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ORIGINAL ARTICLE

Assessment of weight gain in adult patients living with HIV receiving first-line dolutegravir-based or efavirenz-based ART regimens in routine care clinics in Tshwane district, South Africa: An observational study

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Abstract

Introduction: Although dolutegravir (DTG) is deemed stable, safe, cost-effective, and clinically beneficial, it also carries the risk of side effects, including observed weight gain among patients on DTG-based antiretroviral therapy (ART) regimens. We compared weight changes among adults (≥18 years) initiating tenofovir disoproxil fumarate, lamivudine, and dolutegravir (TLD) or tenofovir disoproxil fumarate, emtricitabine, and efavirenz (TEE) regimens and those switching from TEE to TLD (TEE-to-TLD switchers) in three large primary care facilities in South Africa

Methods: We conducted a retrospective longitudinal record review using patient medical records, extracting relevant demographic and clinical data from October 2018 to June 2021 from randomly selected adults who initiated TLD or TEE (initiators) and adult TEE-to-TLD switchers. We assessed weight, body mass index (BMI), and percentage weight changes for both groups and fitted linear regression and generalized linear models to determine factors associated with weight and BMI change and percentage weight change ≥10%, respectively, among treatment initiators. We fitted linear mixed-effect models among TEE-to-TLD switchers to consider repeated measures.

Results: Of 860 initiators, 450 (52.3%) initiated on TEE and 410 (47.7%) on TLD, with median follow-up of 1.4 years and 1.0 year, respectively. At initiation, 43.3% on TEE and 40.8% on TLD were overweight or obese. TLD initiators had an adjusted higher mean weight gain of 1.6 kg ($p < 0.001$) and mean BMI gain of 0.51 kg/m^2 ($p < 0.001$) than TEE initiators. Independent risk factors for higher

mean weight and BMI included age ≥50 years, male, on ART for >12 months, initial BMI of <18.5 kg/m^2, and CD4 counts <200 cells/μL.

Of 298 TEE-to-TLD switchers, 36.6% were overweight or obese at TEE initiation. Comparing before and after TLD switch, TEE-to-TLD switchers had an adjusted mean weight of 1.2 kg less while on TLD ($p = 0.026$). Being overweight and CD4 counts >350 cells/μL were independent risk factors for lower weight gain after TLD switch.

Conclusions: We report more weight gain among TLD than among TEE initiators, although to a lesser extent than previously reported. TEE-to-TLD switchers experienced less weight gain after TLD switch; return to health before receiving TLD may be a contributory factor. The current findings are reassuring for those switching to a DTG-based regimen

KEYWORDS

ART, dolutegravir, HIV, routine care, weight gain

INTRODUCTION

In 2016, the World Health Organization (WHO) first recommended dolutegravir (DTG), a second-generation integrase strand transfer inhibitor, as an alternative to efavirenz (EFV) as a first-line antiretroviral drug for people living with HIV [1]. Benefits of DTG include quicker attainment of viral suppression, a higher genetic barrier to resistance, lower toxicity, longer half-life, lower cost, better tolerability, and fewer documented drug-to-drug interactions than other available antiretrovirals [1, 2]. In July 2019, the WHO updated their recommendation to include DTG-based regimens as the preferred first- and second-line regimen for all populations, including pregnant women and women of child-bearing potential [3, 4]. In October 2019, South Africa's National Department of Health adopted the use of DTG in combination with tenofovir disoproxil fumarate and lamivudine (TLD) as its preferred first-line regimen for men, adolescent boys, older women, and women on contraception initiating antiretroviral therapy (ART) or stable on ART and switching to a DTG-based regimen [5, 6]. In 2021, they extended roll-out of TLD to women of child-bearing potential and pregnant and breastfeeding women [7].

Although DTG is more tolerable than EFV, which is expected to result in improved viral load suppression and to be cost effective [8], it does have side effects [9]. Multiple studies have reported significant increases in weight among people living with HIV receiving an integrase strand transfer inhibitor-based regimen for initial therapy compared with non-nucleoside reverse transcriptase inhibitors or protease inhibitor-based regimens [10–12]. The ADVANCE and NAMSAL (New Antiretroviral and Monitoring Strategies in HIV-infected Adults in Low-income countries) randomized clinical trials first reported significantly higher weight gain with DTG-based than with EFV-based regimens [13, 14]. These trials predominately involved Black African females, raising concerns about the secondary effect of excess weight gain on mortality and long-term morbidity outcomes, including an increased risk of cardiovascular and metabolic diseases [9, 10, 12, 15–17]. The mechanism remains unclear, and more recent studies have postulated that EFV toxicity related to metabolism may instead be responsible for lower weight gain on EFV, which may be skewing the interpretation of DTG-associated weight gain [18].

Although evidence from clinical trials showed that DTG was significantly associated with increased weight gain, evidence from real-world routine care settings among patients initiating ART on a DTG-based regimen or patients switching from EFV- to DTG-based regimens as first-line treatment remains limited. This study compares weight changes among adults living with HIV initiating or switching to a first-line TLD regimen compared with a tenofovir disoproxil fumarate, emtricitabine, and efavirenz (TEE) first-line regimen, who were receiving routine ART services in three public health facilities in the Tshwane Metropolitan Health District, South Africa.

METHODS

Study design and population

We conducted a retrospective longitudinal record review from August 2021 to November 2021, using routinely

collected data extracted from the files of adult (aged ≥18 years) patients who recently started on ART. Medical records from three large primary care HIV treatment centres (i.e., Temba, Stanza Bopape, and Laudium Community Health Centres [CHCs]) in the Tshwane Health District were reviewed if patients had either initiated a TEE or TLD treatment regimen (TEE initiators and TLD initiators) or switched from a first-line (ART initiation) TEE regimen to a first-line TLD regimen (TEE-to-TLD switchers) between October 2018 and January 2021.

Sample size

The sample size for comparing weight gain among TLD and TEE initiators, optimizing available resources while allowing sufficient power to detect small differences in weight gain between groups (standard effect size of 0.3 for independent samples, with an alpha value of 0.05, 80% power, and a design effect of 1.5), was a minimum of 700, with half for each treatment group. The sample size for determining weight gain among TEE-to-TLD switchers was a minimum of 350 (effect size of 0.21 for paired samples and a design effect of 1.5). The minimum number of files to be selected from each facility was based on probability proportional to the number of ART clients per facility (i.e., Stanza CHC: 132, 144, and 180; Laudium CHC: 157, 135, and 95; Temba CHC: 61, 71, and 75 for TEE initiators, TLD initiators, and TEE-to-TLD switchers, respectively).

