ViiV Healthcare's European Webinar

RECENT UPDATES IN THE MANAGEMENT OF HIV

Catch up on the presentations from:
22nd July 2020 - Virtual Meeting

ViiV Healthcare

Dovato
dolutegravir/lamivudine

PM-GB-DLL-PPT-200007 August 2020

THE AGENDA FOR THE LIVE WEBINAR

Time	Session	Speaker	Provided on ViiV Exchange website
16:00–16:05	Welcome and opening	Dr Tia Vincent	No
16:05–16:15	**Metabolic parameters in the TANGO study**	**Dr Jean van Wyk**	**Yes**
16:15–16:25	**Other important topics from AIDS 2020, including summary of COVID-19 conference**	**Prof. José Gatell**	**Yes**
16:25–16:55	Panel discussion on latest data from AIDS 2020 and Q&A	Dr Tia Vincent, Dr Jean van Wyk, Prof. José Gatell, Dr Juan Berenguer and Dr Laura Waters	No
16:55–17:00	Meeting summary and close	Dr Tia Vincent	No

METABOLIC PARAMETERS IN THE TANGO STUDY

Dr Jean van Wyk

Global Medical Lead
Dolutegravir
ViiV Healthcare

CONFLICTS OF INTEREST – JEAN VAN WYK

- I am an employee of ViiV Healthcare

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]

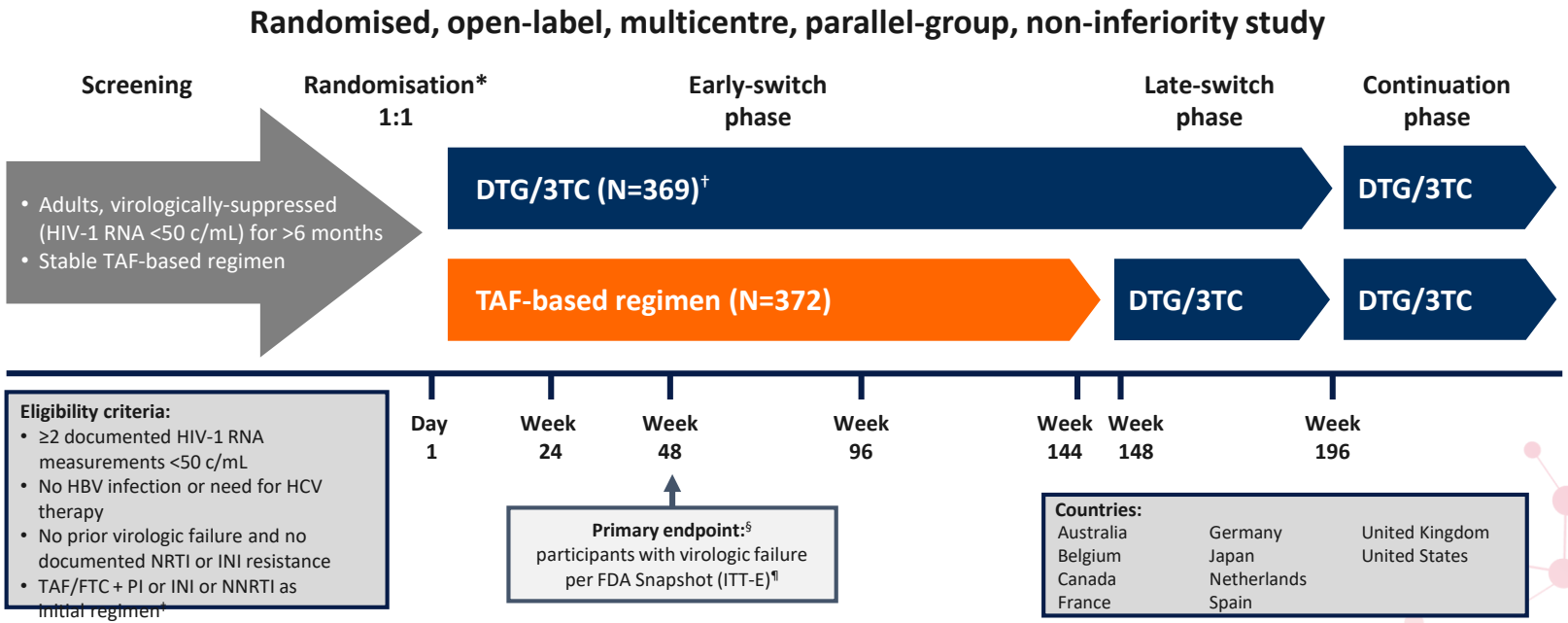
- ARV agents have been associated with weight gain and adverse metabolic health outcomes
  - ART regimens containing the INIs DTG, BIC and EVG/c have been associated with weight gain compared with
    other core agents[2,3]
  - The NRTI TAF has been associated with weight gain in individuals with HIV-1[2–4] and HIV-negative individuals
    taking PrEP[5]
  - In the ADVANCE study, participants receiving DTG + TAF/FTC experienced increases from BL in lipid and glucose levels and increased incidence of metabolic syndrome versus the EFV/TDF/FTC group, and increased
    10-year risk of developing diabetes versus the DTG + TDF/FTC group[3]
  - bPIs have been associated with lipid abnormalities, insulin resistance and central adiposity[6,7]

