Weight Change Following Switch to Dolutegravir for HIV Treatment in Rural Kenya During Country Roll-Out

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Introduction: Switch to dolutegravir (DTG) in treatment-experienced people living with HIV (PLH) is associated with excess weight gain in some settings; data are limited from rural low-income settings with low obesity prevalence.

Methods: In rural Kenya, we conducted a retrospective cohort study at 8 HIV clinics and a single-site prospective cohort study including adults switching to DTG during countrywide transition to DTG/tenofovir DF(TDF)/emtricitabine as first-line HIV treatment. In the retrospective analysis, we used preswitch data to model postswitch weight trajectory had each participant not switched to DTG and contrasted observed vs. predicted postswitch weight. In the prospective analysis, we measured weight post-DTG switch and evaluated predictors of 6-month weight change.

Results: Our retrospective cohort included 4445 PLH who switched to DTG between 2018 and 2020. Mean 12-month weight change was 0.6 kg preswitch and 0.8 kg postswitch. Among those on TDF throughout (n = 3374; 83% on efavirenz preswitch), 12-month postswitch weight was 0.7 kg more than predicted for women (95% CI: 0.4, 1.0) and similar among men (0.04 kg; 95% CI −0.3, 0.4). In our prospective cohort (n = 135, 100% female), mean 6-month weight change was +0.4 kg (IQR −1.1, 2.0 kg). Predicted gain varied by baseline food insecurity: +1.1 kg (95% CI: 0.34, 1.87) among food secure, −0.09 kg (95% CI −0.71, 0.54) among moderate insecure, and +0.27 kg (95% CI −0.82, 1.36) among severe insecurity.

Conclusion: In contrast to some reports of large weight gain following switch to DTG, we observed small weight increases in women and no weight change in men following DTG switch when on TDF throughout. Weight gain may be attenuated by food insecurity, though was modest even among food secure.

Key Words: weight gain, dolutegravir, switch, Kenya

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INTRODUCTION

In 2018, the World Health Organization[1] changed preferred first-line antiretroviral therapy (ART) for HIV treatment to dolutegravir (DTG) in combination with tenofovir disoproxil fumarate (TDF) and lamivudine (3TC), replacing efavirenz (EFV). DTG has several advantages over EFV, including superior viral suppression, higher barrier to resistance, and lower neuropsychiatric toxicity[2,3]; however, DTG may be associated with greater weight gain and treatment-emergent obesity than EFV-based ART.[4,5]

In sub-Saharan Africa, 2 recent randomized controlled trials (RCTs) among ART-naive persons living with HIV (PLH) in South Africa (ADVANCE) and Cameroon (NAMSAL) demonstrated significant weight gain following initiation of DTG when compared with EFV-containing ART.[4–8] Weight gain was most pronounced when combined with tenofovir alafenamide (TAF) among women, though was still greater with DTG than EFV when both were combined with TDF. DTG + TDF was associated with greater treatment-emergent metabolic syndrome than EFV + TDF in NAMSAL, but not in ADVANCE.[8] In both of these studies, approximately one-third of patients were overweight or obese at baseline. Another recent study in rural Kenya, where overweight and obesity is less prevalent, found similar large increases in weight gain after 12 months among treatment-naive individuals after starting DTG compared with nonnucleotide reverse transcriptase inhibitor (NNRTI)-based regimens.[9]

Weight gain on ART initiation may reflect improved health, with reduction of inflammation and catabolic activity and increased appetite. This return-to-health effect is not present for virally suppressed patients switching from one ART class to another; thus, ART switch studies may help better understand drug-specific effects on body weight. Several switch studies suggest greater weight gain with TAF compared with TDF, suggesting either TAF-associated

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weight gain or TDF-associated weight suppression. A recent RCT in Zambia found greater weight gain with switch from TDF to TAF compared with maintaining TDF.[10] Another study in South Africa showed that switch from TAF to TDF resulted in weight loss in women, but not in men, highlighting potential sex-specific effects.[11] Switch from EFV to DTG also may also lead to weight gain, albeit with variable effects in different populations that could be due to heterogeneity in food environment or genetic polymorphisms affecting drug metabolism.[12] Recent studies of switch from EFV to DTG while maintaining other ART components have ranged from a mean 1-year weight gain of 1.1 kg in Zambia[10] to 2.9 kg, nearly 3-fold greater, in South Africa.[11] With recent widespread transition to DTG/TDF/3TC, it is important to understand effects on weight and metabolic disease across different populations and contexts throughout sub-Saharan Africa.

We sought to characterize incident weight gain, diabetes, and metabolic syndrome following countrywide transition to DTG/TDF/3TC in a rural setting in sub-Saharan Africa where obesity is uncommon. We conducted our study in 2 parts. First, we conducted a retrospective cohort study among patients switching to DTG in 8 HIV clinics in rural western Kenya to evaluate weight changes after switch and risk factors for weight gain. Because diabetes and metabolic syndrome screening is not systematically conducted in routine clinical care, we also conducted a prospective cohort study to evaluate incident diabetes and metabolic syndrome following switch to DTG.

