 (3.5) Asian; 289 (77.7) White; 12 (3.2) other | 66 (17.7) Hispanic or Latino; 306 (82.3) not Hispanic or Latino | 720; 74 (19.9) [<500]; 298 (80.1) [≥ 500] | 35.1 (7.0–160.8) |
| TANGO-196, Phase III, randomized, open-label, non-inferiority study | 18th Jan 2018–18th May 2018 | 2DR, DTG/3TC 369 | 40 (20–74) | 25 (6.8) | 50 (13.6) African American/ African heritage; 13 (3.5) Asian; 297 (80.5) White; 9 (2.4) other | 69 (18.7) Hispanic or Latino; 300 (81.3) not Hispanic or Latino | 682; 98 (26.6) [<500]; 271 (73.4) [≥ 500] | 33.8 (7.1–201.2) |
| SALSA-48, Phase III, randomized, open-label, non-inferiority study | 11th Nov 2019–23rd Apr 2021 | 3DR or 4DR, CAR, 247 | 45 (23–83) | 84 (34) | 48 (19) African American/ African heritage; 39 (16) Asian; 144 (58) White; 16 (6) other | 69 (18.7) Hispanic or Latino; 300 (81.3) not Hispanic or Latino | 682; 98 (26.6) [<500]; 271 (73.4) [≥ 500] | 33.8 (7.1–201.2) |
| SWORD-48, Phase III, randomized, open-label, non-inferiority study | 14th Apr 2015–15th Oct 2015 | 3DR or 4DR, CAR, 511 | 43 (22–76) | 108 (21) | 45 (18) African American/ African heritage; 31 (13) Asian; 149 (61) White; 21 (9) other | 69 (18.7) Hispanic or Latino; 306 (82.3) not Hispanic or Latino | 751.4; NS | 34.0 (7.0–160.8) |
| SWORD-100, Phase III, randomized, open-label, non-inferiority study | 14th Apr 2015–15th Oct 2015 | 2DR, DTG/3TC LS, 477 | 43 (22–76) | 96 (20) | 41 (14) African American/ African heritage; 12 (4) Asian; 235 (79) White; 10 (3) other | NS | 702; NS | 33.8 (7.1–201.2) |
| SWORD-148, Phase III, randomized, open-label, non-inferiority study | 14th Apr 2015–15th Oct 2015 | 2DR, DTG/3TC ES, 369 | 40 (20–74) | 25 (6.8) | 50 (13.6) African American/ African heritage; 13 (3.5) Asian; 297 (80.5) White; 9 (2.4) other | NS | 668; 63 (26) [<500]; 184 (74) [≥ 500] | 71 (12–253) |
| DOLAM-48, Phase IV, randomized, open-label study | 23rd Jun 2015–21st Nov 2019 | 3DR or 4DR, CAR, 134 | 45 (22–74) | 108 (44) | 48 (19) African American/ African heritage; 31 (13) Asian; 144 (58) White; 16 (6) other | NS | 675; 60 (24) [<500]; 184 (75) [≥ 500] | 63 (4–240) |
| | | 2DR, DTG/3TC, 246 | 43 (21–79) | 120 (23) | 45 (18) African American/ African heritage; 31 (13) Asian; 149 (61) White; 21 (9) other | 82 (16) Hispanic or Latino; 429 (84) not Hispanic or Latino | 638; NS | 53 (9–270) months |
| | | 3DR or 4DR, CAR, 511 | 43 (22–76) | 108 (21) | 14 (3) American Indian or Alaska native; 50 (10) Asian; 49 (79) African American/ African heritage; 0 native Hawaiian or other pacific islander; 398 (78) White; 2 (<1) other | 67 (13) Hispanic or Latino; 446 (87) not Hispanic or Latino | 611; NS | 51 (9–221) |
| | | 2DR, DTG/3TC, 246 | 43 (21–79) | 120 (23) | 14 (3) American Indian or Alaska native; 38 (7) Asian; 37 (7) African American/ African heritage; 2 (<1) native Hawaiian or other pacific islander; 421 (82) White; 1 (<1) other | 67 (13) Hispanic or Latino; 446 (87) not Hispanic or Latino | 611; 315 (93) [≥ 500] | NS |
| | | 2DR, DTG/3TC ES, 369 | 43 (22–76) | 96 (20) | 11 (2) American Indian or Alaska native; 38 (7) Asian; 37 (7) African American/ African heritage; 2 (<1) native Hawaiian or other pacific islander; 421 (82) White; 1 (<1) other | 76 (16) Hispanic or Latino; 401 (84) not Hispanic or Latino | 611; 314 (90) [≥ 500] | NS |
| | | 2DR, DTG/3TC ES, 513 | 43 (21–79) | 120 (23) | 14 (3) American Indian or Alaska native; 38 (7) Asian; 37 (7) African American/ African heritage; 2 (<1) native Hawaiian or other pacific islander; 421 (82) White; 1 (<1) other | 67 (13) Hispanic or Latino; 446 (87) not Hispanic or Latino | NS | NS |
| | | 2DR, DTG/3TC ES, 513 | 46 (39–51) | 18 (13) | NS | NS | NS | NS |
| | | 2DR, DTG/3TC 131 | 45 (37–53) | 20 (15) | NS | NS | 747; NS | NS |
| | | 2DR, DTG/3TC 131 | 45 (37–53) | 20 (15) | 25 (19) Latino; 105 (78) White; 4 (3) other | NS | 700; NS | NS |
| | | 2DR, DTG/3TC 131 | 45 (37–53) | 20 (15) | 24 (18) Latino; 106 (81) White; 1 (1) other | NS | NS | NS |

3TC = lamivudine, ART = antiretroviral therapy, BR = based-regimen, CAR = current antiretroviral regimen, CD4+ = cluster of differentiation 4 positive cells, DR = drug regimen, DTG = dolutegravir, ES = early switch, LS = late switch, NS = not specified, RPV = rilpivirine, TAF = tenofovir alafenamide.

follow-up was identified from the SLR, and a meta-analysis cannot be performed with data from a single research, data from this Phase IV study were pooled with the 3 Phase III studies. Moreover, additional analyses were conducted excluding the Phase IV study (DOLAM), to evaluate its impact on the overall findings. Lastly, a sensitivity analysis was performed using the alternative method to assess the robustness of the meta-analysis conclusions. Results were reported using a 95% confidence interval (CI), with statistical significance defined as $P < .05$. Data were visually depicted using tables and forest plots. No other variables/outcomes assessment or data conversions were required.

3. Results

From an initial pool of 848 studies, we ultimately included 9 publications in the SLR and 4 in the meta-analysis (Fig. 1).

