IMPROVED METABOLIC PARAMETERS AFTER SWITCHING FROM TAF-BASED 3- OR 4-DRUG REGIMEN TO THE 2-DRUG REGIMEN OF DTG/3TC (DOLUTEGRAVIR/LAMIVUDINE): THE TANGO STUDY

Jean van Wyk,[1] Mounir Ait-Khaled,[1] Jesus Santos,[2] Stefan Scholten,[3] Michael Wohlfeiler,[4] Faiza Ajana,[5] Bryn Jones,[1] Maria Claudia Nascimento,[1] Allan Tenorio,[6] Don E. Smith,[7] Jonathan Wright,[8] Brian Wynne[6]

[1]ViiV Healthcare, Brentford, UK; [2]Hospital Virgen de la Victoria, Málaga, Spain; [3]Praxis Hohenstaufenring, Cologne, Germany; [4]AIDS Healthcare Foundation, Miami Beach, FL, USA; [5]Centre Hospitalier de Tourcoing, Tourcoing, France; [6]ViiV Healthcare, Research Triangle Park, NC, USA; [7]Albion Centre, Sydney, Australia; [8]GlaxoSmithKline, Stockley Park, UK

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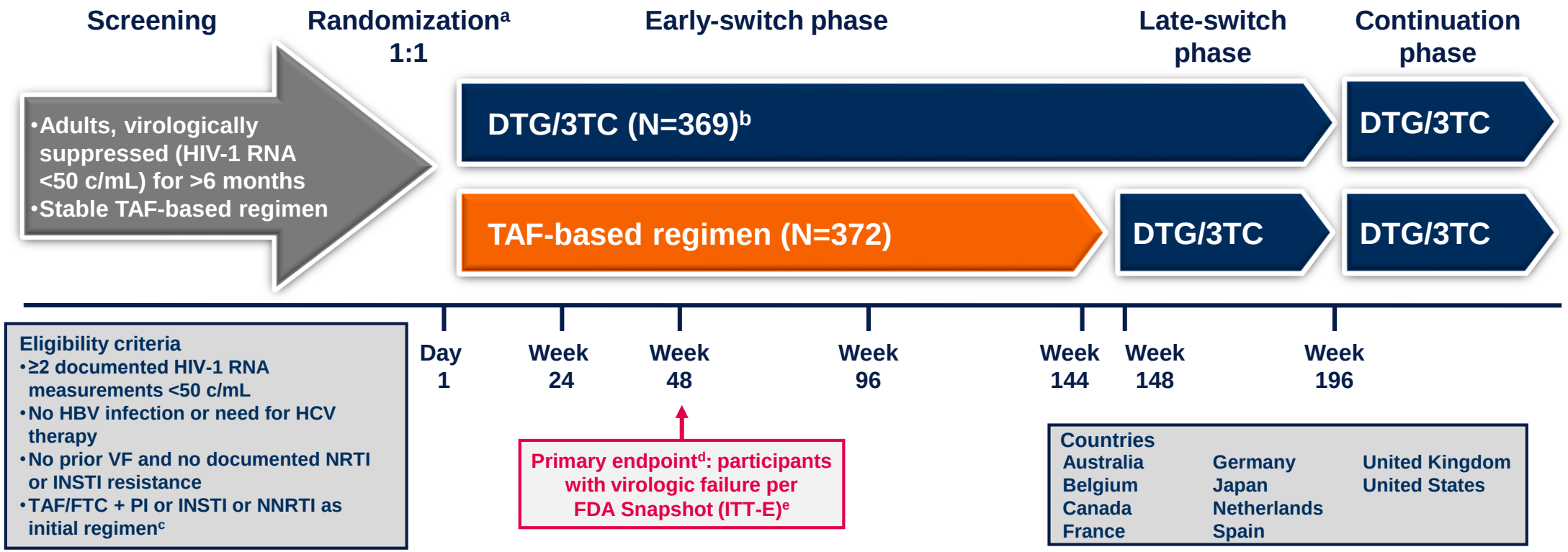
Background

- Primary outcomes at Week 48 of the phase III TANGO study demonstrated that switching to DTG/3TC is non-inferior to continuing a 3- or 4-drug TAF-based regimen for the maintenance of virologic suppression in individuals with HIV-1[1]
- Antiretroviral agents have been associated with weight gain and adverse metabolic health outcomes
  - ART regimens containing the INSTIs DTG, BIC, and EVG/c have been associated with weight gain compared with other core agents[2,3]
  - The NRTI TAF has been associated with weight gain in individuals with HIV-1[2-4] and HIV-negative individuals taking PrEP[5]
  - In the ADVANCE study, participants receiving DTG + TAF/FTC experienced increases from baseline in lipid and glucose levels and increased incidence of metabolic syndrome vs the EVF/TDF/FTC group, and increased 10-year risk of developing diabetes vs the DTG + TDF/FTC group[3]
  - Boosted PIs have been associated with lipid abnormalities, insulin resistance, and central adiposity[6,7]
- Here, we summarize changes in metabolic health outcomes at Week 48 among participants receiving DTG/3TC or a TAF-based regimen in TANGO, including subgroup analyses by baseline boosting status

1. van Wyk et al. *Clin Infect Dis.* 2020 [Epub ahead of print]. **2.** Sax et al. *Clin Infect Dis.* 2019 [Epub ahead of print]. **3.** Hill et al. CROI 2020; Boston, MA. Slides 81. **4.** Schafer et al. *Open Forum Infect Dis.* 2019;6:ofz414. **5.** Ogbuagu et al. CROI 2020; Boston, MA. Slides 92. **6.** DeJesus et al. *Lancet*. 2012;379:2429-2438. **7.** Lake et al. *Clin Infect Dis*. 2017;64:1422-1429.