METHODS

Study Design and Participants

In 2018, Kenya adopted new HIV treatment guidelines recommending that virally suppressed patients on EFV/TDF/3TC switch to the new first-line regimen, DTG/TDF/3TC.[13] We sought to evaluate weight changes and incident metabolic disease following switch to DTG in western Kenya during countrywide transition to DTG-based HIV treatment. Our study included both a retrospective cohort study and a prospective cohort study with additional biometric and laboratory data collection. The retrospective analysis used electronic medical record data from 8 rural HIV clinics. The prospective study recruited adults switching to DTG at a single clinic in rural western Kenya and followed them over the first 6 months postswitch.

The retrospective study included nonpregnant PLH aged ≥25 years who switched to DTG from January 2018 through December 2020; were on ART for ≥1 year before switching to DTG; and had ≥2 weight measurements within 14 months preswitch, a measured weight at or within 2 months preswitch (baseline weight), and ≥1 weight measurement within 14 months postswitch. We excluded individuals on abacavir before switch due to small numbers on this regimen (n = 3) and those who had implausible preswitch weight (<40 kg) or BMI (<14 kg/m^2).

We conducted the prospective cohort study at the Sindo Sub-County Hospital in Kenya, a large public hospital with approximately 3000 adult patients receiving ART. Because of later transition to DTG among reproductive-aged women,[14] nearly all eligible men had already switched to DTG at study start; thus, we focused our study on women. We recruited PLH attending routine HIV visits who switched to DTG on the day of enrollment and met the following eligibility criteria: (1) aged ≥25 years, (2) female sex, (3) not previously on DTG, (4) on ART for ≥6 months, (5) not currently pregnant, and (6) able to provide written informed consent in English, Swahili, or Dholuo. Patients were eligible for DTG switch by country guidelines if they were on a prior first-line regimen and were virally suppressed; we included all individuals switched to DTG by Ministry of Health clinicians even if these criteria were not strictly met. We excluded women who became pregnant during the study due to limitations in comparing weight gain in this population to nonpregnant individuals. Both studies were approved by the institutional review boards at the Kenya Medical Research Institute and University of California, San Francisco.

Measurements

In the retrospective cohort, we reviewed electronic charts to gather data on participant characteristics at the time of DTG switch and all available visit data through October 2021. Data included age, sex, date of HIV diagnosis, date of ART initiation, ART history, clinic visit dates, weight, height, and HIV viral load. All data were collected during routine HIV care visits and were recorded in the medical record by clinical staff.

In the prospective cohort, we collected participant demographic data, HIV treatment history, past medical history, and height. At baseline and 1-, 3-, and 6-month follow-up visits, we collected data on medication adherence, pregnancy, and food insecurity over the prior 4 weeks; we categorized food insecurity as moderate if participants reported ≥5 mild–moderate factors and severe if any severe factor was reported on the 9-item Individual Household Food Insecurity Scale.[15] We also measured weight, blood pressure, and fasting glucose at each visit. We measured weight using a calibrated scale with participants removing shoes and heavy clothing. We measured blood pressure using a standard protocol including a single measurement in all participants following 2 minutes of rest with back and arm supported; those with blood pressure of ≥140/90 mm Hg on initial measurement underwent 2 additional measurements after 2-minute intervals.[16] We measured fasting lipids at baseline and 6 months.

Outcomes

For the retrospective cohort, our primary outcome was the difference between predicted and observed weight change at 12 months postswitch. For the prospective cohort, our primary outcome was mean weight change at 6 months postswitch. Secondary outcomes included incident obesity, diabetes, and metabolic syndrome. Incident obesity was defined as body mass index (BMI) ≥30 kg/m^2 among those without baseline obesity. Incident diabetes was defined as

having fasting blood glucose (FBG) ≥7 mmol/L among those without baseline diabetes. Incident metabolic syndrome was defined as FBG ≥6.1 mmol/L and ≥2 of the following among those without baseline metabolic syndrome: fasting high-density lipoprotein <0.9 mmol/L (men) or <1.0 mmol/L (women), fasting triglycerides ≥1.7 mmol/L, BMI ≥30 kg/m^2, or hypertension defined as blood pressure ≥140/90 on the average of the second and third readings out of 3 repeated measures.[17]

Data Analysis

In the retrospective cohort study, we used linear mixed models based on preswitch weight to predict the postswitch weight trajectory for each participant if they had not switched to DTG, adjusting for sex, age, preswitch regimen, and time. We contrasted the observed vs. predicted weight at 12 months postswitch in all participants and stratified by sex, BMI category (underweight [BMI <18.5 kg/m^2], normal weight [BMI 18.5–24.9 kg/m^2], overweight/obese [BMI ≥25 kg/m^2]), and preswitch HIV viral suppression (<200 copies/mL on the most recent visit within 2 months before switch). Because TDF has been associated with weight loss,[18] we repeated our analysis restricted to those on TDF both preswitch and postswitch. Statistical inference was obtained with the nonparametric bootstrap (1000 repetitions). In the prospective cohort, we summarized incident weight gain, fasting glucose, cholesterol, diabetes, and metabolic syndrome 6 months post-DTG switch and used paired *t* tests to compare changes from baseline to 6 months. We conducted univariable and multivariable linear regression of weight change after 6 months as a function of baseline age, years since HIV diagnosis, BMI, fasting glucose, total cholesterol, and food insecurity. Predictors with univariable $P \leq 0.1$ were included in the multivariable model, which was also used to obtain predicted weight gain under different levels of baseline food insecurity.

