Implications of weight gain with newer antiretrovirals: 10-year predictions of cardiovascular disease and diabetes

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Objective: To evaluate the long-term risks of type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) secondary to weight gain and clinical obesity associated with the initiation of integrase strand transfer inhibitors and tenofovir alafenamide (TAF) in the ADVANCE trial using validated risk equation tools.

Design: Retrospective data analysis.

Methods: In ADVANCE, 1053 treatment-naive participants in South Africa (99% black, 59% female) were randomized to 96 weeks of TAF/emtricitabine + dolutegravir (TAF/FTC + DTG), tenofovir disoproxil fumarate/FTC + DTG (TDF/FTC + DTG), or TDF/FTC + efavirenz (TDF/FTC/EFV). The 5 and 10-year risks of CVD were calculated using D:A:D, QRISK and Framingham, and T2DM risk using QDiabetes, Cambridge Diabetes and Leicester Practice Risk scores. Participants were included in this analysis if they were above 30 years old at baseline.

Results: A total of 217 (TAF/FTC + DTG), 218 (TDF/FTC + DTG), and 215 (TDF/FTC/EFV) participants had 96-week data available. Weight gain was +8.1, +4.2, and +2.4 kg on TAF/FTC + DTG, TDF/FTC + DTG, and TDF/FTC/EFV, respectively. Participants on TAF/FTC + DTG had greatest risk scores for CVD (using QRISK) and T2DM, driven by weight changes. Differences were statistically significant between TAF/FTC + DTG and TDF/FTC/EFV for CVD risk using the QRISK equation, equivalent to one extra case per 1000 people treated over 10 years, and between all treatment groups for T2DM risk. Six extra T2DM cases were predicted on TAF/FTC + DTG vs. TDF/FTC + DTG using QDiabetes.

Conclusion: Obesity, especially with TAF/FTC + DTG, drove increased risk of T2DM, with some evidence of greater CVD risk. However, predictive tools have not been validated in the HIV-positive and black African population.

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Introduction

Overview

Increasing access and availability of anti-retroviral therapy (ART) has significantly reduced HIV-related morbidity and mortality [1]. As life expectancy increases among people living with HIV (PWH), non-communicable diseases (NCDs) have become more prevalent. This growing double burden of HIV and NCD co-morbidities presents a challenge to health systems globally [1]. Compared with the general population, the incidence of cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) is reported to be up to two-times [2–4] and four-times higher [5,6], respectively, in PWH.

Obesity is on the rise in the sub-Saharan Africa; a consequence of urbanization and changing lifestyle [7,8]. In South Africa, 68% of women and 31% of men are overweight or obese [9]. Overweight and obesity are risk factors for metabolic syndrome and NCDs such as hypertension, T2DM, and CVD [10], as well as a range of non-AIDS defining cancers that are linked to a high BMI in PWH [11]. The burden of hypertension is greatest in the African population, contributing to its domination in the global burden from CVD [12].

Recent evidence has emerged of an association between the use of integrase strand transfer inhibitors (INSTIs) in ART regimens and weight gain, including treatment-emergent obesity. Independent and registration trials have observed weight gain and clinical obesity following initiation of INSTIs [13,14] notably dolutegravir (DTG) or bictegravir [14,15]. Similar findings were reported in a pooled analysis of eight randomized controlled trials in participants starting ART and in studies of patients switching from protease inhibitors or non-nucleoside reverse transcriptase inhibitors (NNRTIs) to INSTIs in people virologically suppressed on ART [15–17].

It has also recently been recognized that the new nucleotide reverse transcriptase inhibitor prodrug, tenofovir alafenamide (TAF), is associated with weight gain [14,18–20]. Sax *et al*. showed that TAF had more weight gain compared with other NNRTIs, including tenofovir disoproxil fumarate (TDF) and abacavir. TDF is known to have lipid and weight suppressive effects [21,22]. However, TAF offers safety benefits with favourable biomarkers for bone and renal toxicity [23]; although it is important to note that these had no clinical safety benefit in a recent meta-analysis of TDF vs. TAF [24].

