The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 29, 2019 VOL. 381 NO. 9

Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV

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ABSTRACT

BACKGROUND

Two drugs under consideration for inclusion in antiretroviral therapy (ART) regimens for human immunodeiciency virus (HIV) infection are dolutegravir (DTG) and tenofovir alafenamide fumarate (TAF). There are limited data on their use in low- and middle-income countries.

METHODS

We conducted a 96-week, phase 3, investigator-led, open-label, randomized trial in South Africa, in which we compared a triple-therapy combination of emtricitabine (FTC) and DTG plus either of two tenofovir prodrugs — TAF (TAF-based group) or tenofovir disoproxil fumarate (TDF) (TDF-based group) — against the local standard-of-care regimen of TDF–FTC–efavirenz (standard-care group). Inclusion criteria included an age of 12 years or older, no receipt of ART in the previous 6 months, a creatinine clearance of more than 60 ml per minute (>80 ml per minute in patients younger than 19 years of age), and an HIV type 1 (HIV-1) RNA level of 500 copies or more per milliliter. The primary end point was the percentage of patients with a 48-week HIV-1 RNA level of less than 50 copies per milliliter (as determined with the Snapshot algorithm from the Food and Drug Administration; noninferiority margin, –10 percentage points). We report the primary (48-week) efficacy and safety data.

RESULTS

A total of 1053 patients underwent randomization from February 2017 through May 2018. More than 99% of the patients were black, and 59% were female. The mean age was 32 years, and the mean CD4 count was 337 cells per cubic millimeter. At week 48, the percentage of patients with an HIV-1 RNA level of less than 50 copies per milliliter was 84% in the TAF-based group, 85% in the TDF-based group, and 79% in the standard-care group, findings that indicate that the DTG-containing regimens were noninferior to the standard-care regimen. The number of patients who discontinued the trial regimen was higher in the standard-care group than in the other two groups. In the per-protocol population, the standard-care regimen had equivalent potency to the other two regimens. The TAF-based regimen had less effect on bone density and renal function than the other regimens. Weight increase (both lean and fat mass) was greatest in the TAF-based group and among female patients (mean increase, 6.4 kg in the TAF-based group, 3.2 kg in the TDF-based group, and 1.7 kg in the standard-care group). No resistance to integrase inhibitors was identified in patients receiving the DTG-containing regimens.

CONCLUSIONS

Treatment with DTG combined with either of two tenofovir prodrugs (TAF and TDF) showed noninferior efficacy to treatment with the standard-care regimen. There was significantly more weight gain with the DTG-containing regimens, especially in combination with TAF, than with the standard-care regimen. (ADVANCE ClinicalTrials.gov number, NCT03122262.)

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This article was published on July 24, 2019, at NEJM.org.

N Engl J Med 2019;381:803-15.
DOI: 10.1056/NEJMoa1902824

A Quick Take is available at NEJM.org

A first-line regimen of tenofovir disoproxil fumarate (TDF) with either lamivudine (3TC) or emtricitabine (FTC) plus efavirenz (EFV) for the treatment of human immunodeficiency virus infection (HIV) is recommended by the World Health Organization (WHO) because it can be safely used in pregnancy and during tuberculosis treatment. However, the regimen has a low resistance barrier, and there are relatively high incidences of toxic effects among some patients.[1-4] Other antiretroviral agents are recommended in high-income countries.[5,6]

Two drugs under consideration for inclusion in new regimens are dolutegravir (DTG), to replace EFV, and tenofovir alafenamide fumarate (TAF), to replace TDF, both prodrugs of tenofovir.[7,8] DTG has potency, resistance, and side-effect benefits over EFV, and there are widespread plans to rapidly expand its use in low- and middle-income countries.[7-13] However, associations of DTG with teratogenic effects (specifically, neural-tube defects), neuropsychiatric symptoms, and weight gain have aroused concern, as has the complexity of twice-daily administration with rifampin-containing tuberculosis treatment.[7,14] TAF has similar efficacy to that of TDF, with fewer effects on markers of renal or bone toxicity, but lacks data in low- and middle-income countries and in patients who are receiving rifamycins for tuberculosis therapy and in those who are pregnant. For these reasons, the use of TAF has not yet been included in WHO recommendations.[7,15-18] We conducted an investigator-led, randomized clinical trial, ADVANCE, to evaluate the efficacy and safety of two antiretroviral therapy (ART) combinations, TAF–FTC–DTG and TDF–FTC–DTG, as compared with the current first-line regimen of TDF–FTC (or 3TC)–EFV used in the majority of patients in low- and middle-income countries.[13]

