Clinical Infectious Diseases

BRIEF REPORT

Weight and metabolic changes after switching from tenofovir alafenamide (TAF)/emtricitabine (FTC)+dolutegravir (DTG), tenofovir disoproxil fumarate (TDF)/FTC+DTG and TDF/FTC/efavirenz (EFV) to TDF/lamivudine (3TC)/DTG

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Participants randomised to first-line tenofovir alafenamide (TAF)/emtricitabine (FTC)+dolutegravir (DTG), tenofovir disoproxil fumarate (TDF)/FTC+DTG or TDF/FTC/efavirenz (EFV) for 192 weeks were then switched to TDF/lamivudine (3TC)/DTG for 52 weeks. Participants switching either TAF/FTC+DTG or TDF/FTC/EFV to TDF/3TC/DTG showed statistically significant reductions in weight, low density lipoprotein, triglycerides, glucose and glycated haemoglobin.

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INTRODUCTION

World Health Organization (WHO) guidelines for HIV treatment currently recommend tenofovir disoproxil fumarate (TDF) with either lamivudine (3TC) or emtricitabine (FTC) plus dolutegravir (DTG) as preferred first-line antiretroviral therapy (ART). DTG replaced efavirenz (EFV) in 2019 in first-line regimens due to potency, barrier to resistance, cost, and safety benefits over EFV [1].

Tenofovir alafenamide (TAF), a prodrug of tenofovir, is the recommended alternative to TDF for patients with renal impairment or established osteoporosis but endorsed more broadly in higher income countries [1]. WHO does not currently advocate a wholesale programmatic switch from TDF to TAF, due to associations with increased weight gain, worsened lipid profile, equivalent renal and bone toxicity and virological potency when compared to unboosted TDF, as well as concerns regarding drug interactions, unknown pregnancy outcomes, and high cost [2] [3].

In contrast, some studies have observed the mitigating effect of TDF and EFV on weight gain. EFV has been associated with significant side effects including neuropsychiatric side effects and increases in lipids and serum glucose levels [4]. Weight loss is higher for people with cytochrome polymorphisms resulting in slower metabolism of the drug, this then conferring other neurological and metabolic toxicities [5, 6]. TDF has been associated with a higher risk of weight loss in a recent analysis of HIV-negative people taking pre-exposure prophylaxis therapy [5, 6].

ADVANCE was an investigator-led randomized controlled trial evaluating the efficacy and safety of two newer antiretroviral combinations; TAF/FTC+DTG and TDF/FTC+DTG, as compared with TDF/FTC/EFV [7]. The trial recruited from routine HIV testing sites, based in Johannesburg, South Africa. ADVANCE demonstrated virological non-inferiority at 48, 96 and 192 weeks, with significant weight gain in the two DTG-containing arms, which was especially marked in the TAF/FTC+DTG arm. After week 192, participants were switched to open-label TDF/3TC/DTG as per the national guidelines, and evaluated here after further informed consent processes, following at least 52 weeks of follow up in the state ART programme. The aim of the study, CHARACTERISE, was to evaluate the change in clinical and metabolic parameters after this move to the standard-of-care ART regimen.

METHODS

Study setting

CHARACTERISE enrolled residents of inner-city Johannesburg from July-November 2022 who had previously been part of ADVANCE and were not pregnant at the time of screening.

Study design

CHARACTERISE evaluated outcomes after a minimum of 52 weeks of open label TDF/3TC/DTG. Results were evaluated for weight, lipids, fasting glucose, HbA1C, systolic/diastolic blood pressure and HIV RNA. Participants with elevations in HIV RNA were re-tested at least one month after adherence counselling. The methods of analysis followed the usual procedures for ADVANCE as described in the previous publications [8, 9]. Results for changes in weight and metabolic parameters are displayed as median and interquartile range (IQR). Changes within each treatment group were evaluated using the paired non-parametric Wilcoxon signed-rank test.

The trial was approved by the University of the Witwatersrand Human Research Ethics Committee and received local regulatory approval. All patients provided informed consent prior to any study procedures.

Role of funding source

Unitaid contributed to the study design of CHARACTERISE.

RESULTS

Out of 1053 patients who were randomised to ADVANCE, 172 participated in CHARACTERISE. Results from CHARACTERISE are available for 70 of the 351 participants originally in the TAF/FTC+DTG arm at the end of ADVANCE, 71 of the 351 participants in the TDF/FTC+DTG arm and 31 of the 351 participants in the TDF/FTC/EFV arm. Part of the reason for the low number in the TDF/FTC/EFV arm, was that the local clinics were still transitioning to TDF/3TC/DTG, with much residual stock, and it appeared the local nurses elected to continue EFV-based ART in many of these patients rather than switch to TDF/3TC/DTG. Overall, patients in CHARACTERISE were similar to those not enrolled, in terms of sex (p=0.10), CD4 (p=0.18) and HIV RNA (p=0.93). However, there were significant differences in their weight (p=0.0023). The mean weight of participants in CHARACTERISE was 79 kg and the mean weight of participants who did not enrol in CHARACTERISE was 74 kg.

