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MAJOR ARTICLE

Changes in Inflammatory and Atherogenesis Biomarkers With the 2-Drug Regimen Dolutegravir Plus Lamivudine in Antiretroviral Therapy–Experienced, Virologically Suppressed People With HIV-1: A Systematic Literature Review

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Background. The 2-drug regimen dolutegravir plus lamivudine has demonstrated long-term noninferior efficacy vs 3-/4-drug regimens (3/4DRs) in phase 3 trials. This systematic literature review summarizes clinical trial and real-world evidence evaluating impact of dolutegravir plus lamivudine on inflammatory and atherogenesis biomarkers in people with human immunodeficiency virus type 1 (PWH).

Methods. Using Ovid MEDLINE, Embase, PubMed, and Cochrane library databases and conference proceedings, we searched for studies published from 1 January 2013 to 14 July 2021, reporting changes in inflammatory and atherogenesis biomarkers with dolutegravir plus lamivudine in antiretroviral therapy–experienced, virologically suppressed PWH aged ≥18 years.

Results. Four records representing 2 randomized controlled trials (RCTs) and 6 records of real-world evidence met eligibility criteria. All real-world studies evaluated $CD4^+/CD8^+$ ratio, while only 1 assessed inflammatory biomarkers. Across both RCTs, no consistent pattern of change in biomarkers was observed between dolutegravir/lamivudine and 3/4DR comparators. There were significant changes in soluble CD14 favoring dolutegravir/lamivudine in TANGO at weeks 48 and 144 and SALSA at week 48, and in interleukin-6 favoring the control group in TANGO at weeks 48 and 144. In the real-world study evaluating inflammatory biomarkers, median soluble CD14 significantly decreased 48 weeks postswitch to dolutegravir plus lamivudine ($P < .001$), while other biomarkers remained stable. In all 6 real-world studies, increases in $CD4^+/CD8^+$ ratio were reported after switch to dolutegravir plus lamivudine (follow-up, 12–60 months).

Conclusions. Results show that dolutegravir plus lamivudine has a comparable impact on inflammatory and atherogenesis biomarkers vs 3/4DRs, with no consistent pattern of change after switch in virologically suppressed PWH.

Keywords. dolutegravir plus lamivudine; 2-drug regimen; HIV-1; inflammation.

Effective antiretroviral therapy (ART) has been shown to reduce systemic inflammation caused by human immunodeficiency virus (HIV) infection, although not to the levels of HIV-negative populations [1–4]. Even in the setting of maintained ART-mediated virologic suppression, HIV may be associated with some degree of persistent inflammation, contributing to an increased risk of non-AIDS-related comorbidities such as cardiovascular disease and cancer [2, 3, 5, 6]. HIV-related inflammation may be driven by a variety of factors including ongoing viral replication and persistent low-level viremia (HIV reservoirs and sanctuary sites), coinfections, and bacterial translocation [2, 3, 6, 7]. Moreover, other host-specific considerations such as comorbidities (eg, obesity, diabetes mellitus, metabolic syndrome [eg, insulin resistance and hyperlipidemia], and hypertension), lifestyle factors (eg, smoking and substance abuse), and sex differences (eg, menopause) have also been associated with the pathogenesis of inflammation in people with HIV (PWH) and may further contribute to persistent inflammation

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despite ART-mediated suppression [1, 5, 7, 8]. Finally, irreversible immune damage, generally established before ART initiation, fuels persistent inflammation despite subsequent HIV suppression on ART [1, 5].

Potential biomarkers of HIV-related inflammation (eg, C-reactive protein [CRP], interleukin-6 [IL-6]), monocyte and macrophage activation (eg, soluble CD14 [sCD14], soluble CD163 [sCD163]), and atherogenesis and hypercoagulation (eg, D-dimer) have been linked to increased risk of mortality and non-AIDS-related events in PWH [1, 5, 6]. Observations from the Strategies for Management of Anti-Retroviral Therapy (SMART) study showed that elevated baseline levels of inflammatory biomarkers were independently associated with increased risk of cardiovascular disease and mortality [9,10]. Mediators of other immunological processes such as intestinal barrier dysfunction (eg, fatty acid binding protein-2 [FABP-2]) and endothelial dysfunction (eg, soluble vascular cell adhesion molecule-1 [sVCAM-1]) have also been assessed as biomarkers of inflammation in HIV [5, 11]. Furthermore, persistently low $CD4^+/CD8^+$ ratio (≤0.4) has been associated with systemic inflammation in ART-treated PWH, which may be linked to an increased risk of non-AIDS-defining morbidity and mortality [7, 12]. Other biomarkers of cellular activity such as those for T-cell activation ($HLA\text{-}DR^+$ and $CD38^+$), proliferation (Ki-67), and apoptosis ($annexin\text{-}V^+$) have also been studied in HIV-1 [6, 13]. Although several presumed biomarkers of inflammation and atherogenesis have been investigated in HIV, precise correlations of each marker with specific clinical events are largely unknown and a high degree of overlap exists in the processes they are supposed to monitor [2].

