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MAJOR ARTICLE

Final 192-Week Efficacy and Safety Results of the ADVANCE Trial, Comparing 3 First-line Antiretroviral Regimens

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Background. ADVANCE compared 3 World Health Organization–recommended first-line regimens in participants with HIV who were antiretroviral naive.

Methods. This randomized, open-label, noninferiority trial enrolled participants living with HIV with no antiretroviral exposure in the previous 6 months to 1 of the following arms: tenofovir alafenamide (TAF) / emtricitabine (FTC) + dolutegravir (DTG) (2 tablets), tenofovir disoproxil fumarate (TDF) / FTC + DTG (2 tablets), or a fixed-dose combination of TDF / FTC / efavirenz (EFV) (1 tablet). We report the final safety and efficacy data up to 192 weeks.

Results. Repeat consent from the original 351 participants randomized to each arm was obtained from 230 participants (66%) in the TAF/FTC + DTG arm, 209 (60%) in the TDF/FTC + DTG arm, and 183 (52%) in the TDF/FTC/EFV arm. At 192 weeks, 213 (61%) of the original 351 participants in the TAF/FTC + DTG arm, 195 (56%) in the TDF/FTC + DTG arm, and 172 (49%) in the TDF/FTC/EFV arm had confirmed RNA <50 copies/mL, with low virologic failure in all groups and no significant integrase inhibitor mutations in any arm. Mean weight gain was 8.9 kg (SD, 7.1) in the TAF/FTC + DTG arm, 5.9 kg (SD, 7.1) in the TDF/FTC + DTG arm, and 3.2 kg (SD, 8.1) in the TDF/FTC/EFV arm at 192 weeks from baseline and was greatest among women, those taking TAF, and those with lower baseline CD4 counts. The weight trajectory slowed after week 96. There were few clinical events and minor laboratory changes and differences among arms after 96 weeks. There were no significant differences in treatment-emergent hypertension or pregnancy outcomes by arm.

Conclusions. High viral suppression was seen across arms, with no resistance to DTG. Weight gain continued but slowed after 96 weeks, with few clinical events or laboratory changes.

Keywords. dolutegravir; tenofovir; obesity; suppression; resistance.

Antiretroviral integrase inhibitors (INSTIs) dolutegravir (DTG) and bictegravir have rapidly replaced older INSTIs and non-nucleoside reverse transcriptase inhibitors (NNRTIs) in almost all first-line and most subsequent-line antiretroviral therapy regimens in guidelines [1–3]. The World Health Organization's 2021 guidance to countries includes DTG within the first- and subsequent-line regimens, based on side effects, persistence, and resistance benefits [4]. Almost all treated people living with HIV in low- and middle-income countries have transitioned to regimens containing DTG, most commonly tenofovir disoproxil fumarate (TDF) / lamivudine / DTG (TLD) [5].

Tenofovir alafenamide (TAF) is recommended with TDF in many high-income country guidelines but not yet in the World

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Health Organization's guidelines due to the lipid- and weight-lowering benefits of TDF over TAF, drug interactions, and cost concerns [2, 3].

ADVANCE aimed to demonstrate the noninferiority and safety of DTG- and TAF-containing regimens, designed on the basis of early data pointing to the promising safety profile of both drugs, DTG's benefits in the context of the rising prevalence of efavirenz (EFV) resistance, as well as the potential for lower manufacturing cost if scaled up in generic production. Publication of the initial 48- and 96-week results demonstrated the potency and safety of the DTG-containing regimens but with substantial weight gain [6, 7]. We report the final 192-week virologic and safety data, including secondary cardiometabolic outcomes and pregnancy and infant follow-up data in those aged >19 years.

METHODS

ADVANCE was a randomized, open-label, noninferiority, phase 3 trial in inner-city Johannesburg, South Africa, after participant recruitment from 11 public health clinics. Detailed methods and protocol with 48-week and subsequent 96-week results have been reported [6, 7].

Briefly, participants with HIV-1 infection were aged ≥12 years, weighed ≥40 kg, had no antiretroviral exposure in the previous 6 months, and had a plasma HIV-1 RNA concentration of ≥500 copies/mL and a creatinine clearance >60 mL/min (80 mL/min if age <19 years). Participants who had tuberculosis or were pregnant were excluded.

Participants received a fixed-dose combination of TAF (25 mg), FTC (200 mg), and DTG (50 mg); a fixed-dose combination of TDF (300 mg), FTC (200 mg), and DTG (50 mg); or a coformulation of TDF (300 mg), FTC (200 mg), and EFV (600 mg), all administered orally daily.

Participants were randomly assigned (1:1:1) to the TAF/FTC + DTG group, TDF/FTC + DTG group, or the TDF/FTC/EFV group via a computerized randomization system. Treatment allocation was not masked to staff or participants.

Study visits were performed at weeks 4 and 12 and then every 12 weeks, with side effect questionnaires, physical examination, and laboratory investigations. Investigators were masked to questionnaire results unless a safety concern was identified. Measurement of glycated hemoglobin A1c was added to the protocol in 2019. Renal tubular markers were omitted after week 96, as results were similar to past study results comparing TAF and TDF. No resistance genotyping was performed prior to treatment initiation.

Isoniazid prophylaxis therapy was administered according to local guidelines. The management of pregnancy and tuberculosis is described in detail in the protocol, with participants able to continue within the study. Women who became pregnant had ultrasound assessments for fetal abnormalities; infants were followed until 18 months; and outcomes were added to the Antiretroviral Pregnancy Registry.