The characteristics of the publications included in the SLR are summarized in Table 1. A total of 9 publications were analyzed, encompassing 3 phase III trials: TANGO (three publications), SALSA (one publication) and SWORD (three publications), along with 1 phase IV study, DOLAM (one article). The NICE quality appraisal score analysis indicated a high-quality rating across the selected publications (mean score of 1.67–1.78 out of a maximum of 2). Among them, only 4 publications reported the same follow-up duration (48 weeks), and 3 publications compared early versus late treatment switches. The sample sizes varied across the studies, ranging from 265 to 1024 participants, with well-balanced control and experimental groups in each study. Most participants were male and identified as White, demonstrating stable and comparable CD4 + cell counts (cells/mm³). Additionally, all participants had been on ART for a minimum of 33.8 months.

3.1. Regimens

The baseline third agent class of participants either continuing with 3DR or 4DR or switching to 2DR was generally consistent across study arms in early-switching trials (Table 2). In the

TANGO study, the most common baseline third-agent class used was an INSTI (3DR or 4DR: 79.6%; 2DR: 78.3%), followed by an NNRTI (3DR or 4DR: 12.9%; 2DR: 13.8%) and a protease inhibitor (PI) (3DR or 4DR: 7.5%; 2DR: 7.9%). The SWORD study showed a different trend, with an NNRTI being the most frequent third-agent class (3DR or 4DR: 54 %; DTG/RPV: 50%), followed by a PI (3DR or 4DR: 27 %; 2DR: 26%) and an INSTI (3DR or 4DR: 19 %; 2DR: 20%). In the SALSA study, both treatment arms had an identical distribution, with 50% of participants using an NNRTI as their third-agent class, 40% using an INSTI and 10% using a PI. Similarly, in the DOLAM study, non-nucleoside reverse transcriptase inhibitors were the most common third-agent class (3DR or 4DR: 49 %; 2DR: 51%), with smaller proportions for INSTI (3DR or 4DR: 47 %; 2DR: 54%) and PI (3DR or 4DR: 4 %; 2DR: 5%). The regimens utilized in the late switch studies are outlined in (Table S1, Supplemental Digital Content, <https://links.lww.com/MD/Q302>).

3.2. Adverse events

DRAEs were reported in 7 out of the 9 publications included in the SLR. Across all 7 studies, a higher frequency of DRAEs was consistently observed in participants who switched to a 2DR compared to those who remained on a 3DR or 4DR (12.2 % vs 1.3% in TANGO at 48 weeks, 13.8 % vs 3.2% in TANGO at 96 weeks, 14.9 % vs 4.8% in TANGO at 144 weeks, 19.5 % vs 6.5% in SALSA at 48 weeks, 18.9 % vs 1.7% in SWORD at 48 weeks, and 6.9 % vs 0% in DOLAM at 48 weeks) (Table 3). Additionally, the SWORD study at 100 weeks highlighted a higher incidence of these events in early-switch participants than late-switch participants (20 % vs 12.1%). Similar results were obtained when analyzing DRAEs-LD, with frequencies elevated in participants who switched from 3DR or 4DR to 2DR (2.4 % vs <1% in TANGO at 48 weeks, 3.8 % vs <1% in TANGO at 96 weeks, 3.5 % vs 1.3% in TANGO at 144 weeks, 1.6 % vs <1% in SALSA at 48 weeks, and 2.9 % vs 0% in SWORD at 48 weeks). Nevertheless, SWORD at

Table 2
Baseline third agent class.

| Regimen [n (%)] | TANGO | | SALSA | | SWORD | | DOLAM | |
|--------------------------------|-------------------------------|-------------------------|----------------------------|-------------------------|----------------------------|-------------------------|----------------------------|-------------------------|
| | 3DR or 4DR (TAF-BR) (n = 372) | 2DR (DTG/3TC) (n = 369) | 3DR or 4DR (CAR) (n = 247) | 2DR (DTG/3TC) (n = 246) | 3DR or 4DR (CAR) (n = 511) | 2DR (DTG/RPV) (n = 513) | 3DR or 4DR (CAR) (n = 134) | 2DR (DTG/3TC) (n = 131) |
| INSTI | 296 (79.6) | 289 (78.3) | 98 (40) | 98 (40) | 97 (19) | 105 (20) | 63 (47) | 58 (44) |
| DTG | NS | NS | 41 (17) | 45 (18) | NS | NS | 27 (20) | 21 (16) |
| EVG/COBI | 249 (66.9) | 243 (65.9) | 27 (11) | 24 (10) | NS | NS | 23 (17) | 25 (19) |
| BIC | NS | NS | 26 (11) | 24 (10) | NS | NS | NS | NS |
| RAL | NS | NS | 6 (2) | 4 (2) | 6 (1) | 4 (1) | 13 (10) | 12 (9) |
| NNRTI | 48 (12.9) | 51 (13.8) | 124 (50) | 123 (50) | 278 (54) | 275 (54) | 65 (49) | 67 (51) |
| RPV | 45 (12.1) | 43 (11.7) | NS | NS | NS | NS | NS | NS |
| EFV | NS | NS | 73 (30)* | 79 (32)* | 62 (12) | 62 (12) | NS | NS |
| NRTI | 372 (100)† | 369 (100)† | NS | NS | NS | NS | NS | NS |
| ABC/3TC | NS | NS | NS | NS | NS | NS | 53 (40)‡ | 45 (34)‡ |
| 3TC | NS | NS | 89 (36)* | 96 (39)* | NS | NS | -- | -- |
| TAF | NS | NS | 91 (37)* | 83 (34)* | NS | NS | 35 (26)‡ | 38 (29)‡ |
| TDF | NS | NS | 109 (44)* | 109 (44)* | 359 (70) | 374 (73) | 46 (34)‡ | 48 (37)‡ |
| FTC | NS | NS | 156 (63)* | 149 (61)* | 341 (67) | 352 (69) | -- | -- |
| PI | 28 (7.5) | 29 (7.9) | 25 (10) | 25 (10) | 136 (27) | 133 (26) | 6 (4) | 6 (5) |
| RTV or COBI -boosted darunavir | 27 (7.3) | 25 (6.8) | NS | NS | 6 (1) | 9 (2) | NS | NS |

3TC = lamivudine, ABC = abacavir, BIC = bictegravir, BR = based-regimen, CAR = current antiretroviral regimens, COBI = cobicistat, DR = drug regimen, DTG = dolutegravir, EFV = efavirenz, EVG = elvitegravir, FTC = emtricitabine, INSTI = integrase strand transfer inhibitor, NNRTI = nonnucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, NS = not specified, PI = protease inhibitor, RAL = raltegravir, RPV = rilpivirine, RTV = ritonavir, TAF = tenofovir alafenamide, TDF = tenofovir disoproxil fumarate.