Methods

Trial Oversight

The ADVANCE trial is an open-label, noninferiority, 96-week, phase 3 trial comparing three first-line regimens in patients with HIV type 1 (HIV-1) infection starting ART, with the primary end point (48-week viral suppression) reported here along with safety data.[19] Authors, sponsors, and pharmaceutical companies were involved in the trial design and execution and in the review of the manuscript. Analysis of the data was performed by the authors, with the first author responsible for overall trial management and manuscript preparation. The authors vouch for the completeness and accuracy of the data and for the adherence of the trial to the protocol, available with the full text of this article at NEJM.org. The trial conformed to international and local guidelines based on the Declaration of Helsinki and Good Clinical Practice guidelines of the International Conference on Harmonisation.

Oversight was maintained through the multinational data and safety monitoring board of the National Institutes of Health (NIH), with regular reporting to an academic ethics committee, local regulatory authorities, a scientific advisory committee of senior researchers, a clinical end-point committee, an internal safety committee, and a program advisory committee formed by Unitaid and the U.S. Agency for International Development, chaired by senior members from the WHO and the Global Fund to Fight AIDS, Tuberculosis, and Malaria and including members from treatment activist groups, the Centers for Disease Control and Prevention, the NIH, the Bill and Melinda Gates Foundation, and the Food and Drug Administration (FDA). Additional support was provided by contract research organizations and local experts. The trial was approved by an institutional review board (the human research ethics committee at the University of the Witwatersrand) and received local regulatory approval.

Trial Patients and Intervention

The trial enrolled residents of inner-city Johannesburg from February 2017 through May 2018. Inclusion criteria were an age of 12 years or older, a weight of 40 kg or more, a viral load of 500 copies or more per milliliter, and a creatinine clearance of more than 60 ml per minute (Cockcroft–Gault formula) in patients 19 years of age or older or more than 80 ml per minute (modified Cockcroft–Gault formula) in those younger than 19 years of age. Among the exclusion criteria were more than 30 days of treatment with any form of ART, any ART within the past 6 months, pregnancy, or current treatment for tuberculosis.

The trial drugs were TAF (25 mg, Gilead Sciences), coformulated with FTC (200 mg, Gilead Sciences); TDF (300 mg), coformulated with FTC (generic manufacturers); DTG (50 mg, ViiV Healthcare); and coformulated TDF–FTC plus EFV (600 mg) (generic manufacturers). After written

informed consent was obtained, patients were randomly assigned (in a 1:1:1 ratio) to receive TAF–FTC–DTG, as two tablets daily (TAF-based group); TDF–FTC–DTG, as two tablets daily (TDF-based group); or TDF–FTC–EFV as a single tablet daily (standard-care group). Patients 12 to 19 years of age underwent randomization separately, at the request of the South African regulator and data and safety monitoring board. TAF–FTC was donated by Gilead Sciences, and DTG was donated by ViiV Healthcare. Additional trial drugs were procured from local registered generic suppliers (Mylan and Macleods Pharmaceuticals).

TRIAL END POINTS AND ASSESSMENTS

The primary end point was the percentage of patients with an HIV-1 RNA level of less than 50 copies per milliliter at week 48. Secondary objectives were to evaluate additional viral-load thresholds, CD4 count changes, and side-effect profile and safety, including findings on physical examination, laboratory analyses, and dual-energy x-ray absorptiometry (DXA) scans. Laboratory services were provided by a laboratory (Bio Analytical Research Corporation South Africa) that is accredited by the Division of AIDS, National Institute of Allergy and Infectious Diseases.

There was no testing of HIV resistance at screening. Patients with two confirmed elevations in the HIV-1 RNA level to 1000 copies or more per milliliter after week 24 were tested for drug resistance, together with their stored baseline samples.

Throughout the trial, data were collected from symptom screening, vital-signs measurement, symptom-directed physical examination, laboratory assessments, and multiple questionnaires, including a sleep questionnaire. The trial included visits at screening, enrollment, week 4, week 12, and then every 12 weeks until week 96, with tuberculosis and pregnancy screening at every visit. Female patients who became pregnant could elect to remain in the trial, with active follow-up of infants to 18 months and data entered in the Antiretroviral Pregnancy Registry. Patients receiving the TAF-based regimen in whom tuberculosis developed were switched to the TDF-based regimen, and those receiving the DTG-containing regimens in whom tuberculosis developed had their dose of the drug increased to 50 mg twice daily.