TANGO Phase III Study Design

Randomized, open-label multicenter, parallel-group, non-inferiority study



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[a]Stratified by baseline third agent class (PI, INSTI, or NNRTI). [b]Two participants excluded who were randomized but not exposed to study drug. [c]Participants with initial TDF treatment who switched to TAF ≥3 months before screening, with no changes to other drugs in their regimen, were also eligible. [d]4% non-inferiority margin. [e]Includes participants who changed a background therapy component or discontinued study treatment for lack of efficacy before Week 48, or who had HIV-1 RNA ≥50 c/mL in the 48-week window.

Metabolic Health Outcomes Analyses

- Post hoc analyses were performed to assess the following metabolic health parameters at Week 48 of TANGO:
  - Change from baseline in weight, fasting lipids, glucose, HbA_{1c}, and insulin
  - Prevalence of insulin resistance[a]
  - Prevalence of metabolic syndrome[b]
- Mixed models for repeated measures analysis was performed on change from baseline in metabolic health parameters at Week 48 in subgroups by boosting status of the baseline regimen (boosted vs unboosted)
- Logistic regression analysis was used to assess factors associated with insulin resistance and metabolic syndrome at Week 48

HOMA-IR, homeostatic model assessment of insulin resistance.

[a]Defined as HOMA-IR ≥2. [b]Defined by the International Diabetes Federation as a combination of risk factors for cardiovascular disease, including diabetes, raised fasting plasma glucose, abdominal obesity, high cholesterol, and high blood pressure.[1]

1. International Diabetes Foundation. *The IDF Consensus Worldwide Definition of the Metabolic Syndrome*. 2006.

Demographics and Baseline Characteristics: ITT-E Population

Characteristic, n (%)[a]	DTG/3TC (N=369)	TAF-based regimen (N=372)
Age, median (range), y	40 (20-74)	39 (18-73)
≥50 y	79 (21)	92 (25)
Female	25 (7)	33 (9)
Race		
African American/African heritage	50 (14)	58 (16)
Asian	13 (4)	13 (3)
White	297 (80)	289 (78)
Other	9 (2)	12 (3)
Ethnicity		
Hispanic or Latino	69 (19)	66 (18)
Not Hispanic or Latino	300 (81)	306 (82)
Weight, mean (SD), kg	81.2 (15.4)	81.7 (15.9)[b]
BMI, mean (SD), kg/m^2	26.3 (4.8)	26.7 (5.1)[b]
Diabetes[c]	12 (3)	18 (5)

[a]Unless otherwise indicated. [b]N=371. [c]One participant in each arm had type 1 diabetes.

van Wyk et al. AIDS 2020; Virtual. Slides OAB0606.

Demographics and Baseline Characteristics: ITT-E Population (cont)

Characteristic, n (%)[a]	DTG/3TC (N=369)	TAF-based regimen (N=372)
CD4+ cell count, median (range), cells/mm^3	682 (133-1904)	720 (119-1810)
CD4+ cell count, <350 cells/mm^3	35 (9)	30 (8)
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)
Boosted	272 (74)	277 (74)
Unboosted	97 (26)	93 (25)
Duration of ART before Day 1, median (range), mo	33.8 (7.1-201.2)	35.1 (7.0-160.8)
Duration of TAF before Day 1, median (range), mo	17.7 (3.6-73.7)	18.2 (3.9-71.2)

[a]Unless otherwise indicated.

Baseline Metabolic Health Was Similar Between Treatment Arms

Metabolic health parameter	Overall		Boosted		Unboosted	
	DTG/3TC (N=369)	TAF-based regimen (N=370)	DTG/3TC (N=272)	TAF-based regimen (N=277)	DTG/3TC (N=97)	TAF-based regimen (N=93)
Metabolic syndrome, n (%)[a]	36 (10)	41 (11)	22 (8)	26 (9)	14 (14)	15 (16)
Obesity	63 (17)	77 (21)	39 (14)	52 (19)	24 (25)	25 (27)
Raised triglycerides	116 (31)	98 (26)	92 (34)	76 (27)	24 (25)	22 (24)
Reduced HDL	64 (17)	69 (19)	41 (15)	48 (17)	23 (24)	21 (23)
Raised blood pressure	154 (42)	148 (40)	110 (40)	103 (37)	44 (45)	45 (48)
Raised fasting glucose	89 (24)	88 (24)	65 (24)	59 (21)	24 (25)	29 (31)
Fasting insulin, median (range), pmol/L	72.0 (11-582)	72.0 (11-690)	72.0 (11-582)	72.0 (11-690)	78.0 (11-558)	66.0 (18-420)
HOMA-IR, median (range)[b]	2.80 (0.5-35.4)	2.60 (0.6-35.5)	2.60 (0.5-35.4)	2.60 (0.6-35.5)	3.0 (0.6-22.7)	2.7 (0.9-18.4)
HOMA-IR ≥2, n (%)[c]	222 (73)	210 (72)	—	—	—	—

[a]Participants who have BMI ≥30 kg/m^2 and who satisfy any 2 of the raised/reduced factors within the baseline visit window. Raised triglycerides, ≥150 mg/dL or treatment; reduced HDL, <40 mg/dL (males), <50 mg/dL (females), 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. [b]HOMA-IR = fasting plasma insulin (mU/L) × fasting plasma glucose (mmol/L)/22.5. [c]Percentages based on participants with HOMA-IR data at baseline and Week 48: DTG/3TC, N=303; TAF-based regimen, N=291.