RESULTS

Among 6935 adults aged ≥25 years who switched to DTG/TDF/3TC, 4445 were included in the retrospective study (Fig. S1, Supplemental Digital Content, http://links.lww.com/QAI/C28). Included participants had a total of 40,589 visits with a measured weight within 14 months before and after switch. The median age was 43 years (IQR 35–51 years); 63% of participants were women (n = 2780); 10% were underweight (n = 453), 68% had a normal BMI (n = 3013), 17% were overweight (n = 761), and 5% were obese (n = 218) at the time of switch (Table 1). Before switch, 99.2% of participants were on a nonnucleoside reverse transcriptase inhibitor (NNRTI; n = 4410). Preswitch nucleoside reverse transcriptase inhibitors (NRTIs) included 3TC plus TDF (76%, n = 3374), zidovudine (AZT; 18%, n = 815), or stavudine (d4T; 6%, n = 256). At switch, 24% had a measured viral load (n = 1061), among whom 94% were virally suppressed (<200 copies/mL; n = 999). Among all participants, average weight change was +0.60 kg in the year before switch and +0.76 kg in the year following switch. Restricting to those on TDF before switch (n = 3374), average weight change was +0.54 kg

TABLE 1. Participant Characteristics at the Time of Switch to DTG (n = 4445) in the Retrospective Cohort Study

Baseline Characteristic	On TDF (n = 3374), n (%)	Not on TDF (n = 1071), n (%)	All (N = 4445) n (%)
Median age (yr; median (Q1–Q3))	40 (34–49)	50 (43–57)	43 (35–51)
Weight at switch (kg; median (Q1–Q3))	61 (55–69)	61 (55–68)	61 (55–68)
Women (n, %)	2215 (66%)	565 (53%)	2780 (63%)
Time since ART initiation (yr; median (Q1–Q3))	5.42 (3.67–7.33)	8.75 (7–10.58)	6.25 (4.25–8.5)
BMI at switch (n, %)			
Underweight (<18.5 kg/m^2)	335 (10%)	118 (11%)	453 (10%)
Normal weight (18.5–24.9 kg/m^2)	2270 (67%)	743 (69%)	3013 (68%)
Overweight (25–29.9 kg/m^2)	592 (18%)	169 (16%)	761 (17%)
Obese (≥30 kg/m^2)	177 (5%)	41 (4%)	218 (5%)
Viral load measured in 12 mo before switch (n, %)	768 (23%)	293 (27%)	1061 (24%)
Viral load <200 copies/mL (n, %)	719/768 (94%)	280/293 (96%)	999/1061 (94%)
ART anchor drug at switch (n, %)			
NNRTI	3350 (99%)	1060 (99%)	4410 (99%)
PI	24 (1%)	11 (1%)	35 (1%)
NNRTI at switch (n, %)			
EFV	2900 (86%)	79 (7%)	2979 (67%)
NVP	450 (13%)	981 (92%)	1431 (32%)
NRTI at switch (n, %)			
TDF	3374 (100%)	0 (0%)	3374 (76%)
AZT	0 (0%)	815 (76%)	815 (18%)
d4T	0 (0%)	256 (24%)	256 (6%)

DTG, dolutegravir; TDF, tenofovir disoproxil fumarate; IQR, interquartile range displayed as quartile 1 – quartile 3; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; EFV, efavirenz; NVP, nevirapine; AZT, zidovudine; d4T, stavudine.

TABLE 2. Observed Pre-switch and Post-switch Weight Changes in the Retrospective Cohort, Overall and by Baseline Subgroup

	Participant, n	Mean Weight Change 12 mo Preswitch (kg)	Mean Weight at Switch (kg)	Mean Weight Change 12 mo Postswitch (kg)
All participants	4445	0.60	62.3	0.76
Men	1665	0.50	63.8	0.27
Women	2780	0.64	61.4	1.05
Underweight	453	−0.73	49.5	1.02
Normal weight	3013	0.29	59.9	0.77
Overweight/obese	979	2.26	75.6	0.65
Virally suppressed	999	0.63	62.8	0.67
Participants on TDF throughout	3374	0.54	62.4	0.90
Men	1159	0.53	63.9	0.47
Women	2215	0.54	61.6	1.11
Underweight	335	−0.97	49.4	1.20
Normal weight	2270	0.15	59.8	0.93
Overweight/obese	769	2.46	75.7	0.73
Virally suppressed	719	0.70	62.7	0.72

TDF, tenofovir disoproxil fumarate

preswitch and +0.90 kg postswitch. Women on TDF gained +0.54 kg preswitch and +1.11 kg postswitch. Virally suppressed individuals on TDF preswitch gained +0.70 kg preswitch and +0.72 kg postswitch (Table 2).