Investigators were unaware of renal tubular markers, findings on DXA scans, and questionnaire results unless patient safety concerns were an issue. We derived values for bone mineral density and fat mass using DXA (Hologic Discovery W with APEX software, version 4.6.0.2) for body-composition analysis.[8] In the original protocol, weight loss was graded as an adverse event, but weight gain was not. In the final statistical analysis plan, clinical obesity was defined as a body-mass index (the weight in kilograms divided by the square of the height in meters) of 30 or more. For full details regarding trial conduct, see the protocol and statistical analysis plan, available at NEJM.org.

STATISTICAL ANALYSIS

The primary efficacy variable was a viral load of less than 50 copies per milliliter at the end of week 48 (with a 6-week window on either side) in the intention-to-treat population, which included all the patients who had received at least one dose of trial medication. Patients with missing RNA results at week 48 were considered to have not reached an undetectable level of plasma HIV-1 RNA for the primary efficacy variable, according to the Snapshot algorithm from the FDA. A sample size of 350 patients per group was estimated to provide 80% power to establish noninferior efficacy for the TAF-based regimen as compared with the standard-care regimen and for the TDF-based regimen as compared with the standard-care regimen.[20] The additional comparison of the DTG-containing regimens (TAF-based vs. TDF-based) was also prespecified. These calculations assumed a noninferiority margin of –10 percentage points, as recommended by the FDA,[21] with an assumed 80% efficacy in the standard-care group. After the testing for noninferiority, the treatment groups were compared for differences in efficacy. For these tests, an overall 1.7% significance level ($P=0.017$) was used, to adjust for the three pairwise treatment comparisons being made. The primary analysis was repeated with the exclusion of patients who had missing data on HIV-1 RNA levels (during-treatment analysis). Adverse events and laboratory abnormalities that emerged during treatment were graded according to Division of AIDS criteria.[22]

RESULTS

PATIENTS

Of the 1053 patients who had undergone randomization, 351 were assigned to each group (Fig. S1 and Table S1 in the Supplementary Appendix,

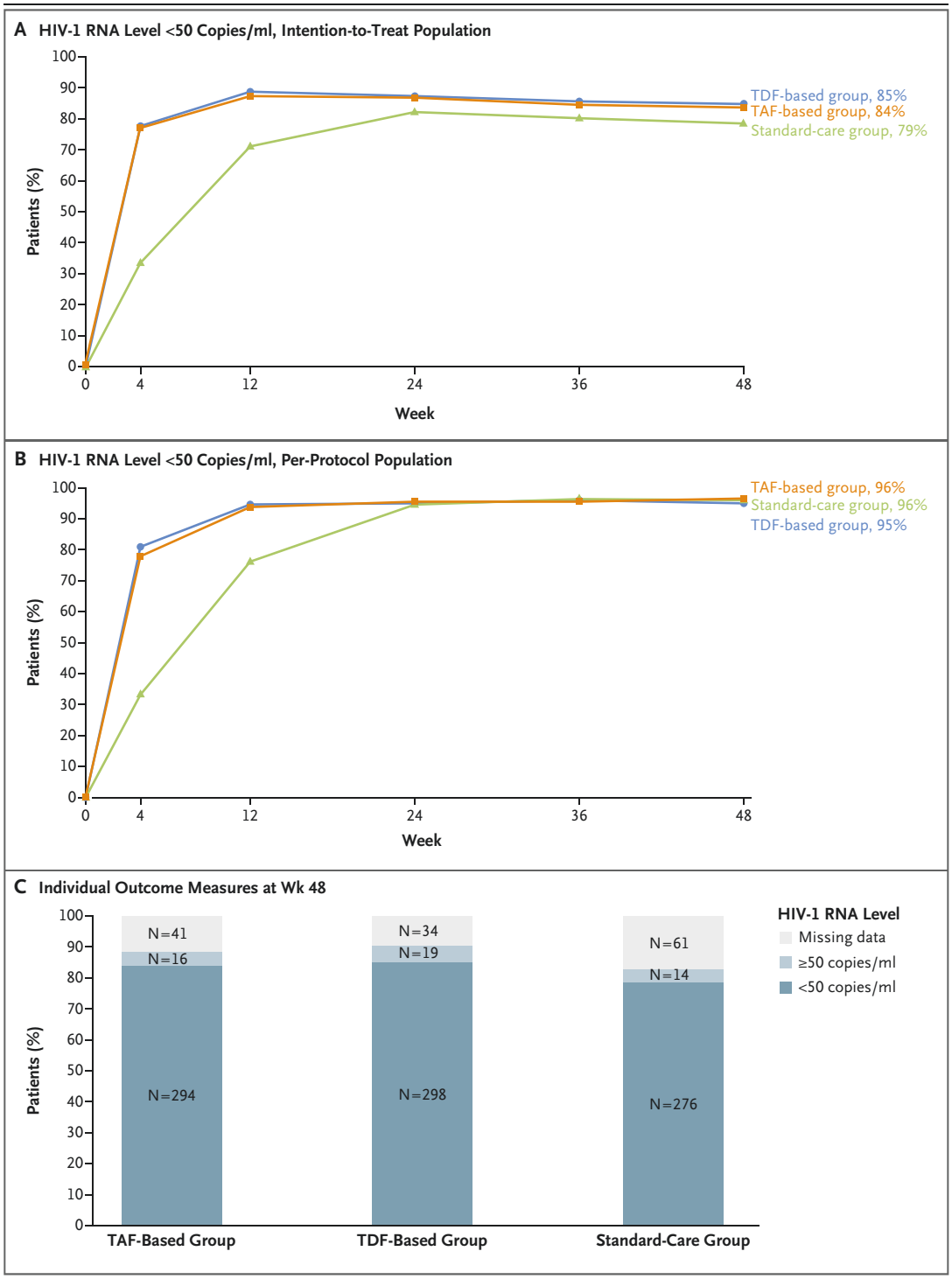
Table 1. Baseline Characteristics of the Patients.*

