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Cardiometabolic Parameters 3 Years After Switch to Dolutegravir/Lamivudine vs Maintenance of Tenofovir Alafenamide–Based Regimens

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Background. Cardiometabolic outcomes were investigated 3 years after switching to the 2-drug regimen dolutegravir/lamivudine (DTG/3TC) vs continuing 3-/4-drug tenofovir alafenamide (TAF)–based regimens in a multicenter phase 3 noninferiority study based on an open-label randomized design.

Method. Adults with virologically suppressed HIV-1 switched to once-daily DTG/3TC (n = 369) or continued TAF-based regimens (n = 372). Cardiometabolic health parameters were assessed through week 144 via mixed-model repeated measures or logistic regression analyses, adjusting for baseline variables.

Results. At week 144, 13% (42/316) of the DTG/3TC group and 12% (37/303) of the TAF-based regimen group had ≥10% weight gain from baseline (adjusted odds ratio, 1.11; 95% CI, .68–1.80). Adjusted change from baseline in serum leptin, a surrogate marker of adiposity, was similar between groups (treatment ratio, 1.00; 95% CI, .89–1.13). The lipid profile generally favored DTG/3TC in the baseline boosted subgroup. Adjusted odds revealed no clinically meaningful differences between groups: homeostatic model assessment of insulin resistance ≥2 (adjusted odds ratio, 0.79; 95% CI, .50–1.26), metabolic syndrome (International Diabetes Federation criteria, 0.99; .59–1.68), hepatic fibrosis (fibrosis-4 index score ≥1.45, 1.39; .63–3.06), and coronary artery disease risk (Framingham risk score ≥10%, 0.92; .56–1.49). Baseline variables and characteristics associated with odds of each cardiometabolic parameter outcome were consistent with known risk factors, including age, sex, race, and some disease characteristics.

Conclusions. Cardiometabolic health 3 years after switching to DTG/3TC was comparable to that for individuals continuing TAF-based regimens, further supporting DTG/3TC as a robust switch option with a stable metabolic profile.

Trial registration. ClinicalTrials.gov NCT03446573

Keywords. 2-drug regimen; cardiometabolic health; insulin resistance; leptin; weight.

As people with HIV (PWH) age on lifelong antiretroviral therapy (ART), risk of comorbidities and polypharmacy increases [1, 2]. Regimen simplification via 2-drug regimens (2DRs) reduces the number of antiretroviral agents used and potentially decreases long-term toxicities, drug-drug interactions, and costs [3]. Older antiretrovirals have been associated with weight

suppression and metabolic toxicity [4, 5]. Although progress has been made in mitigating metabolic toxicity, the holistic and long-term impact of newer antiretrovirals on metabolic health is unclear, particularly for tenofovir alafenamide (TAF) and the second-generation integrase strand transfer inhibitors (INSTIs) dolutegravir (DTG) and bictegravir.

International guidelines recommend that initial ART regimens include an INSTI with ≥1 nucleoside reverse transcriptase inhibitor [6–8]. However, ART regimens containing the INSTIs DTG or bictegravir or the nucleoside reverse transcriptase inhibitor TAF have been independently associated with weight gain [4, 9–12]. The first-generation INSTIs elvitegravir and raltegravir have generally been associated with less weight gain than DTG and bictegravir, underscoring potential differences in metabolic health impact between INSTI generations [13–15]. Understanding the causality and degree of association between any antiretroviral and weight gain is complex and requires consideration of confounders such as lifestyle, concomitant

medications and comorbidities, the return-to-health phenomenon, and effect of prior regimens on weight (eg, suppressive effect of antiretrovirals such as tenofovir disoproxil fumarate [TDF] and efavirenz) [4].

Beyond change in weight, parameters related to body fat, insulin resistance, metabolic syndrome, metabolic-associated liver disease, and cardiovascular disease (CVD) provide a more complete understanding of cardiometabolic health. For example, plasma leptin assesses total fat mass [16], and homeostatic model assessment of insulin resistance (HOMA-IR) indicates insulin sensitivity, which may be predictive of increased CVD risk [17]. Assessing and preventing metabolic syndrome and CVD is important, given the occurrence of obesity in ART-treated individuals and heightened risk of CVD in PWH [18–21].

The 2DR dolutegravir/lamivudine (DTG/3TC) is recommended as initial therapy for most PWH who are ART naive and as a switch option for PWH who are virologically suppressed [6–8], as supported by phase 3 clinical trial evidence in ART-naive (GEMINI-1/-2) and virologically suppressed (TANGO and SALSA) populations for up to 3 years [22–24]. In TANGO, switching to a DTG/3TC fixed-dose combination tablet was noninferior to continuing 3-/4-drug TAF-based regimens for maintenance of virologic suppression, demonstrating durable efficacy, good safety and tolerability, and a high barrier to resistance for 3 years [22]. Change in weight from baseline to week 144 was similar between participants who switched to DTG/3TC (2.2 kg) and those continuing TAF-based regimens (1.7 kg) and between treatment groups across baseline body mass index (BMI) categories [22]. Participants who switched to DTG/3TC had favorable changes in lipid profile, with small and similar changes observed between treatment groups from baseline to week 144 in terms of HOMA-IR and inflammatory biomarkers associated with cardiometabolic disorders [22, 25, 26]. We present in-depth post hoc analyses of cardiometabolic outcomes and baseline variables associated with cardiometabolic outcomes through week 144 of TANGO.

METHODS

Study Design
TANGO (ClinicalTrials.gov NCT03446573) is a phase 3 open-label study based on a randomized noninferiority design that evaluated the efficacy and safety of switching to the 2DR DTG/3TC vs continuing 3-/4-drug TAF-based regimens in adults who are virologically suppressed. Methods have previously been published [22, 27]. Briefly, adults with HIV-1 who were virologically suppressed for >6 months while taking TAF-based regimens were randomized 1:1 (stratified by baseline third agent class) to switch to once-daily DTG (50 mg)/3TC (300 mg) or continue their TAF-based regimen. Switch from TDF to TAF ≥3 months before screening was permitted; during the study, no regimen modifications were allowed in the TAF-based

regimen group, except for switching between ritonavir and cobicistat [22, 27]. The primary endpoint was the proportion of participants with HIV-1 RNA ≥50 copies/mL at week 48.