Table 3 shows the average difference in observed weight gain 12 months postswitch compared with predicted based on preswitch weight trajectories. Restricting to those on TDF throughout, participants gained an average of 0.47 kg (95% CI: 0.20, 0.73) more than expected. Individuals who were underweight had the greatest weight gain compared with expected (2.42 kg, 95% CI: 1.83, 3.09), followed by normal weight individuals (0.95 kg, 95% CI: 0.65, 1.25). Women gained 0.70 kg (95% CI: 0.37, 1.03) greater than expected, and weight for men was not different than expected: 0.04 kg (95% CI −0.30, 0.43). Individuals who were overweight or obese gained 1.82 kg less than predicted postswitch (95% CI −2.42, −1.20; Fig. 1).

Among 145 screened for the prospective study, 140 people were eligible, and 139 people enrolled (Fig. S2, Supplemental Digital Content, http://links.lww.com/QAI/C28). Four participants dropped out or became ineligible during follow-up due to lack of interest (n = 1) and incident pregnancy (n = 3). Among 135 who completed 6 months of follow-up, the median age was 37 (range 26–58; Table S1, Supplemental Digital Content, http://links.lww.com/QAI/C28). All participants were on a regimen combined with TDF and 3TC both before and after switch to DTG; nearly all were on efavirenz before switching (n = 133, 99%), with the remaining participants on boosted atazanavir (n = 2, 1%). At baseline, the median weight was 60.0 kg (Q1–Q3 53.1–69.0). Most participants had a normal baseline BMI (61%), whereas 7% were underweight, 24% were overweight, and 7% were obese. At baseline, 1 participant had a known diagnosis of diabetes and an elevated fasting blood glucose (20 mmol/L) that required medication initiation; 9 participants had fasting glucose ≥7.0 mmol/L at baseline without a known history of diabetes. Nine participants had baseline hypertension (4 by self-report and 5 with blood pressure ≥140/90 mm Hg). One participant had baseline metabolic syndrome.

Mean weight gain over 6 months of follow-up was 0.4 kg (SD 2.8 kg, $P = 0.12$; Table S2, Supplemental Digital Content, http://links.lww.com/QAI/C28). Overall, 12% (n = 16) gained ≥5% of their body weight, and 7% (n = 10) lost ≥5% of their body weight over the 6 months following switch to DTG. One participant developed incident obesity from a baseline BMI of 29.7 kg/m^2 and 1 participant who was obese at baseline lost 6 kg, reducing BMI from 30.1 to 27.7 kg/m^2. Average glucose decreased from 5.7 mmol/L at baseline to 5.2 mmol/L after 6 months ($P < 0.0001$). No participants developed elevations in fasting blood glucose ≥7 mmol/L that were sustained on ≥1 follow-up visit. Eight participants had an elevated fasting glucose at any postbaseline visit; 5 of these had normal fasting glucose on repeat visits without intervention, and 3 had their first abnormal fasting glucose on the 6-

TABLE 3. Contrast of Observed vs Predicted Weight 12 mo Post-switch in the Retrospective Cohort, Overall and by Baseline Subgroup

	All (n = 4445)	On TDF throughout (n = 3374)
	Weight Difference From Predicted (kg; 95% CI)	Weight Difference From Predicted (kg; 95% CI)
All	0.21 (−0.01 to 0.42)	0.47 (0.20–0.73)
Men	−0.23 (−0.54 to 0.06)	0.04 (−0.30 to 0.43)
Women	0.50 (0.20–0.78)	0.70 (0.37–1.03)
Underweight	2.00 (1.51–2.51)	2.42 (1.83–3.09)
Normal weight	0.55 (0.28–0.80)	0.95 (0.65–1.25)
Overweight/obese	−1.7 (−2.26 to −1.18)	−1.82 (−2.42 to −1.20)
Virally suppressed	0.23 (−0.22 to 0.68)	0.37 (−0.21 to 0.91)

