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Regional variation in weight change after the transition to dolutegravir in Uganda and South Africa

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Background: People with HIV (PWH) on integrase inhibitor-based regimens may be at risk of excess weight gain, but it is unclear if this risk is consistent across settings. We assessed weight change over 48 weeks among PWH who were transitioned to tenofovir disoproxil fumarate/lamivudine/dolutegravir (TLD).

Design: We conducted a prospective cohort study at public-sector HIV clinics in Uganda and South Africa.

Methods: Eligible participants were adults who were transitioned to TLD. Weight was measured at enrollment, 24-, and 48-weeks post TLD transition. Our outcomes were weight change, change in waist circumference, and clinically significant weight gain, defined as $\geq$10% increase in weight from baseline, over 48 weeks. We used linear mixed-effects regression models, adjusted for demographic factors, to estimate weight gain and identify risk factors.

Results: Weight data were available for 428 participants in Uganda and 367 in South Africa. The mean weight change was 0.6 kg [95% CI: 0.1–1.0] in Uganda and 2.9 kg [2.3–3.4] in South Africa ($P < 0.001$). The mean change in waist circumference was 0.8 cm [95% CI: 0.0–1.5]) in Uganda and 2.3 cm [95% CI: 1.4–3.2] in South Africa ($P = 0.012$). Clinically significant weight gain occurred in 9.8% [7.0–12.6] of participants in Uganda and 18.0% [14.1–21.9] in South Africa ($P < 0.001$). After adjustment, PWH gained significantly less weight in Uganda than in South Africa.

Conclusions: PWH in South Africa experienced significantly greater weight gain and increases in waist circumference compared to Uganda. Strategies to address weight gain in PWH should be carefully considered and may vary by region.

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Keywords: dolutegravir, HIV, sub-Saharan Africa, tenofovir, waist circumference, weight gain

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Introduction

Modern antiretroviral therapy (ART) regimens in people with HIV (PWH) have been associated with excess weight gain and increased risk of obesity [1,2]. The risk of weight gain has been most tightly linked to use of integrase inhibitors and tenofovir alafenamide (TAF), as well as to transitions off efavirenz (EFV), tenofovir disoproxil fumarate (TDF) and zidovudine (AZT), and has been observed both in new initiators of ART and in those who are "suppressed and transitioned" [3–6]. Moreover, the magnitude of weight change with specific regimens has differed across sub-populations in studies from both high-income countries and in Africa, with women and Black populations most affected [5]. These data notwithstanding, due to its high barrier to resistance, excellent tolerability, and affordability of integrase inhibitors, many countries in Africa, including Uganda and South Africa, have adopted a fixed-dose combination of TDF, lamivudine, and dolutegravir (TLD) as the preferred first-line regimen for all PWH and this remains the World Health Organization's recommended first-line regimen in low- and middle-income countries (LMICs) [7].

Efforts to understand the impact of large-scale TLD implementation on weight gain and the risk of obesity in populations with HIV across Africa may be complicated by differences in the background obesity epidemics that are co-occurring in the general population [8]. The growing burden of obesity in Africa and low- and middle-income countries more generally has been attributed to greater urbanization, changes in diet, and decreasing physical activity that accompany economic development [9]. However, there have been few studies to assess the "real-world" implications of the transition to TLD in terms of weight gain and clinical obesity among PWH in routine care across different contexts. A comprehensive understanding of heterogeneity in the risk of obesity and magnitude of weight gain in PWH is important to tailor policies and programs to safeguard healthy aging on ART, including the prevention of diabetes and downstream cardiovascular disease that can result from excess body weight [10,11].

In this study, we leverage data from a large, multisite prospective cohort study of 1000 PWH on ART, undergoing a program-directed transition to first-line TLD in public sector clinics in Uganda and South Africa, to explore trajectories of body weight change over 48 weeks after transitioning to TLD. In this analysis, we compare differences in risk of incident obesity among PWH in routine care from two distinct African settings with different background obesity epidemics. We first compare changes in body weight and risk of clinically significant weight gain over 48 weeks and then describe demographic and HIV-related factors associated with these outcomes in these two contexts.

Methods

Study population, design, setting, and sample size

The Population Effectiveness of Dolutegravir Implementation in sub-Saharan Africa: a Prospective Observational Cohort Study (DISCO, NCT04066036) was conducted from 2019 to 2023. A total of 999 participants were recruited from public-sector clinics: 500 PWH from Mbarara Regional Referral Hospital Immune Suppression Syndrome Clinic in Mbarara, Uganda and 499 PWH from Mtubatuba Clinic, Somkhele Clinic, Mpukunyoni Clinic, and Nkundusi Clinic in KwaZulu-Natal, South Africa.

Recruitment and eligibility criteria

The inclusion criteria for the cohort were as follows: $\geq$18 years of age, on NNRTI-based (EFV or nevirapine [NVP]), first-line ART for at least 6 months, prescribed a change to TLD by clinic staff, and residing within 100 kilometres of the clinic with no plans to move outside the catchment area. There were no specific exclusion criteria, except that referral for study procedures was made only after the transition to TLD was confirmed.