Patient Consent Statement
TANGO was conducted in accordance with the International Conference on Harmonization's good clinical practice and the Declaration of Helsinki, with protocol approvals obtained before participant screening. All participants provided written informed consent before study initiation.

Metabolic Health Assessments
Metabolic outcomes included change from baseline in weight and BMI and percentage change from baseline in fasting lipids (total cholesterol, low- and high-density lipoprotein cholesterol [LDL-C and HDL-C], total cholesterol/HDL-C ratio, and triglycerides), fasting glucose and insulin, and hemoglobin A_{1c} (HbA$_{1c}$). Insulin resistance was assessed with HOMA-IR and defined as a score ≥2 [28–30]. Metabolic syndrome was defined by criteria of the International Diabetes Federation [31]. Hepatic fibrosis was assessed through fibrosis-4 index (FIB-4) ≥1.45 [32–35]. Framingham risk score ≥10% was used in the present analysis [36, 37]. Data collection timelines and formulas used for analysis are provided in the Supplementary Methods.

Statistics
Adjusted mean change and adjusted geometric mean ratio for log$_e$-transformed endpoints from baseline to week 144 were calculated for weight, leptin, fasting lipids, HOMA-IR, fasting glucose and insulin, HbA$_{1c}$, and FIB-4. Data were compared between treatment groups per mixed-model repeated measures analyses adjusting for relevant baseline variables in the safety population. Multivariable logistic regression models were used for determining adjusted odds ratios (aORs) of relevant baseline variables' association with the following binary endpoints defined at week 144: ≥10% weight gain, metabolic syndrome, HOMA-IR ≥2, FIB-4 ≥1.45, and Framingham risk score ≥10%.

Exploratory subgroup analyses for prior TAF duration (<1 vs ≥1 year), boosting status (presence or absence of pharmacokinetic boosting agent at baseline), and baseline BMI category (kg/m^2; underweight/normal, <25; overweight, 25 to <30; obesity, ≥30) were performed with mixed-model repeated measures or logistic regression as appropriate. Adjustment of baseline variables per analysis is detailed in the figures.

RESULTS

Demographics and Baseline Characteristics
Overall, 743 participants were randomized to switch to DTG/3TC (n = 371) or continue their TAF-based regimen (n = 372), and 369 and 372 participants, respectively, received study treatment (intention-to-treat–exposed population). The median age was 40 and 39 years for the DTG/3TC and TAF-based

Table 1. Demographics and Baseline Characteristics

	Parameter, No. (%)[a]	
	DTG/3TC (n = 369)	TAF-Based Regimen (n = 372)
Age, median (range), y	40 (20–74)	39 (18–73)
Female	25 (7)	33 (9)
Race		
White	297 (80)	289 (78)
African American/African heritage	50 (14)	58 (16)
Asian	13 (4)	13 (3)
Other races[b]	9 (2)	12 (3)
Ethnicity		
Hispanic/Latinx	69 (19)	66 (18)
Not Hispanic/Latinx	300 (81)	306 (82)
CD4+, median (range), cells/mm^3	682 (133–1904)	720 (119–1810)
Baseline third agent class		
INSTI	289 (78)	296 (80)
EVG/c	243 (66)	249 (67)
NNRTI	51 (14)	48 (13)
RPV	43 (12)	45 (12)
PI	29 (8)	28 (8)
bDRV	25 (7)	27 (7)
Baseline boosted regimen	272 (74)	277 (74)
Duration before day 1, median (range), mo		
ART	33.8 (7.1–201.2)	35.1 (7.0–160.8)
TAF-based regimen	17.7 (3.6–73.7)	18.2 (3.9–71.2)
Cardiometabolic characteristics		
Mean (SD)		
Weight, kg	81.2 (15.4)	81.7 (15.9)[c]
BMI, kg/m^2	26.3 (4.8)	26.7 (5.1)[c]
BMI category[d]		
Underweight	3 (<1)	4 (1)
Normal	172 (47)	153 (41)
Overweight	131 (36)	137 (37)
Obesity	63 (17)	77 (21)
Diabetes		
Type 2	12 (3)	18 (5)
Type 1	1 (<1)	1 (<1)
Prevalence of metabolic syndrome[e,f]	36 (10)	41 (11)[g]
Fasting insulin, pmol/L		
Median (range)[f]	72.0 (11–582)	72.0 (11–690)
Geometric mean (95% CI)	73.8 (69.2–78.8)	71.7 (67.4–76.4)
Geometric mean (95% CI)		
Fasting glucose,	5.07 (5.00–5.13)	5.09 (5.02–5.16)
HbA$_{1c}$, %	5.07 (5.02–5.12)	5.13 (5.06–5.20)
HOMA-IR[h]	2.81 (2.62–3.02)	2.74 (2.55–2.93)
HOMA-IR ≥2[i]	193 (72)	186 (72)
Leptin, geometric mean (95% CI)[f]	4.98 (4.47–5.54)	4.97 (4.43–5.58)
BMI: underweight/normal	2.79 (2.43–3.21)	2.49 (2.15–2.89)
BMI: overweight	6.82 (5.98–7.77)	5.67 (4.97–6.48)
BMI: obesity	13.12 (10.61–16.22)	16.18 (13.45–19.47)
FIB-4		
Median (range)[f]	0.869 (0.20–3.08)	0.867 (0.26–3.51)
Geometric mean (95% CI)	0.843 (.804–.884)	0.862 (.824–.903)

Table 1. Continued

	Parameter, No. (%)[a]	
	DTG/3TC (n = 369)	TAF-Based Regimen (n = 372)
Proportion of participants		
Past or current hypertension	59 (16)	59 (16)
Framingham risk score ≥10%[j]	90 (24)	80 (22)

Abbreviations: ART, antiretroviral therapy; bDRV, boosted darunavir; BMI, body mass index; DTG, dolutegravir; EVG/c, elvitegravir/cobicistat; FIB-4, fibrosis-4 index; HbA$_{1c}$, hemoglobin A$_{1c}$; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RPV, rilpivirine; TAF, tenofovir alafenamide; 3TC, lamivudine.

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

[b]Other races included American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, mixed White race, and multiple races.

[c]n = 371.

[d]BMI categories based on World Health Organization classification.