- Here, we summarise changes in metabolic health outcomes at Week 48 among participants

/c, cobicistat boosted; **3TC,** lamivudine; **ART,** antiretroviral therapy; **ARV,** antiretroviral; **BIC,** bictegravir
BL, baseline; **bPI,** boosted protease inhibitor; **DTG,** dolutegravir; **EFV,** efavirenz; **EVG,** elvitegravir
FTC, emtricitabine; **INI,** integrase inhibitor; **NRTI,** nucleoside reverse transcriptase inhibitor
PrEP, pre-exposure prophylaxis; **TAF,** tenofovir alafenamide; **TDF,** tenofovir disoproxil fumarate

1. van Wyk J, et al. Clin Infect Dis 2020 [Epub ahead of print]; **2.** Sax PE, et al. Clin Infect Dis 2019 [Epub ahead of print]
3. Hill A, et al. CROI 2020. Oral presentation 81; **4.** Schafer JJ, et al. Open Forum Infect Dis 2019;6:ofz414
5. Ogbuagu O, et al. CROI 2020. Oral presentation 92; **6.** DeJesus E, et al. Lancet 2012;379:2429–38
7. Lake JE, et al. Clin Infect Dis 2017;64:1462–9; **8.** van Wyk J, et al. AIDS 2020. Oral presentation OAB0606

TANGO PHASE III STUDY DESIGN



*Stratified by BL third-agent class (PI, INI or NNRTI); †Two participants excluded who were randomised but not exposed to study drug; ‡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; §4% non-inferiority margin; ¶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

c/mL, copies/mL; **FDA,** US Food and Drug Administration; **HBV,** hepatitis B virus; **HCV,** hepatitis C virus; **ITT-E,** intention-to-treat exposed **NNRTI,** non-nucleoside reverse transcriptase inhibitor; **PI,** protease inhibitor; **VF,** virologic failure

van Wyk J, et al. Clin Infect Dis 2020 [Epub ahead of print]

METABOLIC HEALTH OUTCOMES ANALYSES

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

*Defined as HOMA-IR ≥2
†Defined by the International Diabetes Federation as a combination of risk factors for CVD, including diabetes, raised fasting
plasma glucose, abdominal obesity, high cholesterol and high blood pressure
CVD, cardiovascular disease; **HbA_{1c},** haemoglobin A_{1C}; **HOMA-IR,** homeostatic model assessment of insulin resistance[1]

1. van Wyk J, et al. AIDS 2020. Oral presentation OAB0606
2. International Diabetes Federation. The IDF Consensus Worldwide Definition of the Metabolic Syndrome. 2006. Available from https://www.idf.org/component/attachments/attachments.html?id=705&task=download [Accessed July 2020]

DEMOGRAPHICS AND BASELINE CHARACTERISTICS: ITT-E POPULATION

Characteristic, n (%)*	DTG/3TC (N=369)	TAF-based regimen (N=372)
Age, median (range), years	40 (20–74)	39 (18–73)
≥50 years	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)†
BMI, mean (SD), kg/m^2	26.3 (4.8)	26.7 (5.1)†
Diabetes‡	12 (3)	18 (5)