TDF, tenofovir disoproxil fumarate

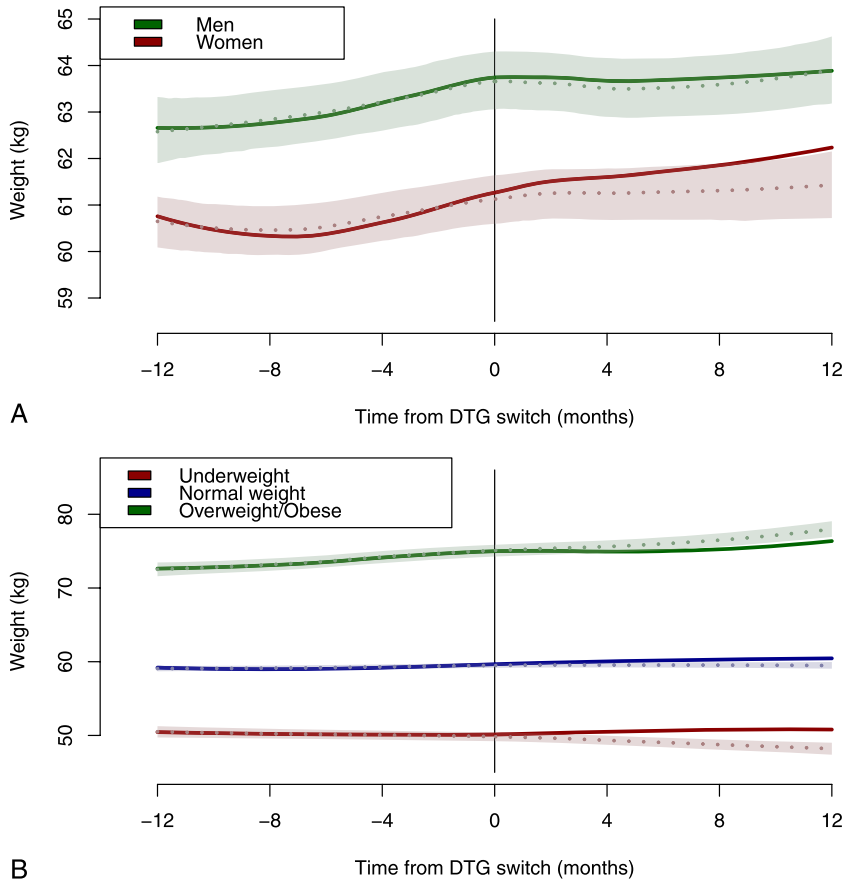

FIGURE 1. Observed (solid line) versus predicted (dashed line) weight trajectories in the retrospective cohort study among those on TDF throughout by sex (panel A) and BMI group (panel B); 95% confidence intervals are shown by the shaded bands. full color online

month visit (range 7.2–7.5 mmol/dL). None required new initiation of diabetes treatment. Of the 9 participants with baseline elevated fasting glucose who did not have known diabetes, all had normal repeat fasting glucose values on all subsequent visits without intervening medication. Three participants (2%) developed incident metabolic syndrome.

Food insecurity was common, with 50% (n = 68) reporting moderate food insecurity and 16% (n = 22) severe food insecurity at baseline. Over 6 months of follow-up, 86% reported at least moderate and 49% reported severe food insecurity at any point during follow-up. Self-reported medication adherence was high, with 88% of participants reporting taking ART every day in the prior week at all study visits and 12% reporting missing ≥1 dose in the prior week at any of the 4 study visits.

In the multivariable regression model, higher baseline BMI was associated with weight loss at 6 months postswitch (−0.2 kg per 1-unit increase in baseline BMI, 95%

TABLE 4. Characteristics Associated With Weight Change at 6 mo Post-switch in the Prospective Cohort

	Univariable			Multivariable*		
Baseline Characteristic	**Weight Change (kg)**	**95% CI**	***P***	**Weight Change (kg)**	**95% CI**	***P***
Age (per 1-yr increase)	−0.02	(−0.09, 0.05)	0.56			
Years since HIV diagnosis	−0.05	(−0.17, 0.07)	0.40			
BMI (kg/m^2)	−0.17	(−0.27, −0.06)	0.002	−0.17	(−0.27, −0.07)	0.001
Fasting glucose (mmol/L)	−0.37	(−0.68, −0.06)	0.02	−0.38	(−0.67, −0.08)	0.013
Total cholesterol (mmol/L)	−0.01	(−0.02, 0.0005)	0.06	−0.01	(−0.02, 0.01)	0.29
Food insecurity			0.12			0.059
None	Ref			Ref		
Moderate	−1.1	(−2.1, −0.05)	0.04	−1.2	(−2.2, −0.21)	0.018
Severe	−0.86	(−2.3, 0.56)	0.23	−0.84	(−2.2, 0.50)	0.22

*Included in the final model of univariable $P < 0.1$.
BMI, body mass index

CI −0.3, −0.1 kg/m^2), as was baseline fasting blood glucose (−0.4 kg weight change per 1 mmol/L increase in glucose, 95% CI −0.7, −0.1) and baseline food insecurity (Table 4). Average predicted weight gain varied by baseline food insecurity; on average, predicted weight change was +1.1 kg (95% CI: 0.34, 1.87) without food insecurity, −0.09 kg (95% CI −0.71, 0.54) with moderate food insecurity, and +0.27 kg (95% CI −0.82, 1.36) with severe food insecurity.