The study was extended to 192 weeks, once the 48-week data were published, with the need for longer-term data on weight gain acknowledged. Culturally appropriate lifestyle advice based on local guidelines regarding weight gain mitigation was intensified for participants experiencing overweight or obesity, although pharmaceutical or surgical interventions were not routinely offered.

Owing to the low enrollment rate in the adolescent group, participants aged <19 years were transferred to routine care. Two participants who had aged beyond 19 years transferred to the adult site as part of the extension.

Due to the COVID-19 pandemic, delayed consent authorization led to incomplete data sets for the 144-week analysis, but full data sets were available for subsequent time points. A local committee of 3 independent HIV and infectious diseases experts acted as the data safety monitoring board beyond 96 weeks. The study was registered at ClinicalTrials.gov (NCT03122262).

Statistical Analysis

We previously reported the primary outcome—the proportion of participants with HIV-1 RNA <50 copies/mL at week 48—and key secondary efficacy end points at the week 96 visit [6, 7]. These results are updated here to 192 weeks, whereupon the participants transitioned back to routine care, where TLD is standard first-line therapy.

Subgroup analyses included age, sex, country of origin, baseline plasma RNA concentration, baseline CD4 count, employment status, and treatment adherence, with safety analyses including physical and vital signs, laboratory analyses, and adverse events during the study.

The sample size justification has been published [6]. Statistical analysis at week 192 followed the same methods as previously reported. Participants with confirmed RNA ≥50 copies/mL or who had missing data for any reason were considered to have treatment failure. Participants who switched to a different treatment were considered to have treatment success if their RNA concentrations were <50 copies/mL.

In addition to the intention-to-treat analysis, we conducted an observed analysis, excluding individuals who did not consent to the trial extension or had missing RNA in the week 192 window. Participants with ongoing virologic failure (ie, 2 RNA results ≥1000 copies/mL after week 24) underwent genotyping. In the absence of clinically relevant resistance mutations, participants with elevated RNA were counseled on adherence and maintained their randomized medication. This allowed evaluation of HIV RNA resuppression during long-term follow-up.

Key cardiometabolic outcomes of interest included changes in body weight, blood pressure, and hemoglobin A1c. Treatment-emergent obesity was defined as a body mass index (BMI) >30 kg/m^2. We examined continuous change in systolic blood

pressure (SBP) in millimeters of mercury from baseline to 192 weeks among those participants who remained untreated for hypertension prior to randomization and over the observation period. We also estimated treatment-emergent hypertension, defined as (1) a measured blood pressure with SBP ≥140 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg at a minimum of 2 study visits between weeks 4 and 192 or (2) the initiation of treatment with an antihypertensive over that same time horizon. Participants were excluded from the calculation of treatment-emergent hypertension if they (1) reported taking antihypertensive medication prior to or at randomization or (2) had a screening and enrollment SBP ≥140 mm Hg or DBP ≥90 mm Hg. Diabetes was defined as a hemoglobin A1c ≥6.5%. The remaining secondary outcomes of interest included pregnancy outcomes and other key adverse events. Changes from baseline in laboratory and other safety parameters were summarized by treatment group with observed on-treatment data. Events of interest at week 192 were calculated as treatment-emergent events over the number of at-risk individuals with evaluable results at week 192, excluding those with the event at baseline, graded according to criteria of the Division of AIDS (National Institute of Allergy and Infectious Diseases).

For continuous data, we calculated *P* values using the Mann-Whitney test, comparing 2 treatment groups at a time. For categorical data, we used the chi-square or Fisher exact test as appropriate. All *P* values for secondary outcomes were exploratory. Of particular interest was the relationship between baseline CD4 count (<100, 100–200, >200–350, ≥350 cells/μL) and subsequent weight gain. We used multivariable linear regression analysis to assess the relationship between CD4 count at baseline and continuous BMI at 96 and 192 weeks. In addition, we used Cox proportional hazards models to assess the relationship between baseline CD4 cell count and time to clinical obesity at 96 and 192 weeks. These models were adjusted for age, sex, treatment group, and baseline BMI. Analyses were conducted with Stata version 14.2 (StataCorp).

Patient Consent Statement

The study protocol was approved by the South African Health Products Regulatory Authority, local authorities, and the Human Research Ethics Committee of the University of the Witwatersrand. All participants provided written informed consent before enrollment and again for the extension to 192 weeks.

RESULTS

Between January 2017 and May 2018, 351 participants were randomized to each treatment group, with similar demographics between arms: the mean age was 32 years (range, 13–62), 623 (59%) were women, 1051 (99%) were Black, and 398 (38%) originated from countries outside of South Africa (Figure 1, Supplementary Table 1). The mean CD4 count was 337 cells/μL (range, 1–1721), and 228 participants (22%) had a baseline RNA concentration >100 000 copies/mL. The 48- and 96-week analyses demonstrated noninferiority of the DTG-containing arms when compared with the TDF/FTC/EFV arm [6, 7].

Repeat consent was obtained for 230 participants (66%) in the TAF/FTC + DTG arm, 209 (60%) in the TDF/FTC + DTG arm, and 183 (52%) in the TDF/FTC/EFV arm from the original 351 participants randomized to each arm. Significantly fewer participants in the TDF/FTC/EFV arm reconsented to continue after week 96 as compared with the combined DTG arms ($P < .001$). Overall, the major reasons for nonparticipation were loss to follow-up, withdrawal of consent, relocation, and transfer for care due to complex comorbidities requiring multiple agents for control (mainly hypertension and diabetes; Figure 1).