Study procedures and data collection

Data collection occurred at three time points: enrollment (the date of transition to TLD), approximately 24 weeks after the transition, and approximately 48 weeks after the transition. At enrollment, study nurses reviewed clinical records to obtain clinical and laboratory history, administered questionnaires about ART adherence, concurrent medication use, and symptoms, and collected physical measurements and blood samples. Study measurements included height (in meters [m]), weight (in kilograms [kg]), and waist circumference (in centimeters [cm]). Measured height and weight were used to calculate body mass index (BMI), defined as weight in kg divided by height in meters squared (kg/m^2). At both follow-up visits, nurses repeated the questionnaires and collection of physical measurements and blood samples.

Outcomes

Our outcomes of interest were: (a) change in body weight (kg) from enrollment to 48 weeks, (b) change in

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waist circumference (cm) from enrollment to 48 weeks, (c) clinically significant weight gain from enrollment to 48 weeks, defined as ≥10% increase in body weight during the observation period, and (d) a combined endpoint of increase in BMI category from normal (18.5–24.9 kg/m^2) to overweight or obese (18.5–24.9 to ≥25 kg/m^2) or from normal or overweight to obese (18.5–29.9 to ≥30 kg/m^2) over the period from enrollment to 48 weeks [12].

Statistical analysis

We first compared crude changes in body weight, waist circumference, incidence of clinically significant weight gain, and incidence of those who changed BMI categories overall and then stratified each of these outcomes by sex and by country. Student's *t*-tests were used to assess differences in continuous variables and Pearson's chi-square tests were used to assess differences in proportions where applicable. To assess for possible confounding, we used a linear mixed-effects regression model with individual random effects to identify factors associated with weight change and, separately, waist circumference over each study visit (as the time scale), and adjusted for age, sex, education, ART duration (in years), and country. Of note, data collected at the 24-week visit were included in these linear mixed-effects models.

We then used multivariable logistic regression to evaluate factors associated with clinically significant weight gain and changes in BMI category over 48 weeks. These models were adjusted for age (categorized as greater versus less than or equal to 47 years old, which is the median age of participants in the cohort), sex, highest educational attainment (no schooling, completion of primary, completion of secondary, or completion of tertiary education), and ART duration (in years). Of note, women who were pregnant during the study period were excluded from these analyses.

A sub-analysis was performed among the Uganda participants only to additionally examine differences in weight change by NNRTI contained in the previous ART regimen (EFV or NVP) prior to TLD transition. In this analysis, we compared weight change over 48 weeks using a linear mixed-effects model, adjusted for age, sex, education, and ART duration, and then adjusted for NNRTI prior to TLD transition as an additional covariate in single-country regression analyses. Finally, a stratified analyses of these relationships in South Africa only was also conducted. These models did not include prior ART regimen for the South Africa cohort because most participants (486/497, 97.8%) switched from a regimen of lamivudine or emtricitabine (XTC), TDF, and EFV to TLD.

Ethical approval

Ethical approval for the study was obtained from Massachusetts General Brigham (2019P000898), the Mbarara University of Science and Technology Research Ethics Committee (16/11–18), the Uganda National Council of Science and Technology, the University of KwaZulu-Natal Biomedical Research Ethics Committee (No. BE485/19), and the South Africa Department of Health. All participants provided written informed consent.

Results

From 999 individuals enrolled in the DISCO cohort, 795 were included in this analysis, including 428 participants in Uganda and 367 in South Africa. Seventy-two (14%) participants from Uganda and 132 (26%) from South Africa were excluded due to missing body weight data at the enrollment and/or 48-week study visits or due to pregnancy that occurred during the follow-up period (South Africa only, N = 37 [7%]) (Supplementary Figure 1, Supplemental Digital Content, http://links.lww.com/QAD/D143). Compared to those who had complete data and thus were included in the analysis, a greater proportion of excluded participants were men ($P = 0.027$) and had a shorter duration of ART use ($P = 0.041$) in Uganda (Supplementary Table 1, Supplemental Digital Content, http://links.lww.com/QAD/D145). In South Africa, the excluded participants were younger ($P = 0.010$), on a shorter duration of ART ($P = 0.017$), and had a different BMI distribution ($P = 0.003$) than those who were included (Supplementary Table 2, Supplemental Digital Content, http://links.lww.com/QAD/D146). Moreover, a greater proportion of the excluded participants in South Africa had a BMI < 18.5 kg/m^2 and a smaller proportion had a BMI ≥ 25 kg/m^2 compared to those who were included. The mean age of participants was 44.9 ± 10.8 years, and 59% were female (43% in Uganda and 78% in South Africa, Table 1). Women were significantly older in Uganda than in South Africa (49.1 ± 6.4 versus 42.4 ± 12.3 years, respectively, $P < 0.001$). There was no significant difference in age among male participants between countries (44.3 ± 10.5 versus 45.6 ± 11.1 years in Uganda and South Africa, respectively, $P = 0.36$). Most participants in Uganda had completed primary school (50%), while many participants in South Africa had completed secondary school (63%). XTC/TDF/EFV was the most common ART regimen prior to TLD transition overall (68%) and within each country (Uganda: 42%, South Africa: 98%), followed by XTC/AZT/NVP (Overall: 22%, Uganda: 40%, South Africa: 0%). Overall, the mean (95% CI) study duration was 55.9 weeks (55.2–56.6). The mean study duration was 58.7 weeks (57.6–59.8) in Uganda and 52.6 weeks (51.8–53.3) in South Africa ($P < 0.001$).