Sample selection

Patient files were randomly selected from three sampling frames of patient files to ensure representativeness of the selected sample: TEE initiators, TLD initiators, and TEE-to-TLD switchers. For TEE and TLD initiators, patients were included if they had a weight measure recorded at ART initiation and at least one additional weight measure ≥4 months after ART initiation. For TEE-to-TLD switchers, patients were included if they initiated first-line ART on a TEE regimen and remained on TEE for ≥6 months before switching to TLD; had a weight measure recorded at TEE initiation and when they switched from TEE to TLD; and had at least one additional weight measure ≥4 months after switching to TLD. Patients weighing <35 kg and females who were pregnant during the study period or less than 6 months postpartum at ART initiation were excluded for both groups. South African guidelines at the time recommended TLD from 35 kg upwards, so we used this weight cut-off. Pregnant women were excluded because pre-pregnancy weight was not routinely available and because of the complexities around interpreting weight gain in pregnancy, which were beyond the scope of this analysis. If a randomly selected file did not meet eligibility criteria, the next file on the sampling frame was chosen as a replacement, and so forth until an eligible file was found. The retrieval of files continued until we reached at least the minimum sample sizes per facility.

Data collection

Relevant demographic and clinical information from patients' clinic records from 1 October 2018 until 30 June 2021 was extracted and recorded directly into a standardized electronic data collection form on a secure REDCap [19] database. We collected information on patients' demographics (age, sex) and full clinical history (including the date of HIV diagnosis, ART history, visit dates, weights, height, comorbidities, chronic conditions, hormonal contraceptives, CD4 absolute counts, concomitant medications for chronic conditions, and – if appropriate – date of treatment switch from TEE to TLD) from the first HIV diagnosis visit until the last clinic visit conducted on or before 30 June 2021. Missing CD4 counts at ART initiation were imputed from the most recent CD4 count closest to the ART initiation date, between 60 days before and up to 1 month after ART initiation.

Data analysis

The distribution of the sample by baseline demographic and clinical factors was determined; frequencies, proportions, and interquartile ranges (IQRs) were calculated for this purpose, depending on the nature of the variable. Outcome variables included change in weight and body mass index (BMI; weight of an individual measured in kg divided by the square of the corresponding height in metres) determined either from the difference in weight between treatment initiation and last recorded visit between TEE initiators and TLD initiators or from change in weight and BMI before TLD switch (from TEE initiation until TLD switch) and after TLD switch (from TLD switch until the last recorded visit). Weight change was also assessed through percentage weight gain by dividing the difference in weight between the last recorded visit on TEE or TLD and the baseline weight on TEE or TLD, respectively, by the weight at baseline.

We conducted descriptive analyses of the mean weight and BMI change, and proportion of weight change ≥10% (with associated 95% confidence intervals [CIs]), by the

aforementioned demographic and clinical factors to assess the distribution of the outcome variables by these factors. Type of contraceptive use, presence of comorbidities, prevalence of chronic conditions, and concomitant medication use could not be included in the analyses because reported data for these variables were lacking.

We fitted linear regression and generalized linear models to determine factors associated with weight and BMI changes because these are continuous variables, and proportion of weight change ≥10% (logit transformation was modelled), respectively, among TEE and TLD initiators. We fitted mixed-effects linear regression and generalized linear mixed-effects models to determine factors associated with changes in weight and BMI, and proportion of weight change ≥10%, respectively, to account for repeated measures among those who switched treatment from TEE to TLD. A mixed-effect modelling approach was conducted since before and after weight changes were considered for each observation. In the multivariable regression analysis, the results were adjusted for ART regimen, age, sex, time on ART, weight and BMI at the time of ART initiation, and baseline CD4 count. The analysis considered the study design was adjusted for level of completeness. In addition, we used the method of inverse probability of treatment weighting to ensure comparability of baseline characteristics such as period on ART, age, sex, CD4 count, and weight [20]. Data analysis was conducted using STATA16 and R 4.1.2 statistical packages.

Ethical considerations

The study protocol was approved by the University of the Witwatersrand's Human Research Ethics Committee (HREC) and the Gauteng Province and District Research Committees. This project was reviewed in accordance with CDC human research protection procedures and was determined to be research, but CDC investigators did not interact with human subjects or have access to identifiable data or specimens for research purposes. These approvals included permission to access patient clinical records and a waiver of informed consent for the use of retrospectively collected data that were de-identified.

RESULTS

Among the 1266 randomly selected records captured, 14 were excluded because of missing data or data inconsistencies that could not be resolved. Of the 897 TEE and TLD initiators, 860 files were included in the analysis; 37 were excluded because patients were not on TEE or TLD for at least 24 weeks (Figure 1). Overall, 298 files were eligible for inclusion in the analysis of TEE-to-TLD switchers. The reasons for excluding 57 files for TEE-to-TLD switchers are shown in Figure 1.

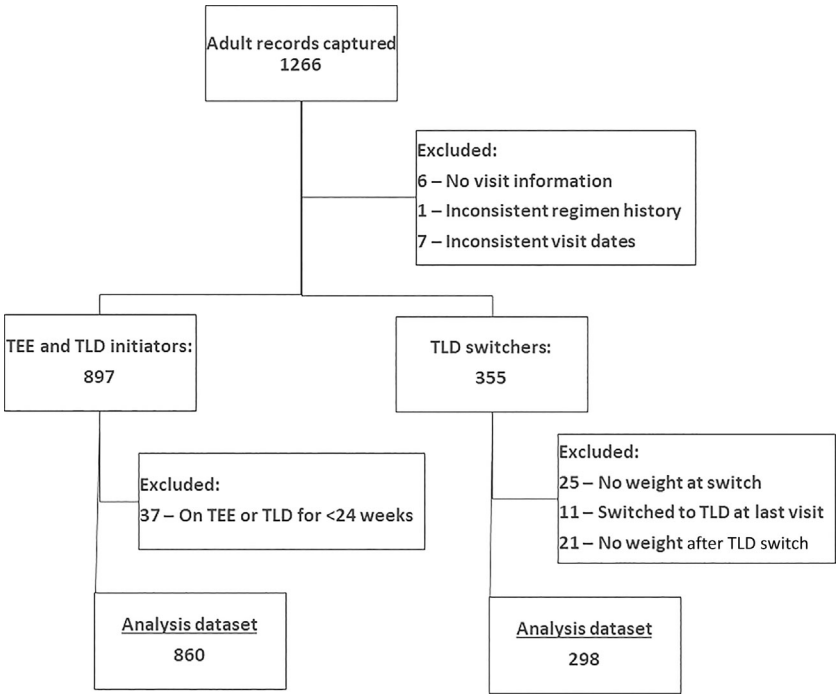

FIGURE 1 Flow diagram of patient files included in analysis datasets. TEE, tenofovir disoproxil fumarate, emtricitabine, and efavirenz; TLD, tenofovir disoproxil fumarate, lamivudine, and dolutegravir.