There were several differences in baseline characteristics between the 622 participants who continued past week 96 and those who discontinued the trial at week 96, as shown in Table 1. Participants who continued post–week 96 were significantly older, were more likely to be male and from countries outside South Africa, and had a higher body weight. In addition, participants who continued in the trial extension were more likely to have HIV RNA suppression at week 96. Other differences between the original and post–96-week cohort are summarized in Table 2.

Virologic Suppression

In the primary intention-to-treat analysis at week 192, 213 (61%) of 351 participants in the TAF/FTC + DTG group, 195 (56%) of 351 in the TDF/FTC + DTG group, and 172 (49%) of 351 in the TDF/FTC/EFV group had achieved RNA <50 copies/mL (Table 3). The difference in the proportion of participants who had achieved RNA <50 copies/mL at week 192 was 12% (98% CI, −3% to 21%; $P = .002$) between the TAF/FTC + DTG group and the TDF/FTC/EFV group, 7% (98% CI, −2% to 16%; $P = .080$) between the TDF/FTC + DTG group and the TDF/FTC/EFV group, and 5% (98% CI, −4% to 14%; $P = .169$) between the TAF/FTC + DTG group and the TDF/FTC + DTG group.

At week 192, <1% in each arm had RNA concentrations ≥50 copies/mL or had discontinued due to poor efficacy (Table 3). In the post hoc "missing data excluded" analysis, at week 192, >97% participants in all groups achieved a confirmed plasma RNA concentration <50 copies/mL (Supplementary Table 3); similar results were observed in the per-protocol analysis. No significant differences among groups were seen in the "missing data excluded" analysis.

There were 9 participants in the TAF/FTC + DTG arm, 12 in the TDF/FTC + DTG arm, and 20 in TDF/FTC/EFV arm who were retrospectively genotyped at the time of elevations in RNA (Table 3). These participants were also genotyped at baseline. Genotyping identified no significant resistance to DTG at the time of viremia on treatment. Two patients had minor INSTI mutations on failure in the TDF/FTC/EFV arm, and both were present at baseline. A significant number of participants

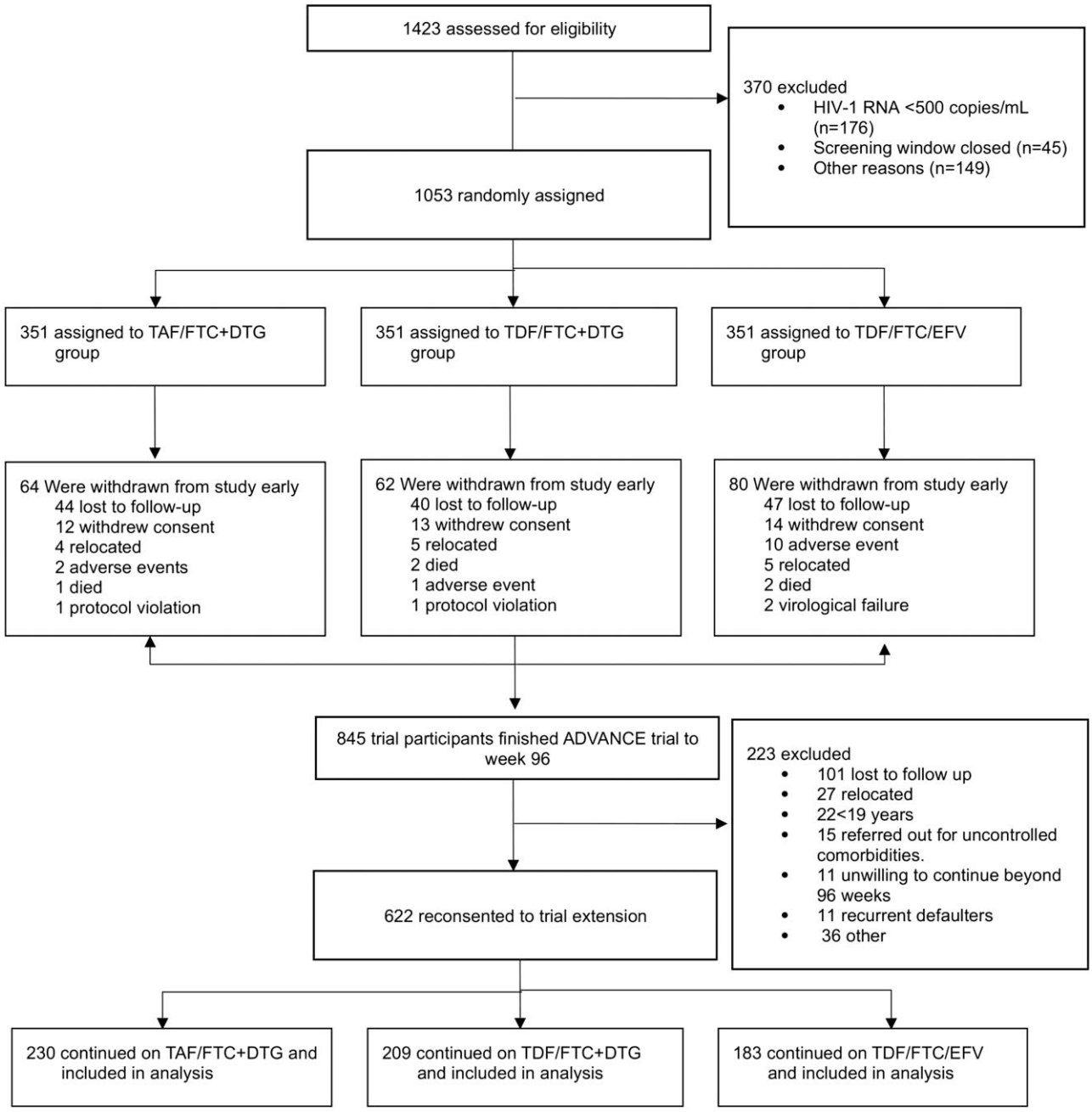

Figure 1. Flowchart for randomization to each treatment group. DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