Overall, the mean weight change from enrollment to the 48-week visit was 1.6 kg (95% CI: 1.3–2.0); when stratified by sex, the mean weight change in men was 0.6 kg and in women was 2.3 kg ($P < 0.001$) (data not shown) (Fig. 1a). There were also differences in weight gain by country; namely, the mean weight change among

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Table 1. Cohort characteristics.

Characteristic	Overall ($n=795$)	Uganda ($n=428$)	South Africa ($n=367$)	P-value*
Age (years), *n* (%)				<0.001
≤47	455 (57)	216 (50)	239 (65)	
48+	340 (43)	212 (50)	128 (35)	
Sex, n (%)				<0.001
Male	324 (41)	244 (57)	80 (22)	
Female	471 (59)	184 (43)	287 (78)	
Education, *n* (%)				<0.001
No schooling	94 (12)	49 (12)	45 (12)	
Primary education	288 (36)	215 (50)	73 (20)	
Secondary education	327 (41)	95 (22)	232 (63)	
Tertiary education	86 (11)	69 (16)	17 (5)	
Weight (kg), *n* (%)				<0.001
≤55	182 (23)	125 (29)	57 (16)	
56–70	352 (44)	197 (46)	155 (42)	
71+	261 (33)	106 (25)	155 (42)	
BMI (kg/m^2), *n* (%)				<0.001
<18.5	68 (8)	49 (11)	19 (5)	
18.5–24.9	436 (55)	272 (64)	164 (45)	
≥25	291 (37)	107 (25)	184 (50)	
ART regimen before switch, n (%)				<0.001
XTC/TDF/EFV	539 (68)	181 (42)	358 (98)	
XTC/AZT/NVP	172 (22)	172 (40)	0 (0)	
Other	84 (10)	75 (18)	9 (2)	
ART duration (years) (IQR)	7.8 (5.2, 11.4)	9.1 (6.0, 12.2)	6.7 (4.4, 10.0)	<0.001

ART, antiretroviral therapy; AZT, zidovudine; EFV, efavirenz; NVP, nevirapine; TDF, tenofovir disoproxil; XTC, lamivudine or emtricitabine.
*P-value indicates comparison between participants in Uganda and South Africa. A chi-squared test was conducted for categorical variables and Student's *t*-tests were conducted for continuous variables, all of which were determined to be approximately normally distributed.

participants in Uganda (0.6 kg [95% CI: 0.1–1.0]) was significantly less than that among participants in South Africa (2.9 kg [95% CI: 2.3–3.4]) ($P<0.001$). When stratified by sex, the mean weight change was significantly lower for both men ($P<0.001$) and women ($P<0.001$) in Uganda (men: 0.1 kg [95% CI: −0.5–0.6]; women: 1.2 kg [95% CI: 0.5–2.0]) as compared to South Africa (Men: 2.3 kg [95% CI: 1.5–3.2]; women: 3.0 kg [95% CI: 2.4–3.7]).

A total of 644 individuals (81% of those with complete body weight data) also had waist circumference data available at baseline and 48 weeks. Changes in waist circumference followed a similar trend as changes in body weight. The mean change in waist circumference overall was 1.6 cm (95% CI: 1.0–2.2); this change was smaller at the Uganda site (0.8 cm [95% CI: 0.0–1.5]) than at the South Africa site (2.3 cm [95% CI: 1.4–3.2) ($P=0.012$). Women in Uganda (0.3 cm [95% CI: −0.7–1.3]) experienced a significantly smaller change in waist circumference than women in South Africa did (2.4 cm [95% CI: 1.4–3.5]) ($P=0.016$), but no significant difference in waist circumference change was observed among men across sites ($P=0.40$; data not shown). In a linear mixed-effects regression model with waist circumference as the outcome and adjusted for potential confounders, increased waist circumference was found among women (7.71 [95% CI: 5.95–9.48], $P<0.001$), people older than 47 years (4.28 [95% CI: 2.47–6.09], $P<0.001$), and those who completed tertiary education (4.36 [95% CI: 0.90–7.82], $P=0.013$) (Supplementary Table 3, Supplemental Digital Content, http://links.lww.com/QAD/D147).