In the CHARACTERISE study, baseline demographics were similar across the original randomised arms (Table 1). Participants were 62% female, 100% Black and 34% from outside of South Africa. Amongst the 34% who were from outside South Africa, 50 were from Zimbabwe,

2 from Malawi, 3 from Mozambique and 4 from other regions. The median baseline CD4 count was 570.5 cells/uL [IQR: 422, 795] with 98% having HIV RNA <50 copies/mL.

Weight

For women switching from TAF/FTC+DTG to TDF/3TC/DTG after week 192, there was a statistically significant reduction in weight (median: -1.6kg, p=0.0125). This change in weight was not significant in men (median: -0.2kg, p=0.2561). There was a statistically significant reduction in BMI for women (median: -0.57 kg/m^2, p=0.0106) but not men (median: -0.08, p=0.2473).

Participants switching from TDF/FTC/EFV to TDF/3TC/DTG, showed a significant increase in body weight (median: +2.9, p=0.02) and BMI (median: +1.01, p=0.0225). This change in weight was significant for the subset of men (median: +2.3, p=0.0464) but not women (median: +2.9, p=0.1127).

For participants in the TDF/FTC+DTG arm switching to TDF/3TC/DTG, there was no significant change in weight and BMI for either women or men.

Lipids, glucose, blood pressure and hba1c

Participants switching from TAF/FTC+DTG to TDF/3TC/DTG after week 192 showed significant reductions in total cholesterol (p=0.0018), LDL (p<0.001), triglycerides (p=0.0254), glucose (p=0.0003) and HbA1C (p=0.0004). The reduction in HDL and increase in systolic and diastolic blood pressure was not significant. Participants switching from TDF/FTC/EFV to TDF/3TC/DTG showed significant decreases in total cholesterol (p=0.0113), LDL (p=0.0012), HDL (p=0.0495), triglycerides (p=0.0575) and HbA1C (p=0.0082). The reduction in glucose and increase in systolic and diastolic blood pressure was not significant. For participants switching from TDF/FTC+DTG to TDF/3TC/DTG, there was a significant increase in total cholesterol (p=0.0009), HDL (p=0.0209) and systolic blood pressure (p=0.0206). However, changes in LDL, triglycerides, glucose, HbA1C and diastolic blood pressure were not significant.

HIV RNA

After at least 52-weeks on TDF/3TC/DTG, HIV RNA was undetectable in 68/68 (100%) participants originally in the TAF/FTC+DTG arm, 68/70 (97%) participants in the TDF/FTC+DTG arm and 25/28 (89%) in the TDF/FTC/EFV arm. There were eight elevations in HIV RNA. Of these, three participants re-suppressed after adherence counselling. However, one participant did not re-suppress and four did not return for their scheduled follow-up visit.

DISCUSSION

Millions of PLWH worldwide have switched from TDF/3TC/EFV or similar regimens, to TDF/3TC/DTG in the last five years. In the CHARACTERISE study, participants who switched from TDF/FTC/EFV to TDF/3TC/DTG gained a median 2.9kg. We also saw small improvements in LDL cholesterol, triglycerides, fasting glucose and HbA1C during the switches from TDF/FTC/EFV to TDF/3TC/DTG. Again, this change is expected, given the previously described metabolic effects of EFV [4].

Women who switched from TAF/FTC+DTG to TDF/3TC/DTG lost a median 1.6kg, and overall, this cohort had a slightly improved glucose and lipid profile. The results from CHARACTERISE are consistent with those seen in other observational studies from Finland and Germany in 292 and 385 participants, respectively [10, 11].

With weight gain persisting as a potentially major health complication with the use of all modern ART, risks for the development of long-term cardiac disorders remain of concern. A previously published analysis on the 5- and 10-year risks of cardiovascular disease (CVD) and diabetes was conducted on the same ADVANCE population at week 96 and demonstrated that participants on the TAF/FTC+DTG regimen had significantly greater risk scores for development of CVD or diabetes, driven by weight gain, in comparison to the TDF-containing groups [12]. A switch from TAF to TDF may be clinically justified in patients, especially women experiencing weight gain and those with glucose or lipid disorders, although it is unclear whether this weight loss will be maintained, or whether other weight loss measures will be required.

Limitations of the CHARACTERISE study include the open-label design and the relatively small sample size: only 16% of the original 1053 participants participated in the trial extension, so the statistical power to evaluate effects of switching in women and men is limited. There was low participation by men, reflective of attrition to HIV care of men in HIV programmes. There is potential for selection bias in those who chose to participate in CHARACTERISE versus those who did not. The trial was conducted in inner-city Johannesburg, with participants coming from across the region and recruited from routine patient care, factors which strengthen the generalisability of the study. This trial was also conducted in a region of highest global genetic diversity. However, this study should be repeated in Asian, Hispanic and Caucasian populations.