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Weight Changes From Baseline at Week 48 Were Small and Comparable Between Treatment Groups

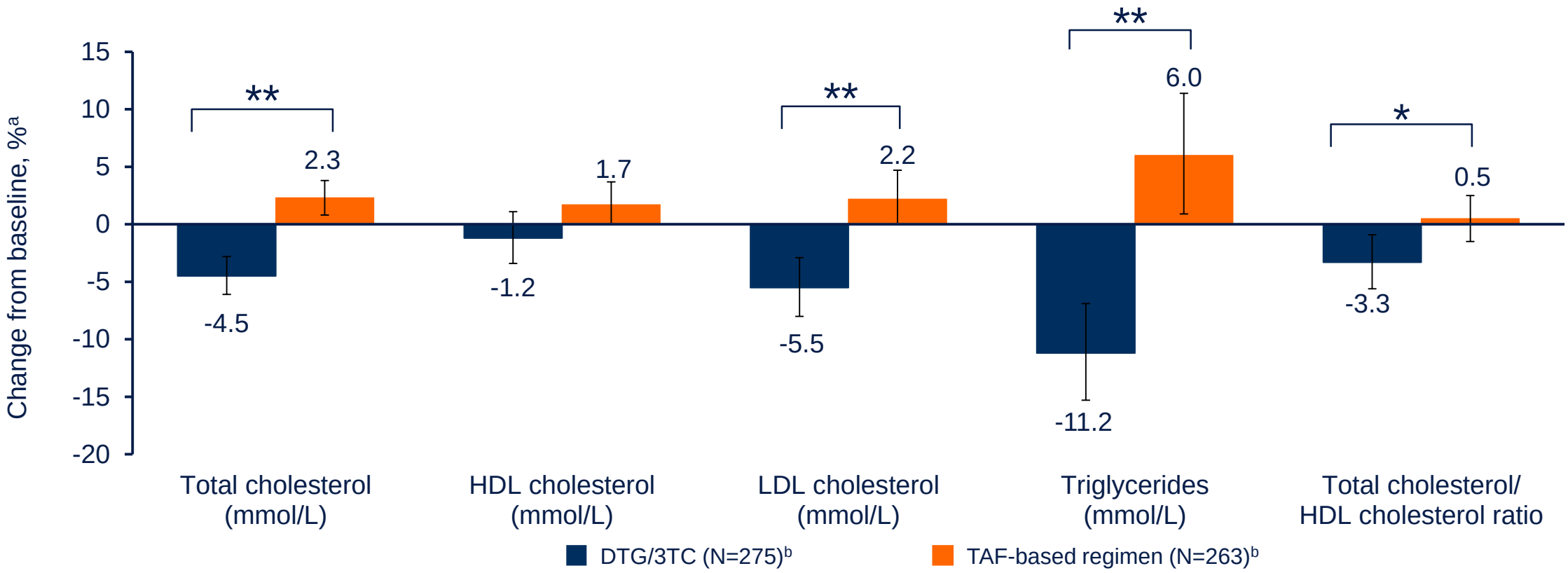
- Adjusted[a] mean (SE) change from baseline in weight (kg) in the DTG/3TC and TAF-based regimen arms, respectively, was 0.81 (0.27) and 0.88 (0.25) in the boosted subgroup and 0.81 (0.45) and 0.40 (0.44) in the unboosted subgroup

Weight parameter	DTG/3TC (N=343)	TAF-based regimen (N=343)
Adjusted[b] change from baseline, mean (SE), kg	0.81 (0.23)	0.76 (0.22)
Prior TAF duration <1 y[c]	1.45 (0.46)	1.35 (0.47)
Prior TAF duration ≥1 y[d]	0.60 (0.26)	0.60 (0.25)
Increased from baseline, n (%)		
≥10%	11 (3)	13 (4)

N, number of participants with available weight data at baseline and Week 48. Comparisons for difference between treatment arms for adjusted mean weight change are not statistically significant.

[a]Adjusted mean is the estimated mean change from baseline at Week 48 in each arm calculated from a repeated measures model. Boosted and unboosted subgroups adjusted for treatment, visit, baseline boosting status, CD4+ cell count (continuous), age (continuous), sex, weight at baseline (continuous), race, treatment-by-visit interaction, baseline-by-visit interaction, treatment-by-boosting status interaction, boosting status-by-visit interaction, and boosting status-by-treatment-by-visit interaction, with visit as the repeated factor. [b]Overall population adjusted for treatment, visit, baseline third agent class, CD4+ cell count (continuous), age (continuous), sex, race, weight at baseline (continuous), treatment-by-visit interaction, and baseline value-by-visit interaction, with visit as the repeated factor. TAF duration subgroups adjusted for same variables as the boosting status subgroups, except baseline boosting status and treatment-by-baseline boosting status interaction was replaced with prior TAF duration (<1 vs ≥1 y) and treatment-by-prior TAF duration interaction, respectively. [c]DTG/3TC, n=83; TAF-based regimen, n=76. [d]DTG/3TC, n=260; TAF-based regimen, n=267.