Relative to standard 3- or 4-drug combination ART regimens (3/4DRs), 2-drug regimens (2DRs) reduce cumulative drug exposure, drug–drug interactions, and costs and may potentially decrease toxicities for PWH taking lifelong ART [2, 14]. The 2DR dolutegravir/lamivudine is a fixed-dose regimen used to treat HIV-1 in both ART-naive and ART-experienced, virologically suppressed PWH with no history of ART failure or known resistance-associated substitutions to the components [15]. In clinical trials, dolutegravir/lamivudine has demonstrated rapid viral load decline and durable, noninferior efficacy compared with 3/4DRs in both ART-naive and ART-experienced, virologically suppressed PWH [16–21]. More stringent analyses of residual viremia (target not detected) and viral blips have demonstrated no difference between dolutegravir/lamivudine and comparator 3/4DRs, suggesting that there are no differences in the level of real viral suppression between 2DRs and 3/4DRs [22, 23]. Studies have also shown no difference in virologic suppression in compartments and sanctuary sites or viral escape from reservoirs with dolutegravir/lamivudine vs 3/4DRs [24, 25].

Several recent studies have focused on investigating the differential effects of suppressive 2DRs on inflammation in PWH [26–30]. However, comprehensive reviews on the impact of switching to dolutegravir/lamivudine on inflammatory biomarkers in virologically suppressed PWH are lacking. Here, we performed a systematic literature search that identified results from clinical trials and real-world evidence published from 1 January 2013 to 14 July 2021, on the effect of dolutegravir plus lamivudine on biomarkers of inflammation and atherogenesis in ART-experienced, virologically suppressed PWH.

METHODS

Literature Search Strategy

Embase and PubMed were used to source articles and congress abstracts published from 1 January 2013 to 7 July 2021, describing randomized controlled trials (RCTs). The terms used for the clinical trial search were "dolutegravir or DTG" and "lamivudine or 3TC."

To identify real-world evidence, results from a prior systematic literature review were updated through 14 July 2021. In brief, Ovid Medline, Embase, PubMed, and Cochrane library databases and conference proceedings were searched for real-world observational studies evaluating the effectiveness and safety of dolutegravir plus lamivudine. The full search strategy including search terms has been previously published [31].

Additional searches were performed to identify any relevant data presented at the 2021 International AIDS Society (IAS) Conference on HIV Science and IDWeek 2021.

This review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [32].

Inclusion and Exclusion Criteria

Eligible studies included observational cohort studies (prospective or retrospective), case-control studies, cross-sectional studies, database studies, and clinical trials of dolutegravir plus lamivudine in ART-experienced, virologically suppressed PWH aged ≥18 years that included data on $CD4^+/CD8^+$ ratio or the inflammatory biomarkers CRP, sCD14, IL-6, sCD163, D-dimer, FABP-2, or sVCAM-1. Articles were only included if biomarker data were summarized for groups or subgroups including those who took dolutegravir plus lamivudine.

Eligibility was independently assessed by 2 reviewers. The screening process included initial review of titles and abstracts, followed by review of full-text articles. Any discrepancies between the decisions of the 2 reviewers at both stages of the screening process were resolved by a third independent reviewer.

For the real-world evidence, linked publications were identified based on trial identifiers in addition to reporting of population, sites, and study period [31]. Studies were reviewed to evaluate potential duplication in reporting the same biomarker outcomes for the same cohort. If duplication was suspected, the publication reporting the highest number of PWH

receiving dolutegravir/lamivudine was included in the analysis [31].

Data Extraction

Data extracted from eligible studies included (1) number of PWH receiving dolutegravir plus lamivudine; (2) baseline demographic characteristics; (3) prior ART duration; (4) prior duration of virologic suppression; and (5) inflammatory and atherogenesis biomarker outcomes. Information was extracted from published material, with no instances of personal communication with authors to confirm or retrieve data. To assess the quality of eligible real-world evidence, a single reviewer evaluated extent of loss to follow-up, methods of selecting PWH, assessment of effectiveness outcomes, and handling of missing data [31].

RESULTS

Randomized Controlled Trials

Of the 773 records identified through database search, 1 study met the full inclusion criteria describing data from RCTs of dolutegravir/lamivudine. In the search of proceedings from the 2021 IAS Conference and IDWeek 2021, 3 additional records were identified that met the inclusion criteria for this analysis (Figure 1). The 4 identified records corresponded to 2 clinical trials (TANGO and SALSA).

TANGO

In the phase 3, open-label TANGO trial, PWH with HIV-1 RNA <50 copies/mL for >6 months were randomized 1:1 to switch to dolutegravir/lamivudine (n = 369) or remain on a tenofovir alafenamide (TAF)–based 3/4DR (n = 372) [18]. Most participants in the dolutegravir/lamivudine group were male (93%) and White (80%) (Table 1) [18]. Switching to the 2DR of dolutegravir/lamivudine was noninferior to continuing TAF-based regimens for maintaining virologic suppression in PWH at every analysis through 144 weeks [17–19]. At 48 weeks, the proportion of participants with HIV-1 RNA ≥ 50 copies/mL after switching to dolutegravir/lamivudine was similar to those continuing TAF-based regimens (0.3% vs 0.5%, respectively; adjusted difference, −0.3% [95% confidence interval (CI), −1.2% to 0.7%]) [18]. Similar efficacy results were observed at 96 weeks (<1% vs 1%, respectively) and 144 weeks (0.3% vs 1.3%, respectively) [17, 19]. The proportions of participants with HIV-1 RNA target not detected were similar between the dolutegravir/lamivudine and TAF-based regimen groups at week 96 (73%