*Drug received at screening in ≥30% of participants. N (% of participants with each of the treatments in each arm). Data on individual treatments are incomplete, reflecting the original sources.

†All patients were on a TAF-based regimen prior to randomization.

‡Backbone regimens (TAF and TDF regimens were combined with FTC).

Table 3
Adverse events.

| Study | Regimen | n | DRAE n (%) | DRAE-LD n (%) | Threshold | Type of DRAE* n (%) | | | | | | | | | | | | Serious AEs n (%) |
|-----------|-----------------------------------|-----|------------|---------------|-----------------|---------------------|------------|-----------|-----------|---------------|----------|----------|--------|------------------|--------|--------|-----------|-------------------|
| | | | | | | Constipation | Depression | Diarrhoea | Fatulence | GFR decreased | Headache | Insomnia | Nausea | Weight increased | | | | |
| TANGO-48 | 3DR or 4DR (TAF-BR) | 372 | 5 (1.3) | 1 (<1) | ≥0.5% | 1 (<1) | | | 0 (0) | | | 0 (0) | | | | | 16 (4.3) | |
| TANGO-96 | 2DR (DTG/3TC) | 369 | 45 (12.2) | 9 (2.4) | ≥0.5% | 2 (<1) | | | 2 (<1) | | | 2 (<1) | | | 4 (1) | | 21 (5.7) | |
| | 3DR or 4DR (TAF-BR) | 372 | 12 (3.2) | 3 (<1) | ≥0.5% | 1 (<1) | 1 (<1) | | 0 (0) | | | 0 (0) | | | 0 (0) | | 35 (9.4) | |
| TANGO-144 | 2DR (DTG/3TC) | 369 | 51 (13.8) | 14 (3.8) | ≥0.5% | 2 (<1) | 3 (<1) | | 2 (<1) | | | 4 (1) | | | 4 (1) | | 42 (11.4) | |
| | 3DR or 4DR (TAF-BR) | 372 | 18 (4.8) | 5 (1.3) | ≥0.5% | 1 (<1) | 1 (<1) | | 0 (0) | | | 0 (0) | | | 0 (0) | 2 (<1) | 44 (11.8) | |
| TANGO-196 | 2DR (DTG/3TC) | 369 | 55 (14.9) | 13 (3.5) | ≥0.5% | 2 (<1) | 2 (<1) | | 2 (<1) | | | 4 (1) | | | 4 (1) | 0 (0) | 57 (15.4) | |
| | 3DR or 4DR (TAF-BR) | 298 | NS | NS | | | | | | | | | | | | | 15 (5) | |
| SALSA-48 | 2DR (DTG/3TC) | 369 | NS | NS | | | | | | | | | | | | | 65 (17.6) | |
| | 3DR or 4DR (CAR) | 247 | 16 (6.5) | 1 (<1) | ≥2 participants | | | | | 0 (0) | | 1 (<1) | | | 1 (<1) | | 16 (6.5) | |
| SWORD-48 | 2DR (DTG/3TC) | 246 | 48 (19.5) | 4 (1.6) | ≥2 participants | | | | | 2 (<1) | | 3 (1) | | | 3 (1) | | 7 (2.8) | |
| | 3DR or 4DR (CAR) | 511 | 9 (1.7) | 1 (<1) | ≥2% | | | | | 1 (<1) | | | | | | | 21 (4.1) | |
| SWORD-100 | 2DR (DTG + RPV) | 513 | 97 (18.9) | 15 (2.9) | ≥2% | | | | | 8 (2) | | | | | 11 (2) | | 27 (5.3) | |
| | 2DR (DTG + RPV) LS (weeks 52–100) | 477 | 58 (12.1) | 8 (1.7) | ≥2% | | | | | 5 (1) | | | | | 8 (2) | 5 (1) | 30 (6.3) | |
| SWORD-148 | 2DR (DTG + RPV) ES (weeks 1–100) | 513 | 103 (20) | 16 (3.1) | ≥2% | | | | | 7 (2) | | | | | 11 (2) | | 58 (11.3) | |
| | 2DR (DTG + RPV) LS (week 52–148) | 477 | NS | 11 (2.3) | | | | | | | | | | | | | 44 (9.2) | |
| DOLAM-48 | 2DR (DTG + RPV) ES (weeks 1–148) | 513 | NS | 18 (3.5) | | | | | | | | | | | | | 72 (14) | |
| | 3DR or 4DR (CAR) | 134 | 0 | NS | | | | | | | | | | | | | 6 (4.5) | |
| | 2DR (DTG/3TC) | 131 | 9 (6.9) | NS | | | | | | | | | | | | | 3 (2.3) | |

3TC = lamivudine, ABC Abacavir, AEs = adverse events, BIC = bictegravir, CAR = current antiretroviral regimens, COBI = cobicistat, DR = drug regimens, DRAEs = drug-related adverse events, DRAEs-LD = drug-related adverse events leading to discontinuation, DTG = dolutegravir, EVG = elvitegravir, ES = early switch, EVG = elvitegravir, FTC = emtricitabine, GFR = glomerular filtration rate, INSTI = integrase strand transfer inhibitor, LS = late switch, M-A = meta-analysis, NNRTI = non nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, NS = not specified, PI = protease inhibitor, RAL = raltegravir, RPV = rilpivirine, RTV = ritonavir, TAF = tenofovir alafenamide, TDF = tenofovir disoproxil fumarate.
*Type of DRAE occurring in a % of participants in either group.

100 weeks (3.1 % vs 1.7%) and SWORD-148 (3.5 % vs 2.3%) studies showed a comparable frequency of DRAEs-LD between early-switch participants and late-switch participants. The most frequently reported DRAEs in these studies included headache, diarrhea and insomnia.

However, these trends did not persist when assessing the frequency of serious AEs. A heterogeneous response was noted among the studies following the switch to 2DR, with no significant differences observed. Finally, studies comparing early and late switches (TANGO at 196 weeks, SWORD at 100 weeks and SWORD at 148 weeks) reported a greater incidence of serious AEs among participants who underwent early switching (5% vs 17.6%, 6.3% vs 11.3% and 9.2% vs 14% respectively). In these studies, the reported temporal window for evaluating AEs was shorter for late-switch participants compared to early-switch participants [TANGO LS (weeks 148–196) vs ES weeks (1–196 weeks); SWORD LS (weeks 52–100/148) vs ES (weeks 1–148)]. Consequently, when comparing the AEs frequency within the first 48 weeks post-switch for both early-switch and late-switch participants, no differences were observed in TANGO (5.7% vs 5%, respectively) and SWORD (5.3% vs 6.3%, respectively) studies.