failing in the DTG arms had NNRTI mutations at baseline (19/24, 79%; Table 3, Supplementary Table 2). At the time of viremia during treatment, 8 of 20 (40%) participants taking TDF/FTC/EFV showed treatment-emergent major International Antiviral Society–USA mutations, while 15 of 20 (75%) had treatment-emergent NNRTI mutations. By contrast, of 21 participants experiencing viremia during treatment in the DTG arms, 3 (14%) developed new nucleoside reverse transcriptase inhibitor (NRTI) mutations, while 1 (5%) developed a new NNRTI mutation.

Weight Change and Cardiometabolic Outcomes

Among participants with available data at week 192, mean weight gain from baseline was 8.9 kg (SD, 7.1) in the TAF/FTC + DTG group, 5.9 kg (SD, 7.1) in the TDF/FTC + DTG group, and 3.2 kg (SD, 8.1) in the TDF/FTC/EFV group, and significant differences in weight gain were identified between the sexes (Figure 2, Supplementary Figure S1, Supplementary Table 13). While there was a plateau in the trajectory of weight gain overall after week 96, there were wide

Table 1. Comparison of Baseline Characteristics: Participants Who Continued vs Discontinued in Trial Extension to Week 192

	Median (IQR) or No. (%)		
	Continued (n = 622)	Discontinued (n = 226)	*P* Value
Age, y	33.0 (28.0–39.0)	30.0 (25.0–37.0)	<.001
Sex			
Female	350 (56.3)	148 (65.5)	.016
Male	272 (43.7)	78 (34.5)	.016
Country of origin			
South Africa	357 (57.4)	155 (68.6)	.003
Other	265 (42.6)	71 (31.4)	.003
Weight, kg	67.0 (59.3–77.4)	65.3 (57.4–76.7)	.040
Body mass index			
<18.5	54 (8.7)	30 (13.3)	.048
18.5–24.9	327 (52.6)	123 (54.4)	NS
25–29.9	159 (25.6)	52 (23.0)	NS
≥30	82 (13.2)	21 (9.3)	NS
HIV-1 RNA level, copies/mL			
≤100 000	480 (77.2)	179 (79.2)	NS
100 001–500 000	125 (20.3)	40 (18.4)	NS
>500 000	17 (2.8)	7 (3.2)	NS
CD4 count, cells/μL	279 (161–427)	337 (193–492)	NS

Abbreviation: NS, not significant.

differences by sex, where women and those with high baseline BMI continued to gain weight steadily after week 96 (Supplementary Table 12). Concomitant medications, appetite, nausea, and insomnia were not associated with weight gain, and quality of life was similar across all groups through 192 weeks.

A sensitivity analysis excluding pregnant women did not affect the weight results (Supplementary Table 13). Treatment-emergent obesity was higher among women and was significantly higher in the TAF/FTC + DTG group than the other groups ($P < .001$). Similarly, those with lower CD4 counts at baseline had greater weight gain and higher risks of clinical obesity (Tables 4 and 5, Supplementary Figure 2). This effect was most prominent in the TAF/FTC/DTG arm, where those with the lowest baseline CD4 counts had body weight significantly higher than the other participants by week 192.

Among all participants, 6% were being treated for hypertension at baseline (Supplementary Tables 10 and 11). Over 192 weeks, we observed the following average changes in SBP by arm: 3.6 mm Hg (95% CI, −1.7 to 5.4), 0.7 mm Hg (95% CI, 1.4–2.7), and −0.4 mm Hg (95% CI, −2.2 to 1.4) in the TAF/FTC + DTG, TDF/FTC + DTG, and TDF/FTC/EFV groups, respectively. These differences in SBP were significant only when the TAF/FTC + DTG and TDF/FTC/EFV groups were compared at 192 weeks ($P = .039$). Moreover, 25.5% (95% CI, 19.3%–31.7%), 20.1% (95% CI, 14.1%–26.1%), and 17.8% (95% CI, 11.5%–24.1%) of participants developed treatment-emergent hypertension in the TAF/FTC + DTG, TDF/FTC + DTG, and TDF/FTC/EFV groups (TAF/FTC + DTG vs TDF/FTC/EFV, $P = .092$; TDF/FTC + DTG vs TDF/FTC/EFV, $P = .602$). Of participants with treatment-emergent hypertension, 95% were given antihypertensives.