DISCUSSION

In our retrospective cohort study, we observed a small increase in body weight compared with expected in rural Kenyan women but not in men following switch to DTG. TDF has been associated with weight suppression,[18] and we observed slightly greater weight gain when restricting to those on TDF before and after DTG switch. Although only one-quarter of participants had a viral load measured at switch, individuals who were virally suppressed maintained a post-switch weight trajectory that was similar to preswitch weight gain. Weight increased the most compared with predicted among underweight individuals—although available data do not provide detailed insight into individual health status, weight gain in this group may reflect improving health. Encouragingly, mean body weight among those obese at switch remained stable and did not increase as expected based on preswitch trajectory. In our complementary prospective analysis with study-measured weights, we also found very small amounts of weight gain among women switching to DTG that was not significantly different at 6 months compared with baseline. Food insecurity was very common in our population and attenuated weight gain after switch, although predicted weight gain was modest even in the absence of food insecurity. Importantly, in both studies, we estimated weight changes with switch to DTG when the NRTI backbone is held constant. Because TDF has been associated with weight suppression,[18] this strengthens our study by eliminating differential influences on weight by concurrent NRTI changes. Together, our findings suggest that although DTG may be associated with small amounts of weight gain following switch from efavirenz in women, increases are not large in settings where obesity is uncommon and may be attenuated by food insecurity.

We observed less weight gain following switch to DTG than most other studies, with a 0.7-kg increase over 1 year postswitch in women and no change in men. In a large study in high income settings, Black individuals gained 0.9 kg, and women gained 1.3 kg per year greater than expected following switch to INSTI-based ART.[19] In sub-Saharan Africa, the AFRICOS cohort study showed a 1.3-kg increase in annual weight gain following switch to DTG in virally suppressed patients. Our findings that women gained more weight than men are consistent with AFRICOS; however, we identified less absolute weight gain and no weight gain in men.

One proposed mechanism is that weight gain associated with switching to DTG may be due to removal of a weight suppressive effect of the prior ART regimen—generally efavirenz in sub-Saharan Africa.[1] In the ADVANCE study, rapid metabolizers of efavirenz gained similar amounts of weight to those on DTG, presumably due to reduced weight-suppressive effect with lower concentrations of efavirenz.[12] Other research has suggested that DTG may have a drug-specific effect on weight gain via activation of melanocortin 4 receptor[20] and may directly promote adipogenesis and insulin resistance.[21,22] Regardless of mechanism, our study suggests that weight gain associated either with removal of EFV or addition of DTG may be attenuated in settings where there is not a widespread obesity epidemic and where food insecurity is common. Variability in pharmacogenetics within and between populations may also contribute to heterogeneous weight gain observed with ART switch between individuals and across settings.[12,23]

Prior studies are inconsistent on the association between INSTIs and incident diabetes or metabolic syndrome when combined with TDF.[24] In Uganda, a study from 2020 found increased signal for new-onset severe hyperglycemia associated with DTG, with 16 of 3417 (0.47%) patients on DTG presenting with symptomatic hyperglycemia, compared with 1 of 3230 patients not on DTG (P = 0.0004).[25] This study prompted changes in Ugandan guidelines to recommend against DTG use in individuals with diabetes.[26] A subsequent case–control study in Uganda found 7-fold increased odds of study-measured hyperglycemia with prior DTG exposure[27]; however, the odds ratio for hyperglycemia with current DTG exposure was 0.07, and discontinuation of DTG in the absence of diabetes was very rare, raising concerns for channeling bias. Modeling estimates from the ADVANCE study estimate that there would be 3 additional cases of incident diabetes per 1000 people on EFV/FTC/TDF than on DTG/FTC/TDF, with risk from modest DTG-associated weight gain offset by improved lipid profile.[28] Large cohort studies in high-income settings have different conclusions about the relationship between INSTIs and diabetes, with some finding a greater diabetes risk[29,30] and others finding no association.[31] Although our prospective study was small, we did not observe any patients with a sustained elevated fasting glucose and observed small declines in average fasting glucose following switch to DTG. Furthermore, in our study, only 2% of participants developed incident metabolic syndrome. These findings suggest that there is not a large signal for increased risk of diabetes or metabolic syndrome following switch to DTG in rural East Africa where DTG-associated weight gain is modest, and obesity is uncommon.

Our study had several limitations. In the retrospective analysis, preswitch viral loads were not available on most participants (76%). Although viral suppression was >90% for those with a measured viral load, we cannot assume that participants with measured viral loads were representative of those with missing viral loads. High viral load is associated with weight gain on ART initiation,[32] and thus, we may have overestimated weight gain by including some with an unsuppressed viral load at the time of switch. For the retrospective cohort, we used routinely collected clinic data, which may be less accurate than study-measured data. We supplemented these data with study-measured weight in a prospective cohort study, which demonstrated similar magnitude of weight changes. In our prospective cohort study, the population was limited to women due to the timing of the study and the later transition of women of reproductive age to DTG.[14] However,

numerous other studies have shown that women may be at higher risk for DTG-associated weight gain than men[4,5,19,32–34]; thus, focusing on women offers important insights. DTG switch was not randomized, and thus, our analyses are subject to confounding. In our retrospective cohort study, we addressed this limitation using preswitch weight trajectories for each individual to predict their weight trajectory had they not switched to DTG, adjusting for sex, age, preswitch regimen, and time. Use of preswitch weight change has its own limitations. Weight gain is often greatest in the first year after ART initiation[35]; thus, patients with shorter duration on ART may have steeper preswitch weight trajectory, leading to overestimation of expected postswitch weight. However, by including patients on ART for at least 1 year before DTG switch (median ART duration 6.25 years), the impact on our analysis should be minimal. Finally, the COVID-19 pandemic may have worsened food insecurity,[36–38] further attenuating observed weight gain, although this would not invalidate our overall conclusions of low amounts of weight gain in the context of a high degree of food insecurity.