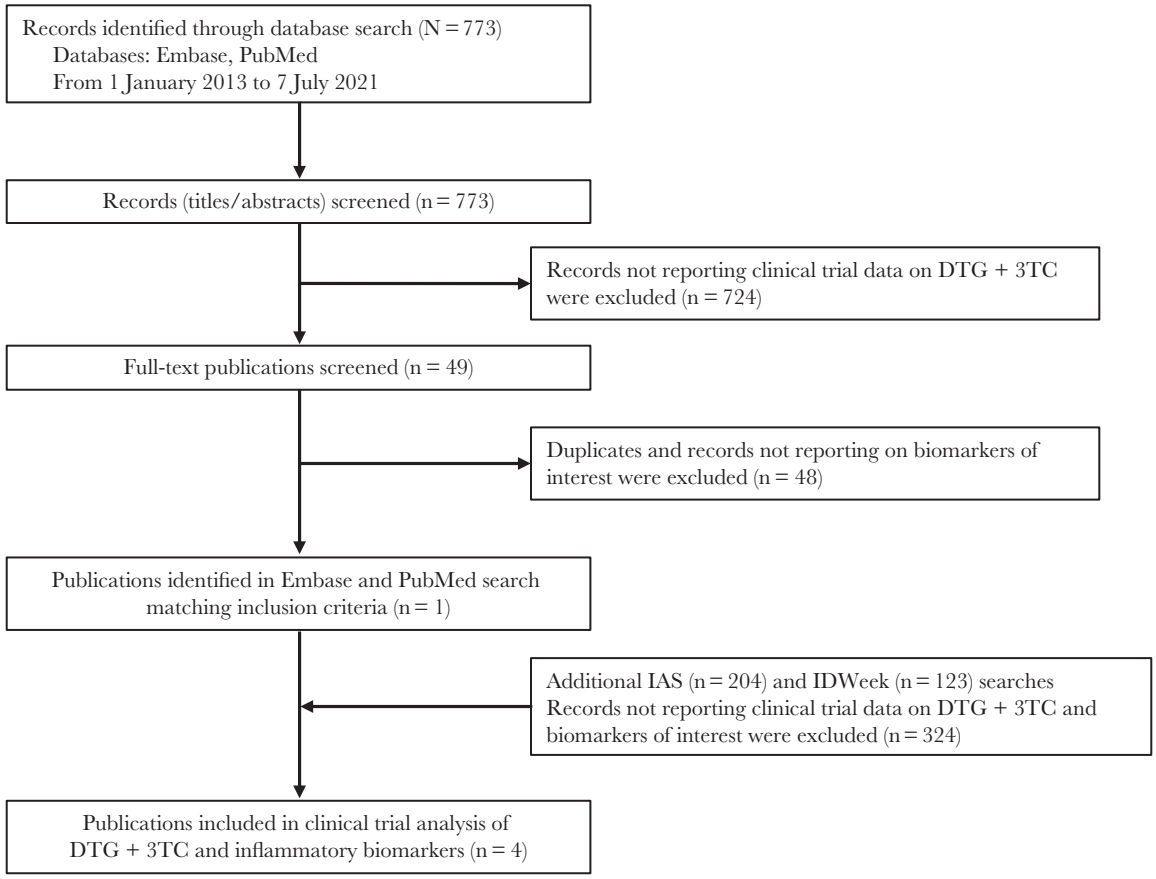

Figure 1. Flow diagram of randomized controlled trial literature search for systematic review. 3TC, lamivudine; DTG, dolutegravir; IAS, International AIDS Society.

Table 1. Demographics and Baseline Characteristics for People With HIV-1 Receiving Dolutegravir/Lamivudine Versus Comparator in Randomized Controlled Trials

Characteristic	TANGO [18]		SALSA [20]	
	DTG/3TC (n = 369)	TAF-Based Regimen (n = 372)	DTG/3TC (n = 246)	CAR (n = 247)
Age				
Median (range), y	40 (20–74)	39 (18–73)	45 (22–74)	45 (23–83)
Age ≥50 y	79 (21)	92 (25)	98 (40)	95 (38)
Female	25 (7)	33 (9)	108 (44)	84 (34)
Race				
African American/African heritage	50 (14)	58 (16)	45 (18)	48 (19)
Asian	13 (4)	13 (3)	31 (13)	39 (16)
White	297 (80)	289 (78)	149 (61)	144 (58)
$CD4^+$ cell count, median (range), cells/μL	682 (133–1904)	720 (119–1810)	675 (154–2089)	668 (94–1954)
Duration of ART before day 1, median (range), mo	34 (7–201)	35 (7–161)	63 (4–240)	71 (12–253)
Baseline third agent class				
INSTI	289 (78)	296 (80)	98 (40)	98 (40)
NNRTI	51 (14)	48 (13)	123 (50)	124 (50)
PI	29 (8)	28 (8)	25 (10)	25 (10)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ART, antiretroviral therapy; CAR, current antiretroviral therapy regimen; DTG/3TC, dolutegravir/lamivudine; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TAF, tenofovir alafenamide.