Changes From Baseline in Lipids Generally Favored the DTG/3TC Arm in the Overall Population



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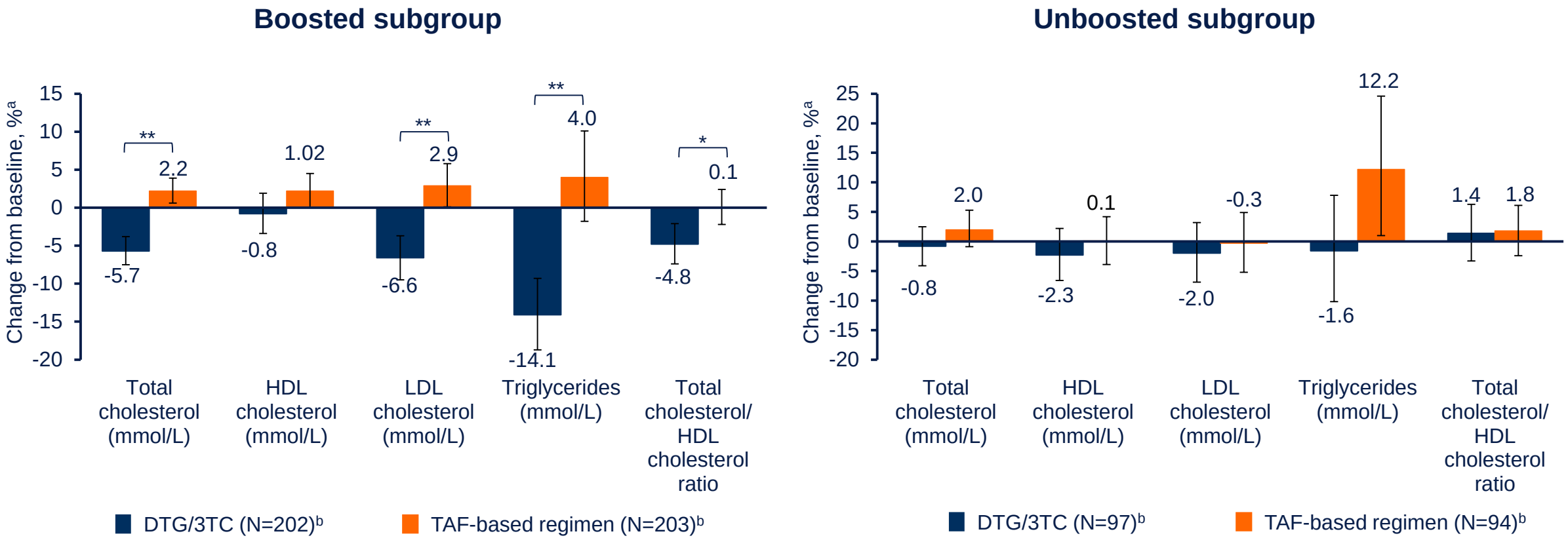
[a]Percent change from baseline with 95% CIs based on adjusted geometric mean ratio (Week 48 to baseline) in each arm calculated from a repeated measures model applied to change from baseline in $\log_e$-transformed data adjusting for the following: treatment, visit, baseline third agent class, CD4+ cell count (continuous), $\log_e$-transformed baseline value (continuous), treatment-by-visit interaction, and baseline value-by-visit interaction, with visit as the repeated factor. [b]Number of participants with non-missing fasting lipid data at baseline and Week 48, removing those with lipid-modifying agent administered at baseline.

**P*=0.017. ***P*<0.001.

Changes From Baseline in Lipids Generally Favored the DTG/3TC Arm in the Boosted Subgroup



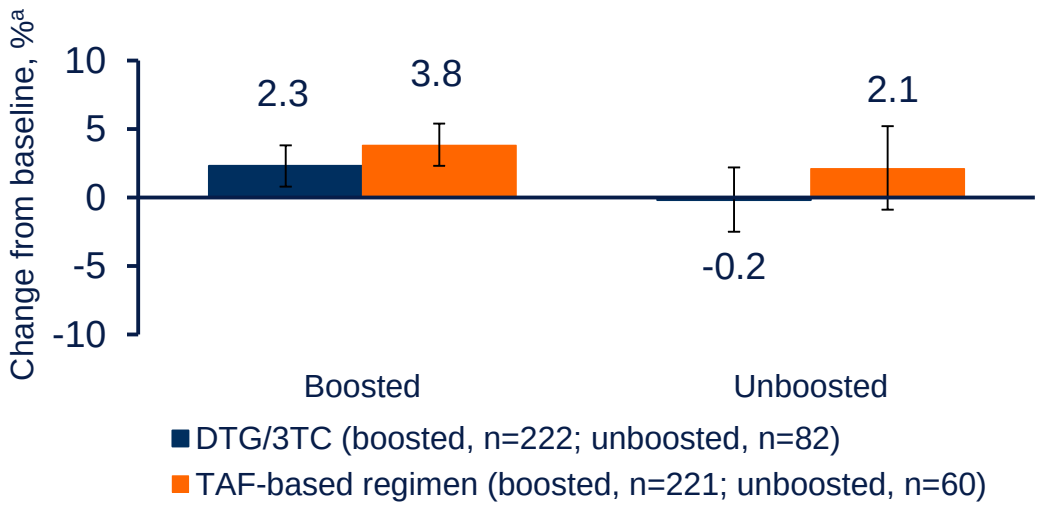
[a]Percent change from baseline with 95% CIs based on adjusted geometric mean ratio (Week 48 to baseline) in each arm calculated from a repeated measures model applied to change from baseline in $\log_e$-transformed data adjusting for the following: treatment, visit, baseline boosting status, CD4+ cell count (continuous), $\log_e$-transformed baseline value (continuous), treatment-by-visit interaction, baseline value-by-visit interaction, treatment-by-baseline boosting status interaction, baseline boosting status-by-visit interaction, and baseline boosting status-by-treatment-by-visit interaction, with visit as the repeated factor. [b]Number of participants with non-missing fasting lipid data at baseline and Week 48, removing those with lipid-modifying agent administered at baseline.