TABLE 1 Demographic and clinical characteristics of adults initiating ART on either TEE or TLD regimens and remaining on their respective regimens.

	Total		TEE initiators		TLD initiators	
Characteristics	***n***	**%**	***n***	**%**	***n***	**%**
Total (*N*)	860		450	52.3%	410	47.7%
Age, median (IQR)	35.2 (30.4–42.3)		33.9 (28.4–40.3)		37.5 (32.1–44.1)	
Age groups (years)						
18–24	81	9.4%	62	13.8%	19	4.6%
25–34	310	36.0%	181	40.2%	129	31.5%
35–49	388	45.1%	174	38.7%	214	52.2%
≥50	81	9.4%	33	7.3%	48	11.7%
Sex						
Male	412	47.9%	160	35.6%	252	61.5%
Female	448	52.1%	290	64.4%	158	38.5%
Facility						
Laudium CHC	341	39.7%	187	41.6%	154	37.6%
Stanza Bopape CHC	332	38.6%	157	34.9%	175	42.7%
Temba CHC	187	21.7%	106	23.6%	81	19.8%
Time on ART						
Median years (IQR)	1.08 (0.83–1.51)		1.36 (0.94–2.03)		1.00 (0.75–1.20)	
<12 months	343	39.9%	140	31.1%	203	49.5%
12–17 months	298	34.7%	116	25.8%	182	44.4%
≥18 months	219	25.5%	194	43.1%	25	6.1%
Weight at ART initiation (kgs)						
35.0–50.0	77	9.0%	43	9.6%	34	8.3%
50.1–60.0	241	28.0%	139	30.9%	102	24.9%
61.1–70.0	222	25.8%	105	23.3%	117	28.5%
70.1–80.0	170	19.8%	84	18.7%	86	21.0%
>80	150	17.4%	79	17.6%	71	17.3%
BMI at ART initiation (kg/m^2)						
Underweight (<18.5)	87	10.1%	50	11.1%	37	9.0%
Normal (18.5–24.9)	411	47.8%	205	45.6%	206	50.2%
Overweight (25.0–29.9)	214	24.9%	108	24.0%	106	25.9%
Obese (≥30.0)	148	17.2%	87	19.3%	61	14.9%
CD4+ cell count (cells/μL)						
Median (IQR)	289 (157–479)		266.5 (146–465.5)		305 (170–494)	
<200	176	20.5%	94	20.9%	82	20.0%
200–349	144	16.7%	75	16.7%	69	16.8%
350–499	83	9.7%	38	8.4%	45	11.0%
≥500	124	14.4%	59	13.1%	65	15.9%
None recorded	333	38.7%	184	40.9%	149	36.3%

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CHC, community health centres; IQR, interquartile range; TEE, tenofovir disoproxil fumarate, emtricitabine, and efavirenz; TLD, tenofovir disoproxil fumarate, lamivudine, and dolutegravir.

TABLE 2 Mean changes in weight, BMI, and proportion of patients with ≥10% weight gain from ART initiation until last recorded visit among TEE and TLD initiators, stratified by demographic and clinical characteristics at ART initiation.

	Mean weight changes in kg (95% CI)		Mean BMI changes in kg/m^2 (95% CI)		% with weight gain ≥10% (95% CI)	
Characteristics	**TEE initiators**	**TLD initiators**	**TEE initiators**	**TLD initiators**	**TEE initiators**	**TLD initiators**
All	2.78 (2.92–3.38)	3.56 (3.38–3.74)	1.11 (1.05–1.17)	1.29 (1.22–1.35)	21.26% (20.39–22.13)	25.39% (24–26.78)
Age groups (years)						
18–24	4.72 (4.28–5.17)	1.74 (1.45–2.03)	1.86 (1.68–2.03)	0.65 (0.54–0.76)	31.07% (28.34–33.8)	5.34% (1.95–8.74)
25–34	2.58 (2.36–2.79)	3.32 (3.02–3.62)	1.10 (0.99–1.22)	1.21 (1.1–1.32)	22.11% (20.72–23.49)	22.95% (20.5–25.4)
35–49	2.55 (2.31–2.78)	3.58 (3.31–3.84)	0.97 (0.88–1.06)	1.28 (1.19–1.38)	17.34% (16.04–18.64)	25.48% (23.51–27.45)
≥50	2.78 (2.64–2.92)	3.56 (3.38–3.74)	0.58 (0.46–0.69)	1.78 (1.55–2.01)	19.63% (16.43–22.83)	39.59% (34.86–44.32)
Sex						
Male	2.62 (2.39–2.84)	3.99 (3.76–4.23)	0.93 (0.85–1.01)	1.38 (1.3–1.47)	21.62% (20.13–23.12)	30.31% (28.4–32.21)
Female	2.87 (2.69–3.05)	2.89 (2.6–3.17)	1.21 (1.12–1.3)	1.14 (1.02–1.25)	21.07% (19.99–22.15)	17.58% (15.58–19.58)
Time on ART (months)						
<12	2.20 (2–2.4)	3.33 (3.08–3.57)	0.86 (0.78–0.94)	1.19 (1.1–1.28)	16.89% (15.45–18.34)	21.09% (19.19–22.98)
12–17	3.22 (2.96–3.48)	3.69 (3.41–3.96)	1.45 (1.29–1.62)	1.32 (1.22–1.42)	21.15% (19.43–22.86)	30.95% (28.71–33.18)
≥18	2.94 (2.69–3.19)	4.54 (3.6–5.48)	1.09 (0.99–1.18)	1.84 (1.47–2.2)	24.42% (23.03–25.8)	19.89% (14.55–25.23)
CD4+ cell count (cells/μL)						
<200	4.02 (3.69–4.36)	5.21 (4.76–5.66)	1.78 (1.59–1.97)	1.83 (1.67–1.99)	27.04% (25–29.08)	40.05% (36.45–43.65)
200–349	2.67 (2.39–2.94)	3.86 (3.38–4.34)	0.95 (0.84–1.07)	1.34 (1.17–1.51)	20.27% (18.16–22.37)	25.88% (22.42–29.34)
350–499	0.40 (−0.03–0.82)	2.40 (1.88–2.92)	0.13 (−0.04–0.29)	0.86 (0.67–1.06)	10.88% (8.64–13.12)	19.9% (15.88–23.91)
≥500	0.99 (0.67–1.31)	2.67 (2.29–3.05)	0.42 (0.3–0.54)	0.98 (0.83–1.12)	13.19% (11.2–15.18)	13.57% (10.74–16.39)
Weight at ART initiation (kg)						
35.0–50.0	7.46 (6.75–8.17)	6.89 (5.91–7.87)	2.83 (2.57–3.1)	2.60 (2.25–2.95)	47.5% (43.99–51)	47.28% (41.53–53.04)
50.1–60.0	3.65 (3.4–3.91)	4.40 (4.06–4.73)	1.58 (1.43–1.72)	1.61 (1.5–1.73)	28.04% (26.29–29.79)	38.88% (35.67–42.1)
61.1–70.0	2.02 (1.79–2.25)	3.32 (3–3.64)	0.81 (0.72–0.9)	1.19 (1.07–1.3)	17.5% (15.82–19.18)	20.35% (17.87–22.83)
70.1–80.0	1.83 (1.58–2.07)	2.87 (2.52–3.23)	0.67 (0.58–0.76)	0.95 (0.82–1.08)	13.95% (12.27–15.64)	19.61% (16.74–22.47)
>80	0.80 (0.48–1.11)	2.07 (1.67–2.47)	0.25 (0.13–0.38)	0.78 (0.62–0.93)	8.64% (7.22–10.07)	11.07% (8.58–13.56)
BMI at ART initiation (kg/m^2)						
Underweight (<18.5)	6.67 (6.04–7.3)	6.91 (5.97–7.84)	2.41 (2.18–2.64)	2.36 (2.03–2.69)	41.34% (38.16–44.51)	51.36% (45.88–56.85)
Normal (18.5–24.9)	2.90 (2.71–3.09)	3.84 (3.62–4.06)	1.09 (1.02–1.16)	1.36 (1.28–1.44)	22.86% (21.53–24.19)	27.41% (25.35–29.46)
Overweight (25.0–29.9)	1.72 (1.48–1.97)	2.72 (2.42–3.02)	0.69 (0.6–0.78)	1.01 (0.9–1.12)	13.6% (12.12–15.08)	18.69% (16.17–21.21)
Obese (≥30.0)	1.49 (1.18–1.8)	2.03 (1.51–2.55)	0.90 (0.67–1.13)	0.83 (0.61–1.04)	15.57% (13.8–17.34)	14.62% (11.57–17.66)