In conclusion, our large multiclinic studies in rural Kenya demonstrated slightly greater than expected weight change following switch to DTG in women, but not in men. Individuals who were virally suppressed at switch did not gain weight on DTG, compared with expected based on preswitch trajectory. In a small complementary prospective cohort study, mean glucose declined after DTG switch, and only 2% developed incident metabolic syndrome. Food insecurity was common and may have attenuated DTG-associated weight gain. Our findings suggest that DTG may not be associated with significant weight gain or metabolic complications among individuals switching to DTG-containing ART in rural sub-Saharan African settings where obesity is uncommon.

REFERENCES

1. World Health Organization. *Updated Recommendations on First-Line and Second-Line Antiretroviral Regimens and Post-Exposure Prophylaxis and Recommendations on Early Infant Diagnosis of HIV*. World Health Organization; 2018.
2. Walmsley SL, Antela A, Clumeck N, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. *N Engl J Med.* 2013; 369:1807–1818.
3. Walmsley S, Baumgarten A, Berenguer J, et al. Brief report: dolutegravir plus abacavir/lamivudine for the treatment of HIV-1 infection in antiretroviral therapy-naive patients: week 96 and week 144 results from the SINGLE randomized clinical trial. *J Acquir Immune Defic Syndr.* 2015;70:515–519.
4. Venter WDF, Moorhouse M, Sokhela S, et al. Dolutegravir plus two different prodrugs of tenofovir to treat HIV. *New Engl J Med.* 2019;381: 803–815.
5. The NAMSAL ANRS 12313 Study Group. Dolutegravir-based or low-dose efavirenz–based regimen for the treatment of HIV-1. *New Engl J Med.* 2019;381:816–826.
6. Venter WDF, Sokhela S, Simmons B, et al. Dolutegravir with emtricitabine and tenofovir alafenamide or tenofovir disoproxil fumarate versus efavirenz, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection (ADVANCE): week 96 results from a randomised, phase 3, non-inferiority trial. *Lancet HIV*. 2020;7:e666–e676.
7. Calmy A, Tovar Sanchez T, Kouanfack C, et al. Dolutegravir-based and low-dose efavirenz-based regimen for the initial treatment of HIV-1 infection (NAMSAL): week 96 results from a two-group, multicentre, randomised, open label, phase 3 non-inferiority trial in Cameroon. *Lancet HIV*. 2020;7:e677–e687.
8. Hill A. *Treatment Optimisation: Lessons from ADVANCE, DolPHIN 2 and NAMSAL trials*. 24th International AIDS Conference, Montreal Canada, July 2022.
9. Bourgi K, Ofner S, Musick B, et al. Weight gain among treatment-naïve persons with HIV receiving dolutegravir in Kenya. *J Acquir Immune Defic Syndr.* 2022;91:490–496.
10. Mulenga LB, Fwoloshi S, Mweemba A, et al. *Dolutegravir With Recycled Nrtis Is Noninferior To Pi-Based Art: Visend Trial*. Conference on Retroviruses and Opportunistic Infections, Denver CO, March 2022.
11. Bosch B, Akpomiemie G, Chandiwana N, et al. 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. *Clin Infect Dis.* 2022. Online ahead of print.
12. Griesel R, Maartens G, Chirehwa M, et al. CYP2B6 genotype and weight gain differences between dolutegravir and efavirenz. *Clin Infect Dis.* 2021;73:e3902–e3909.
13. National AIDS Control Council. *Guidelines on Use of Antiretroviral Drugs for Treating and Preventing HIV Infection in Kenya – 2018 Edition*; 2018. Available at: http://cquin.icap.columbia.edu/wp-content/uploads/2017/04/ICAP_CQUIN_Kenya-ARV-Guidelines-2018-Final_20thAug2018.pdf. Accessed February 25, 2020.
14. Romo ML, Patel RC, Edwards JK, et al. Disparities in dolutegravir uptake affecting females of reproductive age with HIV in low- and middle-income countries after initial concerns about teratogenicity : an observational study. *Ann Intern Med.* 2022;175:84–94.
15. Natamba BK, Kilama H, Arbach A, et al. Reliability and validity of an individually focused food insecurity access scale for assessing inadequate access to food among pregnant Ugandan women of mixed HIV status. *Public Health Nutr.* 2015;18:2895–2905.
16. Unger T, Borghi C, Charchar F, et al. 2020 international Society of hypertension global hypertension practice guidelines. *Hypertension*. 2020;75:1334–1357.
17. Balkau B, Charles MA. Comment on the provisional report from the WHO consultation. European group for the study of insulin resistance (EGIR). *Diabetic Med a J Br Diabetic Assoc.* 1999;16:442–443.
18. Shah S, Pilkington V, Hill A. Is tenofovir disoproxil fumarate associated with weight loss? *AIDS.* 2021;35(suppl 2):S189–S195.
19. Lake JE, Wu K, Bares SH, et al. Risk factors for weight gain following switch to integrase inhibitor-based antiretroviral therapy. *Clin Infect Dis.* 2020;71:e471–e477.
20. Eckard AR, McComsey GA. Weight gain and integrase inhibitors. *Curr Opin Infect Dis.* 2020;33:10–19.
21. Gorwood J, Bourgeois C, Pourcher V, et al. The integrase inhibitors dolutegravir and raltegravir exert pro-adipogenic and profibrotic effects and induce insulin resistance in human/simian adipose tissue and human adipocytes. *Clin Infect Dis.* 2020;71:e549–e560.
22. Jung I, Tu-Sekine B, Jin S, et al. Dolutegravir Suppresses thermogenesis via disrupting uncoupling protein 1 expression and mitochondrial function in Brown/Beige adipocytes in preclinical models. *J Infect Dis.* 2022;226:1626–1636.
23. Leonard MA, Cindi Z, Bradford Y, et al. Efavirenz pharmacogenetics and weight gain following switch to integrase inhibitor-containing regimens. *Clin Infect Dis.* 2021;73:e2153–e2163.
24. Shah S, Hill A. Risks of metabolic syndrome and diabetes with integrase inhibitor-based therapy. *Curr Opin Infect Dis.* 2021;34:16–24.
25. Lamorde M, Atwiine M, Owarwo NC, et al. Dolutegravir-associated hyperglycaemia in patients with HIV. *Lancet HIV*. 2020;7:e461–e462.
26. *Consolidated Guidelines For The Prevention And Treatment Of Hiv And Aids In Uganda*. Ministry of Health, Republic of Uganda; 2020. Available at: https://differentiatedservicedelivery.org/Portals/0/adam/Content/HvpzRP5yUUSdpCe2m0KMdQ/File/Uganda_Consolidated%20HIV%20and%20AIDS%20Guidelines%202020%20June%2030th.pdf. Accessed October 27, 2022.
27. Namara D, Schwartz JI, Tusubira AK, et al. The risk of hyperglycemia associated with use of dolutegravir among adults living with HIV in Kampala, Uganda: a case-control study. *Int J STD AIDS.* 2022;33: 1158–1164.
28. McCann K, Shah S, Hindley L, et al. Implications of weight gain with newer anti-retrovirals: 10-year predictions of cardiovascular disease and diabetes. *AIDS.* 2021;35:1657–1665.