3.3. Meta-analysis

Phase III studies TANGO, SALSA, SWORD 1 to 2, and Phase IV study DOLAM with a 48-week follow-up duration were included in the meta-analysis. The analysis of the RoB indicated that all studies included had an overall low risk of bias, making them suitable for the analysis (Fig. 2).

3.4. Relative risk of developing DRAEs

Initially, the meta-analysis was conducted to determine the RR of developing DRAEs in virologically suppressed PLWH switching from 4DR or 3DR to a 2DR. A high heterogeneity was observed among the studies ($I^2 = 71.5\%$, $P = .015$) (Table 4 and Fig. 3). The analysis showed that participants who switched to a 2DR oral INSTIs for 48 weeks presented a significantly higher RR of developing DRAEs compared to those who continued with a 3DR or 4DR (RR = 6.92; CI: 3.02–15.86, $P < .001$). Similar results were observed when only phase III clinical trials were analyzed; heterogeneity ($I^2 = 79.6\%$, $P = .008$), (RR = 6.41; CI: 2.65–15.64, $P < .001$) (Table 4 and Fig. S1, Supplemental Digital Content, <https://links.lww.com/MD/Q303>).

3.5. Relative risk of developing DRAEs-LD

A low heterogeneity among the studies ($I^2 = 42.3\%$, $P = .177$) (Table 4 and Fig. 4). The analysis excluding phase IV trial DOLAM revealed a significantly higher RR of developing DRAEs-LD in those participants performing treatment simplification (RR = 4.41; CI: 1.77–10.99, $P = .001$) (Table 4).

3.6. Relative risk of developing serious AEs

The analysis detected a moderate heterogeneity among the studies ($I^2 = 48.8\%$, $P = .118$) and a similar RR of developing these serious events when comparing between arms (RR = 1.01; CI: 0.7–1.45, $P = .973$) (Table 4 and Fig. 5). Consistent results were obtained after excluding the phase IV study (heterogeneity, $I^2 = 58.7\%$, $P = .089$), with no changes in the RR (RR = 1.06;

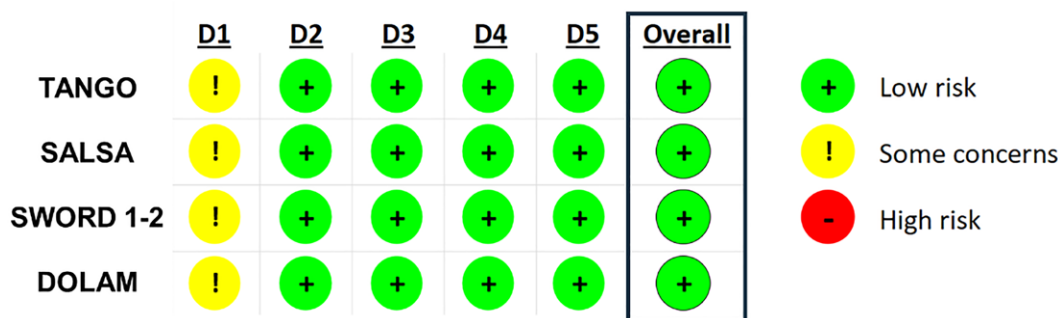


Figure 2. Risk of bias of studies included in the meta-analysis. Figure detailing the risk of bias from the randomization process due to deviated interventions, missing outcome data, measurements of the outcome, or the selection of the reported results of the 4 studies included in the meta-analysis. D1, Bias arising from the randomization process; D2, Bias due to deviations from intended interventions; D3, Bias due to missing outcome data; D4, Bias in measurement of the outcome; D5, Bias in the selection of the reported result.

Table 4
Summary of the meta-analysis results including 48 weeks-follow-up studies.

| Outcomes* excluding DOLAM* | No. of studies (name) | No. of participantsexperimental/control group | N° (%) of events experimental/control group | RR | 95% Confidence Interval | P-value | I ² %, P-value |
|----------------------------|--------------------------------|---|---|--------------|--------------------------|----------------|----------------------------|
| DRAEs | 4 (TANGO, SALSA, SWORD, DOLAM) | 1259/1264*, 1128/1130* | 199/30*, 190/30* | 6.92*, 6.41* | 3.02–15.86*, 2.65–15.64* | <.001*, <.001* | 71.5%, .015*, 79.6%, .008* |
| DRAEs-LD | 3 (TANGO, SALSA, SWORD) | 1128/1130 | 28/2 | 4.41 | 1.77–10.99 | .001 | 42.3%, .177 |
| Serious AEs | 4 (TANGO, SALSA, SWORD, DOLAM) | 1259/1264*, 1128/1130* | 28/32*, 25/30* | 1.01*, 1.06* | 0.7–1.45*, 0.73–1.55* | .973*, .763* | 48.8%, .118*, 58.7%, .089* |
| | 3 (TANGO, SALSA, SWORD) | | | | | | |

AEs = adverse events, DRAEs = drug-related adverse events, DRAEs-LD = drug-related adverse events leading to discontinuation, I² = heterogeneity index, RR = relative risk.

Values in

*indicate results of an additional analysis excluding the DOLAM study.