The mean incidence of clinically significant weight gain (≥10%) overall was 13.6% (95% CI: 11.3–16.2); there was a significantly lower incidence in men (8.3% [95% CI: 5.3–11.3]) than in women (17.2% [95% CI: 13.8–20.6%]) ($P<0.001$; data not shown), and a significantly lower incidence in Uganda (9.8% [95% CI: 7.0–12.6]) compared to South Africa (18.0% [95% CI: 14.1–21.9]) ($P<0.001$). There were differences in incidence of clinically significant weight gain between Uganda and South Africa for men (7.0% v. 12.5%, $P=0.12$) and women (13.6% v. 19.5%, $P=0.096$) but these did not reach statistical significance (Fig. 1b).

The mean incidence of increase in BMI category from normal to either overweight or obese or from normal or overweight to obese was 14.0% (95% CI: 11.6–16.8); this incidence was significantly higher in women than in men (16.4% v. 10.3%, $P=0.021$; data not shown) and lower among participants in Uganda (10.8% [95% CI: 7.7–13.9]) compared to South Africa (17.5% [95% CI: 13.5–21.5]) ($P=0.009$). When comparing men and women across countries, there were no significant differences in incidence of change in BMI category by sex (Men: $P=0.29$; Women: $P=0.11$; Fig. 1c).

In linear mixed-effects regression models with weight as the outcome and adjusted for potential confounders, the increased weight seen among women (4.55 [95% CI:

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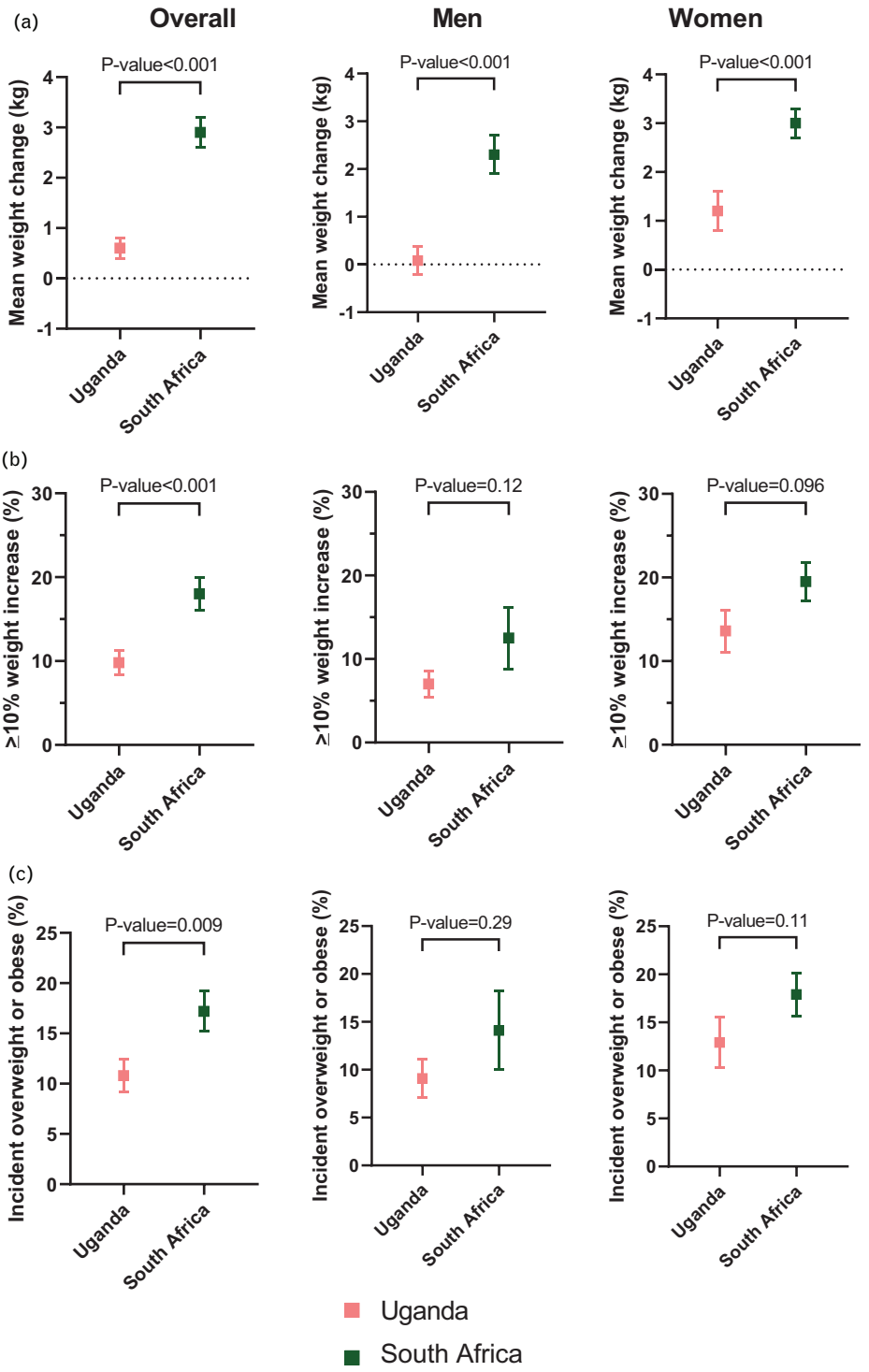


Fig. 1. Comparison of (a) mean changes in body weight, (b) incidence of clinically significant weight gain, and (c) incidence of those who changed BMI categories of DISCO participants. From left to right: overall, men, women.