Weight gain can have serious clinical implications; a recent study found increases in BMI in PWH across all baseline categories were associated with an increased risk of T2DM [25], although increases in BMI were not consistently associated with CVD [25]. However, these results were based on PWH who were not taking INSTI-based ART regimens.

A number of validated risk tools in the general population can be used to estimate CVD and T2DM risk. These risk tools are derived using cross-sectional or longitudinal cohorts and take into account a number of risk factors for both T2DM and CVD. Although, assessment of risk using these tools in PWH must be exercised with caution due to the high likelihood of underestimation resulting from the additional CVD and T2DM risk factors present in PWH.

The ADVANCE trial in South Africa was one of the first independent phase 3 randomized controlled trials of DTG with treatment-naïve participants in a middle-income country setting, along with the NAMSAL trial of Cameroon [19,26]. The ADVANCE trial compared the (at the time) standard regimen of TDF/emtricitabine + efavirenz (TDF/FTC/EFV) to TAF/FTC + DTG or TDF/FTC + DTG, and showed comparable virologic efficacy [19]. Both studies reported treatment-emergent obesity and weight gain, which has been more pronounced on the DTG-arms of both trials and was highest in the TAF-containing arm and among women [19,26]. Although previous studies have reported associations between BMI and the increased risk of T2DM and CVD, the implications of weight gain linked to INSTIs have not yet been studied [27]. This study aims to evaluate weight gain observed in the ADVANCE trial by quantifying changes in metabolic laboratory parameters, incidence of metabolic syndrome, and the risk of developing CVD and T2DM using validated risk equations.

Methods

Study design and participants

The ADVANCE trial is an open-label, non-inferiority, 192-week, phase 3 clinical trial comparing three first-line anti-retroviral regimens in treatment-naive individuals with HIV-1 infection in Johannesburg, South Africa. The full study protocol and 48 and 96-week results are available online [19,28]. This analysis presents metabolic changes and the risk of developing T2DM or CVD from baseline to week 96. CVD was defined as stroke, transient ischemic attack, myocardial infarction or heart attacks, or angina. T2DM was defined as a metabolic disorder resulting in hyperglycaemia.

Randomization and procedures

Participants were randomized to receive a once-daily three-drug regimen of either TAF/FTC + DTG, TDF/FTC + DTG, or TDF/FTC/EFV. Treatment assignment was electronically generated, and medications were administered in an open-label design. Written, informed consent was obtained for all participants.

Study visits for all participants were planned at screening, baseline (week 0), and at weeks 4, 12, and every 12 weeks thereafter until week 96, and included baseline height and visit weight measurement, as well as laboratory measurements [19].

Statistical analysis

Statistical analysis was conducted using STATA/IC version 16 (StataCorp LLC, College Station, TX, USA). Outcomes were evaluated at baseline, week 48, and week 96 including weight, BMI, HDL, LDL, triglycerides, total cholesterol (TC), cholesterol ratio, fasting glucose, SBP, and DBP. Mean, median, and interquartile range were calculated at all time points, and changes from baseline to week 96 were assessed in all participants at least 30 years old at baseline. A two-sample *t* test was used to establish differences between groups.

Patient-level data were used to calculate the risk of developing CVD and T2DM at baseline, week 48, and week 96 in all participants at least 30 years old at baseline. The Framingham equation is only valid in at least 30-year olds; hence, an age cut-off of 30 years was used to make valid comparisons between all the equations. Differences between groups were tested using non-parametric Mann–Whitney *U* tests. QRISK3-2018 [29], Framingham [30], and reduced D:A:D [31] equations were used to quantify the risk of CVD. QDiabetes-2018 [32], Cambridge Diabetes Risk Score [33], and Leicester Practice Risk score [34] were used to quantify the risk of developing T2DM. Participants with type 1 (T1DM) or T2DM at any point in the study or consecutive fasting glucose measurements more than 7 mmol/l were excluded from the T2DM risk analysis at baseline. T1DM and T2DM were defined as any participant with a previous diagnosis. A summary of variables included in each risk equation calculation are displayed in the Supplementary Appendix, Table S1/S2, http://links.lww.com/QAD/C128.