vs 69%, respectively) and week 144 (76% vs 72%, respectively) [22, 33]. Furthermore, the occurrence of blips (viral load between 50 and 200 copies/mL with adjacent values <50 copies/mL) was infrequent and similar between the dolutegravir/lamivudine (4%) and TAF-based regimen (6%) groups through 96 weeks [22]. At week 48, changes in inflammatory biomarkers were small (Figure 2), with significant differences in sCD14 favoring the dolutegravir/lamivudine group (visit to baseline ratio: dolutegravir/lamivudine, 0.953; TAF-based regimen, 0.982; $P = .048$) and in IL-6 favoring the control group (visit to baseline ratio: dolutegravir/lamivudine, 0.990; TAF-based regimen, 0.852; $P = .006$), with no differences in D-dimer, CRP, or sCD163 [18]. Median change in $CD4^+/CD8^+$ ratio at week 48 was +0.03 in the dolutegravir/lamivudine group and +0.05

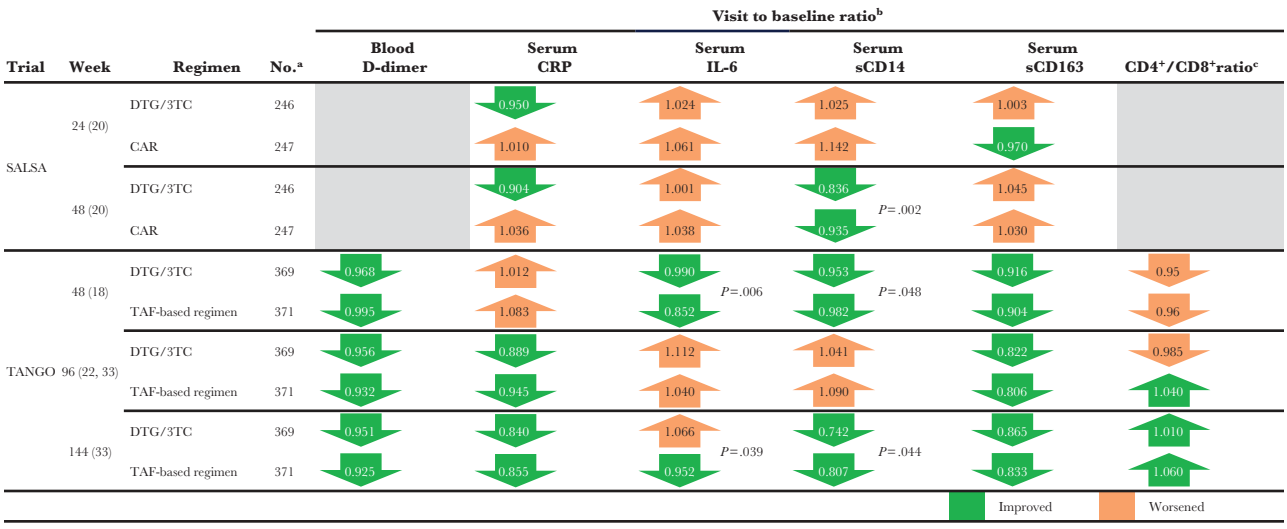

Figure 2. Reported inflammatory and atherogenesis outcomes in people with human immunodeficiency virus receiving dolutegravir/lamivudine vs comparator in randomized controlled trials. *P* values are for treatment comparison. *P* values were not reported for SALSA 24-week data or for TANGO $CD4^+/CD8^+$ ratio data. Other *P* values that are not shown were not significant. [a]Ratio is the estimated adjusted ratio in each group calculated using mixed-model repeated measures applied to change from baseline in $\log_e$-transformed data adjusting for treatment, visit, baseline third agent class, $CD4^+$ cell count (continuous), age (continuous), sex, race, body mass index (continuous), smoking status, hepatitis C virus coinfection status, $\log_e$-transformed baseline biomarker value (continuous), treatment-by-visit interaction, and baseline value-by-visit interaction, with visit as the repeated factor. [b]Participant numbers for individual inflammatory biomarkers vary. [c]Median value at specified time point. Abbreviations: 3TC, lamivudine; CAR, current 3- or 4- drug antiretroviral therapy regimen; CRP, C-reactive protein; DTG, dolutegravir; IL-6, interleukin-6; sCD14, soluble CD14; sCD163, soluble CD163; TAF, tenofovir alafenamide.

in the TAF-based regimen group (significance not reported) [18]. Comparable results between groups for the 5 biomarkers were observed at 96 weeks [22]. At 144 weeks, significant differences in sCD14 favored dolutegravir/lamivudine (visit to baseline ratio: dolutegravir/lamivudine, 0.742; TAF-based regimen, 0.807; $P = .044$) and in IL-6 favoring the control group (visit to baseline ratio: dolutegravir/lamivudine, 1.066; TAF-based regimen, 0.952; $P = .039$) [33].