[e]Participants who have BMI ≥30 kg/m^2 and satisfy any 2 of the raised/reduced factors within the baseline visit window: raised triglycerides, ≥150 mg/dL or treatment; reduced HDL cholesterol, <40 mg/dL (men), <50 mg/dL (women), or treatment; raised blood pressure, systolic ≥130 mm Hg or diastolic ≥85 mm Hg, or treatment for hypertension; fasting glucose ≥100 mg/dL or previous diagnosis of type 2 diabetes.

[f]Post hoc analysis.

[g]n = 370.

[h]HOMA-IR = fasting plasma insulin (mU/L) × fasting plasma glucose (mmol/L) / 22.5.

[i]Percentages based on participants with HOMA-IR data at baseline and week 144: DTG/3TC, n = 268; TAF-based regimen, n = 257.

[j]DTG/3TC, n = 368; TAF-based regimen, n = 370.

regimen groups, respectively (Table 1). Most participants were male and White. The most common baseline third agent class was INSTI, with elvitegravir/cobicistat being the most common INSTI used (66% and 67% for the DTG/3TC and TAF-based regimen groups). Most participants used boosted regimens at baseline (74% in each group). Baseline weight (kg, mean [SD]: DTG/3TC, 81.2 [15.4]; TAF-based regimen, 81.7 [15.9]) and cardiometabolic characteristics were similar between treatment groups.

Changes in Weight, BMI, and Leptin

At week 144, weight gain was generally similar between treatment groups, with ≥5% gain from baseline in 39% (123/316) switching to DTG/3TC and 31% (94/303) continuing a TAF-based regimen and ≥10% gain in 13% (42/316) switching to DTG/3TC and 12% (37/303) continuing a TAF-based regimen (aOR, 1.11; 95% CI, .68–1.80; Figure 1A). Older age (per 10-year increase) was associated with lower odds of ≥10% weight gain (aOR, 0.78; 95% CI, .62–.98). At week 144, 12% (69/577) of male participants and 24% (10/41) of female participants had ≥10% weight gain (aOR, 2.06; 95% CI, .92–4.66). In subgroup analyses based on baseline BMI, adjusted odds of ≥10% weight gain were highest among participants with obesity at baseline, although the 95% CI overlapped with 1 for all BMI categories (aOR [95% CI]: underweight/normal, 0.97 [.48–1.95]; overweight, 1.04 [.45–2.40]; obesity, 1.76 [.56–5.58]).
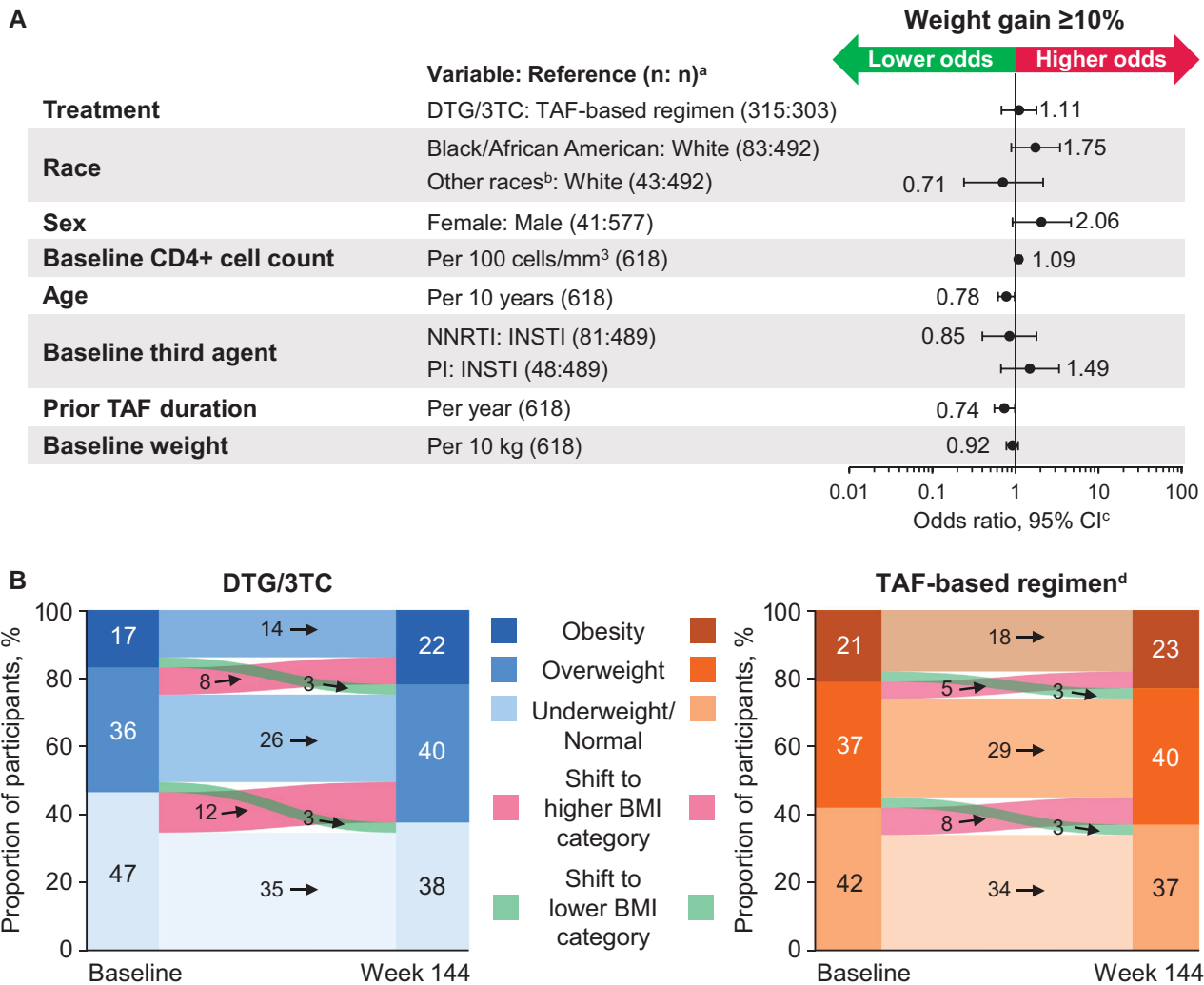
Figure 1. (*A*) Adjusted odds (95% CI) of ≥10% weight gain by relevant parameters and (*B*) change in BMI category in the DTG/3TC and TAF-based regimen groups (post hoc analyses). BMI, body mass index; DTG, dolutegravir; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TAF, tenofovir alafenamide; 3TC, lamivudine. [a]Odds ratios are presented in relation to the reference variable; the number of participants included in final model with covariate data at baseline and weight data at baseline and week 144. [b]Other races included American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, mixed White race, and multiple races. [c]Odds ratios and 95% CIs were calculated with a logistic regression model adjusting for treatment, race, sex, baseline CD4+ cell count (continuous), age (continuous), baseline weight (continuous), baseline third agent class, and prior TAF duration (continuous). [d]In the TAF-based regimen group, 1 (<1%) participant with obesity at baseline had a normal BMI at week 144, and 1 (<1%) participant with a normal BMI had obesity at week 144.