All participants were assumed to have no family history of heart attack or T2DM, as these data were not consistently collected. The QDiabetes/QRISK equations require a UK postcode, which did not apply to this study population and therefore was excluded. Glycated haemoglobin (HbA1c) was not collected at baseline and was excluded from the QDiabetes calculation for consistency. Detailed information on the verification and methods for these equations has been published previously [29–34].

The number of participants with hypertension, T2DM, a previous heart attack/stroke/or transient ischaemic attack, regular steroid use, and regular statin use were calculated at baseline, week 48, and week 96. Hypertension was defined as a previous diagnosis of hypertension with at least 1 week of treatment with an antihypertensive drug. Regular steroid and statin use were defined as any participants taking these drugs daily for at least 1 week during each time window. Smoking status was categorized as non-smoker, exsmoker, light smoker (1–9 cigarettes/day), moderate smoker (10–19 cigarettes/day), or heavy smoker (≥20 cigarettes/day). Smoking status was measured at baseline and assumed to stay constant over the study period.

The presence of metabolic syndrome was determined at baseline, week 48, and week 96 using the International Diabetes Federation worldwide definition [35]. Metabolic syndrome was diagnosed in participants aged at least 30 years for consistency with the risk equation analysis, as well as in all age groups for completeness. Participants were considered to have metabolic syndrome if they had central obesity and any two of the following factors: raised triglycerides, reduced HDL, raised blood pressure or raised fasting glucose. Central obesity was assumed for all participants with a BMI at least 30 kg/m^2. Two sample *t* test was used to establish differences between groups.

Results

Baseline characteristics

A total of 1053 participants were enrolled in ADVANCE, with 351 in each group. For this analysis, 650 participants were included who were at least 30 years old. The full consort diagram can be found in Supplementary Table S3, http://links.lww.com/QAD/C128. Baseline characteristics were well balanced between the groups: mean age was 37 years (SD ±5.9), 54% were women, 99% were black, and 68% were of South African origin. Mean baseline $CD4^+$ cell count was 337 cells/μl (SD ±227) and 22% had a baseline HIV viral load more than 100 000 copies/ml. Detailed characteristics of the full study population have been published elsewhere [19]. The baseline characteristics between the less than 30s and at least 30s can be found in Supplementary Table S4, http://links.lww.com/QAD/C128.

Overall, 49% of participants had a normal BMI at baseline, 10% were underweight, 28% were overweight, and 13% were obese. Female weight and BMI were significantly higher than males at baseline (26.5 vs. 22.0 kg/m^2; $P < 0.001$). Mean SBP was similar across groups (124 mmHg ±16) as well as median DBP (82 mmHg ±12).

Most participants were non-smokers (77%), with a larger percentage of men (40%) categorized as any type of smoker (including exsmokers) compared with women (9%). 52 (8%) of participants were being treated for hypertension and 12 (2%) had T2DM at baseline. There were no significant differences between groups at baseline.

Change in weight

Participants at least 30 years old at baseline showed a larger increase in weight compared with younger participants.

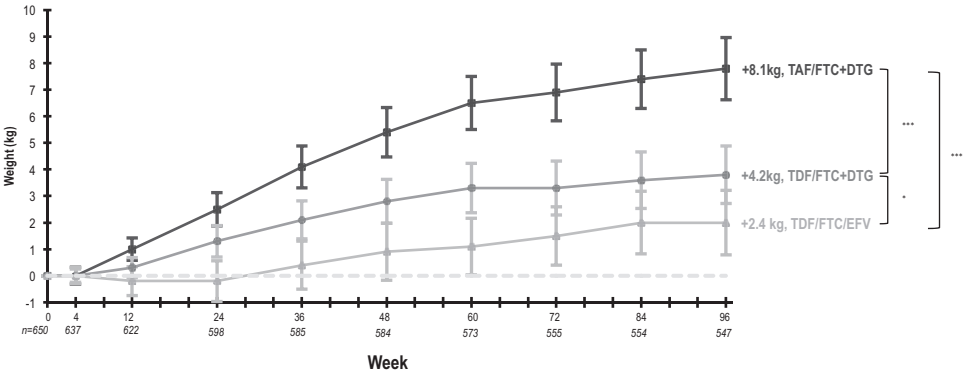

Fig. 1. Changes in weight from baseline to week 96: all participants at least 30 years old at baseline. *P* values from two-sample *t* test, ***$P < 0.001$, **$P < 0.01$, *$P < 0.05$. TAF/FTC + DTG, tenofovir alafenamide/emtricitabine + dolutegravir ($n = 217$); TDF/FTC/EFV, tenofovir disoproxil fumarate/emtricitabine/efavirenz ($n = 215$); TDF/FTC + DTG, tenofovir disoproxil fumarate/emtricitabine + dolutegravir ($n = 218$).