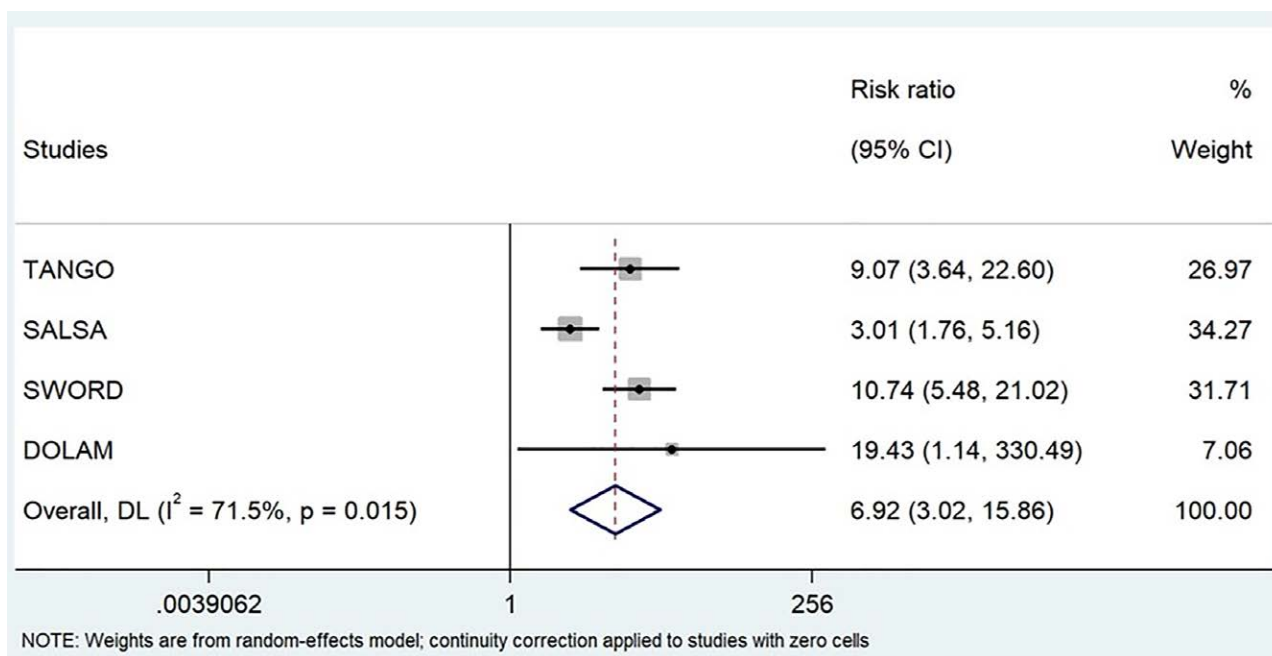


Figure 3. Relative risk of developing DRAEs. Forest plot displaying the risk ratios of developing drug-related adverse events and the relative weights of the 4 studies included in the meta-analysis. Studies included: 4. Participants included: 2523. Continuity correction of 0.5 applied to DOLAM study in zero values. Patients included: 2523. CI = confidence intervals, DRAEs = drug-related adverse events, DL = DerSimonian-Laird estimate of τ^2 , I^2 = heterogeneity index.

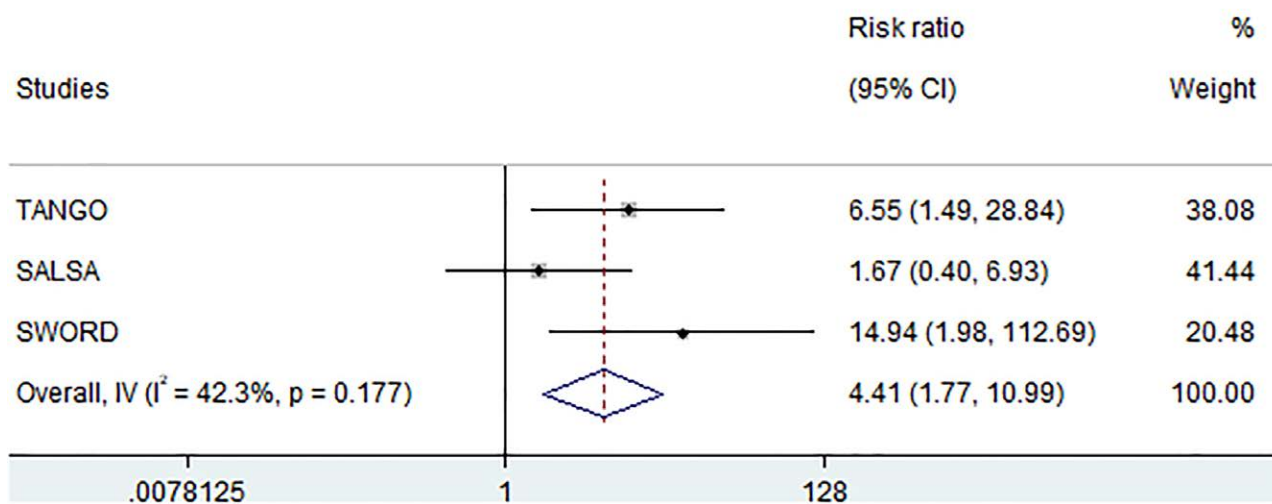


Figure 4. Relative risk of developing DRAEs-LD. Forest plot displaying the risk ratios of developing drug-related adverse events leading to discontinuation and the relative weights of the 3 studies included in the meta-analysis. Studies included: 3. Participants included: 2258. CI = confidence intervals, DRAEs-LD = drug-related adverse events leading to discontinuation, I^2 = heterogeneity index, IV = inverse variance.

CI: 0.73–1.55, $P = .763$) (Table 4 and Fig. S1, Supplemental Digital Content, <https://links.lww.com/MD/Q303>).

3.7. Sensitivity analyses

The sensitivity analysis yielded similar results to the primary findings (Fig. S2, Supplemental Digital Content, <https://links.lww.com/MD/Q303>).

4. Discussion

Despite a trend towards 2DR for enhanced safety and tolerability in PLWH, the impact of switching from 3DR on these

outcomes remains uncertain and warrants further investigation. Current studies suggest that while 2DRs, such as dolutegravir/lamivudine, show good safety profiles, the long-term effects and potential risks associated with switching from established 3DRs require more comprehensive research to fully understand their implications on patient health and treatment efficacy.

Our findings indicate that the switch from continuous 3DR or 4DR to 2DR is not associated with a decreased RR of DRAEs. This conclusion is supported by the findings of the 4 clinical trials analyzed (TANGO, SALSA, SWORD and DOLAM), where DRAEs were consistently higher in 2DR participants than in those on 3DR or 4DR (12.2% vs 1.3%, 19.5% vs 6.5%, 18.9% vs 1.7% y 6.9% vs 0% respectively).^[4,13,15,21] During this manuscript preparation, another clinical trial (DYAD) with