Characteristic	TAF-Based Group (N=351)	TDF-Based Group (N=351)	Standard-Care Group (N=351)
Female sex — no. (%)	214 (61)	208 (59)	201 (57)
Age — yr	33±7.8	32±8.1	32±7.4
Race — no. (%)†			
Black	349 (99)	351 (100)	351 (100)
Mixed race	2 (1)	0	0
Country of origin — no. (%)			
South Africa	213 (61)	223 (64)	219 (62)
Zimbabwe	116 (33)	108 (31)	115 (33)
Other	22 (6)	20 (6)	17 (5)
Body weight — kg			
Male patients	67.9±10.9	67.1±11.2	67.3±11.9
Female patients	68.8±14.8	69.5±16.2	70.2±16.5
Body-mass index			
Male patients	21.7±3.7	21.6±3.3	21.8±3.6
Female patients	25.6±5.0	26.1±6.1	26.1±6.2
Categories of body-mass index — no./total no. (%)			
<18.5: underweight	42/350 (12)	35/351 (10)	37/351 (11)
18.5 to <25: normal	177/350 (51)	190/351 (54)	193/351 (55)
25 to <30: overweight	96/350 (27)	78/351 (22)	77/351 (22)
≥30: obese	35/350 (10)	48/351 (14)	44/351 (13)
CD4 count — cells/mm^3	349±225.3	323±234.3	337±221.6
HIV-1 RNA level — no. (%)			
≤100,000 copies/ml	274 (78)	280 (80)	271 (77)
100,001–500,000 copies/ml	66 (19)	62 (18)	72 (21)
>500,000 copies/ml	11 (3)	9 (3)	8 (2)

* Plus–minus values are means ±SD. Patients were randomly assigned to receive tenofovir alafenamide fumarate (TAF)–emtricitabine (FTC)–dolutegravir (DTG) (TAF-based group), tenofovir disoproxil fumarate (TDF)–FTC–DTG (TDF-based group), or TDF–FTC–efavirenz (standard-care group). Percentages may not total 100 owing to rounding. HIV-1 denotes human immunodeficiency virus type 1.
† Race was reported by the patients.

Figure 1 (facing page). Efficacy Data According to Trial Visit and Individual Outcome Measures.
Panel A shows the percentage of patients with a human immunodeficiency virus type 1 (HIV-1) RNA level of less than 50 copies per milliliter according to trial visit. These values were calculated with the use of the Snapshot algorithm from the Food and Drug Administration (FDA) in the intention-to-treat population: 351 patients assigned to receive tenofovir alafenamide fumarate (TAF)–emtricitabine (FTC)–dolutegravir (DTG) (TAF-based group), 351 assigned to receive tenofovir disoproxil fumarate (TDF)–FTC–DTG (TDF-based group), and 351 assigned to receive TDF–FTC–efavirenz (standard-care group). Panel B shows the percentage of patients with an HIV-1 RNA level of less than 50 copies per milliliter according to trial visit in the per-protocol population (291 patients in the TAF-based group, 300 in the TDF-based group, and 278 in the standard-care group). Patients were excluded from the per-protocol analysis according to criteria from the statistical analysis plan, available with the protocol. Panel C shows the possible outcomes according to the Snapshot algorithm from the FDA at week 48 in the intention-to-treat population.