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CI, confidence interval; TEE, tenofovir disoproxil fumarate, emtricitabine, and efavirenz; TLD, tenofovir disoproxil fumarate, lamivudine, and dolutegravir.

TEE and TLD Initiators–ART-naïve patients initiating ART on either TEE or TLD regimens

Of the 860 initiators who met eligibility criteria, 450 (52.3%) initiated ART on TEE and 410 (47.7%) initiated on TLD (Table 1). Patients remained on their respective regimens for a median of 1.4 years on TEE and 1.0 year on TLD. Most patients initiating ART in the study period were aged 25–49 years (81.1%), 9.4% were aged 18–25 years, and 52.1% were females. Most females (64.4%) initiated on a TEE regimen; most males (61.5%) initiated on TLD. At ART

TABLE 3 Unadjusted and adjusted mean change in weight gain and BMI among TEE and TLD initiators.

	Mean change in weight (kg)				Mean change in BMI (kg/m^2)				Odds ratio for weight gain of ≥10%			
	Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted	
Characteristic	Mean	*p*-value	Mean	*p*-value	Mean	*p*-value	Mean	*p*-value	Odds ratio	*p*-value	Odds ratio	*p*-value
ART regimen												
TEE	Reference		Reference		Reference		Reference		Reference		Reference	
TLD	0.89	<0.001	1.64	<0.001	0.26	0.002	0.51	<0.001	1.37	0.001	1.33	0.004
Age groups (years)												
18–24	Reference		Reference		Reference		Reference		Reference		Reference	
25–34	−1.51	<0.001	0.33	0.179	−0.56	<0.001	0.33	0.004	0.85	0.112	1.10	0.544
35–49	−0.92	<0.001	0.29	0.254	−0.39	<0.001	0.16	0.108	0.87	0.143	1.04	0.795
≥50	1.04	0.09	2.36	<0.001	0.21	0.323	0.85	<0.001	1.56	0.005	2.22	<0.001
Sex												
Male	0.37	0.06	−0.35	0.080	−0.02	0.785	−0.07	0.365	1.36	<0.001	1.4	<0.001
Female	Reference		Reference		Reference		Reference		Reference		Reference	
Months on ART												
<12	−0.50	<0.001	−0.31	0.096	−0.19	<0.001	−0.03	0.716	0.82	0.01	0.97	0.784
12–17	0.63	0.003	1.21	<0.001	0.34	<0.001	0.69	<0.001	1.47	<0.001	1.67	<0.001
≥18	Reference		Reference		Reference		Reference		Reference		Reference	
Weight at ART initiation (kgs)												
35.0–50.0	Reference		Reference		Reference		Reference		Reference		Reference	
50.1–60.0	−3.66	<0.001	−3.10	<0.001	−1.37	<0.001	−1.18	<0.001	0.26	<0.001	0.26	<0.001
61.1–70.0	−4.21	<0.001	−4.45	<0.001	−1.64	<0.001	−1.94	<0.001	0.15	<0.001	0.09	<0.001
70.1–80.0	−4.47	<0.001	−4.93	<0.001	−1.83	<0.001	−2.53	<0.001	0.17	<0.001	0.06	<0.001
>80	−5.39	<0.001	−6.49	<0.001	−2.16	<0.001	−3.45	<0.001	0.06	<0.001	0.02	<0.001
BMI at ART initiation (kg/m^2)												
Underweight (<18.5)	2.33	<0.001	0.77	0.027	0.82	<0.001	0.00	0.997	2.69	<0.001	0.80	0.234
Normal (18.5–24.9)	Reference		Reference		Reference		Reference		Reference		Reference	
Overweight (25.0–29.9)	−0.60	0.065	1.51	<0.001	−0.19	0.104	1.01	<0.001	0.82	0.083	3.08	<0.001
Obese (≥30.0)	−1.19	<0.001	1.04	<0.001	−0.27	0.003	1.39	<0.001	0.42	<0.001	2.71	<0.001
CD4+ cell count (cells/μL)												
<200	Reference		Reference		Reference		Reference		Reference		Reference	
200–349	−1.73	<0.001	−1.22	<0.001	−0.79	<0.001	−0.65	<0.001	0.60	<0.001	0.72	<0.001
350–499	−4.22	<0.001	−3.09	<0.001	−1.69	<0.001	−1.35	<0.001	0.22	<0.001	0.31	<0.001
≥500	−3.36	<0.001	−2.77	<0.001	−1.31	<0.001	−1.24	<0.001	0.30	<0.001	0.40	<0.001

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; TEE, tenofovir disoproxil fumarate, emtricitabine, and efavirenz; TLD, tenofovir disoproxil fumarate, lamivudine, and dolutegravir.

initiation, 43.3% of patients on TEE and 40.8% of those on TLD were overweight or obese. Of the 61% of patients who had CD4 cell counts recorded at ART initiation, 60.7% (320/527) had CD4+ cell counts of <350 cells/μL (Table 1).