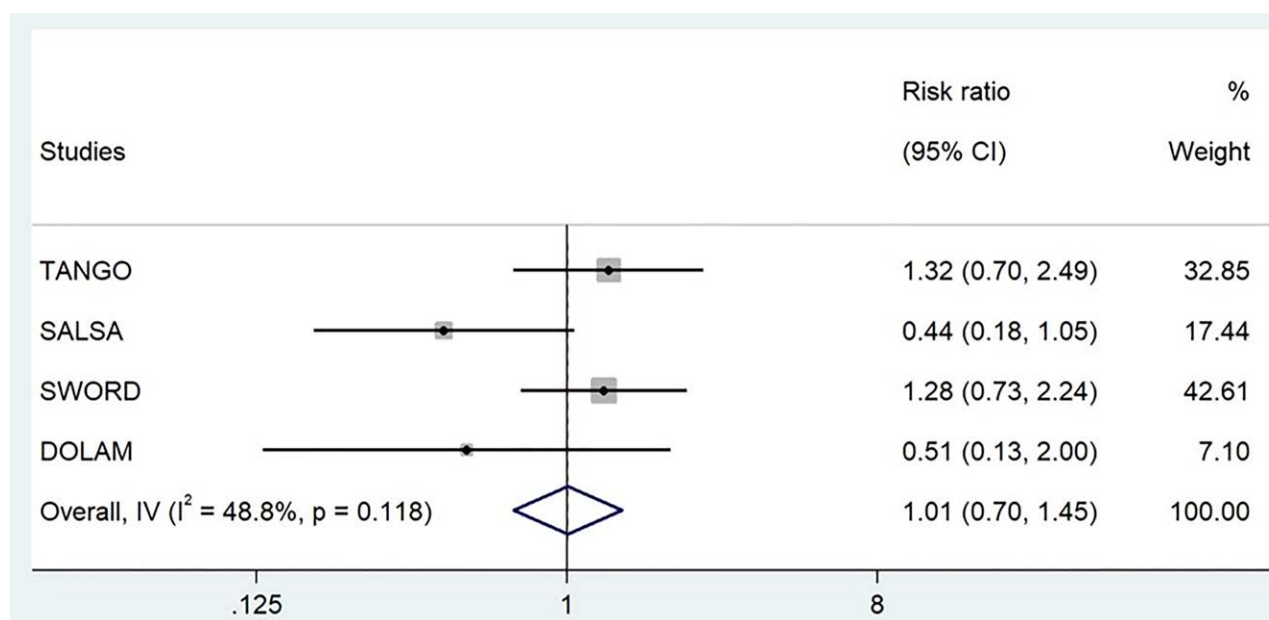


Figure 5. Relative risk of developing serious AEs. Forest plot displaying the risk ratios of developing serious adverse events and the relative weights of the 4 studies included in the meta-analysis. Studies included: 4. Participants included: 2523. AEs = adverse events, CI = confidence intervals, I^2 = heterogeneity index, IV = inverse variance.

a similar study design to those included in our meta-analysis also reported an increased frequency of DRAEs among 2DR participants (21% vs 3%).^[22] These outcomes further align with those reported in studies involving different formulation strategies. Clinical trials assessing the switch to injectable 2DR therapies (SOLAR and FLAIR) reported higher numbers for DRAEs compared to participants who continued on 3DR or 4DR (72% vs 1% in SOLAR trial and 83% vs 10% in FLAIR trial).^[23,24] Although authors suggest that the increased incidence of DRAEs could be linked to the administration route when an injectable is employed, the proportions are still higher in 2DR participants excluding injection-site reactions DRAEs (20% vs 0% in SOLAR trial and 28% vs 10% in FLAIR trial).^[23,24]

Similar results were obtained when examining the RR of DRAEs-LD. Data from the 3 phase III clinical trials (TANGO, SALSA and SWORD) showed a higher incidence in 2DR participants than those maintaining the 3DR or 4DR (2 vs < 1%, 1.6 vs 1% and 2.9% vs 0%, respectively).^[4,13,21] These results align with those reported in the DYAD study (4% vs 0%), and in studies investigating non-oral switching strategies (2% vs 0% in SOLAR trial and 3% vs 1% in FLAIR trial), with authors suggesting that injectable administrations may also play a role in these rates.^[23,24] Evidence on the long-term risks of developing DRAEs remains limited, however, some studies gathered in this work included extended follow-up periods.^[12,25] Across these studies, DRAEs and DRAEs-LD frequencies were consistently higher in 2DR participants than those in 3DR or 4DR. Importantly, our findings showed no increase in the RR of serious AEs, consistent with previous results^[22] and the literature on oral and injectable regimens.^[23,24] A recent retrospective study reported higher discontinuation rates of participants switching to 2DR than those who switched to 3DR (19% vs 11%), with toxicity defined as a potential contributing factor.^[26]

This study analyzed multiple clinical trials with diverse pre- and post-switch treatments, which helps mitigate potential bias associated with the introduction of novel drugs. Notably, prior research has shown a shorter time for discontinuation ($P = .002$) and a higher discontinuation tendency in participants on 2DR, with these individuals showing a 2.3-fold higher likelihood of treatment discontinuation post-switch although reported discontinuations were not due to an increase in AEs.^[27] It is worth

noting that 2DR have been associated with elevated plasma levels of inflammatory markers, such as interleukin-6, C-reactive protein, and D-Dimer, ($P = .001$, $P = .003$ and $P = .001$, respectively),^[28] also reported in clinical trials,^[6,29] and 2DR therapy has correlated with glucose and lipid metabolism disruptions, potentially leading to heightened cardiovascular or metabolic risks.^[30]

Additionally, 2DR have been associated with elevated levels of exhausted lymphocytes (arm–time interaction $P = .02$) and increased monocyte levels (3DR with -6.7 cells/mm³; 95% CI: $-16 - +2.6$; interaction between arm and time $P = .03$), which account for endothelial affection.^[31] The hypothesis suggested by the authors defines that regimen simplification may impact viral reservoir control, particularly in “sanctuary” organs such as the central nervous system and lymphoid organs, where drug penetration is limited, potentially allowing viral persistence.^[30]

Overall, the observations reported here differ from another meta-analysis, which concluded that switching does not affect treatment failure, virological failure, DRAEs-LD or the appearance of mutations after 96 weeks.^[32] Their analysis, which included 9 studies (some overlapping with those used in our analysis), also incorporated observational studies,^[33,34] naïve participants,^[35] or non-oral switching strategies.^[24] To provide a more precise representation of switching effects in clinical settings, we focused on comparable studies in design, switching strategy, and follow-up duration. Notably, those results align with ours when restricted to clinical trials, as it was reported an elevated RR for DRAEs-LD in participants on 2DR compared to those on 3DR (RR 3.38; CI: 1.58–7.24, $P = .002$).

Recently, Fairhead et al published a letter discussing a similar analysis on switching to 2DR; however, the study with complete data has not yet been published.^[36] The conclusions drawn from the available evidence suggest that current research does not confirm that 2DR are safer than 3-drug regimens (3DR). They included trials (SALSA, TANGO, and DOLAM) also analyzed here, assessing DRAEs for up to 48 weeks. Nevertheless, the analysis incorporated studies that were excluded in our study to maintain methodological consistency, since GEMINI-1/2 trials do not assess therapy switching^[10] and PASODOBLE trial had a different design.^[37]

Our findings carry important clinical implications, particularly regarding the current trend of regimen simplification as a default strategy in virologically suppressed PLWH. Healthcare professionals should carefully weigh the potential risks and benefits of switching to simplified strategies on an individual basis, especially in patients with comorbidities, established tolerance to 3DR, or a history of AEs. The incidence of symptoms such as headache, diarrhea, and insomnia reported in the included studies may be clinically relevant, as these symptoms are already prevalent among PLWH.^[38–40] Insomnia, in particular, has been linked to increased depressive symptoms, reduced medication adherence, and poorer overall health status, thereby significantly affecting quality of life.^[41] Headache affects nearly half of PLWH,^[40] and diarrhea occurs at a rate approximately ten times higher than in the general population, with potentially severe consequences in immunocompromised individuals.^[39] These symptoms have been shown to cluster in PLWH, further underscoring their cumulative impact on quality of life.^[42] Consequently, even modest increases in the frequency or severity of these AEs could meaningfully compromise patient well-being and functional status. Clinicians should assess if, in certain cases, simplification may exacerbate rather than alleviate symptom burden.