SALSA

In the phase 3, open-label SALSA trial, PWH on a 3/4DR with HIV-1 RNA <50 copies/mL for >6 months were randomized to switch to dolutegravir/lamivudine (n = 246) or continue their current ART (CAR; n = 247) [20]. In the dolutegravir/lamivudine switch group, 44% of participants were female, 61% were White, and median age was 45 years (Table 1). Switching to the 2DR of dolutegravir/lamivudine demonstrated noninferior virologic efficacy to 3/4DRs through 48 weeks (proportion of participants with HIV-1 RNA ≥50 copies/mL: dolutegravir/lamivudine, <1% vs CAR, 1%; adjusted difference, −0.8% [95% CI, −2.4% to 0.8%]) [20]. Changes from baseline to week 48 in CRP, IL-6, and sCD163 were small and generally similar between the dolutegravir/lamivudine and CAR groups, while changes in sCD14 (Figure 2) favored dolutegravir/lamivudine (week 24 to baseline ratio: dolutegravir/lamivudine, 1.025; CAR, 1.142; week 48 to baseline ratio: dolutegravir/lamivudine, 0.836; CAR, 0.935; $P = .002$) [20]. Analysis of D-dimer could not be performed as the vast majority of participants in both groups had levels below the limit of quantification.

Real-World Evidence

Of the 74 records previously identified and published in a systematic literature review on dolutegravir plus lamivudine, 13 met the inclusion criteria for reporting data on markers of inflammation and atherogenesis in virologically suppressed PWH [31]. In the update to this literature search conducted on 14 July 2021, an additional 316 records were identified, 2 of which were eligible for this analysis. In the search of proceedings from the 2021 IAS Conference and IDWeek 2021, 1 additional record was identified. After excluding duplicate cohorts and studies not reporting data specifically for dolutegravir/lamivudine, 6 studies remained for inclusion in this analysis (Figure 3). All studies assessed changes in $CD4^+/CD8^+$ ratio, while only 1 study evaluated changes in biomarkers of inflammation and atherogenesis.

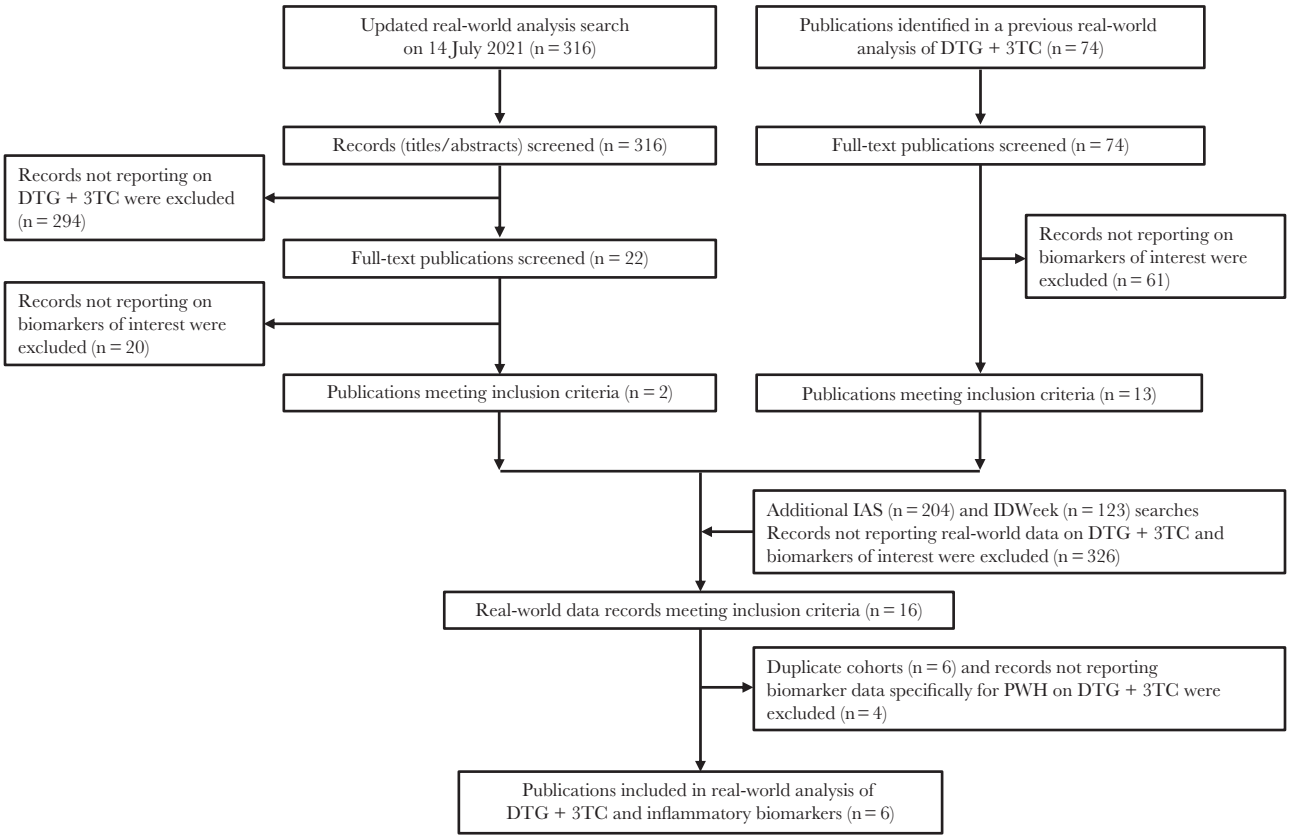

Figure 3. Flow diagram of real-world evidence literature search for systematic review. Abbreviations: 3TC, lamivudine; DTG, dolutegravir; IAS, International AIDS Society; PWH, people with human immunodeficiency virus type 1.