At week 96, weight change was 8.1, 4.2, and 2.4 kg in TAF/FTC + DTG, TDF/FTC + DTG, and TDF/FTC/EFV (Fig. 1), showing no plateau from changes observed at week 48. Treatment emergent obesity at week 96 was higher among women than men across all groups ($P < 0.001$). Treatment emergent obesity at week 96 was 38, 16, and 15% of women taking TAF/FTC + DTG, TDF/FTC + DTG, and TDF/FTC/EFV respectively, with statistically significant differences between TAF/FTC + DTG and other groups (TAF/FTC + DTG vs. TDF/FTC/EFV, $P < 0.001$; TAF/FTC + DTG vs. TDF/FTC + DTG, $P < 0.01$) (Supplementary Table S5, http://links.lww.com/QAD/C128).

Change in metabolic parameters

Lab parameters were similar across all groups at baseline (Table 1).

TC increased by 0.3 mmol/l (TAF/FTC + DTG), 0.0 mmol/l (TDF/FTC + DTG), and 0.4 mmol/l (TDF/FTC/EFV) to week 96, with greater changes in the TAF/FTC + DTG and TDF/FTC/EFV arms compared with TDF/FTC + DTG ($P < 0.01$). Cholesterol ratio decreased by −0.3 (TAF/FTC + DTG), −0.3 (TDF/FTC + DTG), and −0.5 (TDF/FTC/EFV) from baseline to week 96 across all treatment arms with no significant differences between groups. Triglycerides showed little change from baseline to week 96 across all treatment arms. Fasting glucose increased significantly across all treatment arms to week 96, with a 0.6 (TAF/FTC + DTG), 0.4 (TDF/FTC + DTG), and 0.5 (TDF/FTC/EFV) change from baseline, but there were no statistically significant differences between groups. Full findings are shown in Table 2.

Metabolic syndrome

51 (5%) participants had metabolic syndrome at baseline, with no differences among groups. Treatment emergent metabolic syndrome was 11.1% (TAF/FTC + DTG), 8.1% (TDF/FTC + DTG), and 5.4% (TDF/FTC/EFV) at week 96 for all participants at least 30 years old, with no statistically significant differences between groups. Significant differences were observed between TAF/FTC + DTG and TDF/FTC + DTG ($P < 0.05$, 95% confidence interval 4.6–8.6), when all participants, including under 30s, were included in the analysis. The incidence of treatment-emergent metabolic syndrome was higher among women ($n = 38$, 8.3%) compared with men ($n = 11$, 3.2%) at week 96 (Fig. S6, http://links.lww.com/QAD/C128). The results for

Table 1. Summary of baseline characteristics: all participants at least 30 years old at baseline.

	TAF/FTC + DTG	TDF/FTC + DTG	TDF/FTC/ EFV
n	217	218	215
Smoking, *n* (%)			
Non-smoker	167 (77.0)	165 (75.7)	171 (79.2)
Exsmoker	4 (1.8)	–	–
Light smoker	37 (17.1)	43 (19.7)	38 (17.6)
Moderate smoker	7 (3.2)	8 (3.7)	7 (3.2)
Heavy smoker	2 (0.9)	2 (0.9)	–
Diabetes, *n* (%)	2 (0.9)	6 (2.8)	4 (1.9)
Hypertension, *n* (%)	20 (9.2)	16 (7.3)	20 (9.3)
Depression, *n* (%)	1 (0.5)	1 (0.5)	1 (0.5)
Steroid use, *n* (%)	2 (0.9)	–	2 (0.9)
Erectile dysfunction, *n* (%)	1 (0.5)	3 (1.4)	1 (0.5)
Weight (kg), mean (SD)	70.4 (13.4)	69.9 (13.9)	70.6 (14.3)
BMI (kg/m^2), mean (SD)	24.4 (5.1)	24.5 (5.5)	24.4 (5.6)
Lab parameters, mean (SD) (mmol/l)			
Cholesterol ratio	3.7 (1.1)	3.6 (1.2)	3.6 (1.3)
Cholesterol	3.9 (0.9)	3.9 (0.8)	3.81 (0.8)
LDL	2.5 (0.8)	2.38 (0.7)	2.40 (0.8)
HDL	1.1 (0.3)	1.12 (0.3)	1.14 (0.4)
Glucose	4.3 (0.7)	4.47 (1.7)	4.30 (1.3)
Triglycerides	1.0 (0.6)	0.95 (0.4)	1.04 (0.6)