Our study has several strengths worth noting. Our study selection provides a broad representation of participants undergoing switching therapy, overcoming some sampling limitations such as the underrepresentation of women and the predominance of White-skin participants.^[4,29] Besides, we focused exclusively on clinical trials, minimizing the selection bias often present in observational studies. This study uniquely analyzes DRAEs in an accurately representative clinical context, with comparable populations, follow-up durations, and reported outcomes. Importantly, we focused on participants with prior ART exposure, excluding ART-naïve individuals, to model the switching effects on a population already following these regimens. However, it is also important to consider some limitations. The 48-week follow-up does not allow robust conclusions regarding the benefits in reducing the accumulated toxicity of 2DR switching over extended periods. Besides, participants from the experimental arms in switching studies often stop the regimen when experiencing side-effects, increasing dropout rates. Nevertheless, although different therapeutic combinations were included in the study potentially affecting the observed outcomes, the drugs introduced in the switching strategy were already commercial options. Moreover, some studies evaluating treatment switching have shown improvements in safety and quality of life outcomes.^[43] It is also important to acknowledge that the studies included in our analyses did not provide detailed information on the concomitant treatments among their study populations. Therefore, a potential influence of these additional therapies on the observed AEs cannot be ruled out.

5. Conclusions

In conclusion, data from phase III and IV clinical trials indicate that therapy simplification does not appear to enhance safety and tolerability profiles at 48 weeks. This study underscores the need for further research to explore the potential safety advantages of 2DR regimens, thereby informing clinical decision-making and optimizing patient care.

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References

- [1] Antela A, Rivero A, Llibre JM, Moreno S; RET Group. Redefining therapeutic success in HIV patients: an expert view. *J Antimicrob Chemother.* 2021;76(10):2501–2518.
- [2] European AIDS Clinical Society. EACS guidelines version 12.1. 2024. Available from <https://eacs.sanfordguide.com/>.
- [3] Allegranzi B, Zayed B, Bischoff P, et al; WHO Guidelines Development Group. New WHO recommendations on intraoperative and postoperative measures for surgical site infection prevention: an evidence-based global perspective. *Lancet Infect Dis.* 2016;16:e288–303.
- [4] Llibre JM, Hung CC, Brinson C, et al. Efficacy, safety, and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomised, non-inferiority SWORD-1 and SWORD-2 studies. *Lancet.* 2018;391:839–49.
- [5] Punekar YS, Parks D, Joshi M, et al. Effectiveness and safety of dolutegravir two-drug regimens in virologically suppressed people living with HIV: a systematic literature review and meta-analysis of real-world evidence. *HIV Med.* 2021;22:423–33.
- [6] Achhra AC, Mwasakifwa G, Amin J, Boyd MA. Efficacy and safety of contemporary dual-drug antiretroviral regimens as first-line treatment or as a simplification strategy: a systematic review and meta-analysis. *Lancet HIV.* 2016;3:e351–60.
- [7] Adolescents PoAGfAa. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Department of Health and Human Services. 2025. Available from <https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/>. [Accessed January 2025]
- [8] Arnold MJ. Treatment and prevention of HIV infection: recommendations from the International Antiviral Society-USA panel. *Am Fam Physician.* 2024;109:93A–C.
- [9] Sobre el Sida PN; Panel de expertos de GeSIDA. Documento de consenso de GeSIDA/Plan Nacional sobre el Sida respecto al tratamiento antirretroviral en adultos infectados por el virus de la inmunodeficiencia