All 6 studies reported an increase from baseline in $CD4^+$/$CD8^+$ ratio after switch to dolutegravir plus lamivudine over different follow-up periods (12–60 months; Figure 4) [29, 34–38].

A single-center cohort study assessed virologic efficacy of switching to dolutegravir plus lamivudine in 27 PWH on a stable ART regimen with HIV-1 RNA <50 copies/mL for >12 months [37]. After 48 months of follow-up postswitch to dolutegravir plus lamivudine, median change from baseline in $CD4^+$/$CD8^+$ ratio was +0.14 (interquartile range [IQR], −0.02 to +0.30; significance not reported) [37].

A multicenter, observational, retrospective study (DOLAMA) of 177 PWH pretreated for >6 months with virologic suppression and no history of virologic failure evaluated the effectiveness and safety of switch to dolutegravir plus lamivudine [38]. Mean $CD4^+$/$CD8^+$ ratio increased significantly from baseline (0.87 [SD, 0.47]) to week 48 postswitch (0.93 [SD, 0.48]; $P = .023$) [38].

A retrospective observational study of virologically suppressed PWH (N = 556) from 9 Italian clinical centers assessed long-term efficacy and tolerability of switch to dolutegravir plus lamivudine [36]. Median duration of virologic suppression was 88 months. At 144 weeks postswitch, median change in $CD4^+$/$CD8^+$ ratio was +0.10 ($P = .002$) [36].

A prospective, multicenter, cohort study assessed durability of dolutegravir plus lamivudine in 218 PWH on stable ART and confirmed HIV-1 RNA <50 copies/mL for >6 months. Median duration of virologic suppression was 75 months [34]. Sixty months after switch to dolutegravir plus lamivudine, there was a significant increase in $CD4^+$/$CD8^+$ ratio (+0.21; $P < .0001$) [34].

A multicenter, prospective study of the Surveillance Cohort Long-Term Toxicity Antiretrovirals (SCOLTA) cohort compared changes from baseline in $CD4^+$/$CD8^+$ ratio between dolutegravir plus lamivudine (N = 22) and other ART regimens (other dolutegravir-based 2DRs, dolutegravir plus tenofovir disoproxil fumarate/emtricitabine [TDF/FTC], and dolutegravir/abacavir/lamivudine [DTG/ABC/3TC]) [35]. For the 16 participants with available data on dolutegravir plus lamivudine at 1 year, $CD4^+$/$CD8^+$ ratio increased significantly from baseline (+0.26; $P < .05$), and this increase was greater than those observed with dolutegravir plus TDF/FTC (+0.10; n = 41) and DTG/ABC/3TC (+0.09; n = 147). Mean changes

			Demographics and BL characteristics							Change from BL in CD4+/CD8+ ratio	
Study	No.	Time point	Age, y	Female, No. (%)	Race, No. (%)	Nadir CD4+ cell count, cells/μL	Baseline CD4+/CD8+ ratio	Time on ART, median (IQR)	BL regimen used in ≥5% of participants, No. (%)		
Lombardi 2019 (29)	67	48 wk	Median (IQR), 49.4 (41.2-54.9)	18 (27)[a]	White, 67 (100)	Median (IQR), 237 (64-306)	Median (IQR), 0.83 (0.70-1.00)	10.9 (4.8-16.4) y	DRV/r, 43 (64); ATV/r, 18 (27); LPV/r, 6 (9)	0.03[d]	NS
Hidalgo-Tenorio 2019 (38)	177	48 wk	Mean (SD), 48.5 (14.2)	40 (23)[a]	NR	Mean (SD), 252.2 (494.2)	Mean (SD), 0.87 (0.5)	3 (4-18) y	DRV/r or COBI, 27 (15); ATV/r + 3TC, 12 (7)[c]	0.06[d]	$P = .023$
Taramasso 2019 (35)	22	12 mo	NR	NR	NR	NR	NR	NR	NR	0.26[d]	$P < .05$
Baldin 2019 (36)	556	96 and 144 wk	Median (IQR), 51.7 (45.3-57.4)	165 (30)	NR	Median (IQR), 230 (98-328)	Median (IQR), 0.85 (0.61-1.13)[e]	11.5 (6.1-18.3) y	FTC/TDF-containing, 231 (42); 3TC + PI-containing, 171 (31); DTG-containing, 52 (9)	0.06[b] 0.10[b]	96 wk $P = .001$ 144 wk $P = .002$
Reynes 2020 (37)	27	48 mo	Median, 59	NR (26)[a,f]	White (100)[f]	Median (range), 167 (8-450)	Median, 0.84	215 (22-329) mo	PI/r-containing, 22 (81); TDF-containing, 13 (48); RAL-containing, 7 (26)	0.14[b]	*P* value NR
Maggiolo 2021(34)	218	60 mo	Median (IQR), 52 (12)	NR (25)[f]	NR	Median (IQR), 669 (446)[g]	Median (IQR), 0.93 (0.70)	10.2 (13) y	NR	0.21[b]	$P < .0001$
											Improved