In subgroup analyses evaluating prior TAF duration as a continuous variable, adjusted odds of ≥10% weight gain were lower with longer prior TAF duration (aOR, 0.74; 95% CI, .56–.99). When prior TAF duration was evaluated categorically, adjusted odds of ≥10% weight gain were slightly higher between treatment groups in the <1-year category (1.35; .53–3.44) vs ≥1 year (1.02; .58–1.80), although the 95% CI overlapped with 1 for both categories. Proportions of participants with an adverse event of increased weight were similar between treatment groups: DTG/3TC, 5% (17/369); TAF-based regimen, 5% (19/371; Supplementary Table 1).

Changes in BMI categories from baseline to week 144 were similar between treatment groups, with 8% (24/316) and 6% (17/303) shifting from baseline BMI <30 (underweight, normal, and overweight) to postbaseline ≥30 (obesity) in the DTG/3TC and TAF-based regimen groups, respectively (Figure 1B).

Adjusted percentage change in leptin from baseline through week 144 was comparable between the DTG/3TC (21.4%; 95% CI, 11.2%–32.5%; n = 285) and TAF-based regimen (21.2%; 12.1%–31.0%; n = 260) groups (treatment ratio, 1.00; 95% CI, .89–1.13). Change from baseline in leptin was comparable between treatment groups within each BMI category (Figure 2A), with a higher percentage change from baseline in leptin observed with a higher baseline BMI. Change in weight was positively correlated with change in leptin levels

in both treatment groups among women (DTG/3TC, $r = 0.54$; TAF, $r = 0.34$; Figure 2B) and men (DTG/3TC, $r = 0.58$; TAF, $r = 0.57$; Figure 2C).

Change in Lipid Profile

At week 144, the proportion of participants with desirable or optimal lipid levels was numerically higher in the DTG/3TC group for total cholesterol, LDL-C, and triglycerides (Supplementary Table 2). In the baseline boosted subgroup, changes in lipid profile favored DTG/3TC for total cholesterol, LDL-C, and triglycerides and favored TAF-based regimens for HDL-C, with no difference between groups for total cholesterol/HDL-C ratio (Figure 3). No significant differences in lipid changes were observed between treatment groups in the baseline unboosted subgroup.

Insulin Resistance

Adjusted percentage change from baseline through week 144 in fasting serum glucose was −0.4% (95% CI, −1.6% to .9%) and 0.5% (−.9% to 1.9%) in the DTG/3TC and TAF-based regimen groups, respectively (treatment ratio, 0.99; 95% CI, .97–1.01). Percentage change from baseline in fasting serum insulin was 14.2% (95% CI, 8.0%–20.7%) and 12.1% (5.9%–18.7%) in the DTG/3TC (n = 272) and TAF-based regimen (n = 258) groups (treatment ratio, 1.02; 95% CI, .94–1.10). Percentage change from baseline in serum HbA_{1c} was 3.6% (95% CI, 2.8%–4.3%) and 2.9% (2.1%–3.8%) in the DTG/3TC and TAF-based regimen groups (treatment ratio, 1.01; 95% CI, 1.00–1.02). The proportions of participants with an adverse event of type 2 diabetes were low and similar between treatment groups: DTG/3TC, <1% (2/369); TAF-based regimen, <1% (1/371; Supplementary Table 1).

Adjusted percentage change from baseline in HOMA-IR was similar in the DTG/3TC (11.5%; 95% CI, 4.7%–18.7%) and TAF-based regimen (10.2%; 3.7%–17.2%) groups (treatment ratio, 1.01; 95% CI, .93–1.10). The proportions of participants with HOMA-IR ≥2 at baseline were 72% (193/268) and 72% (186/257) in the DTG/3TC and TAF-based regimen groups, respectively, and 78% (208/268) and 82% (211/257) at week 144 (aOR, 0.79; 95% CI, .50–1.26). Higher baseline HOMA-IR (1.81; 1.43–2.29) and BMI (1.13; 1.05–1.22) were associated with higher odds of HOMA-IR ≥2 at week 144 (Figure 4A). The odds of HOMA-IR ≥2—when analyzed by baseline boosting status (aOR [95% CI]: boosted, 0.81 [.47–1.40]; unboosted, 0.74 [.29–1.90]) and baseline BMI (underweight/normal, 0.74 [.42–1.31]; overweight, 0.79 [.28–2.20]; obesity, 1.05 [.21–5.28])—were generally similar between the DTG/3TC and TAF-based regimen groups.

Metabolic Syndrome Assessed by International Diabetes Federation Criteria

Proportions of participants with metabolic syndrome were similar between treatment groups at baseline (DTG/3TC,

10% [36/369]; TAF-based regimen, 11% [41/370]) and week 144 (DTG/3TC, 14% [43/298]; TAF-based regimen, 16% [46/287]; aOR, 0.99 [95% CI, .59–1.68]; Figure 4B). Female sex (aOR, 4.20; 95% CI, 1.65–10.68), the presence of baseline hypertension (5.22; 2.72–10.04), and baseline HOMA-IR (2 to <3, 2.68 [1.00–7.17]; 3 to <4, 3.25 [1.17–9.02]; ≥4, 5.73 [2.29–14.32]) were associated with higher odds of metabolic syndrome at week 144, whereas high baseline HDL-C (aOR, 0.43; 95% CI, .19–.96) was associated with lower odds. Odds of metabolic syndrome were generally similar in the DTG/3TC and TAF-based regimen groups when analyzed by baseline boosting status (aOR [95% CI]: boosted, 0.93 [.51–1.72]; unboosted, 1.14 [.42–3.05]).