**P*=0.007. ***P*<0.001.

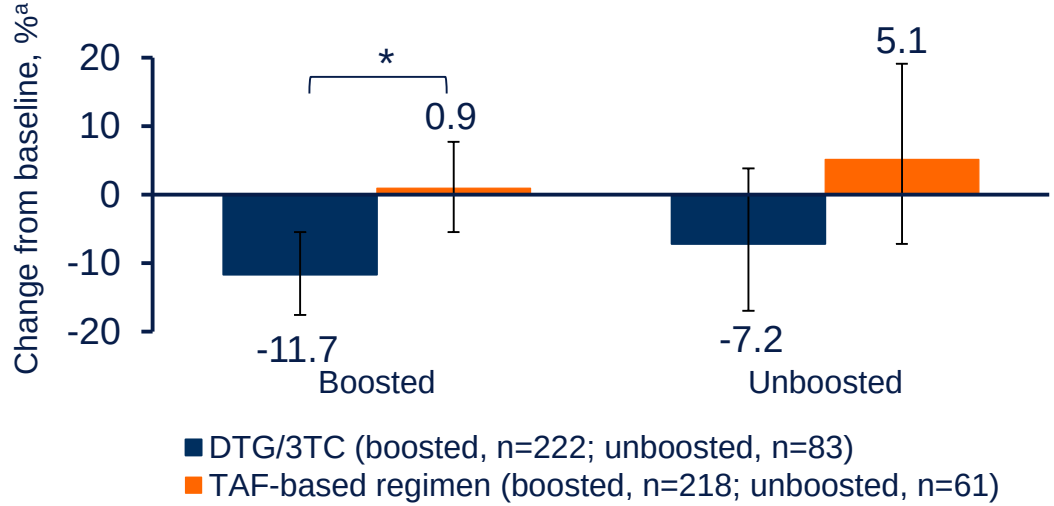
Changes From Baseline in Fasting Glucose, HbA_{1c}, and Insulin

- Median changes from baseline in HbA_{1c} (DTG/3TC, 5.3%; TAF-based regimen, 5.4%) and adjusted mean changes from baseline in fasting glucose were small and similar across treatment arms
- Adjusted mean change in fasting insulin favored the DTG/3TC arm in both the boosted and unboosted subgroups and was significant for the boosted subgroup

Change from baseline in fasting glucose



Change from baseline in fasting insulin



n, number of participants with available data at baseline (including all covariate data) and Week 48. [a]Percent change from baseline with 95% CIs based on adjusted geometric mean ratio (Week 48 to baseline) in each arm calculated from a repeated measures model applied to change from baseline in $\log_e$- transformed data adjusting for the following: treatment, visit, baseline boosting status, CD4+ cell count (continuous), $\log_e$-transformed baseline value (continuous), treatment-by-visit interaction, baseline-by-visit interaction, treatment-by-boosting status interaction, boosting status-by-visit interaction, and boosting status-by-treatment-by-visit interaction, with visit as the repeated factor.