Figure 4. Demographics, baseline (BL) characteristics, and change from BL in $CD4^+$/$CD8^+$ ratio in people with human immunodeficiency virus type 1 (PWH) receiving dolutegravir/lamivudine in studies of real-world evidence. [a]Number of women calculated by subtracting originally reported data for men from total population. [b]Median. [c]Triple ART was used by 66% of participants, but regimens were not specified; values listed in table reflect dual or monotherapies used by ≥5% of total PWH. [d]Mean. [e]Study also reported proportion of participants with $CD4^+$/$CD8^+$ ratio ≥1 at baseline vs week 96 (39/125 [31%] vs 51/125 [41%]; $P < .001$) and at baseline vs week 144 (13/53 [25%] vs 20/53 [38%]; $P < .001$). [f]Source only reported percentage (not number). [g]Source does not specify value as nadir $CD4^+$ cell count. Abbreviations: 3TC, lamivudine; ART, antiretroviral therapy; ATV, atazanavir; BL, baseline; COBI, cobicistat; DRV, darunavir; DTG, dolutegravir; FTC, emtricitabine; IQR, interquartile range; LPV, lopinavir; NR, not reported; NS, not significant; PI, protease inhibitor; r, ritonavir; RAL, raltegravir; SD, standard deviation; TDF, tenofovir disoproxil fumarate.

from baseline in $CD4^+/CD8^+$ ratio were not significant for participants on other dolutegravir-based 2DRs [35].

One retrospective, case-crossover study assessed the impact of switching from a 2DR of lamivudine plus ritonavir-boosted protease inhibitors to dolutegravir plus lamivudine on inflammatory biomarkers in 67 PWH. Median duration of virologic suppression was 7 years. Median $CD4^+/CD8^+$ ratio showed a trend toward improvement from baseline (0.83 [IQR, 0.70–1.00]) to 48 weeks postswitch to dolutegravir plus lamivudine (0.86 [IQR, 0.68–1.06]) but did not reach statistical significance ($P = .060$). Median sCD14 levels significantly decreased postswitch (6.04 $\log_{10}$ pg/mL) to week 48 (5.95 $\log_{10}$ pg/mL) ($P < .001$) [29]. Levels of the other 4 biomarkers (IL-6, CRP, intestinal-FABP, and D-dimer) remained stable through 48 weeks after switch to dolutegravir plus lamivudine [29].

DISCUSSION

In this systematic literature search of RCTs and real-world evidence, changes in inflammatory and atherogenesis biomarkers were analyzed in virologically suppressed PWH who switched to dolutegravir plus lamivudine 2DR from other ART regimens. Overall, there were no consistent patterns of change from baseline in inflammatory and atherogenesis biomarkers, with minimal changes observed after ART switch. There were significant decreases in sCD14 from baseline after switching to dolutegravir plus lamivudine in both clinical trials [18, 20, 33] and in one study of real-world evidence [29]. Overall changes in IL-6 were small and did not show a consistent trend. The minimal biomarker changes observed are as expected, given similar outcomes in viral replication demonstrated in clinical trials that showed no significant difference in rates of virologic suppression, residual viremia, and viral blips with dolutegravir/lamivudine 2DR vs comparator 3/4DRs [17–20, 22]. The clinical significance of these small fluctuations in inflammatory biomarkers is unknown and data have not demonstrated a difference in AIDS-related or non-AIDS-related clinical endpoints between 3/4DRs and 2DRs [39, 40]. Changes in $CD4^+/CD8^+$ ratio were similar between dolutegravir/lamivudine vs comparator postswitch in randomized controlled trials. Consistent increases in $CD4^+/CD8^+$ ratios were observed in real-world evidence after switch to dolutegravir plus lamivudine.

These results are consistent with findings in ART-naive PWH. In the phase 3 GEMINI–1 and GEMINI-2 studies comparing first-line ART with dolutegravir plus lamivudine vs the 3DR dolutegravir plus TDF/FTC in ART-naive PWH, there were minimal or no changes from baseline to 144 weeks in median levels of IL-6 (both groups, 0.0 [IQR, 0.0–0.0] ng/L) and CRP (dolutegravir plus lamivudine, 0.0 [IQR, –0.9 to 0.8] mg/L; dolutegravir plus TDF/FTC, –0.2 [IQR, –0.9 to 0.5] mg/L) in both groups [41].

These results are also strengthened by findings from other studies of dolutegravir-based 2DRs that mostly reported data from PWH receiving dolutegravir plus lamivudine but were not eligible for inclusion in this systematic review because they did not separately summarize data for those on dolutegravir plus lamivudine. In a small, randomized, open-label study of virologically suppressed PWH (n = 50; at baseline, 45 PWH were taking dolutegravir plus lamivudine and 5 dolutegravir plus rilpivirine) either continuing the dolutegravir-based 2DR (n = 25) or switching to elvitegravir (EVG)/cobicistat (COBI)/FTC/TAF (n = 25), changes in CRP, IL-6, and D-dimer did not show any significant change with a switch from dolutegravir-based 2DRs to EVG/COBI/FTC/TAF through 96 weeks [42]. In a retrospective analysis of virologically suppressed PWH who switched to any dolutegravir-based 3DR or dolutegravir plus lamivudine 2DR (N = 133; 89 switched to dolutegravir plus lamivudine), plasma levels of sCD14 decreased significantly through 48 weeks after switch ($P < .001$) when compared with baseline, while changes in IL-6, CRP, and D-dimer were not significant (all $P > .2$) [43].