Hepatic Fibrosis as Measured by FIB-4

Adjusted percentage change from baseline in FIB-4 showed a decrease in both treatment groups and was similar between the DTG/3TC (−11.9%; 95% CI, −14.5% to −9.2%; n = 299) and TAF-based regimen (−10.6%; −13.3% to −7.9%; n = 289) groups (treatment ratio, 0.99; 95% CI, .95–1.03). The proportions of participants with FIB-4 ≥1.45 were similar between treatment groups at week 144: DTG/3TC, 8% (25/299); TAF-based regimen, 7% (21/289; aOR, 1.39 [95% CI, .63–3.06]; Supplementary Figure 1A). Parameters associated with higher odds of FIB-4 ≥1.45 at week 144 were Black/African American vs White race (aOR, 4.52; 95% CI, 1.68–12.16), older age (1.91; 1.24–2.94), and higher baseline FIB-4 (28.68; 9.49–86.71). Adjusted odds of FIB-4 ≥1.45 between treatment groups were generally similar to the overall analysis when analyzed by baseline boosting status (aOR [95% CI]: boosted, 1.62 [.58–4.49]; unboosted, 1.16 [.32–4.17]).

Coronary Artery Disease Risk as Measured by Framingham Risk Score ≥10%

The proportions of participants with Framingham risk score ≥10% were similar between treatment groups at baseline (DTG/3TC, 24% [90/368]; TAF, 22% [80/370]) and week 144 (DTG/3TC, 24% [58/238]; TAF, 25% [57/231]; aOR, 0.92 [95% CI, .56–1.49]; Supplementary Figure 1B). At week 144, the presence of baseline hypertension (aOR, 11.25; 95% CI, 5.22–24.26) and higher baseline total cholesterol (1.02; 1.01–1.03) were associated with higher odds of Framingham risk score ≥10%, whereas higher baseline HDL-C (0.98; 0.96–0.99) was associated with lower odds. The proportions of participants with hypertension and other cardiac adverse events were generally similar between treatment groups (Supplementary Table 3).