2.38–6.73]) persisted (Table 2, Fig. 2). After adjusting for age, sex, education, and ART duration, the weight gain experienced at each visit by people living in Uganda was less than that by those living in South Africa ($P < 0.001$ for all visits) (Fig. 2). In a logistic regression model with clinically significant weight gain as the outcome, being female (adjusted odds ratio [aOR] 1.97 [95% CI: 1.19–3.26]) and living in South Africa as compared to Uganda (aOR 1.81 [95% CI: 1.09–2.99]) were associated with significant weight gain (Table 3).

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Table 2. Linear mixed-effects regression model to identify factors associated with weight change over 48 weeks.

Covariate	$n=795$	Point estimate (95% CI)	*P*-value
Age (years)			
≤47 years	455	-ref-	
48+	340	1.69 (−0.54–3.93)	0.14
Sex			
Male	324	-ref-	
Female	471	4.55 (2.38–6.73)	<0.001
Education			
No schooling	94	-ref-	
Primary education	288	2.44 (−0.89–5.77)	0.15
Secondary education	327	3.48 (0.06–6.90)	0.046
Tertiary education	86	7.58 (3.31–11.85)	<0.001
ART duration (years)	795	−0.15 (−0.42–0.12)	0.27
Visit and country			
24 Weeks | Uganda	374	-ref-	
24 Weeks | South Africa	320	1.84 (1.20–2.49)	<0.001
48 Weeks | Uganda	428	-ref-	
48 Weeks | South Africa	367	2.30 (1.69–2.92)	<0.001

ART, antiretroviral therapy; CI, confidence interval.

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In Uganda, 239 participants were switched from an EFV-containing regimen and 189 were switched from an NVP-containing regimen. In analyses restricted to the Uganda site, differences in weight change by prior NNRTI regimen were not significant (EFV: 0.9 kg [0.2–1.5], NVP: 0.2 kg [−0.4–0.8], $P=0.13$ for difference) (Supplementary Figure 2, Supplemental Digital Content, http://links.lww.com/QAD/D144). There was also no significant difference in weight change by prior NRTI regimen (TDF: 0.8 kg [95% CI: 0.1–1.5], AZT: 0.4 kg [95% CI: −0.2–1.0], $P=0.35$ for difference). In an adjusted linear mixed-effects model limited to participants in Uganda only, women (5.21 [95% CI: 2.74–7.68], $P<0.001$) and those who completed tertiary education (7.21 [95% CI: 2.70–11.73], $P=0.002$) experienced greater weight gain; prior NNRTI-use ($P=0.86$) and regimen prior to switch ($P=0.25$) were nonsignificant (Supplementary Table 4, Supplemental Digital Content, http://links.lww.com/QAD/D148 and Supplementary Table 5, Supplemental Digital Content, http://links.lww.com/QAD/D149). When limited to South Africa participants only, women (4.49 [95% CI: 0.49–8.49], $P=0.028$), those 48 years and older (6.73 [95% CI: 2.18–11.27], $P=0.004$), and those who completed secondary (6.55 [95% CI: 0.59–12.51], $P=0.031$) and tertiary education (12.36 [95% CI: 2.75–21.97], $P=0.012$) experienced greater weight gain in an adjusted linear mixed-effects model, while no covariates were associated with significant weight gain in a logistic regression model with clinically significant weight gain as the outcome

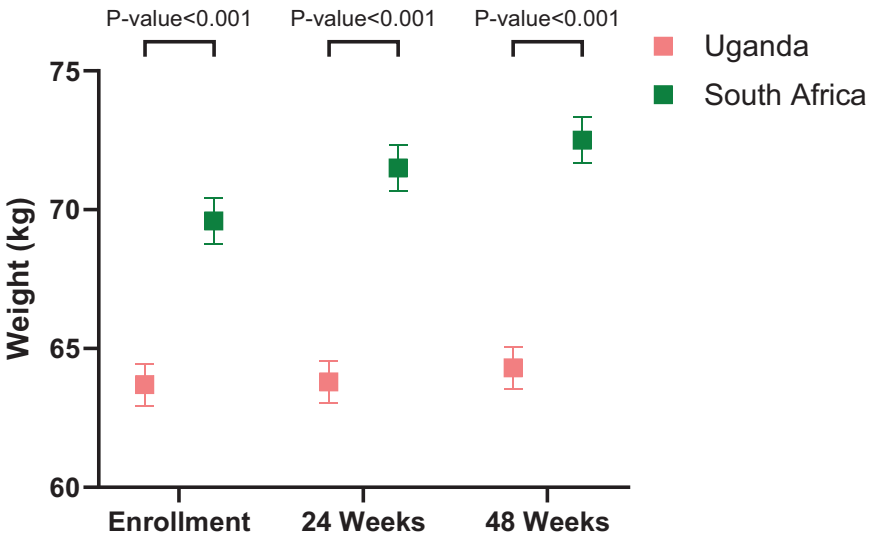


Fig. 2. Predicted body weight at the enrollment, 24-week, and 48-week study visits after adjusting for age, sex, education, and prior ART duration.