TAF/FTC + DTG, tenofovir alafenamide/emtricitabine + dolutegravir ($n = 217$, 61.8% of all randomized); TDF/FTC/EFV, tenofovir disoproxil fumarate/emtricitabine/efavirenz ($n = 215$, 61.3% of all randomized); TDF/FTC + DTG, tenofovir disoproxil fumarate/emtricitabine + dolutegravir ($n = 218$, 62.1% of all randomized).

Table 2. Summary of changes in metabolic parameters (mmol/l): all participants at least 30 years old at baseline.

Metabolic parameters	Group 1 (TAF/FTC + DTG)		Group 2 (TDF/FTC + DTG)		Group 3 (TDF/FTC/EFV)		*P* value Group 1 vs. Group 3	*P* value Group 2 vs. Group 3	*P* value Group 1 vs. Group 2
	n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)			
Cholesterol (mmol/l)									
Baseline	217	3.91 (1.0)	218	3.87 (0.8)	215	3.84 (0.9)			
Week 96	180	+0.25 (0.8)	189	+0.04 (0.6)	176	+0.40 (0.8)	n.s.	$P < 0.001$	$P < 0.01$
HDL (mmol/l)									
Baseline	217	1.12 (0.3)	218	1.12 (0.3)	215	1.12 (0.4)			
Week 96	180	+0.15 (0.3)	189	+0.11 (0.3)	176	+0.28 (0.3)	$P < 0.001$	$P < 0.001$	n.s.
LDL (mmol/l)									
Baseline	217	2.46 (0.8)	218	2.47 (0.7)	215	2.38 (0.7)			
Week 96	180	+0.20 (0.6)	189	+0.02 (0.5)	176	+0.19 (0.6)	n.s.	$P < 0.01$	$P < 0.01$
Cholesterol ratio (mmol/l)									
Baseline	217	3.78 (1.6)	218	3.69 (1.1)	215	3.74 (1.3)			
Week 96	180	−0.30 (1.5)	189	−0.33 (0.8)	176	−0.46 (1.0)	n.s.	n.s.	n.s.
Triglycerides (mmol/l)									
Baseline	217	1.07 (0.6)	218	0.97 (0.4)	215	1.10 (0.7)			
Week 96	180	+0.01 (0.7)	189	−0.05 (0.4)	176	+0.07 (0.6)	n.s.	$P < 0.05$	n.s.
Glucose (mmol/l)									
Baseline	217	4.25 (0.7)	218	4.51 (1.5)	215	4.41 (1.4)			
Week 96	180	+0.56 (0.8)	189	+0.43 (1.5)	177	+0.54 (1.3)	n.s.	n.s.	n.s.

TAF/FTC + DTG, tenofovir alafenamide/emtricitabine + dolutegravir ($n = 217$); TDF/FTC/EFV, tenofovir disoproxil fumarate/emtricitabine/efavirenz ($n = 215$); TDF/FTC + DTG, tenofovir disoproxil fumarate/emtricitabine + dolutegravir ($n = 218$). *P values from two-sample t test.

metabolic syndrome are given in full in Supplementary Appendix S6, http://links.lww.com/QAD/C128.

Cardiovascular disease and type 2 diabetes mellitus risk predictions

The changes from baseline to week 96 across all risk equations are shown in Table 3 and summarized below.