*Unless otherwise indicated; †N=371; ‡One participant in each arm had type 1 diabetes
BMI, body mass index; **SD**, standard deviation

van Wyk J, et al. AIDS 2020. Oral presentation OAB0606

DEMOGRAPHICS AND BASELINE CHARACTERISTICS: ITT-E POPULATION (CONT'D)

Characteristic, n (%)*	DTG/3TC (N=369)	TAF-based regimen (N=372)
CD4+ cell count, median (range), cells/mm^3	682 (133–1,904)	720 (119–1,810)
CD4+ cell count, <350 cells/mm^3	35 (9)	30 (8)
BL third-agent class		
INI	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), months	33.8 (7.1–201.2)	35.1 (7.0–160.8)
Duration of TAF before Day 1, median (range), months	17.7 (3.6–73.7)	18.2 (3.9–71.2)

*Unless otherwise indicated
bDRV, boosted darunavir; **CD4**, cluster of differentiation 4; **RPV**, rilpivirine

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 (%)*	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)†	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 (%)‡	222 (73)	210 (72)	—	—	—	—

†HOMA-IR = fasting plasma insulin (mU/L) × fasting plasma glucose (mmol/L)/22.5; ‡Percentages based on participants with HOMA-IR data at baseline and Week 48: DTG/3TC, N=303; TAF-based regimen, N=291

HDL, high-density lipoprotein

van Wyk J, et al. AIDS 2020. Oral presentation OAB0606

WEIGHT CHANGES FROM BASELINE AT WEEK 48 WERE SMALL AND COMPARABLE BETWEEN TREATMENT GROUPS

- Adjusted* mean change (SE) from BL 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† change from BL, mean (SE), kg	0.81 (0.23)	0.76 (0.22)
Prior TAF duration <1 year‡	1.45 (0.46)	1.35 (0.47)
Prior TAF duration ≥1 year§	0.60 (0.26)	0.60 (0.25)
Increased from BL, n (%)		
≥10%	11 (3)	13 (4)

N, number of par . significant

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

SE, standard error

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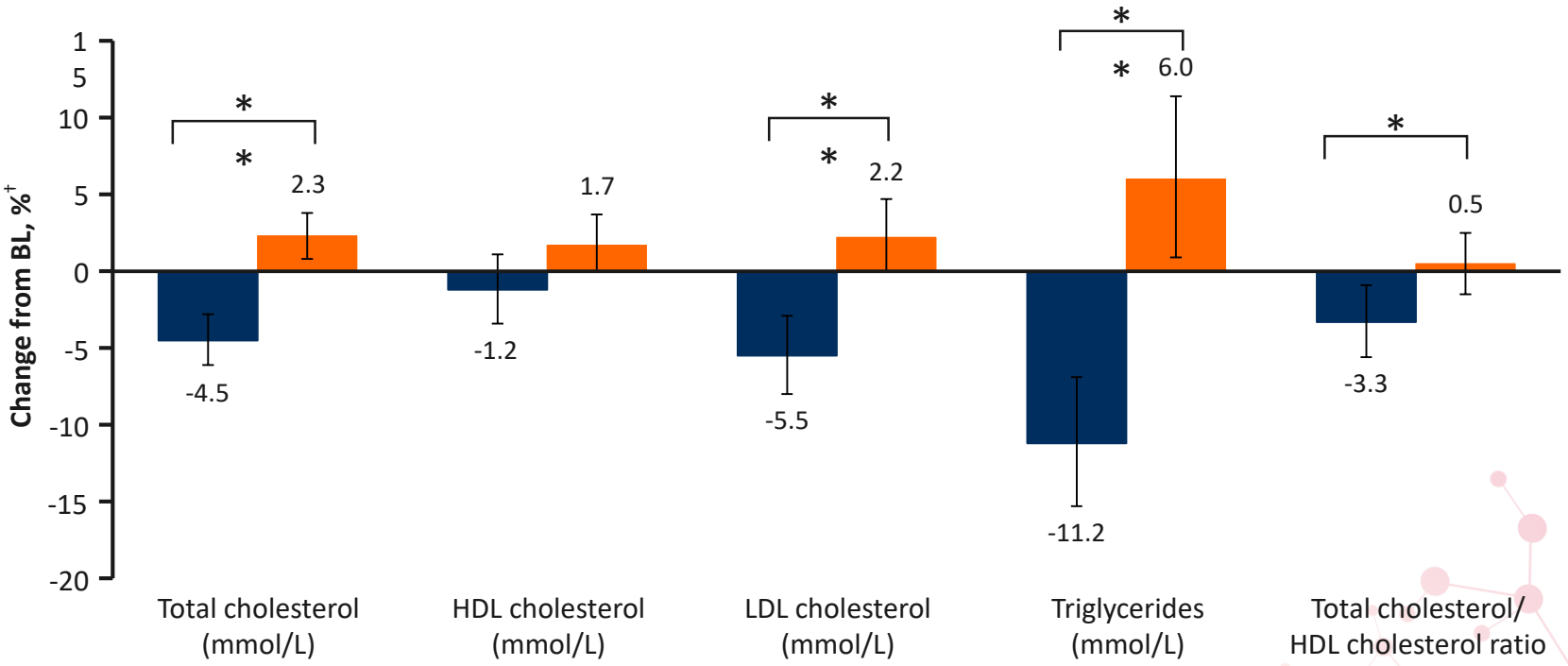
CHANGES FROM BASELINE IN LIPIDS GENERALLY FAVOURED THE DTG/3TC ARM IN THE OVERALL POPULATION