Table 2. Comparison of Week 96 Outcomes: Participants Who Continued vs Discontinued in Trial Extension to Week 192

	No. (%) or Median (IQR)		
	Continued (n = 622)	Discontinued (n = 226)	*P* Value
HIV-1 RNA copies/mL			
<50	605 (97.3)	191 (84.5)	<.001
≥50	11 (1.8)	26 (11.5)	<.001
Missing data at week 96	5 (0.8)	8 (3.5)	.004
CD4 change to week 96	172 (74–267)	168 (84 to 294)	.670
Weight			
Change to week 96, kg	3.8 (0.5–8.8)	2.4 (−1.5 to 7.4)	.002
Emergent obesity any time point	109 (17.5)	29 (12.8)	.102

Pregnancy Outcomes and Adverse Events

During the entire 192-week follow-up, 133 pregnancies occurred among 118 women: 48 in the TAF/FTC + DTG group, 40 in the TDF/FTC + DTG group, and 45 in the TDF/FTC/EFV group (Supplementary Table 13), with follow-up of all infants completed. Medical events were scattered across arms, with no clear pattern. Six congenital anomalies were reported: 3 children with umbilical hernias, 1 child with partial aposthia, 1 child with polydactyly, and 1 child with a microphallus and bilateral undescended testes. No neural tube defects were recorded at any time during the study, nor was there any new neonatal death after 96 weeks.

Other adverse events are summarized in Supplementary Tables 3 to 8. Between baseline and week 192, there were more grade 3 or 4 clinical adverse events in the TDF/FTC/EFV arm (31%) as compared with the TAF/FTC + DTG and TDF/FTC + DTG arms (19% overall). More nervous system and psychiatric grade 1–4 clinical adverse events occurred in the TDF/FTC/EFV arm as compared with the DTG arms (Supplementary Table 4). There were also more grade 3 or 4 liver enzyme elevations and reports of abnormal weight loss in the TDF/FTC/EFV arm when compared with the combined DTG arms (Supplementary Table 5). Finally, 7 bone fractures, all traumatic, were reported as serious adverse events during the 192 weeks of follow-up: 1 in the TAF/FTC + DTG arm, 4 in the TDF/FTC + DTG arm, and 2 in the TDF/FTC/EFV arm (Supplementary Table 6).

No meaningful differences in hematology or chemistry occurred (Supplementary Tables 7–9). There were similar slight rises in creatinine in the 2 DTG-containing arms, with no change in the TDF/FTC/EFV group (Supplementary Figure 2). No cases of renal dysfunction requiring interruption or substitution of tenofovir occurred after week 96. CD4 count increases

Table 3. HIV RNA Suppression at Week 192

	No. (%) or % (98.3% CI)		
	TAF/FTC + DTG	TDF/FTC + DTG	TDF/FTC/EFV
Primary efficacy at week 192 (ITT)			
HIV RNA, copies/mL			
<50	213 (61)	195 (56)	172 (49)
≥50	5 (1)	5 (1)	2 (1)
No virologic data	12 (3)	9 (3)	9 (3)
At last visit, copies/mL			
<50	10 (3)	9 (3)	9 (3)
≥50	2 (1)	…	…
Did not reconsent	121 (34)	142 (40)	168 (48)
Treatment difference (primary efficacy) vs			
TDF/FTC/EFV	+11.7 (2.8 to 20.6)	+6.6 (−2.4 to 15.5)	
P value	.002	.08	
TDF/FTC + DTG	+5.1 (−3.7 to 14.0)		
P value	.169		
Missing: excluded at week 192			
HIV RNA, copies/mL			
<50	213 (98)	195 (98)	172 (99)
≥50	5 (2)	5 (3)	2 (1)
Major treatment-emergent IAS-USA mutations			
Genotyped at baseline and VF	9	12	20
INSTI	0	0	0
NRTI	0	3 (25)	8 (40)
NNRTI	1 (11)	1 (8)	15 (75)

Abbreviations: DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; IAS, International Antiviral Society; INSTI, integrase inhibitor; ITT, intention to treat; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; VF, virological failure.