Cardiovascular disease risk

The median baseline 10-year CVD risk given by the QRISK equation was 0.6 (TAF/FTC + DTG), 0.5 (TDF/FTC + DTG), and 0.5 (TDF/FTC/EFV). At week 96, CVD risk increased by +0.20 (TAF/FTC + DTG and TDF/FTC + DTG) and +0.10 (TDF/FTC/EFV). The difference of 0.1% between

Table 3. Summary of risk equations changes from baseline to week 96: all participants at least 30 years old at baseline.

Risk equations	Group 1 (TAF/FTC + DTG)		Group 2 (TDF/FTC + DTG)		Group 3 (TDF/FTC/EFV)		*P* value Group 1 vs. Group 3	*P* value Group 2 vs. Group 3	*P* value Group 1 vs. Group 2
	n	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)			
Cardiovascular									
Framingham									
Baseline	217	2.2 (1.4, 3.8)	218	2.4 (1.4, 4.3)	215	2.1 (1.3, 3.5)			
Change to week 96	180	+0.6 (0.0, 2.0)	189	+0.4 (−0.2, 1.6)	176	+0.4 (−0.1, 1.4)	n.s.	n.s.	n.s.
QRISK									
Baseline	216	0.60 (0.3, 1.0)	218	0.50 (0.3, 1.1)	215	0.50 (0.3, 1.0)			
Change to week 96	179	+0.20 (0.1, 0.6)	189	+0.2 (0.0, 0.5)	176	+0.1 (0.0, 0.4)	$P < 0.01$	n.s.	n.s.
D:A:D									
Baseline	217	0.65 (0.36, 1.07)	218	0.63 (0.35, 1.07)	215	0.59 (0.35, 1)			
Change to week 96	179	+0.07 (−0.04, 0.18)	188	+0.035 (−0.09, 0.14)	176	+0.04 (−0.03, 0.17)	n.s.	n.s.	n.s.
T2DM									
QDiabetes									
Baseline	213	0.30 (0.1, 0.7)	210	0.30 (0.1, 1.0)	211	0.3 (0.1, 0.9)			
Change to week 96	175	+1.1 (0.3, 2.1)	179	+0.5 (0.1, 1.5)	173	+0.8 (0.3, 2.5)	n.s.	$P < 0.01$	$P < 0.01$
Cambridge									
Baseline	213	2.79 (1.33, 5.87)	210	2.85 (1.26, 6.15)	212	2.57 (1.25, 6.32)			
Change to week 96	177	+3.00 (0.47, 7.28)	181	+0.98 (0.29, 4.68)	172	+0.58 (0.18, 3.22)	$P < 0.001$	$P < 0.05$	$P < 0.01$
Leicester									
Baseline	212	4.35 (4.01, 4.72)	210	4.28 (3.94, 4.67)	212	4.25 (3.95, 4.72)			
Change to week 96	175	+0.36 (0.20, 0.65)	181	+0.24 (0.14, 0.50)	172	+0.16 (0.05, 0.37)	$P < 0.001$	$P < 0.001$	$P < 0.001$

IQR, interquartile range; T2DM, type 2 diabetes mellitus; TAF/FTC + DTG, tenofovir alafenamide/emtricitabine + dolutegravir; TDF/FTC/EFV, tenofovir disoproxil fumarate/emtricitabine/efavirenz; TDF/FTC + DTG, tenofovir disoproxil fumarate/emtricitabine + dolutegravir.

TAF/FTC + DTG and TDF/FTC/EFV was significant ($P < 0.01$), equivalent to one extra CVD event per 1000 treated with TAF/FTC + DTG over a 10-year period.

There were no statistically significant differences between the treatment groups using the D:A:D and Framingham equations.

Across all CVD risk equations, men had a larger increase in the risk of developing CVD from baseline to week 96 compared with women (Supplementary Table S7, http://links.lww.com/QAD/C128).

Type 2 diabetes mellitus risk

The median baseline 10-year T2DM risk given by the QDiabetes equation was 0.3 across all treatment groups. At week 96, a significant 0.6% increase in 10-year risk was predicted on TAF/FTC + DTG compared with TDF/FTC + DTG ($P < 0.01$). This is equivalent to six additional T2DM cases per 1000 people. An extra three T2DM cases per 1000 were predicted on TDF/FTC/EFV over TDF/FTC + DTG ($P < 0.01$).