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Table 3. Multivariable logistic regression model to assess predictors of clinically significant weight gain (≥10%) over 48 weeks.

	Incidence	Univariable model		Multivariable model	
Covariate	*n* (%)	OR (95% CI)	*P*-value	AOR (95% CI)	*P*-value
Age					
≤47 years	70 (15)	-ref-			
48+ years	38 (11)	0.69 (0.45–1.06)	0.088	0.66 (0.40–1.08)	0.097
Sex					
Male	27 (8)	-ref-			
Female	81 (17)	2.28 (1.44–3.62)	<0.001	1.97 (1.19–3.26)	0.008
Education					
No schooling	12 (13)	-ref-			
Primary education	38 (13)	1.04 (0.52–2.08)	0.91	1.26 (0.62–2.59)	0.52
Secondary educ.	48 (15)	1.18 (0.60–2.32)	0.64	0.86 (0.41–1.83)	0.70
Tertiary education	10 (12)	0.90 (0.37–2.20)	0.82	1.20 (0.46–3.09)	0.71
ART duration (years)	0.18 (0.11–0.28)	<0.001	1.01 (0.95–1.07)	0.76	
Country					
Uganda	42 (10)	-ref-			
South Africa	66 (18)	2.02 (1.33–3.05)	<0.001	1.81 (1.09–2.99)	0.021

AOR, adjusted odds ratio; ART, antiretroviral therapy; CI, confidence interval; OR, odds ratio.

(Supplementary Table 6, Supplemental Digital Content, http://links.lww.com/QAD/D150 and Supplementary Table 7, Supplemental Digital Content, http://links.lww.com/QAD/D151).

Discussion

In this study, we identified substantial geographic heterogeneity in weight gain among PWH who were transitioned to first-line TLD in in Uganda as compared to South Africa. While PWH in Uganda gained an average of 0.6 kg over 48 weeks, those in South Africa gained an average of 2.9 kg. Furthermore, in Uganda only about one in ten study participants gained ≥10% of their body weight from baseline, whereas nearly one in five participants in South Africa experienced this weight increase. These differences were largely robust to sex-stratification, adjustment for demographic factors, and the prior duration of ART. Additionally, waist circumference increased differentially in these two groups, suggesting that the observed increases in weight may also portend differential increases in abdominal adiposity and in turn, cardiometabolic risk, between these two groups [13]. Taken together, these results indicate that weight change associated with TLD is not uniform across locations; locally tailored approaches to prevent weight gain will be important to address obesity in PWH.

The large differences in the magnitude of weight gain between participants at these two sites may reflect - at least in part - differences in the underlying obesity epidemic across contexts. Notably, our findings are consistent with obesity trends in the general population of these two countries [8,14]. For instance, in South Africa, recent estimates indicate that half of adults are overweight or obese [15]. The community in which this study site is situated is one that is rural with relatively high unemployment. In contrast, similar data from Uganda have suggested that only about one-third of adults are overweight or obese and that obesity, while increasing, still falls below the regional average [16]. In addition, HIV-related factors may also play a role in these findings. Though we did not find differences in weight gain for those transitioned from EFV to TLD compared to those transitioned from NVP to TLD in Uganda, we were unable to explore heterogeneity in weight gain by other HIV-treatment factors such as CYP2B6 polymorphisms, as these data were not collected from this cohort [17]. Finally, differences in the demographic composition of the sample may contribute to these findings, including the slightly more educated and predominantly female sample in South Africa. Higher education (as a proxy for socioeconomic status) has been associated with a higher risk of obesity in some LMICs due to greater access to processed foods [18].

Our findings have important implications for programs and policies related to the long-term holistic care of PWH on modern ART. First, the substantial weight gain experienced by PWH should prompt an increased focus on both behavioral and pharmacologic interventions to prevent and treat obesity and its complications. This is especially true in South Africa where 18% of people gained over 10% of their body weight within 48 weeks of TLD initiation. To this end, there is a growing arsenal of promising therapies such as glucagon-like-peptide-1 receptor agonists (GLP-1 RAs) that are becoming increasingly available to treat obesity in the general population [19]. These have not been widely studied in PWH to date but should be prioritized as an important area of investigation within HIV medicine, including in Africa, and likely integrated into usual care for obese PWH. Transitioning to alternative ART regimens has also been considered for this purpose, but studies have not demonstrated weight loss with this strategy, and it is currently not recommended in local guidelines [20].