29. Rebeiro PF, Jenkins CA, Bian A, et al. Risk of incident diabetes mellitus, weight gain, and their relationships with integrase inhibitor-based initial antiretroviral therapy among persons with human immunodeficiency virus in the United States and Canada. *Clin Infect Dis official Publ Infect Dis Soc Am.* 2021;73:e2234–e2242.
30. Ursenbach A, Max V, Maurel M, et al. Incidence of diabetes in HIV-infected patients treated with first-line integrase strand transfer inhibitors: a French multicentre retrospective study. *J Antimicrob Chemother.* 2020; 75:3344–3348.
31. O'Halloran JA, Sahrmann J, Parra-Rodriguez L, et al. Integrase strand transfer inhibitors are associated with incident diabetes mellitus in people with HIV. *Clin Infect Dis.* 2022;75:2060–2065.
32. Sax PE, Erlandson KM, Lake JE, et al. Weight gain following initiation of antiretroviral therapy: risk factors in randomized comparative clinical trials. *Clin Infect Dis.* 2019;71:1379–1389.
33. Bakal DR, Coelho LE, Luz PM, et al. Obesity following ART initiation is common and influenced by both traditional and HIV-/ART-specific risk factors. *J Antimicrob Chemother.* 2018;73:2177–2185.
34. Kerchberger AM, Sheth AN, Angert CD, et al. Weight gain associated with integrase Stand transfer inhibitor use in women. *Clin Infect Dis.* 2020;71:593–600.
35. Bourgi K, Jenkins CA, Rebeiro PF, et al. Weight gain among treatment-naïve persons with HIV starting integrase inhibitors compared to non-nucleoside reverse transcriptase inhibitors or protease inhibitors in a large observational cohort in the United States and Canada. *J Int AIDS Soc.* 2020;23:e25484.
36. Maredia MK, Adenikinju A, Belton B, et al. COVID-19's impacts on incomes and food consumption in urban and rural areas are surprisingly similar: evidence from five African countries. *Glob Food Sec.* 2022;33:100633.
37. Merchant EV, Fatima T, Fatima A, et al. The influence of food environments on food Security resilience during the COVID-19 pandemic: an examination of urban and rural difference in Kenya. *Nutrients*. 2022;14:2939.
38. Tabe-Ojong MP Jr, Gebrekidan BH, Nshakira-Rukundo E, et al. COVID-19 in rural Africa: food access disruptions, food insecurity and coping strategies in Kenya, Namibia, and Tanzania. *Agric Econ.* 2022; 53:719–738.