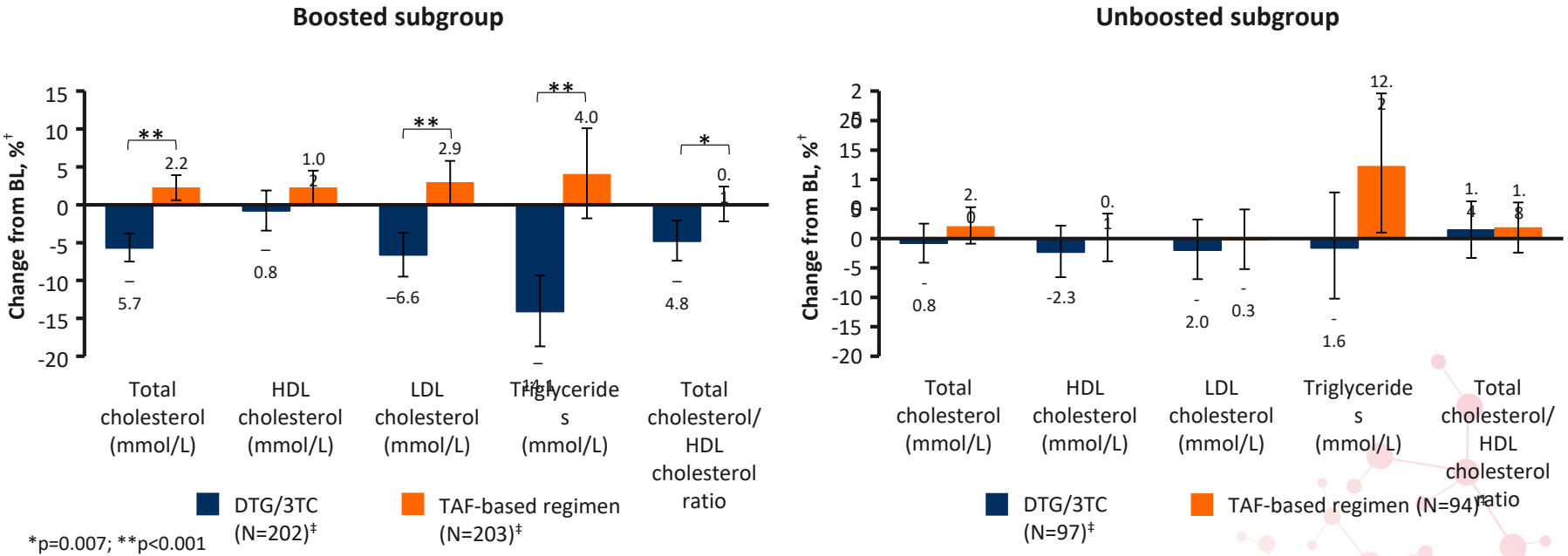
*p=0.017; **p<0.001

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

CI, confidence interval; **LDL,** low-density lipoprotein

van Wyk J, et al. Clin Infect Dis 2020 [Epub ahead of print]