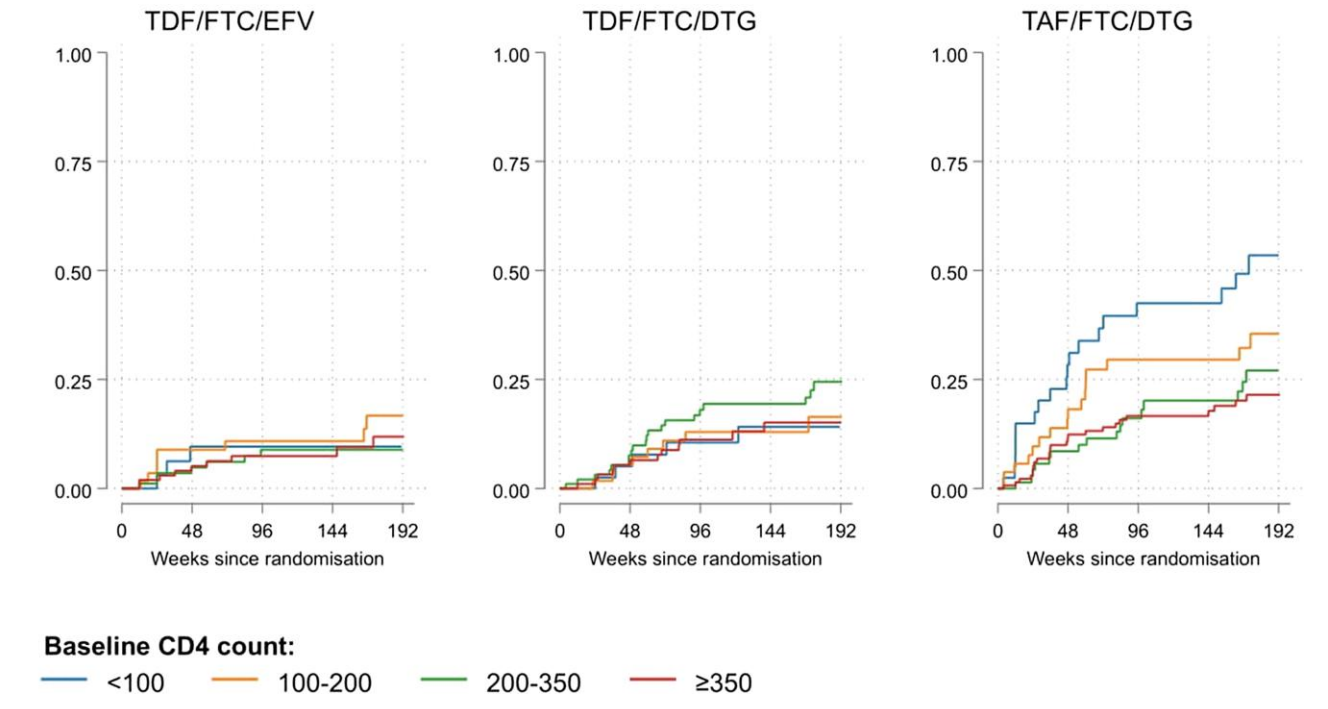

Figure 2. Time to clinical obesity by treatment arm and baseline CD4 count. DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Table 4. Predictors of BMI at Weeks 96 and 192 by Linear Regression

	Week 96 (n = 849)		Week 192 (n = 575)	
	Simple Regression	Multiple Regression	Simple Regression	Multiple Regression
Treatment arm				
TDF/FTC/EFV	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
TDF/FTC/DTG	0.53 (−.45 to 1.50)	0.63 (.23 to 1.02)	0.77 (−.50 to 2.03)	0.85 (.33 to 1.38)
TAF/FTC/DTG	1.57 (.59 to 2.56)	1.70 (1.30 to 2.10)	1.63 (.39 to 2.87)	2.04 (1.52 to 2.55)
Age, y	0.12 (.06 to .17)	−0.00 (−.02 to .02)	0.11 (.04 to .18)	−0.01 (−.04 to .02)
Female sex	5.07 (4.34 to 5.81)	1.14 (.78 to 1.50)	5.55 (4.64 to 6.46)	1.32 (.86 to 1.77)
Baseline CD4 category, cell/mm^3				
<100	−0.16 (−1.49 to 1.18)	2.48 (1.93 to 3.03)	−1.50 (−3.16 to .16)	2.31 (1.61 to 3.01)
100–200	0.16 (−.97 to 1.29)	1.34 (.88 to 1.80)	−0.25 (−1.67 to 1.18)	1.58 (.99 to 2.18)
>200–350	0.29 (−.68 to 1.26)	0.77 (.38 to 1.16)	−0.12 (−1.34 to 1.10)	0.91 (.41 to 1.42)
≥350	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Baseline BMI	1.01 (.98 to 1.05)	0.99 (.96 to 1.03)	1.04 (1.00 to 1.08)	1.03 (.98 to 1.07)

Data are presented as β (95% CI).

Abbreviations: BMI, body mass index; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Table 5. Predictors of Obesity by Weeks 96 and 192 by Cox Proportional Hazards Model

	Week 96 (n = 905)		Week 192 (n = 905)	
	Simple Regression	Multiple Regression	Simple Regression	Multiple Regression
Treatment arm				
TDF/FTC/EFV	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
TDF/FTC/DTG	1.58 (.94–2.65)	1.25 (.73–2.14)	1.61 (1.00–2.59)	1.41 (.86–2.30)
TAF/FTC/DTG	2.72 (1.69–4.38)	2.74 (1.68–4.47)	2.69 (1.73–4.18)	3.15 (2.00–4.98)
Age, y	1.02 (.99–1.04)	0.97 (.95–.99)	1.02 (1.00–1.04)	0.97 (.95–.99)
Female sex	4.80 (2.98–7.75)	1.95 (1.19–3.19)	4.74 (3.08–7.30)	1.93 (1.24–3.01)
Baseline CD4 category, cell/mm^3				
<100	1.92 (1.14–3.24)	6.92 (3.91–12.25)	1.70 (1.05–2.75)	6.64 (3.92–11.25)
100–200	1.48 (.90–2.44)	1.83 (1.11–3.02)	1.39 (.89–2.19)	1.79 (1.13–2.84)
>200–350	1.29 (.82–2.44)	1.56 (.98–2.48)	1.19 (.78–1.80)	1.49 (.98–2.28)
≥350	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Baseline BMI	1.76 (1.62–1.91)	1.89 (1.72–2.08)	1.72 (1.60–1.85)	1.86 (1.71–2.02)

Participants obese at baseline are excluded from the analysis. Data are presented as β (95% CI).

Abbreviations: BMI, body mass index; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

were significantly greater in the TAF/FTC + DTG arm (Supplementary Table 11).

No additional TB cases occurred after 96 weeks (1 case occurred between 48 and 96 weeks). We did not previously report isoniazid prophylaxis therapy usage, with 1043 of the 1053 participants receiving any isoniazid prophylaxis therapy and 894 of these receiving at least 6 months.

DISCUSSION

ADVANCE demonstrated the high efficacy and safety of DTG-based first-line oral regimens combined with tenofovir prodrugs, with few participants interrupting their regimen due to side effects over 192 weeks and with almost no sustained virologic failures, no INSTI resistance, and limited metabolic effects. The EFV-containing arm had predictable toxicities, but all treatment discontinuations for toxicity occurred in the first 48 weeks, with virologic failures and resistance seen in a small number of participants. There was a single case of tuberculosis after 48 weeks, which was the only HIV-related event after 48 weeks in the cohorta testament to the potency of isoniazid prophylaxis therapy and antiretroviral therapy–mediated immune reconstitution.