Overall, the mean weight gain since initiation was 2.8 kg (95% CI 2.9–3.4) among TEE initiators and 3.6 kg (95% CI 3.4–3.7) among TLD initiators. Among those aged 18–24 years, TEE initiators experienced higher mean weight

gain (4.7 kg) than did TLD initiators (1.74 kg) ($p < 0.001$). Conversely, those aged 35–49 years initiating TLD experienced significantly higher mean weight gains (3.6 kg on TLD vs. 2.6 on TEE, $p < 0.001$). Males initiating TLD had higher mean weight gain than TEE initiators (3.9 kg vs. 2.6 kg, $p < 0.001$), respectively. Compared with TEE initiators, TLD initiators experienced higher mean weight gains if on ART for ≥18 months (4.5 kg vs. 2.9 kg, $p = 0.001$). As with mean weight gain, mean BMI increases were higher for older age groups, males, and those with a longer time on TLD regimens (Table 2).

A quarter (25.4%) of TLD initiators and 21.2% of TEE initiators experienced weight gain of ≥10%, and rates were higher among people who were underweight than among those who were overweight or obese. Older patients on TLD appeared to be disproportionately affected by weight gain of ≥10%. Among those aged ≥50 years, 39.6% of TLD initiators had weight gain of ≥10% compared with 19.6% of TEE initiators, whereas 5.4% of those aged 18–24 years on TLD and 31.1% on TEE had weight gain of ≥10%. Among TLD initiators, 30.3% (95% CI 28.4–32.2) of males and 17.6% (95% CI 15.6–19.6) of females experienced weight gain of ≥10%, whereas for those on TEE, weight gain of ≥10% was almost the same by sex (Table 2).

After adjusting for sex, age, duration on ART, weight at ART initiation, BMI at ART initiation, and CD4 count at ART initiation, adults initiating ART on a TLD regimen had a mean weight gain 1.64 kg higher and a mean BMI gain 0.51 kg/m^2 higher ($p < 0.001$) than did those who initiated ART on a TEE regimen ($p < 0.001$). TLD initiators had a significantly higher likelihood of experiencing weight gain of ≥10% (odds ratio 1.33; $p < 0.001$) than did TEE initiators after adjusting for sex, age, duration on ART, weight at ART initiation, BMI at ART initiation, and CD4+ cell count at ART initiation. Independent risk factors for higher mean weight gain, higher mean BMI gains, and a higher odds of experiencing weight gain >10% included age ≥50 years, male, BMI <18.5 kg/m^2 at initiation, low CD4+ cell counts (<200 cells/μL vs ≥200 cells/μL) at initiation, and remaining on either TEE or TLD for longer than 12 months (Table 3).

TEE-to-TLD switchers–Patients who initiated ART on TEE and switched to TLD

The majority of TEE-to-TLD switchers were aged 35–49 years (53.4%), and 10.4% were aged ≥50 years (Table 4). More males switched from TEE to TLD than females (55.4 vs. 44.6%, respectively). At TEE initiation, 36.6% of patients were overweight or obese, and 8.7% were underweight. Of the 174 (58%) patients who had CD4 cell counts recorded at TEE initiation, 60% (105/174) had CD4 <350 cells/μL. The median time on TEE before switching to TLD was 1.0 year (IQR 0.7–1.5),

TABLE 4 Demographic and clinical characteristics of TEE-to-TLD switchers at the time of ART initiation, stratified by demographic and clinical characteristics at ART initiation.

	Switched from TEE to TLD	
Characteristics	***n***	**%**
Total (*N*)	298	
Age groups (years)		
18–24	17	5.70%
25–34	91	30.54%
35–49	159	53.36%
≥50	31	10.40%
Sex		
Male	165	55.37%
Female	133	44.63%
Facility		
Laudium CHC	86	28.86%
Stanza Bopape CHC	139	46.64%
Temba CHC	73	24.50%
Months on ART from TEE initiation until last recorded visit		
<12	12	4.03%
12–17	56	18.79%
≥18	230	77.18%
Weight (kgs)		
35–50.0	29	9.73%
50.1–60.0	78	26.17%
60.1–70.0	80	26.85%
70.1–80.0	65	21.81%
>80	46	15.44%
BMI (kg/m^2)		
Underweight (<18.5)	26	8.72%
Normal (18.5–24.9)	163	54.70%
Overweight (25.0–29.9)	62	20.81%
Obese (≥30.0)	47	15.77%
CD4+ cell count (cells/μL)		
<200	66	22.15%
200–349	39	13.09%
350–499	25	8.39%
≥500	44	14.77%
None recorded	124	41.61%

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CHC, community health centres; TEE, tenofovir disoproxil fumarate, emtricitabine, and efavirenz; TLD, tenofovir disoproxil fumarate, lamivudine, and dolutegravir.

TABLE 5 Mean changes in weight, BMI, and proportion of patients with ≥10% weight gain before and after TLD switch, stratified by baseline demographic and clinical characteristics.