CHANGES FROM BASELINE IN LIPIDS GENERALLY FAVOURED THE DTG/3TC ARM IN THE BOOSTED SUBGROUP



*p=0.007; **p<0.001

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

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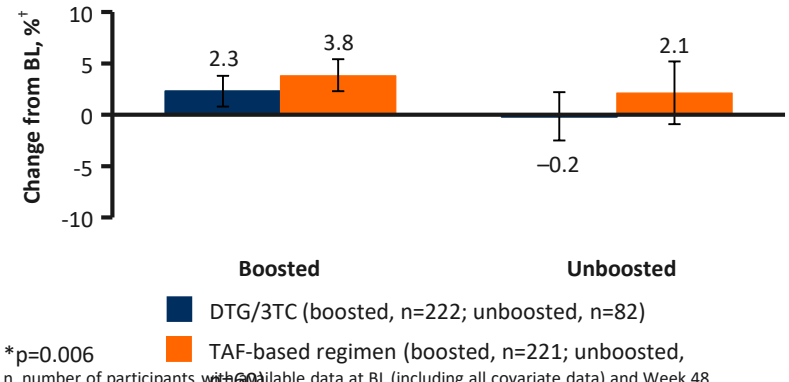
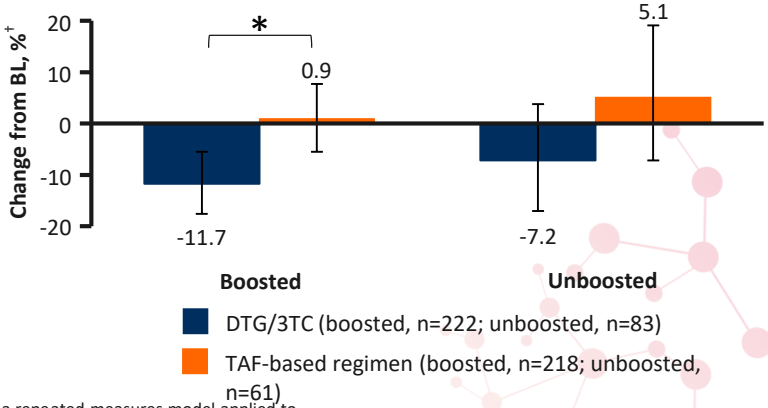
CHANGES FROM BASELINE IN FASTING GLUCOSE, HBA_{1C} AND INSULIN

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

Change from BL in fasting glucose



Change from BL in fasting insulin



*p=0.006

n, number of participants with available data at BL (including all covariate data) and Week 48

†Percent change from BL with 95% CIs based on adjusted geometric mean ratio (Week 48 to BL) in each arm calculated from a repeated measures model applied to change from BL in log_e-transformed data adjusting for the following: treatment, visit, BL boosting status, CD4+ cell count (continuous), log_e-transformed BL value (continuous), treatment-by-visit interaction,
BL-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

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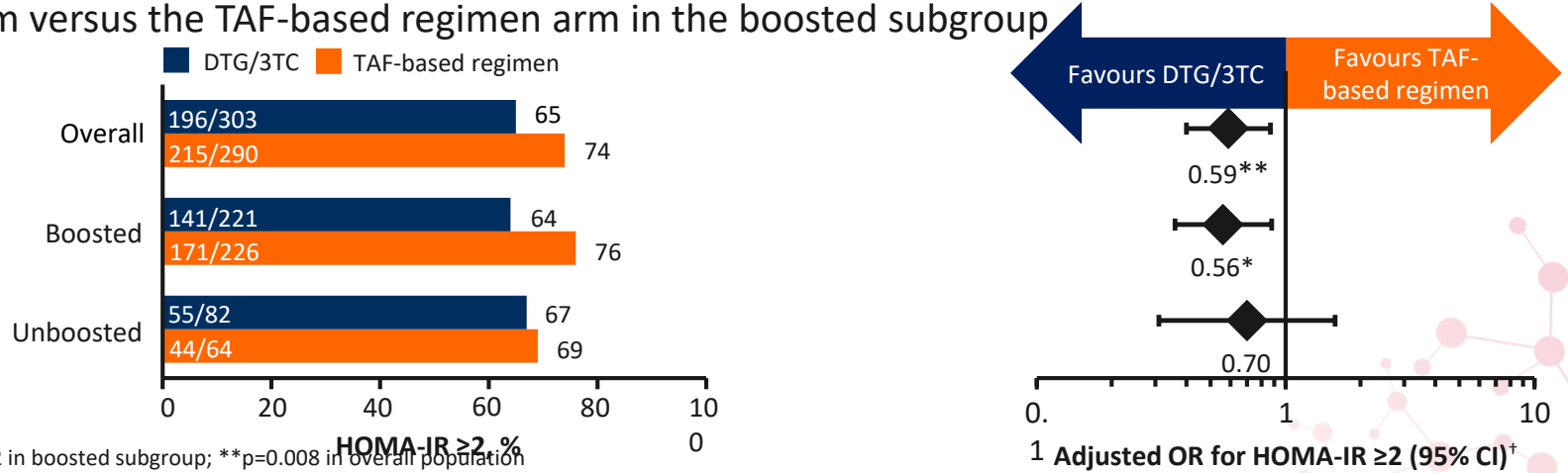
INSULIN RESISTANCE AT WEEK 48