**P*=0.006.

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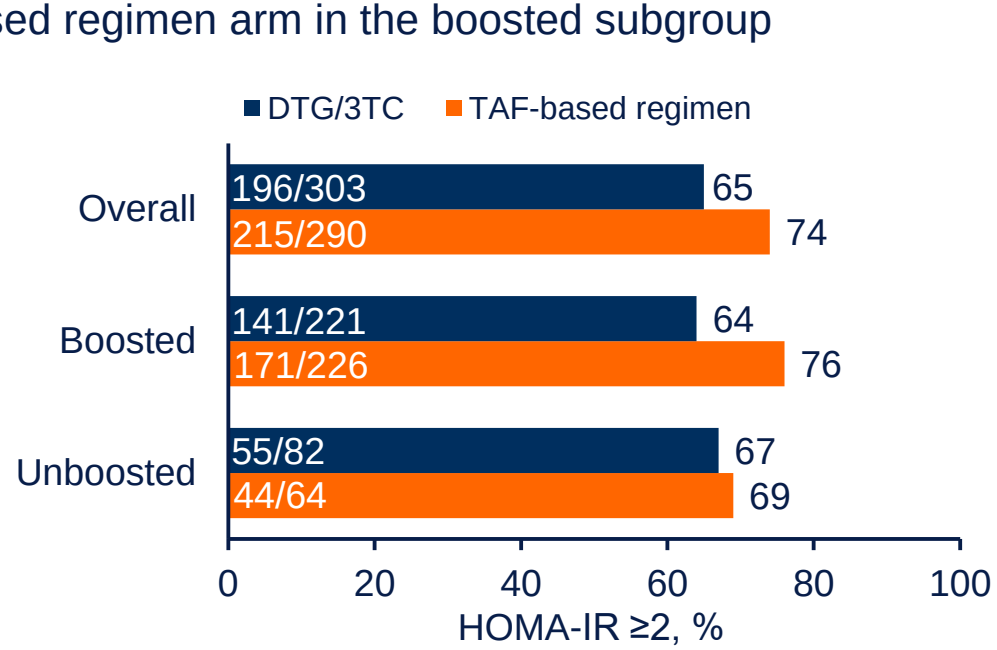
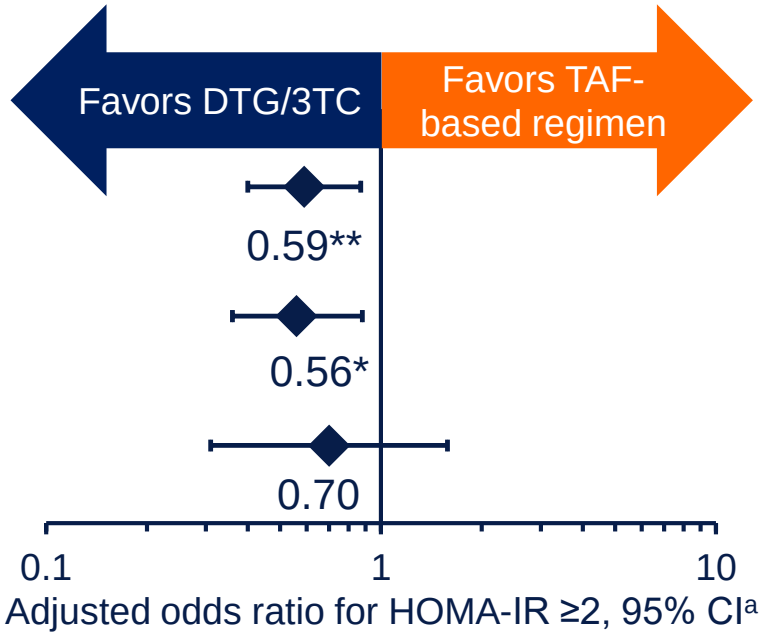
Insulin Resistance at Week 48

- Change from baseline in adjusted geometric mean HOMA-IR was −9.7% in the DTG/3TC arm and 4.5% in the TAF-based regimen arm (*P*=0.001)
- Odds of insulin resistance (HOMA-IR ≥2; adjusted odds ratio) was significantly lower in the DTG/3TC arm vs the TAF-based regimen arm in the boosted subgroup





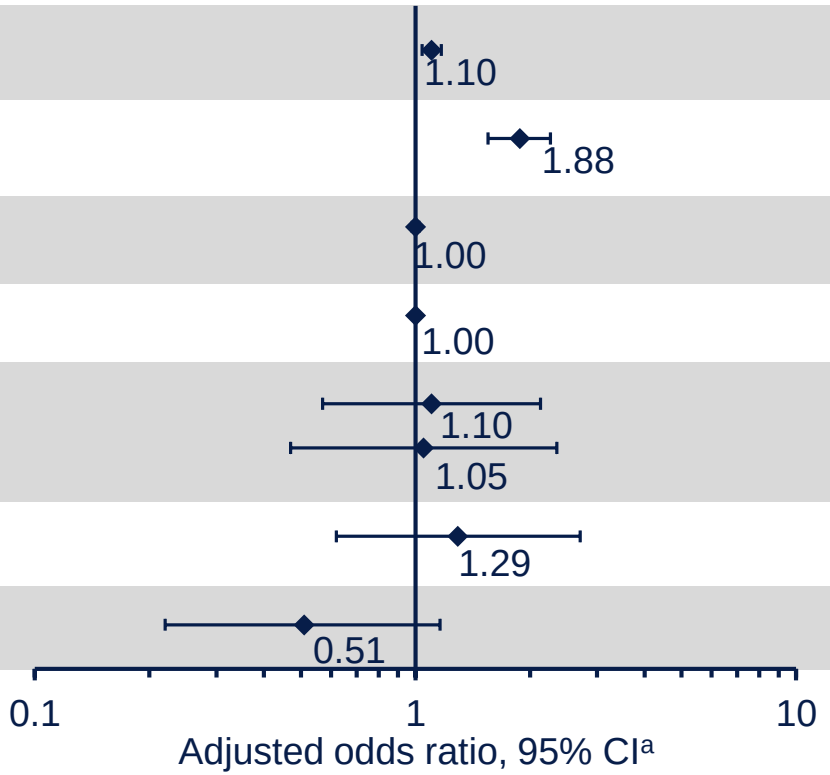
[a]Odds ratios and 95% CIs were calculated using a logistic regression model. Overall population adjusted for treatment, baseline third agent class, CD4+ cell count (continuous), age (continuous), sex, race, baseline BMI (continuous), baseline hypertension, baseline smoking status, log-transformed baseline HOMA-IR (continuous), and treatment-by-baseline third class agent interaction. Boosted and unboosted subgroups adjusted for treatment regimen (DTG/3TC vs TAF-based regimen), baseline boosting status (boosted vs unboosted), race (black, other vs white), sex (female vs male), baseline BMI (continuous), baseline CD4+ cell count (continuous), age (continuous), baseline hypertension (yes vs no), log-transformed baseline HOMA-IR (continuous), and treatment-by-baseline boosting status interaction.