A small study nested in a nonrandomized cohort (Spanish HIV Research Network [CoRIS]) assessed changes in inflammatory biomarkers in archived samples over 3 years in suppressed PWH who started ART between 2004 and 2018 and switched to a 2DR (n = 58, 7 on dolutegravir plus lamivudine) or remained on 3-drug ART (n = 90). Increases in CRP and D-dimer were observed in the long-term follow-up modeled trajectories after switch, with no changes in IL-6, sCD14, sCD163, or FABP-2 [28, 40]. However, it is difficult to interpret the validity of this nested study due to several limitations, including small sample size, potential bias, and unmeasured confounders.

Both the randomized clinical trials and real-world evidence suggest an improvement in sCD14 at 48 weeks after switching to dolutegravir plus lamivudine. Soluble CD14 is a marker of monocyte and macrophage activation and a strong predictor of morbidity and mortality as well as cardiovascular disease in PWH [44]. Elevated plasma levels of sCD14 are observed in many chronic diseases associated with inflammation [44, 45]. However, this improvement is not seen in other biomarkers that potentially capture similar mechanisms of underlying inflammation (including CRP and sCD163).

To our knowledge, this is the first systematic literature review investigating the impact of a specific ART regimen on inflammatory and atherogenesis biomarkers in virologically suppressed PWH. The primary strengths of this review are the inclusion of 2 large, phase 3, randomized trials and the sizeable sample of PWH on dolutegravir plus lamivudine analyzed from both real-world evidence (N = 1000) and clinical trials (TANGO, n = 369; SALSA, n = 246). Further, this analysis investigated a wide variety of biomarkers of inflammation and atherogenesis representing multiple underlying pathways, although there are other cellular biomarkers (eg, $CD38^+$) and T-cell subsets (eg,

$CD8^+$) that were not investigated in this review. Additionally, there are limitations in the assessment of inflammatory biomarkers with ART. First, the heterogeneity of real-world studies may affect the generalizability of findings, although the data from these studies are fairly consistent (eg, a consistent increase in $CD4^+/CD8^+$ ratio postswitch to dolutegravir/lamivudine). Second, although studies have evaluated changes in several markers that have been presumed to be surrogate markers for inflammation or atherogenesis in HIV, the confirmed correlation of these markers with specific clinical events has yet to be clearly established. Third, inflammatory biomarkers are primarily used in a research setting, and their clinical relevance is unknown. Guidelines do not recommend use of biomarkers for monitoring inflammation in clinical practice because there are no determined cutoff values (ie, what defines a meaningful change and how this varies by biomarker) or approved standardized methods for measurement, and biomarkers can significantly fluctuate in PWH due to non-HIV-related factors [46]. Regulatory agencies also do not require biomarker information to support ART approval [47]. Moreover, biomarkers such as CRP and D-dimer are broad, nonspecific indicators of inflammatory response [5, 48, 49]. Finally, most studies assessing changes in inflammatory biomarkers with ART do not account for host characteristics or comorbidities, such as coinfections and lifestyle factors, which may independently induce or modulate inflammation [48]. For example, sex can factor into residual HIV activity, cellular immune activation, and disease outcomes [50–53]. In a recent analysis from the US Women's Interagency HIV Study, postmenopausal women had higher plasma sCD14 and sCD163 levels compared with premenopausal women after adjusting for relevant baseline covariates, suggesting that menopause (particularly during menopausal transition) may increase innate immune activation [8]. In the present analysis, female participants represented 39% of the overall SALSA study population (44% of dolutegravir/lamivudine participants) but only 8% of the TANGO study population. In the included real-world evidence studies, women represented approximately 25% of each study population. Underrepresentation of women in the existing literature is a common limitation in many studies and underscores the need for increased diversity in HIV studies.

In conclusion, switching to the 2DR dolutegravir plus lamivudine was not associated with consistent changes in inflammatory or atherogenesis biomarkers in 2 large, randomized, phase 3 trials (TANGO, n = 369; SALSA, n = 246) or in 1 real-world study (N = 67) in PWH who were virologically suppressed. Dolutegravir plus lamivudine has demonstrated durable, noninferior virologic efficacy, with no differences in low-level viremia and viral blips, or virologic control in sanctuary sites and reservoirs vs 3/4DRs. The data suggest a lack of impact of the number of drugs in an ART regimen as long as virologic suppression is maintained. HIV-associated inflammation is multifactorial, with comorbidities, lifestyle factors, coinfections, long-term immune damage, and ongoing viral replication and persistence all contributing to the inflammatory landscape. Although the clinical significance of inflammation in HIV is currently unknown, further studies are warranted to shed light on causes of underlying persistent inflammation in PWH with suppressed viremia and potential mitigation strategies.

Notes

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