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Several aspects of our findings are consistent with those from recent prior studies. First, studies of PWH who were transitioned to dolutegravir-based ART in high-income countries have shown average overall weight gain of 0.6 kg to 1.6 kg over 48 weeks after regimen switch [3,5]. Moreover, one of these studies also found that 6.4% of those who were switched gained ≥10% of their baseline body weight. In addition, there have been several retrospective analyses from observational cohorts that describe body weight change across other African contexts after implementation of TLD. For instance, one study of 4445 PWH in rural Kenya found a preswitch weight gain of 0.6 kg and a postswitch weight gain of 0.8 kg annually across all participants [21]. In a second analysis from the African Cohort Study (AFRICOS), including participants from Kenya, Tanzania, Uganda, and Nigeria, PWH who switched to TLD experienced an average adjusted weight gain of 0.35 kg per year prior to switch and a weight increase of 1.46 kg in the year following the switch [22]. Several prior studies have also observed greater weight gain in women, including the aforementioned studies [21,22]. Here, we also found that women had twice the risk of clinically significant weight gain as men in both countries after the switch to TLD [5,23]. However, our findings regarding the risk of greater weight gain with transitions off EFV compared to NVP are inconsistent with a prior analysis from Kenya as we did not find a significant difference when comparing these two prior regimens [24].

Our study has several limitations. First, our study sites in Uganda and South Africa were both located in rural or peri-urban settings. Hence, our findings may not be generalizable to urban populations in Africa. However, one strength of this design is that the two settings are geographically similar and use a parallel study design. Second, we did not collect data on blood pressure or blood glucose, and thus could not study trajectories of these health indicators alongside changes in body weight. However, we were able to describe changes in waist circumference. Waist circumference is typically used to assess abdominal obesity, and has been closely associated with greater visceral fat and increased cardiometabolic health risks [25]. Third, our cohort had missingness in body weight at either enrolment or the 48-week visit in 14% of participants in Uganda and 21% of participants in South Africa. However, we provide a detailed overview of the distribution of key characteristics among those with complete body weight data, as compared to those with missing data (Supplementary Tables 1, Supplemental Digital Content, http://links.lww.com/QAD/D145 and 2, http://links.lww.com/QAD/D146). Fourth, though visits were conducted at about 24 and 48 weeks after the transition, there was some heterogeneity in the exact timing of the visits. Fifth, there is the possibility of unmeasured confounding due to factors that were not captured in this study (e.g. diet). Sixth, the South Africa site enrolled more women than the Uganda site. While we found site-based differences in some measures when sex-stratifying, it is possible that these differences in sample composition may still impact our findings (Supplementary Tables 8, Supplemental Digital Content, http://links.lww.com/QAD/D153 and 9, http://links.lww.com/QAD/D154). Finally, we lack a group of PWH who were not switched or HIV-negative comparator group to contextualize the extent to which this weight change is due to ART versus other factors.

In conclusion, this study uncovered important geographic heterogeneity in the magnitude of weight gain experienced by PWH who were transitioned to TLD in routine care. While participants from both countries experienced weight gain and increases in waist circumference, these increases were much greater in South Africa. These findings should motivate tailored policies and programs for prevention and treatment of obesity and its complications among PWH on TLD.

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Conflicts of interest

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References

1. Venter WDF, Moorhouse M, Sokhela S, Fairlie L, Mashabane N, Masenya M, *et al*. **Dolutegravir plus two different prodrugs of tenofovir to treat HIV.** *N Engl J Med* 2019; **381**:803–815.