- humana (Actualización enero 2022). *Enferm Infecc Microbiol Clín.* 2022;32:446.e1–446.e42.
- [10] Cahn P, Madero JS, Arribas JR, et al; GEMINI Study Team. Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naïve adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. *Lancet.* 2019;393:143–55.
- [11] Cahn P, Madero JS, Arribas JR, et al. Durable efficacy of dolutegravir plus lamivudine in antiretroviral treatment-naïve adults with HIV-1 infection: 96-week results from the GEMINI-1 and GEMINI-2 randomized clinical trials. *JAIDS J Acquir Immune Defic Syndr.* 2020;83:310–8.
- [12] Osiyemi O, De Wit S, Ajana F, et al. Efficacy and safety of switching to dolutegravir/lamivudine versus continuing a tenofovir alafenamide-based 3- or 4-drug regimen for maintenance of virologic suppression in adults living with human immunodeficiency virus type 1: results through week 144 from the phase 3, noninferiority TANGO randomized trial. *Clin Infect Dis.* 2022;75:975–86.
- [13] Llibre JM, Brites C, Cheng CY, et al. Efficacy and safety of switching to the 2-drug regimen dolutegravir/lamivudine versus continuing a 3- or 4-drug regimen for maintaining virologic suppression in adults living with human immunodeficiency virus 1 (HIV-1): week 48 results from the phase 3, noninferiority SALSA randomized trial. *Clin Infect Dis.* 2023;76:720–9.
- [14] van Wyk J, Orkin C, Rubio R, et al. Brief report: durable suppression and low rate of virologic failure 3 years after switch to dolutegravir + rilpivirine 2-drug regimen: 148-Week results from the SWORD-1 and SWORD-2 randomized clinical trials. *J Acquir Immune Defic Syndr.* 2020;85:325–30.
- [15] Rojas J, de Lazzari E, Negro E, et al; DOLAM study group. Efficacy and safety of switching to dolutegravir plus lamivudine versus continuing triple antiretroviral therapy in virologically suppressed adults with HIV at 48 weeks (DOLAM): a randomised non-inferiority trial. *Lancet HIV.* 2021;8:e463–73.
- [16] Chandler J, Cumpston M, Li T, Page MJ, Welch VJHW. *Cochrane handbook for systematic reviews of interventions.* Hoboken: Wiley; 2019;4:14651858.
- [17] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* 2021;372:n71.
- [18] National Institute for Health and Care Excellence. *Methods for the development of NICE Public Health Guidance.* National Institute for Health and Care Excellence (NICE); 2012.
- [19] Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ.* 2019;366:l4898.
- [20] Deeks JJ, Higgins JP, Altman DG, Cochrane Statistical Methods Group. Analysing data and undertaking meta-analyses. In *Cochrane handbook for systematic reviews of interventions.* 2019:241–284.
- [21] van Wyk J, Ait-Khaled M, Santos J, et al. Brief report: improvement in metabolic health parameters at week 48 after switching from a tenofovir alafenamide-based 3- or 4-drug regimen to the 2-drug regimen of dolutegravir/lamivudine: the TANGO study. *J Acquir Immune Defic Syndr.* 2021;87:794–800.
- [22] Rolle CP, Castano J, Nguyen V, Hinestrosa F, DeJesus E. Efficacy, safety, and tolerability of switching from bicitegravir/emtricitabine/tenofovir alafenamide to dolutegravir/lamivudine among adults with virologically suppressed HIV: the DYAD study. *Open Forum Infect Dis.* 2024;11:ofae560.
- [23] Ramgopal MN, Castagna A, Cazanave C, et al. Efficacy, safety, and tolerability of switching to long-acting cabotegravir plus rilpivirine versus continuing fixed-dose bicitegravir, emtricitabine, and tenofovir alafenamide in virologically suppressed adults with HIV, 12-month results (SOLAR): a randomised, open-label, phase 3b, non-inferiority trial. *Lancet HIV.* 2023;10:e566–77.
- [24] Orkin C, Arasteh K, Górgolas Hernández-Mora M, et al. Long-acting cabotegravir and rilpivirine after oral induction for HIV-1 infection. *N Engl J Med.* 2020;382:1124–35.
- [25] Van Wyk J, Ajana F, Bisshop F, et al. Switching to DTG/3TC fixed-dose combination (FDC) is non-inferior to continuing a TAF-based regimen (TBR) in maintaining virologic suppression through 96 weeks (TANGO study). In *Oral O441 HIV Drug Therapy Glasgow.* 2020:5–8.
- [26] Pierone G, Fusco JS, Brunet L, et al. Virologically suppressed switch to Dolutegravir/Lamivudine 2-Drug regimen versus switch to commonly prescribed 3-Drug regimens in the United States. *AIDS Res Ther.* 2024;21:76.
- [27] Teira R, Diaz-Cuervo H, Aragão F, et al. Shorter time to discontinuation due to treatment failure in people living with hiv switched to dolutegravir plus either rilpivirine or lamivudine compared with integrase inhibitor-based triple therapy in a large Spanish Cohort. *Infect Dis Ther.* 2022;11:1177–92.
- [28] Serrano-Villar S, López-Huertas MR, Jiménez D, et al. Long-term changes of inflammatory biomarkers in individuals on suppressive three-drug or two-drug antiretroviral regimens. *Front Immunol.* 2022;13:848630.
- [29] Van Wyk J, Ajana F, Bisshop F, et al. Efficacy and safety of switching to dolutegravir/lamivudine fixed-dose 2-drug regimen vs continuing a tenofovir alafenamide-based 3-or 4-drug regimen for maintenance of virologic suppression in adults living with human immunodeficiency virus type 1: phase 3, randomized, noninferiority TANGO study. *Clin Infect Dis.* 2020;71:1920–9.
- [30] de Lazzari E, Negro E, Domingo P, et al. Multiomics plasma effects of switching from triple antiretroviral regimens to dolutegravir plus lamivudine. *J Antimicrob Chemother.* 2024;79:1133–41.
- [31] Cossarizza A, Cozzi-Lepri A, Mattioli M, et al. Evaluating immunological and inflammatory changes of treatment-experienced people living with HIV switching from first-line triple cART regimens to DTG/3TC vs. B/F/TAF: the DEBATE trial. *Front Immunol.* 2023;14:1279390.
- [32] Russo A, Martini S, Pisaturo M, et al. Efficacy and tolerability of INI-based 2-drug regimen in virologically suppressed persons living with HIV: a systematic review and meta-analysis. *Infect Chemother.* 2024;56:395–405.
- [33] De Socio GV, Tordi S, Altobelli D, Gidari A, Zoffoli A, Francisci D. Dolutegravir/lamivudine versus tenofovir alafenamide/emtricitabine/bicitegravir as a switch strategy in a real-life cohort of virologically suppressed people living with HIV. *J Clin Med.* 2023;12:7759.
- [34] Borghetti A, Alkhatib M, Dusina A, et al. Virological outcomes with dolutegravir plus either lamivudine or two NRTIs as switch strategies: a multi-cohort study. *J Antimicrob Chemother.* 2022;77:740–6.
- [35] Fabbiani M, Rossetti B, Ciccullo A, et al; ODOACRE Study Group. Efficacy and durability of two- vs. three-drug integrase inhibitor-based regimens in virologically suppressed HIV-infected patients: data from real-life ODOACRE cohort. *HIV Med.* 2021;22:843–53.
- [36] Fairhead C, Levi J, Ramesh N, Hill A. Results from systematic review and meta-analysis of the efficacy and safety of two-drug versus three-drug (tenofovir/lamivudine/dolutegravir; TLD) regimens for HIV treatment. *Clin Infect Dis.* 2025;80:1173–5.
- [37] Ryan P, Blanco JL, Masia M, et al. Non-inferior efficacy and less weight gain when switching to DTG/3TC than when switching to BIC/FTC/TAF in virologically suppressed people with HIV (PWH): the PASODOBLE (GeSIDA 11720) randomized clinical trial. In *Journal of the International Aids Society.* John Wiley & Sons; 2024;27:90–1.
- [38] Reiser H, Miner B, Farhadian S. Sleep deficiency among people living with human immunodeficiency virus: a growing challenge. *HIV Med.* 2024;25:5–15.
- [39] Sanchez TH, Brooks JT, Sullivan PS, et al; Adult/Adolescent Spectrum of HIV Disease Study Group. Bacterial diarrhea in persons with HIV infection, United States, 1992–2002. *Clin Infect Dis.* 2005;41:1621–7.
- [40] Kirkland KE, Kirkland K, Many WJ Jr, Smitherman TA. Headache among patients with HIV disease: prevalence, characteristics, and associations. *Headache.* 2012;52:455–66.
- [41] Rogers BG, Bainter SA, Smith-Alvarez R, et al. Insomnia, health, and health-related quality of life in an urban clinic sample of people living with HIV/AIDS. *Behav Sleep Med.* 2021;19:516–32.
- [42] Wilson NL, Hoffman TJ, Heath SL, Saag MS, Miaskowski C. HIV symptom clusters are similar using the dimensions of symptom occurrence and distress. *J Pain Symptom Manage.* 2022;63:943–52.
- [43] Wohl D, Clarke A, Maggiolo F, et al. Patient-reported symptoms over 48 weeks among participants in randomized, double-blind, phase III non-inferiority trials of adults with HIV on co-formulated bicitegravir, emtricitabine, and tenofovir alafenamide versus co-formulated abacavir, dolutegravir, and lamivudine. *Patient.* 2018;11:561–73.