These safety, potency, and efficacy data of DTG-containing regimens are reassuring, with most people with HIV globally currently on similar combinations [5]. Only minor INSTI resistance mutations were seen during virologic failure, in the EFV arm, and at baseline. A significant number of participants failing treatment had major NNRTI resistance mutations at baseline, probably due to circulating resistance or having failed EFV-based therapy and not informing the study team. While the post hoc analysis of ADVANCE demonstrates the relative

potency and safety of EFV, there seems little reason to recommend the drug over second-generation INSTIs. However, weight gain continued between 96 and 192 weeks among women and those taking TAF, making this a major ongoing concern since emerging as a signal in 2017 [8].

Data from ADVANCE's pharmacokinetic substudies demonstrated that medium and fast metabolizers of EFV gained weight at the same rate as those taking DTG, while EFV slow metabolizers were the participants who contributed to the slower weight gain in the overall cohort [9, 10]. This suggests that EFV is responsible for the lower weight trajectory seen in the TDF/FTC/EFV arm in ADVANCE, over the DTG-containing arms, as opposed to DTG being responsible for the weight gain. Slow metabolizers are at risk for developing other EFV-linked side effects, many serious, such that substituting DTG with EFV in those experiencing weight gain is ill-advised.

Weight loss has long been recognized with the thymidine analogues and more recently associated with EFV and TDF [11]. TDF has a modest mitigating impact on weight gain in ADVANCE and other treatment, switch, and prophylaxis studies [11, 12]. The ADVANCE arm containing TAF saw the most weight gain, but a causative association would imply an off-target and previously undescribed mechanism of action. Study results comparing new regimens without NRTIs will be illuminating, especially those containing new agents, such as islatravir and lenacapavir, as compared against TAF, FTC, and bictegravir combinations. If they show no difference, it may be that mechanisms other than drug side effects are driving weight gain.

The greater weight gain in those starting with a lower CD4 count is perplexing (Figure 2, Supplementary Figure 1). It is not entirely clear yet whether people with HIV gain weight at a greater pace than people without HIV, but the difference within these immunologic categories suggest that HIV status does make a difference to weight trajectories. It is plausible that the inflammatory milieu HIV creates and subsequent recovery, damage to the gastrointestinal absorption processes, or other as-yet unexplained factors, in the presence of an obesogenic environment alters weight gain trajectories. It also may be that social determinants contribute to late presentation and obesity. Older drugs with recognized impact on weight gain (stavudine, zidovudine, and other nucleoside analogues), as well as EFV and TDF more recently, may have masked our recognition of this weight gain.

Participants received ongoing and culturally appropriate lifestyle advice, including diet, which appeared to make little or no impact on the weight trajectory. This is unsurprising given current understandings of obesity pathophysiology, which suggests minimal impact of lifestyle interventions in most people [13, 14].

While weight gain was associated with little or no change in blood pressure, lipids, glucose, and hemoglobin A1c, longer follow-up may be needed to see the full metabolic consequences [15–17]. We saw minimal rise in SBP and DBP, significant in other studies, possibly due to high levels of antihypertensive use at diagnosis of elevated blood pressure in ADVANCE [18, 19].

The study's limitations include the open-label, single-site design and differing pill burdens across arms. Reconsenting procedures and exclusions at week 96 may have introduced bias. The participants who continued the ADVANCE trial after week 96 showed several key differences in baseline characteristics and on-treatment HIV RNA suppression when compared with those who discontinued (Tables 1 and 2). The number of participants with data available at week 192 was below the prespecified sample size to demonstrate noninferiority. It is difficult to interpret the intention-to-treat analysis at week 192 with missing data classified as failure: in particular, participants randomized to TDF/FTC/EFV could have discontinued this treatment and switched to TLD outside the trial, as part of routine clinical practice (ie, South Africa transitioned to use of TLD during the ADVANCE trial).

We were unable to recruit sufficient adolescents to study this important group. Strengths include recruitment from routine services, limited inclusion and exclusion criteria, and high representativity of women. ADVANCE, with high regional participation, recruited from an area with high genetic variability, again a strength in terms of representation [20].

Future research should address weight mitigation for people with HIV that embraces increasingly accepted therapeutics, including weight loss drugs and bariatric surgery for those with established obesity, as ADVANCE suggests that most will require intervention [21]. The magnitude of the overall weight gain suggests that additional interventions beyond changing antiretroviral regimens will be required, although a move to TDF from TAF has been shown decrease weight in women [12]. Obesity is now well recognized not only as a progressive state, with strong associations as diverse as diabetes and cancer, but also as a risk factor for nonresponsiveness to the first generations of injectable antiretrovirals [22, 23]. Weight gain for those on established antiretroviral therapy continues to be a major challenge for the field.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Author contributions. W. D. F. V., A. H., M. Moorhouse, P. C., and S. S. developed the protocol. W. D. F. V., S. S., B. B., and A. H. wrote this initial manuscript draft, with data assistance from B. B. W. D. F. V. oversaw the study with assistance from S. S., N. M., N. A., G. A., M. Masenya, L. F., M. Moorhouse, B. B., and N. C. K. M., B. S., and A. Q. performed the statistical analysis under the supervision of A. H. All authors reviewed the manuscript, suggested edits, and approved the final version.