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2. Kouanfack C, Mpoudi-Etame M, Omgba Bassega P, Eymard-Duvernay S, Leroy S, Boyer S, *et al*. **Dolutegravir-based or low-dose efavirenz-based regimen for the treatment of HIV-1.** *N Engl J Med* 2019; **381**:816–826.
3. Erlandson KM, Carter CC, Melbourne K, Brown TT, Cohen C, Das M, *et al*. **Weight change following antiretroviral therapy switch in people with viral suppression: pooled data from randomized clinical trials.** *Clin Infect Dis* 2021; **73**:1440–1451.
4. Lake JE, Trevillyan J. **Impact of Integrase inhibitors and tenofovir alafenamide on weight gain in people with HIV.** *Curr Opin HIV AIDS* 2021; **16**:148–151.
5. Lake JE, Wu K, Bares SH, Debroy P, Godfrey C, Koethe JR, *et al*. **Risk factors for weight gain following switch to integrase inhibitor-based antiretroviral therapy.** *Clin Infect Dis* 2020; **71**:e471–e477.
6. Mallon PW, Brunet L, Hsu RK, Fusco JS, Mounzer KC, Prajapati G, *et al*. **Weight gain before and after switch from TDF to TAF in a U.S. cohort study.** *J Int AIDS Soc* 2021; **24**:e25702.
7. World Health Organization, Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, H.a.S.T.I.P. Department of Global HIV, 2021, World Health Organization.
8. Jaacks LM, Vandevijvere S, Pan A, McGowan CJ, Wallace C, Imamura F, *et al*. **The obesity transition: stages of the global epidemic.** *Lancet Diabetes Endocrinol* 2019; **7**:231–240.
9. Popkin BM, Adair LS, Ng SW. **Global nutrition transition and the pandemic of obesity in developing countries.** *Nutr Rev* 2012; **70**:3–21.
10. Herrin M, Tate JP, Akgün KM, Butt AA, Crothers K, Freiberg MS, *et al*. **Weight gain and incident diabetes among HIV-infected veterans initiating antiretroviral therapy compared with uninfected individuals.** *J Acquir Immune Defic Syndr* 2016; **73**:228–236.
11. McCann K, Shah S, Hindley L, Hill A, Qavi A, Simmons B, *et al*. **Implications of weight gain with newer antiretrovirals: 10-year predictions of cardiovascular disease and diabetes.** *AIDS* 2021; **35**:1657–1665.
12. Verburgh ML, Wit FWNM, Boyd A, Verboeket SO, Reiss P, van der Valk M. **One in 10 virally suppressed persons with HIV in the Netherlands experiences ≥10% weight gain after switching to tenofovir alafenamide and/or integrase strand transfer inhibitor.** *Open Forum Infectious Diseases* 2022; **9**:.
13. Neeland IJ, Ross R, Després JP, Matsuzawa Y, Neeland IJ, Yamashita S, *et al*. **Visceral and ectopic fat, atherosclerosis, and cardiometabolic disease: a position statement.** *Lancet Diabetes Endocrinol* 2019; **7**:715–725.
14. Ajayi IO, Adebamowo C, Adami HO, Dalal S, Diamond MB, Bajunirwe F, *et al*. **Urban-rural and geographic differences in overweight and obesity in four sub-Saharan African adult populations: a multicountry cross-sectional study.** *BMC Public Health* 2016; **16**:1126.
15. Boachie, M., *Obesity costs South Africa billions. We did the sums*, in *The Conversation*. 2022.
16. Ayoola A, Ssekubugu R, Grabowski MK, Ssekasanvu J, Kigozi G, Mustapha A, *et al*. **Overweight and obesity in south central Uganda: a population-based study.** *PLOS Global Public Health* 2022; **2**:e0001051.
17. Griesel R, Maartens G, Chirehwa M, Sokhela S, Akpomiemie G, Moorhouse M, *et al*. **CYP2B6 genotype and weight gain differences between dolutegravir and efavirenz.** *Clin Infect Dis* 2021; **73**:e3902–e3909.
18. Monteiro CA, Moura EC, Conde L, Popkin BM. **Socioeconomic status and obesity in adult populations of developing countries: a review.** *Bull World Health Organ* 2004; **82**:940–946.
19. Wang JY, Wang QW, Yang XY, Yang W, Li DR, Jin JY, *et al*. **GLP-1 receptor agonists for the treatment of obesity: Role as a promising approach.** *Front Endocrinol* 2023; **14**:1085799.
20. Nel J, Dlamini S, Meintjes G, Burton R, Black JM, Davies NECG, *et al*. **Southern African HIV Clinicians Society guidelines for antiretroviral therapy in adults: 2020 update.** *South Afr J HIV Med* 2020; **21**:1115.
21. Hickey MD, Wafula E, Ogachi SM, Ojwando H, Orori G, Adede RO, *et al*. **Weight change following switch to dolutegravir for HIV treatment in rural kenya during country roll-out.** *J Acquir Immune Defic Syndr* 2023; **93**:154–161.
22. Esber AL, Chang D, Iroezindu M, Bahemana E, Kibuuka H, Owuoth J, *et al*. **Weight gain during the dolutegravir transition in the African Cohort Study.** *J Int AIDS Soc* 2022; **25**:e25899.
23. Bourgi K, Ofner S, Musick B, Griffith B, Diero L, Wools-Kaloustian K, *et al*. **Weight gain among treatment-naïve persons with hiv receiving dolutegravir in Kenya.** *J Acquir Immune Defic Syndr* 2022; **91**:490–496.
24. Bourgi K, Ofner S, Musick B, Wools-Kaloustian K, Diero L, Yiannoutsos CT, Gupta S. Weight gain among participants switching to a dolutegravir-based HIV regimen in Kenya [CROI Abstract 674], in Conference on Retroviruses and Opportunistic Infections. 2023: Washington. p. 236.
25. Ross R, Neeland IJ, Yamashita S, Seidell J, Magni P, Santos RD, *et al*. **Waist circumference as a vital sign in clinical practice: a consensus Statement from the IAS and ICCR Working Group on Visceral Obesity.** *Nature Rev Endocrinol* 2020; **16**:177–189.

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