**P*=0.012 in boosted subgroup. ***P*=0.008 in overall population.

Association of Other Baseline Factors With Insulin Resistance at Week 48

- In addition to treatment effects, increases from baseline in BMI and HOMA-IR were associated with significantly increased odds of HOMA-IR ≥2 at Week 48

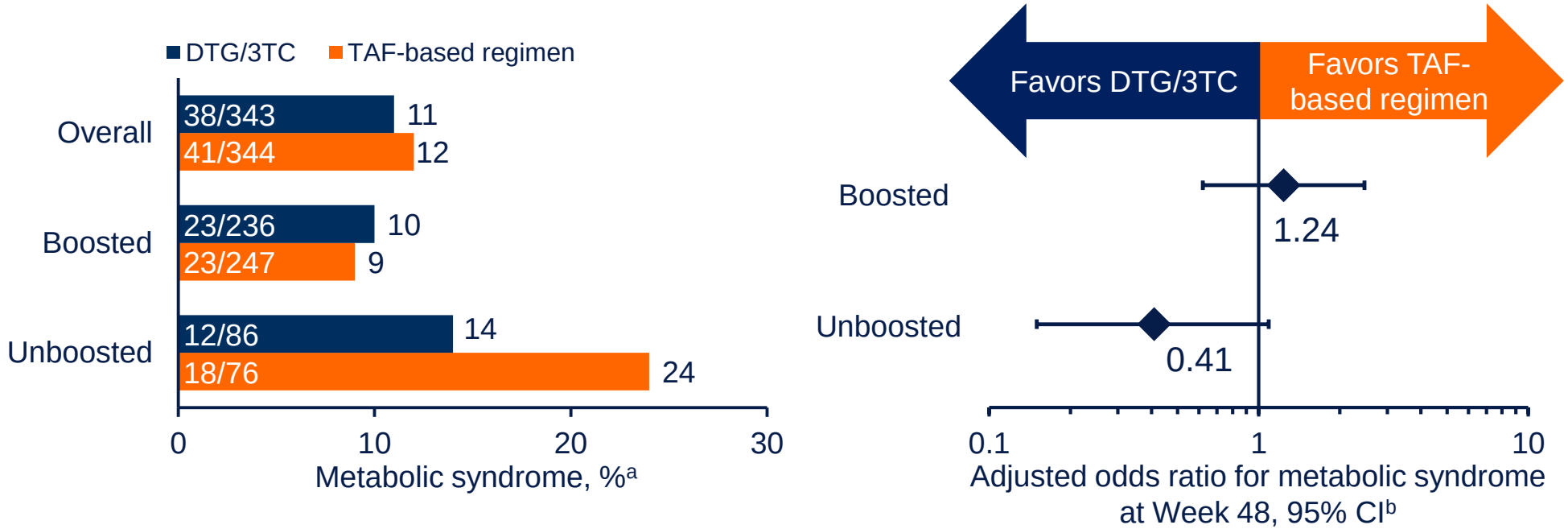
BMI	Continuous (per unit increase)	1.10	*P*=0.001
HOMA-IR	Continuous (per unit increase)	1.88	*P*<0.001
Age	Continuous (per unit increase)	1.00	*P*=0.944
CD4+ cell count	Continuous (per unit increase)	1.00	*P*=0.553
Race (vs white)	Black or African American	1.10	*P*=0.771
	Other	1.05	*P*=0.899
Hypertension status	Yes	1.29	*P*=0.498
Sex (vs male)	Female	0.51	*P*=0.108



[a]Odds ratios and 95% CIs were calculated using a logistic regression model adjusting for treatment regimen (DTG/3TC vs TAF-based regimen), baseline boosting status (boosted vs unboosted), race (black, other vs white), sex (female vs male), baseline BMI (continuous), baseline CD4+ cell count (continuous), age (continuous), baseline hypertension (yes vs no), baseline HOMA-IR (continuous), and treatment-by-baseline boosting status interaction.