Significant changes were observed between all treatment arms of the Cambridge and Leicester scores, with greatest risk on the TAF/FTC + DTG arm.

Across all T2DM risk equations, median change in risk to week 96 was greater in women compared with men, largely due to weight differences (Supplementary Table S8, http://links.lww.com/QAD/C128).

Discussion

We demonstrate an accumulating T2DM risk, with some evidence of a raised CVD risk in the ADVANCE trial, particularly in participants on the TAF/FTC + DTG arm, when risk was assessed using validated CVD and T2DM risk calculators. Increases in risk, and differences between treatment groups, were largely driven by weight gain. Treatment associated weight gain, especially within the context of individuals with traditional CVD and T2DM risk factors present, represents an increased risk of developing CVD or diabetes. With mass upscaling of TAF/FTC + DTG, treatment associated weight gain may pose major challenges to health systems worldwide.

As these calculators have not been validated in the local population, the results must be interpreted with caution [36]. The equations were developed using cohorts with low HIV prevalence in high-income countries, and do not account for the differences in cause of CVD and T2DM in PWH, and hence may under-estimate risk in this study population [37]. However, it should be noted that the calculators are widely used in populations where they have not been validated, including in Africa, where they are used to make treatment decisions and inform local guidelines.

QRISK and QDiabetes account for more risk factors, such as co-morbidities and concomitant medications, than other predictive equations and can be adjusted for black African ethnicity [29,32]. Consequently, these equations may show more accurate 10-year risk predictions of CVD and T2DM risk in the ADVANCE trial compared with other risk equations. In particular, the D:A:D (HIV-specific equation) and the Framingham equation were derived from a white, male-dominated cohort [30,31] and may not represent the black, mixed-sex population of ADVANCE.

The QDiabetes equation has shown superior sensitivity over other equations [32], predominantly due to inclusion of fasting glucose. It was therefore able to discriminate and detect the elevated T2DM risk of EFV, which is known to increase plasma glucose [38], over the Cambridge and Leicester scores. The latter were derived using cross-sectional methods, and only give us the probability of T2DM in an undiagnosed patient. In addition, they have previously shown poor discrimination for African ethnicities [39,40].

A higher predicted CVD and T2DM risk was seen on the TAF/FTC + DTG arm compared with TDF/FTC + DTG arm. This is likely due to two reasons. First, weight gain and treatment-emergent obesity has been greatest in participants taking TAF/FTC + DTG. Second, we found TAF to increase metabolic parameters, compared with TDF. Although TAF has generally been found to be lipid-neutral, with a similar lipid profile to abacavir in one randomized trial [41], TDF has demonstrated lipid suppressive effects [21,42]. Our QRISK finding of raised CVD risk on TAF/FTC + DTG corresponds to another analysis which found a 13% increase in adjusted Atherosclerotic CVD risk score in participants switched from TDF to TAF [43].

Emerging evidence links weight gain with INSTIs and T2DM. When switching to INSTIs, HbA1c has been found to be raised in the INSTI group vs. the non-INSTI group [44,45]. In another cohort study, participants initiating INSTIs (in particular raltegravir) were more likely to develop T2DM compared with NNRTIs [46]. However, this was non-significant in participants initiating DTG. In the EMERALD trial, TAF was significantly associated with treatment emergent T2DM compared with TDF ($P < 0.05$) [47,48].

Substantial sex differences were observed. Women showed greater increases in T2DM risk, whereas men showed greater increases in CVD risk. As high BMI is a risk factor for T2DM, the greater weight gain seen in women compared with men on ADVANCE may explain the higher T2DM risk in women [49]. The greater

weight gain among women on ADVANCE could be reflective of the greater average weight of women in South Africa compared with men [50]. Conversely, CVD develops 7–10 years later in women than men, and in the relatively young ADVANCE cohort weight changes might have had a greater impact on male CVD risk than females [51].