- Change from BL 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 OR) was significantly lower in the DTG/3TC arm versus the TAF-based regimen arm in the boosted subgroup



*p=0.012 in boosted subgroup; **p=0.008 in overall population

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

OR, odds ratio

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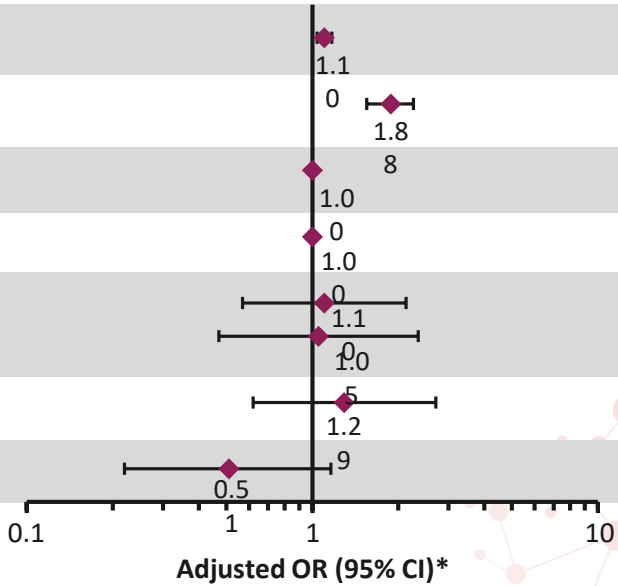
ASSOCIATION OF OTHER BASELINE FACTORS WITH INSULIN RESISTANCE AT WEEK 48

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

		p-value
BMI	Continuous (per unit increase)	0.001
HOMA-IR	Continuous (per unit increase)	<0.001
Age	Continuous (per unit increase)	0.944
CD4+ cell count	Continuous (per unit increase)	0.553
Race (vs white)	Black or African-American	0.771
	Other	0.899
Hypertension status	Yes	0.498
Sex (vs male)	Female	0.108