Metabolic Syndrome at Week 48

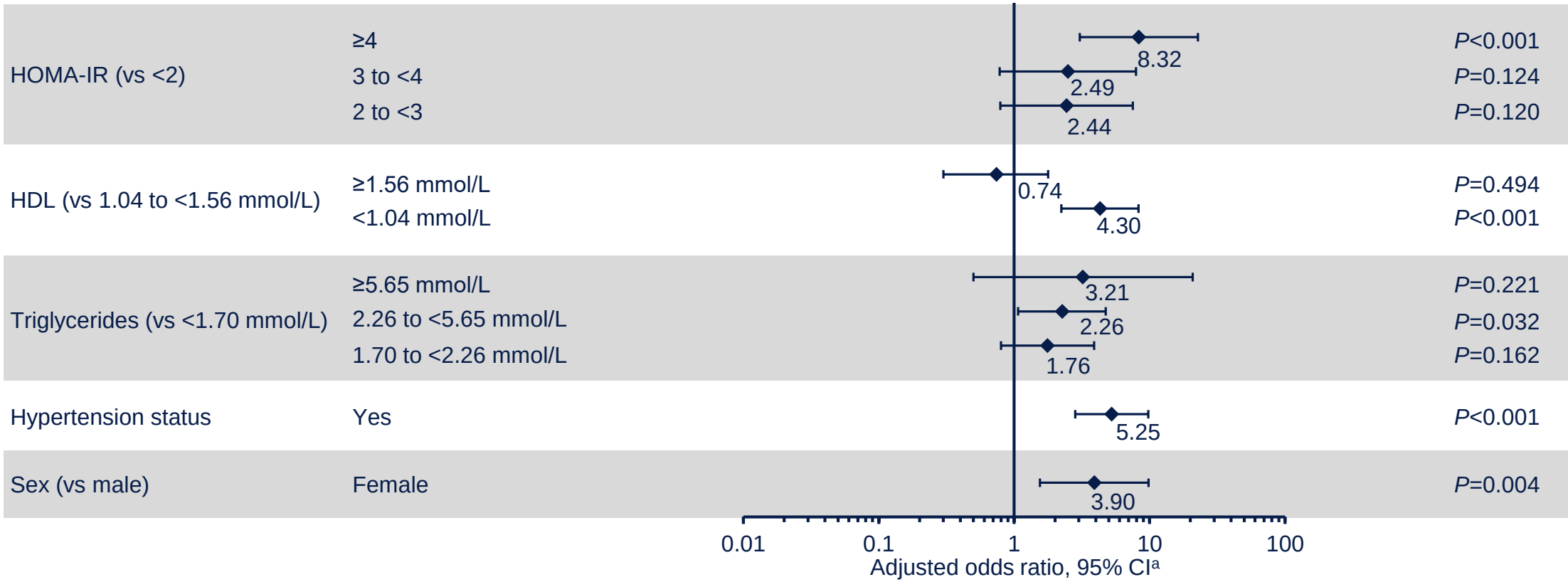
- Proportions of participants with metabolic syndrome were 11% and 12% in the DTG/3TC and TAF-based regimen arms, respectively
- The odds of metabolic syndrome (adjusted odds ratio) was lower in the DTG/3TC arm vs the TAF-based regimen arm in the unboosted subgroup but did not reach statistical significance (*P*=0.075)



[a]Overall population includes participants with Week 48 metabolic syndrome data; boosting status subgroups include participants with Week 48 metabolic syndrome data and no missing baseline covariate data used in the logistic regression model. [b]Odds ratios and 95% CIs were calculated using a logistic regression model adjusting for treatment regimen (DTG/3TC vs TAF-based regimen), baseline boosting status (boosted vs unboosted), sex (female vs male), baseline hypertension (yes vs no), baseline triglycerides (borderline high, high, very high vs normal), baseline HDL (low, high vs normal), baseline HOMA-IR (2 to <3, 3 to <4, ≥4 vs <2), and treatment-by-baseline boosting status interaction.

Association of Baseline Factors With Metabolic Syndrome at Week 48

- In addition to treatment effects, increased odds of metabolic syndrome at Week 48 were observed for female participants and those with hypertension, high triglycerides, low HDL, and HOMA-IR ≥4 at baseline



[a]Odds ratios and 95% CIs were calculated using a logistic regression model adjusting for treatment regimen (DTG/3TC vs TAF-based regimen), baseline boosting status (boosted vs unboosted), sex (female vs male), baseline hypertension (yes vs no), baseline triglycerides (borderline high, high, very high vs normal), baseline HDL (low, high vs normal), baseline HOMA-IR (2 to <3, 3 to <4, ≥4 vs <2), and treatment-by-baseline boosting status interaction.

Adverse Events Related to Metabolic Health Were Low in Both Treatment Arms

Metabolic AE, n (%)[a]	Overall		Boosted		Unboosted	
	DTG/3TC (N=306)	TAF-based regimen (N=293)	DTG/3TC (N=233)	TAF-based regimen (N=225)	DTG/3TC (N=73)	TAF-based regimen (N=68)
Investigations						
Weight decreased	0	1 (<1)	0	0	0	1 (1)
Weight increased	1 (<1)	0	1 (<1)	0	0	0
Metabolism and nutrition disorders						
Hyperlipidemia	1 (<1)	0	0	0	1 (1)	0
Type 1 diabetes	1 (<1)	0	1 (<1)	0	0	0
Type 2 diabetes	2 (<1)	0	2 (<1)	0	0	0

[a]Percentages are based on number of participants not obese at baseline.

Conclusions

- Switching from a 3- or 4-drug TAF-based regimen to the 2-drug regimen of DTG/3TC led to similar small increases in weight, but overall improvements in other metabolic health parameters, over 48 weeks
- More pronounced differences favoring the DTG/3TC arm were observed in the boosted subgroup for lipids, fasting insulin, and insulin resistance
- In the unboosted subgroup, there was a trend observed in favor of DTG/3TC for prevalence of metabolic syndrome at Week 48, although this did not reach statistical significance
- Metabolic health is multi-factorial and complex; clinical trials specifically designed to assess the potential long-term metabolic health impact of removing TAF from ART regimens are needed