	Mean weight changes (95% CI)		Mean BMI changes (95% CI)		% with weight gain of ≥10% (95% CI)	
Characteristics	**Pre-TLD switch**	**Post-TLD switch**	**Pre-TLD switch**	**Post-TLD switch**	**Pre-TLD switch**	**Post-TLD switch**
All	2.86 (2.72–3.00)	2.01 (1.87–2.16)	1.05 (1.00–1.10)	0.50 (0.46–0.53)	20.00% (18.97–21.04)	7.37% (6.66–8.09)
Age groups (years)						
18–24	1.19 (0.72–1.65)	1.81 (1.34–2.28)	0.40 (0.21–0.58)	0.73 (0.55–0.91)	12.99% (9.19–16.79)	13.15% (9.46–16.84)
25–34	2.74 (2.47–3.00)	1.20 (1.00–1.39)	0.99 (0.89–1.09)	0.45 (0.38–0.52)	18.53% (16.64–20.42)	6.78% (5.55–8.01)
35–49	3.02 (2.82–3.22)	1.27 (1.14–1.39)	1.09 (1.01–1.16)	0.46 (0.42–0.51)	20.05% (18.57–21.53)	6.60% (5.67–7.53)
≥50	3.33 (2.89–3.77)	1.93 (1.62–2.24)	1.46 (1.29–1.63)	0.66 (0.53–0.80)	28.53% (24.57–32.48)	9.83% (7.19–12.46)
Sex						
Male	3.11 (2.94–3.28)	1.12 (0.99–1.25)	1.26 (0.99–1.52)	0.37 (0.33–0.41)	26.67% (19.87–33.46)	9.09% (4.67–13.51)
Female	2.54 (2.30–2.78)	1.62 (1.47–1.78)	1.43 (0.99–1.88)	0.65 (0.59–0.71)	24.06% (16.74–31.38)	8.27% (3.55–12.99)
Months on ART from TEE initiation until last recorded visit						
<12	3.26 (2.76–3.77)	0.88 (0.29–1.48)	1.24 (1.05–1.42)	0.38 (0.16–0.60)	21.51% (15.49–27.53)	13.43% (8.43–18.43)
12–17	3.19 (2.86–3.52)	1.68 (1.41–1.96)	1.28 (1.15–1.41)	0.60 (0.49–0.71)	27.71% (24.78–30.64)	14.97% (12.62–17.31)
≥18	2.76 (2.60–2.92)	1.29 (1.18–1.39)	0.99 (0.93–1.05)	0.48 (0.44–0.52)	18.20% (17.06–19.33)	5.38% (4.69–6.07)
CD4+ cell count (cells/μL)						
<200	4.64 (4.25–5.03)	2.57 (2.26–2.88)	1.63 (1.49–1.78)	0.95 (0.84–1.06)	39.32% (36.27–42.37)	16.31% (14.00–18.63)
200–349	2.79 (2.40–3.18)	2.12 (1.85–2.39)	1.01 (0.86–1.17)	0.79 (0.69–0.89)	15.28% (12.60–17.95)	10.93% (8.59–13.27)
350–499	0.85 (0.38–1.32)	2.08 (1.79–2.37)	0.34 (0.17–0.52)	0.77 (0.67–0.87)	16.25% (12.51–19.99)	10.91% (7.70–14.12)
≥500	2.13 (1.77–2.50)	1.19 (1.00–1.39)	0.81 (0.67–0.96)	0.49 (0.41–0.58)	8.62% (6.51–10.72)	5.72% (4.00–7.44)
Weight at ART initiation (kg)						
35–50	4.29 (3.93–4.66)	1.32 (1.01–1.63)	1.70 (1.55–1.86)	0.48 (0.37–0.58)	31.42% (27.26–35.58)	10.38% (7.68–13.08)
50.1–60	4.1 (3.78–4.41)	1.40 (1.20–1.60)	1.52 (1.40–1.65)	0.55 (0.48–0.63)	29.46% (26.76–32.15)	10.96% (9.13–12.79)
61.1–70	2.62 (2.31–2.94)	1.09 (0.90–1.29)	0.89 (0.78–1.01)	0.42 (0.35–0.50)	19.48% (17.45–21.51)	6.40% (5.13–7.68)
70.1–80	1.75 (1.52–1.97)	1.37 (1.17–1.58)	0.62 (0.54–0.70)	0.49 (0.42–0.56)	12.13% (10.29–13.97)	6.26% (4.87–7.65)
>80	2.41 (2.05–2.77)	1.63 (1.39–1.87)	0.94 (0.80–1.09)	0.56 (0.47–0.66)	13.74% (11.54–15.94)	4.42% (3.12–5.72)
BMI at ART initiation (kg/m^2)						
Underweight (<18.5)	3.91 (3.6–4.22)	0.62 (0.18–1.07)	1.35 (1.23–1.46)	0.21 (0.06–0.36)	23.96% (19.93–27.99)	16.04% (12.67–19.41)
Normal (18.5–24.9)	3.51 (3.3–3.73)	1.32 (1.19–1.46)	1.26 (1.18–1.34)	0.46 (0.42–0.51)	24.01% (22.41–25.62)	8.19% (7.14–9.24)
Overweight (25.0–29.9)	1.52 (1.26–1.77)	1.27 (1.09–1.46)	0.52 (0.43–0.62)	0.49 (0.42–0.56)	13.14% (11.23–15.04)	4.28% (3.15–5.42)
Obese (≥30.0)	2.13 (1.75–2.5)	1.86 (1.6–2.12)	0.98 (0.82–1.14)	0.75 (0.64–0.87)	15.16% (12.79–17.54)	4.69% (3.31–6.07)

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CI, confidence interval; TEE, tenofovir disoproxil fumarate, emtricitabine, and efavirenz; TLD, tenofovir disoproxil fumarate, lamivudine, and dolutegravir.

and the median time on TLD after switching until last recorded visit was 0.8 years (IQR 0.5–1.1) (Table 4).

Table 5 shows that the overall mean weight gain was 2.9 kg (95% CI 2.7–3.0) before TLD switch and 2.0 kg (95% CI 1.9–2.2) after TLD switch ($p = 0.000$). Apart from those aged 18–24 years, all other age groups experienced higher weight gain before than after TLD switch. After TLD switch, males had a mean weight gain of 2.0 kg less than before their TLD switch, whereas females had a 0.92 kg mean weight gain difference. Mean weight gain was consistently higher before TLD switch, regardless of time on ART. The overall mean BMI change

TABLE 6 Unadjusted and adjusted mean weight and BMI change, and odds ratio for weight gain ≥10% after TLD switch.