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

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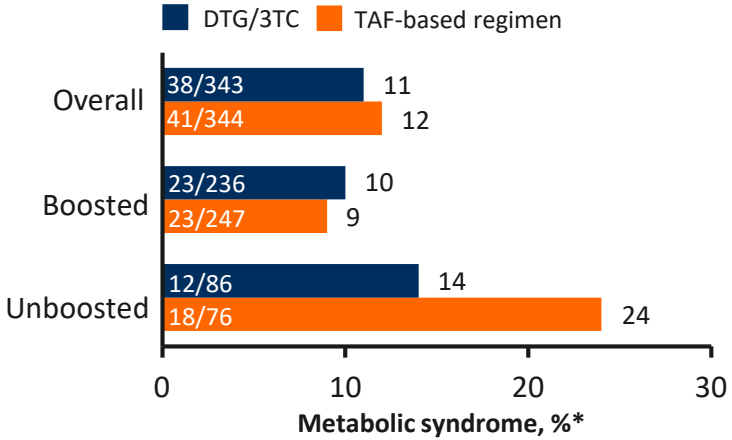
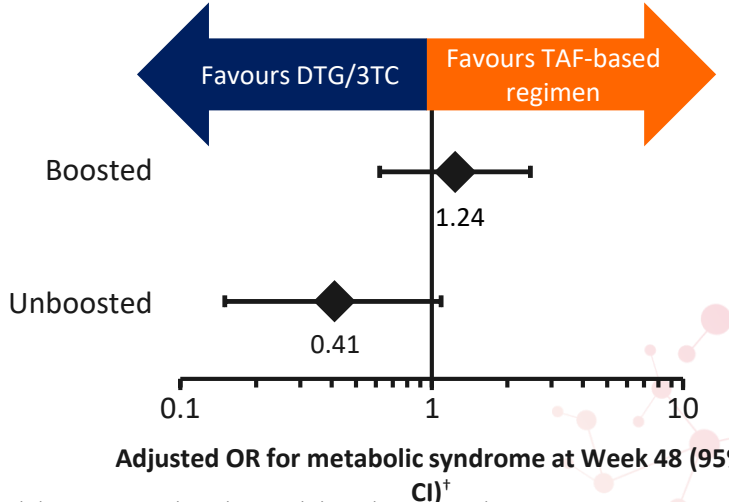
METABOLIC SYNDROME AT WEEK 48

- 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 OR) was lower in the DTG/3TC arm versus the TAF-based regimen arm in the unboosted subgroup but did not reach statistical significance (p=0.075)





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

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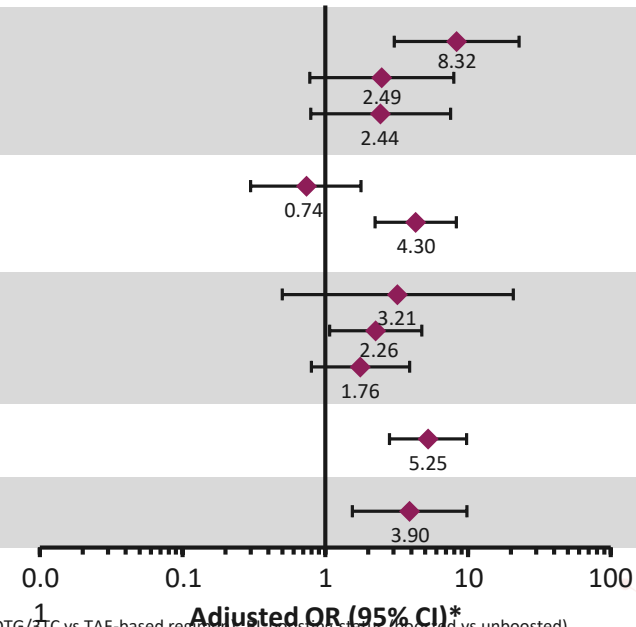
ASSOCIATION OF BASELINE FACTORS WITH METABOLIC SYNDROME AT WEEK 48

- 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 BL

		p-value
HOMA-IR (vs <2)	≥4	<0.001
	3 to <4	0.124
	2 to <3	0.120
HDL (vs 1.04 to <1.56 mmol/L)	≥1.56 mmol/L	0.494
	<1.04 mmol/L	<0.001
Triglycerides (vs <1.70 mmol/L)	≥5.65 mmol/L	0.221
	2.26 to <5.65 mmol/L	0.032
	1.70 to <2.26 mmol/L	0.162
Hypertension status	Yes	0.001
Sex (vs male)	Female	0.004



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

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ADVERSE EVENTS RELATED TO METABOLIC HEALTH WERE LOW IN BOTH TREATMENT ARMS

	Overall		Boosted		Unboosted	
Metabolic AE, n (%)*	**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

*Percentages are based on number of participants not obese at BL

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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 favouring 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 favour of DTG/3TC for prevalence of metabolic syndrome at Week 48, although this did not reach statistical significance
- Metabolic health is multifactorial and complex; clinical trials specifically designed to assess the potential long-term metabolic health impact of removing TAF from ART regimens are needed

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THANK YOU FOR CATCHING UP ON THE WEBINAR

This presentation is provided from the live webinar hosted by ViiV Healthcare on the 22nd of July.

Also available, from the same webinar, on ViiV Exchange website is Prof. José Gatell's presentation covering: '**Other important topics from AIDS 2020, including summary of COVID-19 conference**'.

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