Data sharing. Deidentified data, with data labels, can be made available from the corresponding author for further analysis with appropriate motivation for academic research.

Disclaimer. Unitaid, USAID, Gilead Sciences, and ViiV Healthcare contributed to the study design. All study funders reviewed the manuscript, and the authors had the final decision on the content. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Dovato
dolutegravir/lamivudine

EVIDENCE SUPPORTS THE HIGH BARRIER TO RESISTANCE OF DOVATO UP TO 5 YEARS[1-3]

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Treatment-naïve resistance rates, with up to **3 years of evidence**[5–7]

0% (n=0/1,885)*,[4]
REAL-WORLD EVIDENCE

0.1% (n=1/953)**,†,‡,§,5–7
RANDOMISED CONTROLLED TRIALS

Treatment-experienced resistance rates, with up to **5 years of evidence**[1–3]

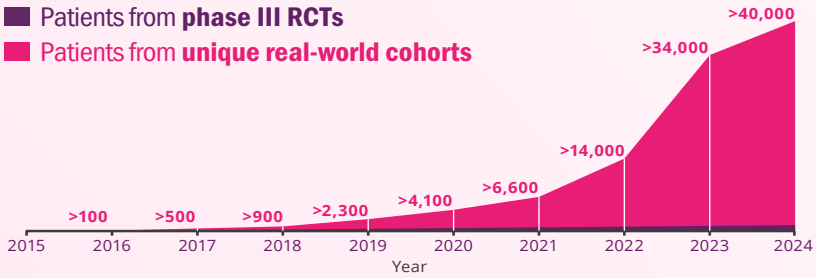
0.03% (n=10/35,888)*,[4]
REAL-WORLD EVIDENCE

0% (n=0/615)||,¶,#,8,9
RANDOMISED CONTROLLED TRIALS

>300,000 PEOPLE LIVING WITH HIV HAVE BEEN TREATED WITH DOVATO GLOBALLY[10]

DOVATO is supported by a wealth of evidence, with the outcomes of **>40,000** people living with HIV captured within clinical trials and real-world evidence, including those with:[4–9,11,12]

- **NO PRIOR TREATMENT EXPERIENCE**[13]
- **NO BASELINE RESISTANCE TESTING**[13]
- **HIGH BASELINE VIRAL LOAD** (>100,000 copies/mL and even >1M copies/mL)[6,13]
- **LOW CD4 + COUNT** (≤200 cells/mm³)[13]



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ABBREVIATIONS

3TC, lamivudine; **CD4,** cluster of differentiation 4; **DTG,** dolutegravir; **FDA,** United States Food and Drug Administration; **FTC,** emtricitabine; **HIV,** human immunodeficiency virus; **ITT-E,** intention-to-treat exposed; **NRTI,** nucleoside/nucleotide reverse transcriptase inhibitor; **RCT,** randomised controlled trial; **RNA,** ribonucleic acid; **TAF,** tenofovir alafenamide fumarate; **TDF,** tenofovir disoproxil fumarate; **XTC,** emtricitabine.

FOOTNOTES

*Data extracted from a systematic literature review of DTG+3TC real-world evidence. Overlap between cohorts cannot be fully excluded.

**The reported rate reflects the sum-total of resistance cases calculated from GEMINI I and II (n=1/716, through 144 weeks), STAT (n=0/131, through 52 weeks), and D2ARLING (n=0/106, through 24 weeks).[5–7]

†GEMINI I and II are two identical 148-week, phase III, randomised, double-blind, multicentre, parallel-group, non-inferiority, controlled clinical trials testing the efficacy of DTG/3TC in treatment-naïve patients. Participants with screening HIV-1 RNA ≤500,000 copies/mL were randomised 1:1 to once-daily DTG/3TC (n=716, pooled) or DTG + TDF/FTC (n=717, pooled). The primary endpoint of each GEMINI study was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).[13]

‡STAT is a phase IIIb, open-label, 48-week, single-arm pilot study evaluating the feasibility, efficacy, and safety of DTG/3TC in 131 newly diagnosed HIV-1 infected adults as a first line regimen. The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 24.[6]

§D2ARLING is a randomised, open-label, phase IV study designed to assess the efficacy and safety of DTG/3TC in treatment-naïve people with HIV with no available baseline HIV-1 resistance testing. Participants were randomised in a 1:1 ratio to receive DTG/3TC (n=106) or DTG + TDF/XTC (n=108). The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48.[7] Results at week 24 of the study.

||The reported rate reflects the sum-total of resistance cases calculated from TANGO (n=0/369, through 196 weeks) and SALSA (n=0/246, through 48 weeks).[8,9]

¶TANGO is a randomised, open-label, trial testing the efficacy of DOVATO in virologically suppressed patients. Participants were randomised in a 1:1 ratio to receive DOVATO (n=369) or continue with TAF-containing regimens (n=372) for up to 200 weeks. At Week 148, 298 of those on TAF-based regimens switched to DOVATO. The primary efficacy endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL (virologic non-response) as per the FDA Snapshot category at Week 48 (adjusted for randomisation stratification factor).[8,13]

#SALSA is a phase III, randomised, open-label, non-inferiority clinical trial evaluating the efficacy and safety of switching to DTG/3TC compared with continuing current antiretroviral regimens in virologically suppressed adults with HIV. Eligible participants were randomised 1:1 to switch to once-daily DTG/3TC (n=246) or continue current antiretroviral regimens (n=247). The primary endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).[9]

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