	Mean change in weight (kg)				Mean change in BMI (kg/m^2)				Odds ratio weight gain ≥10% after TLD switch			
	Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted	
Characteristics	**Mean**	***p*-value**	**Mean**	***p*-value**	**Mean**	***p*-value**	**Mean**	***p*-value**	**Odds ratio**	***p*-value**	**Odds ratio**	***p*-value**
ART regimen												
TLD	−1.51	<0.001	−1.20	0.026	−0.76	<0.001	−0.58	0.006	0.08	<0.001	0.20	<0.001
Age groups (years)												
18–24	Reference				Reference				Reference			
25–34	0.46	0.586	0.42	0.716	0.29	0.401	0.47	0.297	1.13	0.938	3.78	0.460
35–49	0.65	0.427	0.40	0.712	0.33	0.331	0.53	0.225	1.17	0.916	3.57	0.464
≥50	1.13	0.247	0.54	0.706	0.61	0.128	0.85	0.129	3.74	0.472	27.44	0.146
Sex												
Male	0.03	0.946	−0.18	0.769	−0.21	0.172	−0.23	0.314	1.26	0.731	1.52	0.648
Female	Reference				Reference				Reference			
Months on ART from TEE initiation until last recorded visit												
<12	−0.47	0.405	1.24	0.125	−0.27	0.244	0.31	0.335	0.18	<0.001	1.41	0.311
12–17	−0.35	0.575	1.00	0.257	−0.10	0.686	0.46	0.191	0.72	0.281	1.44	0.333
≥18	Reference				Reference				Reference			
CD4+ cell count												
<200	Reference				Reference				Reference			
200–349	−1.13	0.095	−1.08	0.140	−0.11	0.682	−0.12	0.667	0.10	0.035	0.11	0.062
350–499	−2.12	0.009	−2.20	0.009	−0.46	0.139	−0.61	0.105	0.14	0.121	0.13	0.123
≥500	−1.92	0.004	−1.87	0.011	−0.46	0.078	−0.45	0.105	0.03	<0.001	0.04	0.004
Weight at ART initiation (kgs)												
35–50	Reference				Reference				Reference			
50.1–60	−0.06	0.939	−0.30	0.780	−0.22	0.434	−0.44	0.281	0.37	0.513	0.08	0.149
61.1–70	−0.95	0.185	−1.14	0.312	−0.45	0.114	−0.59	0.183	0.17	0.250	0.11	0.242
70.1–80	−1.24	0.088	−1.14	0.363	−0.63	0.031	−0.83	0.088	0.11	0.164	0.08	0.224
>80	−0.79	0.299	−1.04	0.449	−0.51	0.099	−1.01	0.070	0.08	0.130	0.02	0.084
BMI at ART initiation												
Underweight (<18.5)	−0.15	0.828	−0.42	0.692	−0.10	0.727	−0.28	0.490	2.52	0.503	2.92	0.522
Normal (18.5–24.9)	Reference				Reference				Reference			
Overweight (25.0–29.9)	−1.02	0.031	−0.65	0.450	−0.31	0.110	−0.11	0.731	0.41	0.303	0.82	0.880
Obese (≥30.0)	−0.43	0.424	−0.12	0.912	−0.05	0.839	0.29	0.503	0.34	0.277	1.56	0.789

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; TEE, tenofovir disoproxil fumarate, emtricitabine, and efavirenz; TLD, tenofovir disoproxil fumarate, lamivudine, and dolutegravir.

before TLD switch (1.05; 95% CI 1.0–1.10) was higher than after (0.5; 95% CI 0.46–0.53). Higher mean BMI changes were seen before TLD switch for both males and females aged >25 years, those with CD4+ cell counts of <350 cells/μl and ≥500 cells/μl, any time on ART from TEE initiation until last recorded visit, any weight at ART initiation, and any BMI at ART initiation when compared with after TLD switch (Table 5).

One-fifth of all patients (20.0%; 95% CI 19.0–21.0) before TLD, and <10% (7.4%; 95% CI 6.7–8.1) after TLD, experienced a weight increase of ≥10%. Almost 30% and 10% of patients aged ≥50 years had weight gain of ≥10% before and after TLD switch, respectively. Before TLD switch, both females and males had similarly high proportions (24.1% and 26.7%, respectively) with weight gain of ≥10%; this dropped to <10% after TLD switch for both sexes. Almost 40% of patients with a CD4 count of <200 cells/μl at ART initiation experienced weight gain ≥10% while on TEE; this decreased to 16.3% after TLD switch. Similarly, patients with low weight at TEE initiation gained more weight on their TEE regimen than after TLD switch (31.4% vs. 10.4%) (Table 5).

After TLD switch, the unadjusted mean change in weight was −1.51 kg and BMI −0.76 kg/m^2 ($p < 0.001$). Independent risk factors for lower mean weight gain after TLD switch included overweight and high CD4+ cell counts (>350 cells/μl). Being on ART for <12 months and a high CD4+ cell count (≥500 cells/μl) at ART initiation were independent risk factors for lower odds of weight gain of ≥10% after TLD switch. After adjusting for sex, age, duration on ART, weight at ART initiation, BMI at ART initiation, and CD4 at ART initiation, adults switching from TEE to TLD had a mean weight change of −1.20 kg ($p = 0.026$) and a mean change in BMI of −0.58 kg ($p = 0.006$) (Table 6). Switching from TEE to TLD showed a decreased adjusted odds of having weight gain of ≥10% (odds ratio 0.20; $p < 0.001$) after than before TLD switch.

DISCUSSION

This study from South Africa, which currently has one of the largest HIV treatment programmes in the world [21], adds to the existing body of evidence on weight changes related to DTG-based first-line ART regimens in routine real-world clinical settings. In this retrospective record review of adults living with HIV, we investigated weight gain, BMI gain, and the proportion of patients with ≥10% weight gain in two groups: those who initiated ART on TEE or TLD, and those who initiated ART on first-line TEE and switched to first-line TLD after at least 6 months on TEE. We found significantly higher adjusted mean weight gain and mean BMI gain and a significantly higher likelihood of experiencing weight gain of ≥10% among TLD initiators compared with TEE initiators. Conversely, TEE-to-TLD switchers exhibited significantly less mean weight change and mean BMI change after TLD switch, with fewer patients having weight gain of ≥10% after than before TLD switch.

The mean weight gain of 3.6 kg among TLD initiators in our cohort is slightly lower than the 4.3 kg mean weight gain (standard deviation 6.7) reported in the ADVANCE trial conducted among 1053 ART-naïve patients in Johannesburg [22], with similar mean weight gains among TEE initiators in both studies (2.8 kg in ADVANCE vs. 2.3 kg in this study). In a smaller randomized controlled trial among 589 ART-naïve participants, the NAMSAL study reported a median weight increase of 5.0 kg (IQR 1.0–8.0) in those on a DTG-based regimen compared with 3.0 kg (IQR 0.0–7.0) on the EFV-based regimen, though with very wide CIs around these estimates [13]. A network meta-analysis of 73 studies comparing DTG- and EFV-based regimens found that the mean weight differences between arms were stable up to week 96 after ART initiation but increased from week 96 to week 144 [23]. Our study showed a similar pattern of mean weight gain among TLD initiators who were on TLD for up to 18 months, with a slight tendency towards higher mean weight gain after 18 months on ART. Compared with the ADVANCE, NAMSAL, and network meta-analysis studies, which reported significantly higher weight gain among female than among male TLD initiators [13, 22, 23], we found higher mean weight and BMI gain among males than among females initiating TLD. This could be because our cohort of TLD initiators included more males (61.5%) who were initiated on TLD earlier and were therefore on TLD for longer than females. This was because of the staggered implementation of the TLD roll-out in South Africa starting in October 2019: implementation of TLD as a preferred regimen in women of child-bearing potential was delayed because of concerns over the development of foetal neural tube defects in infants exposed to DTG around conception [5, 7]. It is also possible that the ADVANCE and NAMSAL studies were underpowered to detect weight gain differences by sex.