It should be acknowledged that a proportion of weight gain could be attributed to 'return-to-health'. Average bodyweight in South Africa is considerably higher than the global average [52], which might in part explain the substantial weight gain seen across all treatment arms in ADVANCE. However, it is unlikely that the weight gain in ADVANCE can be solely attributed to return-to-health. There were non-significant differences in $CD4^+$ cell count and virological suppression between treatment groups at baseline, suggesting that return-to-health would have equivalent impact across each treatment arm [19]. However, clear differences in weight gain were observed between treatment arms in ADVANCE.

Mechanisms for INSTI-related weight gain are poorly understood. INSTIs have been shown to promote adipogenesis, lipogenesis, and insulin resistance [53]. INSTIs may also interfere with the melanocortin system and central nervous system appetite regulation via the melanocortin-4 receptor (MC4R) [54]. However, antagonism of the MC4R receptor occurs at a much greater drug concentration than clinical exposure [55]. It is unclear whether TAF contributes to weight gain, or merely doesn't suppress DTG-induced weight gain, as TDF does. The differences in weight gain observed in ADVANCE may be linked to the CYP2BR mutation, a genetic susceptibility more common in individuals of African ancestry. In a subanalysis of ADVANCE, this mutation was linked to slow metabolism of EFV and impaired weight gain [56].

T2DM and CVD are leading causes of mortality in low-middle income countries, countries which also carry much of the HIV burden. It is becoming increasingly appropriate to incorporate NCD screening and management into routine HIV care. Clinicians prescribing DTG or TAF must closely monitor participants for associated metabolic complications or treatment-induced weight gain. Patients with significant risk factors for T2DM and CVD should be identified and avoid initiation with TAF/FTC + DTG, as well as undergo counselling for modifiable risk factor reduction, with guidance for participants on weight management, diet and lifestyle, in line with global recommendations. Health promotion interventions may be challenging in resource limited settings, especially where current public health efforts are focused on affluent communities. Nevertheless, policy-makers should leverage existing infectious disease infrastructure to scale-up community-level programmes for NCDs [57,58].

Finally, obesity has been implicated in increasing risks of cancer, degenerative arthritis, and Alzheimer's disease, among other conditions [10]. The effects of treatment-emergent obesity on these diseases should be explored and could pose further risk to PWH.

Limitations

Some limitations must be considered. The study populations were relatively young, and therefore at low background risk from CVD and T2DM. The Framingham equation is only valid in individuals over 30; therefore, 403 of participants on the ADVANCE trial were excluded, lowering the sample size. Pregnant women were also excluded from our analysis. Our estimates are likely to be underestimations as longer term weight data from ADVANCE shows that weight gain has increased past week 96 (Supplementary Table S9, http://links.lww.com/QAD/C128). Family history and HbA1c were not included in these predictions, which may affect estimations of risk. Considering the importance of family history in determining risk of both CVD and T2DM, this is a limitation.

Human error in the manual calculation of the QRISK-3 and QDiabetes risks is a possibility, although these were cross-checked by independent researchers. As a retrospective data analysis, the trial was not powered to test the differences in CVD or T2DM risk. The equations were derived in locations with differing demographics and epidemiology to the ADVANCE trial, and therefore may not be valid for use, as discussed above.

These results are from a single study and further analysis of CVD and T2DM risk should be conducted for ongoing trials on diverse populations reporting INSTI-related weight gain for external validation. However, it is important to recognize that this study sample is representative of the region, as a substantial minority of participants were not from South Africa (48%), and importantly, representative of the HIV epidemic.

The analysis should also be repeated on HIV-switch trials, where DTG-associated weight gain has been less pronounced [17,59]. Finally, the analysis should be repeated on pre-exposure prophylaxis trials of TAF/FTC and TDF/FTC to contribute to the discussion around the comparative safety of TAF compared with TDF.

Conclusion

In the ADVANCE trial, weight gain associated with initiating TAF/FTC + DTG increased the incidence of treatment-emergent metabolic syndrome and the long-term risks of T2DM. There was also an increased CVD risk using the QRISK-3 calculator. A risk equation validated in PWH must be developed for reliable and accurate prediction and monitoring of CVD and T2DM risk in this population. Long-term follow-up will be essential to attain a comprehensive analysis of T2DM and

CVD incidence in PWH on either TAF or DTG and to compare the predictions to real endpoints.

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Conflicts of interest

There are no conflicts of interest.

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