Current WHO recommendations for TDF/3TC/DTG as the preferred first-line regimen appear to be further substantiated by our study and are very reassuring for the participants switched from EFV-based regimens. Ultimately, countries such as Botswana that are moving away from TDF/3TC/DTG in favour of TAF/FTC+DTG, may want to consider preservation of TDF-

containing regimens as an option for patients with ongoing, significant weight gain and metabolic disease, sadly a significant proportion, of this population.

NOTES

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Table 1: Baseline characteristics and changes in weight and metabolic parameters from switch to TDF/3TC/DTG by original treatment received: CHARACTERISE trial

Group	TAF/FTC+DTG (n=70)	TDF/FTC+DTG (n=71)	TDF/FTC/EFV (n=31)
Baseline characteristics*			
Sex (% Female)	41/70 (59%)	41/71 (58%)	24/31 (77%)
Country (% South Africa)	42/70 (60%)	51/71 (72%)	20/31 (64%)
Weight (kg)	81.1 [71.5, 89.1]	72.9 [61.7, 86.3]	74.3 [61.8, 100.5]
BMI (kg/m^2)	28.0 [23.9, 31.8]	25.9 [22.5, 30.6]	25.6 [23.6, 33.1]
HIV RNA <50 copies/mL (%)	66/67 (98%)	62/64 (97%)	23/23 (100%)
CD4 count (cells/uL)	560 [424, 787]	549 [407.5, 743.5]	677 [544, 882]
Cholesterol (mmol/L)	3.9 [3.5, 4.8]	3.7 [3.2, 4.3]	4.5 [3.6, 4.91]
LDL (mmol/L)	2.6 [2.2, 3.1]	2.3 [1.9, 2.9]	2.8 [2.3, 3.27]
HDL (mmol/L)	1.1 [0.9, 1.3]	1.1 [0.9, 1.3]	1.3 [1.0, 1.6]
Triglycerides (mmol/L)	0.9 [0.7, 1.2]	0.8 [0.6, 1.0]	0.9 [0.7, 1.3]
Fasting glucose	4.9 [4.5, 5.2]	4.9 [4.6, 5.1]	4.7 [4.5, 5.1]

(mmol/L)			
HbA1c (mmol/L)	5.5 [5.1, 5.7]	5.5 [5.2, 5.7]	5.5 [5.2, 5.7]
Systolic blood pressure (mmHg)	127 [119, 134]	122 [117, 132]	118 [113, 126]
Diastolic blood pressure (mmHg)	83 [78, 88]	82 [77.5, 86]	76 [72, 83]
Changes from switch*			
Weight (kg)	-1.2 [-3.8,1], p=0.0057	-0.1 [-2.1, 2.2] (n.s.)	+2.9 [-0.7, 4.9], p=0.02
BMI (kg/m^2)	-0.4 [-1.3, 0.3], p=0.0048	-0.05 [-0.7, 0.7] (n.s.)	+1.0 [-0.2, 1.9], p=0.0225
Total cholesterol (mmol/L)	-0.2 [-0.5, 0.1], p=0.0018	+0.2 [-0.1, 0.4], p=0.0009	-0.3 [-0.8, 0.01], p=0.0113
LDL cholesterol (mmol/L)	-0.3 [-0.6, -0.01], p=0.000	-0.01 [-0.2, 0.2] (n.s.)	-0.3 [-0.5, -0.1], p=0.0012
HDL (mmol/L)	-0.03 [-0.2, 0.1] (n.s.)	+0.04 [-0.1, 0.2], p=0.0209	-0.1 [-0.3, 0.05], p=0.0495
Triglycerides (mmol/L)	-0.1 [-0.3, 0.09], p=0.0254	-0.02 [-0.2, 0.2] (n.s.)	-0.1 [-0.3, 0.05], p=0.0575
Fasting glucose (mmol/L)	-0.2 [-0.5, 0.1], p=0.0003	0 [-0.3, 0.2] (n.s.)	-0.1 [-0.3, 0.1] (n.s.)
HbA1c (mmol/L)	-0.1 [-0.3, 0], p=0.0004	-0.1 [-0.3, 0.1] (n.s.)	-0.15 [-0.2, 0], p=0.0082
Systolic blood pressure (mmHg)	+1.5 [-6, 14] (n.s.)	+3 [-2.5, 10], p=0.0206	+6 [-10, 13] (n.s.)
Diastolic blood pressure (mmHg)	+2 [-4, 6] (n.s.)	+0.5 [-5.5, 4.5] (n.s.)	+2 [-4, 11] (n.s.)
HIV RNA<50 copies/mL at or after week 52 (%)	68/68 (100%)	68/70 (97%)	25/28 (89%)

*Note:
Continuous variables are displayed as Median and interquartile range (IQR). Count variables are displayed as n/N and %
n.s. = not significant