In line with Kanters' meta-analysis [23], our study also found that low CD4 count and low BMI at ART initiation were associated with higher mean weight and BMI gain in both descriptive and univariable analyses. Since both low BMI and low CD4 counts are indicative of more advanced HIV disease, it is likely that much of the weight gain experienced by these people was driven by the decrease in HIV-related inflammatory responses, a return to normal catabolism, improved appetite, and nutrient absorption [23, 24]. These metabolic changes reduce the overall metabolic cost of HIV infection [24] and could therefore be a result of a return to health scenario rather than merely excessive weight gain [25]. This is also evidenced by the finding that weight gain in patients initiating EFV and then switching to TLD was higher before than after the switch, suggesting that weight gain in this instance was likely related to initial return to health, rather than to DTG. Recent evidence has shown that, in contrast to concerns

regarding increased weight gain on DTG, lower weight gain on EFV may be more problematic, due to cellular and neuropsychological toxicity effects [18]. Metabolism differs according to cytochrome p450 enzyme metabolism pathway, with genetic mutations categorizing people into slow, intermediate, and extensive metabolisers. Around 20% of South Africans are slow metabolisers, resulting in increased EFV concentrations and associated toxicity [25]. Although our cohort of ART initiators reported that 42% of people living with HIV were overweight or obese, the 2016 Demographic and Health Survey in South Africa reported that 31% of men and 62% of women in the general population were either overweight or obese [26]. Although being overweight or obese were not risk factors for weight gain after TLD initiation, the high proportion of people living with HIV who were overweight or obese is concerning because it may lead to several adverse health outcomes, worsened by the cultural drivers of the acceptability of being overweight or obese in the Black South African population [27, 28].

The ADVANCE sub-study, CHARACTERIZE, demonstrated a significant increase in median body weight of 2.9 kg after TLD switch among 172 participants [15]; the AFRICOS study reported a mean change in weight of 0.35 kg before TLD switch and 1.46 kg after TLD switch after adjustment for confounders among 1433 adults [29]. In addition, a propensity score-matched prospective study by Brennan et al [16] reported a higher adjusted mean weight change of 1.78 kg after TLD switch compared with those remaining on EFV-based regimens. Unlike these studies [15, 16, 29], our cohort of patients who initiated ART on TEE and transitioned to TLD demonstrated consistently higher mean weight and BMI gains before than after TLD switch (2.86 kg vs. 2.01 kg and 1.05 kg/m^2 vs. 0.50 kg/m^2). Similarly, fewer patients demonstrated weight gain of >10% after TLD (7.37%) compared with before TLD (20.00%). After adjusting for potential confounders, the mean weight change experienced after TLD was 1.20 kg less than before the TLD switch. Despite experiencing lower mean changes after than before TLD switch, the mean weight gained while on TLD was similar to those reported in the studies mentioned above.

Limitations

The data from this study should be interpreted in the context of several limitations. This includes the use of routine clinical data that are prone to transcription errors from laboratory results or from using non-standardized scales measuring weight or height, possible incomplete longitudinal records due to files being misplaced, and missing data on CD4 test results, contraception in women of child-bearing potential, and possible comorbidities. We attempted to mitigate some of these potential limitations by only including records that contained ≥6 months on either regimen under investigation with at least one height and weight recorded at ART initiation and ≥4 months after switching from the TEE to the TLD regimen (where applicable). The follow-up time of this cohort was limited and varied by regimen, with more observed follow-up time on TEE (1.36 years) than on TLD (1.0 year). Longer follow-up would be ideal to gauge long-term effects of DTG-based regimens in this cohort of patients. Implementation of TLD during the study period may have been slower than expected because of the COVID-19 pandemic and delayed approval and implementation of TLD among women of child-bearing potential. Our data are therefore skewed toward more males being initiated on TLD and switched to TLD and more females initiated on TEE. Lastly, since our study results are from three public health clinics in Tshwane that serve a predominantly Black African population and includes only those accessing treatment in public health facilities, generalizability may be limited; however, this study adds to the overall body of knowledge on weight gains experienced in people on DTG-based regimens in real-life settings.

CONCLUSIONS

Similar to clinical trials, this study confirmed more weight gain in TLD initiators than in TEE initiators, although to a lesser extent, where EFV toxicity likely impaired weight gain among TEE initiators. This is in contrast to TEE-to-TLD switchers, who experienced lower weight gain after TLD switch, where return to health before receiving TLD may be a key contributory factor. The current findings are particularly reassuring for both TLD initiations and switching to a DTG-based regimen, supporting current recommendations from the WHO and South Africa's National Department of Health. With such a large proportion of people living with HIV who were either obese or overweight at ART initiation, large cohort studies with follow-up of at least 5 years from routine clinical settings are required to determine any long-term effects of TLD on cardiac and metabolic disorders and to elucidate other mechanisms of weight gain, including lifestyle changes among a healthier population of adults living with HIV.

AUTHOR CONTRIBUTIONS

JI, KA, SS, GM, MBH, MvW-H, SM, LT, JA-D, CM, and LF conceptualized the study. JI is the principal investigator. SS and SSh led the project set-up and conduct. SS,

SSh, and NM managed the data and assisted with data quality control. KA prepared the randomization lists. SS, SSh, and NM managed the study and assisted with training, team operations, and data abstraction. SS verified data and prepared it for analysis. KA analyzed the data. JB, MBH, MvW-H, and SM contributed to sponsor oversight of study. LT and JA-D managed stakeholder relations during the study. SS wrote the first drafts of the manuscript, and all authors critically reviewed and edited the manuscript. All authors approved the final version of manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author (SS) upon reasonable request.

ETHICS STATEMENT

The study protocol was approved by the University of the Witwatersrand's Human Research Ethics Committee (HREC) and the Gauteng Province and District Research Committees. This project was reviewed in accordance with CDC human research protection procedures and was determined to be research, but CDC investigators did not interact with human subjects or have access to identifiable data or specimens for research purposes.

DISCLAIMER

The findings and conclusions in this manuscript are those of the authors and do not necessarily represent the official position of the funding agencies.

PATIENT CONSENT STATEMENT

Ethics approvals included permission to access patient clinical records and a waiver of informed consent for the use of retrospectively collected data that were de-identified.

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