DISCUSSION

At week 144 in the TANGO study, the adjusted mean change in weight from baseline was similar between participants who switched to DTG/3TC and continued TAF-based regimens through 3 years and was consistent with the annual rate
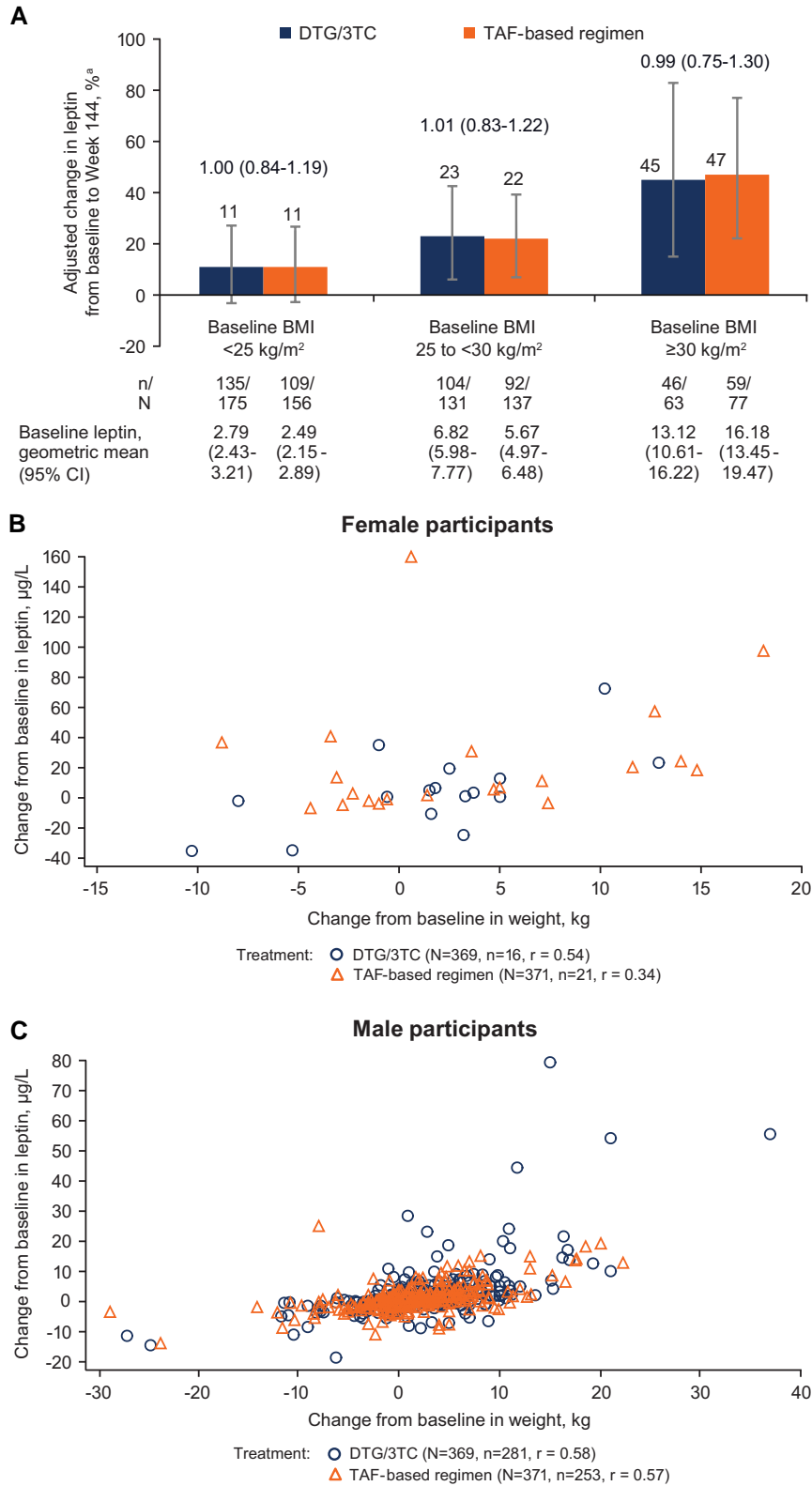
Figure 2. (A) Adjusted percentage change from baseline in leptin and correlation between change from baseline in leptin and body weight in (B) female and (C) male participants (post hoc analysis). BMI, body mass index; DTG, dolutegravir; TAF, tenofovir alafenamide; 3TC, lamivudine. [a]Percentage change from baseline and 95% CI based on adjusted ratio (week 144 to baseline) in each group were calculated via a mixed-model repeated measures analysis applied to change from baseline in $\log_e$-transformed data, adjusting for the following: treatment, baseline BMI category, baseline third agent class, prior TAF duration (continuous), $\log_e$-transformed baseline leptin (continuous), baseline insulin (continuous), baseline CD4+ cell count (continuous), age (continuous), sex, treatment × visit, $\log_e$-transformed baseline leptin × visit, treatment × baseline BMI category, baseline BMI category × visit, and baseline BMI category × treatment × visit—with visit as the repeated factor. Treatment ratio (95% CI) is shown above the bars in panel A.
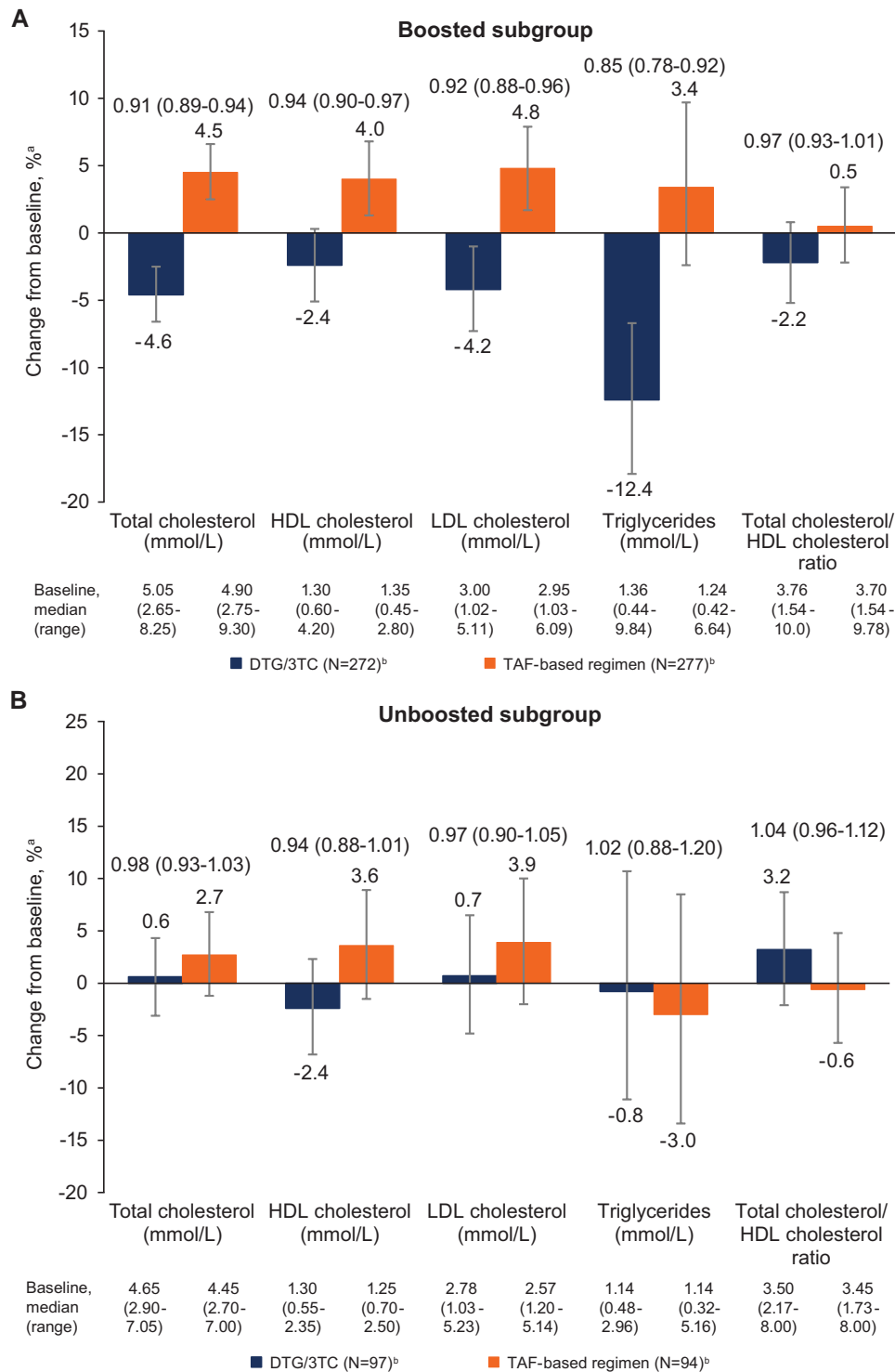
Figure 3. Adjusted percentage change from baseline (95% CI) in lipids in the baseline (*A*) boosted and (*B*) unboosted subgroups (post hoc analysis). BMI, body mass index; DTG, dolutegravir; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TAF, tenofovir alafenamide; 3TC, lamivudine. [a]Percentage change from baseline and 95% CI based on adjusted ratio (week 144 to baseline) in each group were calculated via mixed-model repeated measures analysis applied to change from baseline in $\log_e$-transformed data, adjusting for the following: treatment, baseline boosting status, CD4+ cell count (continuous), age (continuous), $\log_e$-transformed baseline value (continuous), race, baseline BMI (continuous), treatment × visit, baseline value × visit, treatment × baseline boosting status, baseline boosting status × visit, and baseline boosting status × treatment × visit—with visit as the repeated factor. [b]Number of participants with nonmissing fasting lipid data at baseline and week 144, removing those with lipid-modifying agent administered at baseline. Treatment ratio (95% CI) is shown above the bars.
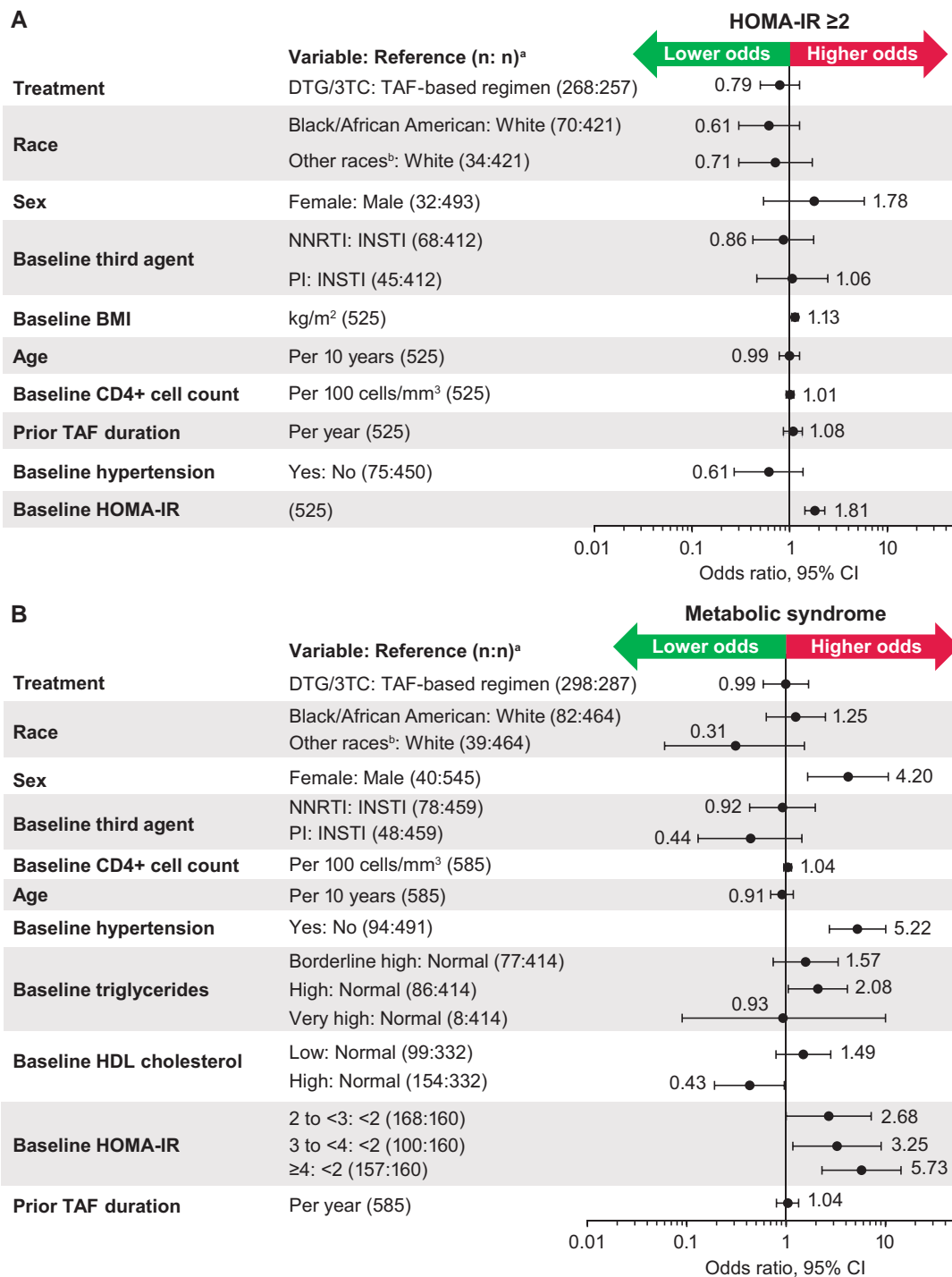
Figure 4. Adjusted odds (95% CI) of (*A*) HOMA-IR ≥2 and (*B*) metabolic syndrome (post hoc analysis). Each logistic regression adjusted for all variables assessed within the analysis. BMI, body mass index; DTG, dolutegravir; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TAF, tenofovir alafenamide; 3TC, lamivudine. [a]Odds ratios are presented in relation to the reference variable; the number of participants included in final model with covariate data at baseline and outcome data at baseline and week 144. Participants with evidence of prestudy diabetes were excluded. [b]Other races included American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, mixed White race, and multiple races.

expected in the general population (0.5–1.0 kg/y) [22, 38]. Shift in BMI category was similar between treatment groups, with similar odds of ≥10% weight gain in the DTG/3TC and TAF-based regimen groups. Increases in leptin from baseline to week 144 were similar between treatment groups (∼21%). Leptin is predominantly secreted by white adipose tissue;

circulating levels positively correlate with amount of body fat [16, 39–41]. Plasma leptin measurement allows for evaluation of whether weight gain is fat or lean muscle mass [16, 41]. Across groups, magnitude of leptin increase was aligned with baseline BMI, and there was a positive correlation between change from baseline in serum leptin and weight in male and female participants. Together, these data suggest a similar change in total fat mass over 3 years between treatment groups.

More female than male participants gained ≥10% weight, which is consistent with other studies reporting female sex as a risk factor for greater weight gain on INSTI-based regimens, including after switch to INSTIs [12, 13, 42]. In the ADVANCE trial of PWH initiating ART (N = 1053), greater weight gain was observed in female participants, particularly among those taking DTG + TAF/emtricitabine [43]. Older age was associated with lower odds of ≥10% weight gain, similar to findings from a retrospective observational study of PWH who were virologically suppressed who switched to INSTIs (N = 2272), reporting that younger age (<50 years) was associated with greater risk of weight gain [44]. Shorter prior TAF duration, when evaluated as a continuous variable, was associated with higher odds of weight gain. Shorter prior TAF duration may indicate shorter overall ART duration, and return to health characterized by weight gain has been well described in PWH initiating ART [4]. Additionally, the inclusion criteria allowed participants a TDF-to-TAF switch ≥3 months before randomization; these participants would have shorter prior TAF durations and could have experienced weight gain associated with a TDF-to-TAF switch, which has been demonstrated to be greatest during the first 6 to 12 months, followed by a plateau [9].

In the overall TANGO population, DTG/3TC had a generally favorable lipid profile as compared with TAF-based regimens at week 144, particularly for total cholesterol, LDL-C, and triglycerides [22]. The present study showed favorable changes in lipids after switch to DTG/3TC in the baseline boosted subgroup, with the exception of HDL-C, whereas changes were comparable between groups in the baseline unboosted subgroup. The differences observed within the boosted subgroup may be explained by increased TAF exposure when given with cobicistat—even when dosed at 10 mg, as in elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (EVG/c/FTC/TAF), the most common baseline regimen in this study—and/or by a direct effect of the booster drug. In a study assessing the effect of switch from TDF to TAF on LDL-C (N = 221), use of cobicistat with TAF was associated with an increased risk of LDL-C above the cardiovascular target (aOR, 2.4; 95% CI, 1.0–5.1; P = .03) [45].

At week 144 in TANGO, similar proportions of participants in the DTG/3TC (78%) and TAF-based regimen (82%) groups had insulin resistance (HOMA-IR ≥2) [22]. The present analyses support this finding by showing that changes from baseline in markers of insulin resistance were comparable between the DTG/3TC and TAF-based regimen groups through week 144, including HOMA-IR, glucose, insulin, and HbA$_{1c}$. Furthermore, switching to DTG/3TC vs continuing TAF-based regimens was associated with similar odds of HOMA-IR ≥2. Of note, at week 48 of TANGO, the odds of HOMA-IR ≥2 were lower with DTG/3TC (aOR, 0.59; 95% CI, .40–.87) [46]. However, between weeks 48 and 144, differences in HOMA-IR between groups were no longer apparent. Baseline BMI and HOMA-IR were associated with higher odds of HOMA-IR ≥2 at week 144. A post hoc analysis demonstrated that a greater proportion of participants continuing TAF-based regimens with obesity at baseline were referred for diet/weight management counseling, which may have influenced weight fluctuations and changes in HOMA-IR through week 144 [22]. Visceral adipose tissue, which is strongly associated with HOMA-IR [47], was not measured in TANGO, yet leptin data indicate that body fat increase was similar between groups.

We observed higher odds of metabolic syndrome in women, consistent with a prior study in 1861 PWH reporting that female sex increased odds of metabolic syndrome (aOR, 2.24; 95% CI, 1.69–2.97) [21]. Change in FIB-4 from baseline was similar between DTG/3TC (−11.9%) and TAF-based regimens (−10.6%), with older age associated with greater odds of hepatic fibrosis. Data from 1137 PWH in the ICONA Foundation Study support this finding, reporting that each 10-year increase in age was associated with a greater likelihood of FIB-4 progression (adjusted relative hazard, 1.40; 95% CI, 1.20–1.64; P < .001) [48]. Proportions of participants with Framingham risk score ≥10% were similar between treatment groups (DTG/3TC, 24%; TAF, 25%). The presence of baseline hypertension was associated with considerably higher odds of Framingham risk score ≥10% (aOR, 11.25), whereas higher baseline HDL-C was associated with odds just under 1 (aOR, 0.98). Overall, the baseline characteristics associated with lower or higher risk of various cardiometabolic parameters in the current analysis are consistent with the literature. These baseline characteristics may help inform cardiometabolic profiling to proactively identify PWH who would benefit from focused cardiometabolic health counseling.

There are several limitations to this analysis. Notably, the TANGO study population was primarily composed of White male participants. Although female sex and Black race were associated with higher odds of metabolic syndrome and FIB-4 ≥1.45, respectively, higher INSTI-related weight gain has been observed in Black PWH [12], and the relatively low number of participants in these groups may have affected the ability to detect associations with other cardiometabolic health outcomes as well as the precision of the odds ratio point estimates. The SALSA study recruited a more diverse population switching to DTG/3TC vs continuing 3-/4-drug current antiretroviral regimens [24]. Generally similar changes in insulin resistance

and lipids were observed through 1 year in SALSA; however, comparing cardiometabolic endpoints between TANGO and SALSA is complicated by the significant heterogeneity of baseline regimens, as well as SALSA being limited to 1 year of follow-up. It remains important that clinical trials recruit diverse populations to help ensure appropriate efficacy and safety assessments of therapies in participants representing the global diversity of PWH. Given the low numbers of female participants and participants of Black race in this analysis, findings may not be as generalizable to the majority of PWH worldwide.

Another limitation is that many of the analyses were post hoc. While a 144-week follow-up is lengthy for a clinical trial, cardiometabolic parameters that fluctuate over time (eg, weight) are not completely captured in an analysis at a single time point, and longer follow-up is needed for a comprehensive understanding of the impact of ART on metabolic health. The majority of participants switched from EVG/c/FTC/TAF to DTG/3TC, limiting generalizations for switch from other INSTI-based regimens. Similar to many large analyses of this nature, several potential confounders were not adequately measured, including diet, lifestyle, and risk factors before ART initiation [10]. Finally, proportions of participants with ≥10% weight increase over 3 years were relatively small (12%–13%) —although in line with a 2022 study reporting that ∼10% of PWH who were virologically suppressed experienced ≥10% weight gain within 2 years of switching to TAF or INSTIs [49]—and analyses of the association between this postbaseline status and week 144 cardiometabolic health parameters were not performed due to statistical methodology challenges. Conversely, the strengths of the current analyses include the relatively large sample size, with high retention over 3 years, regular assessments every 12 weeks, and the randomized nature of the comparison between treatment groups. Additionally, the comprehensive nature of this metabolic health evaluation, which included assessment of diet/exercise counseling and leptin levels, is novel for a contemporary clinical trial of a second-generation INSTI.

Our findings support that cardiometabolic parameters in PWH who switched to DTG/3TC were similar to those who continued TAF-based regimens and were generally stable for both groups over 3 years of follow-up, except for lipids, which favored DTG/3TC in the boosted subgroup. Furthermore, demographic and cardiometabolic risk factors known to be associated with lower or higher odds of each cardiometabolic parameter examined were aligned in the TANGO population, underscoring their importance in clinical management and prevention of adverse outcomes in PWH receiving lifelong ART. As the 2DR DTG/3TC has been shown to be potent with durable efficacy, a high barrier to resistance, and good safety, including a comprehensive evaluation of laboratory parameters and inflammatory biomarkers associated with cardiometabolic health [22–24], the long-term use of an additional third antiretroviral agent for the treatment of HIV should be justified. Our findings, in combination with previously demonstrated 3-year durable efficacy and good safety and tolerability, support the 2DR DTG/3TC as a robust switch option [22].

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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