available at NEJM.org). Baseline characteristics were balanced across the groups (Table 1). The mean age was 32 years (range, 13 to 62); 14 patients were younger than 19 years of age. A total of 59% of the patients were female, more than 99% were black, and 62% were from South Africa. The mean CD4 count was 337 cells per cubic millimeter (range, 1 to 1721), and 78% of the



patients had a baseline HIV-1 RNA level of less than 100,000 copies per milliliter. By week 48, the number of patients who had discontinued treatment or who had missing data was 41 (12%) in the TAF-based group, 39 (11%) in the TDF-based group, and 55 (16%) in the standard-care group.

EFFICACY

In the primary efficacy analysis, the percentage of patients with an HIV-1 RNA level of less than 50 copies per milliliter was 84% in the TAF-based group, 85% in the TDF-based group, and 79% in the standard-care group (Fig. 1A). Both DTG-containing regimens showed noninferior efficacy to the standard-care regimen. There was no significant difference in efficacy between groups in the three pairwise comparisons, at the prespecified significance level of 0.017. With respect to the prevalence of HIV-1 RNA suppression at week 48, the difference between the TAF-based group and the standard-care group was 5.1 percentage points (98.3% confidence interval [CI], −1.9 to 12.2; P=0.08), the difference between the TDF-based group and the standard-care group was 6.3 percentage points (98.3% CI, −0.1 to 13.2; P=0.03), and the difference between the TAF-based group and the TDF-based group was −1.1 percentage points (98.3% CI, −7.7 to 5.4; P=0.68).

Differences in efficacy between the groups were driven by a higher number of discontinuations in the standard-care group than in the other two groups, with 61 patients classified as having missing data or having discontinued treatment, as compared with 41 in the TAF-based group and 34 in the TDF-based group (Fig. 1C, and Table S2 in the Supplementary Appendix). In the per-protocol analysis, the percentage of patients with an HIV-1 RNA level of less than 50 copies per milliliter was similar across the groups at week 48 (96% in the TAF-based group, 95% in the TDF-based group, and 96% in the standard-care group) (Fig. 1B). The time to viral suppression at an HIV-1 RNA level of less than 50 copies per milliliter was longer in the standard-care group than in the other two groups, but an HIV-1 RNA level of less than 1000 copies per milliliter at week 4 was achieved in 90% of the patients (as compared with 98% in the TAF-based group and 97% in the TDF-based group), with similar virologic control across the groups by 24 weeks at a level of less than 50 copies per milliliter.

After virologic failure, no resistance to integrase inhibitors was observed in patients receiving the DTG-containing regimens; four patients receiving EFV and one patient receiving DTG showed new resistance to nucleoside reverse-transcriptase inhibitors (NRTIs) or nonnucleoside reverse-transcriptase inhibitors (NNRTIs) during viremic episodes (Table S3 in the Supplementary Appendix). In multivariate logistic-regression analysis, the strongest predictors of viral suppression at week 48 were older age and employment (Fig. 2). Most patients with an HIV-1 RNA level of 50 copies or more per milliliter at week 48 showed resuppression at a level of less than 50 copies per milliliter in longer-term follow-up with no change in regimen, after interventions to improve adherence.

SAFETY

At 48 weeks, there was one death in the TAF-based group, one in the TDF-based group and two in the standard-care group (Table S4 in the Supplementary Appendix); none were judged by the investigator to be related to the trial medication. One patient in the TAF-based group discontinued the trial regimen owing to presumed DTG-related asymptomatic laboratory-measured increases in aminotransferase levels (Table 2). There were eight EFV-linked discontinuations for toxicity: five with liver dysfunction (two symptomatic), two with rash, and one with neuropsychiatric manifestations; two patients in the standard-care group had the trial regimen changed owing to renal side effects thought to be unrelated to EFV. The only major between-group difference in clinical and laboratory grade 3 or 4 events was a higher percentage of patients in the standard-care group having weight loss, dizziness, or an elevated level of γ-glutamyltransferase than in the other two groups (Table 2, and Table S6 in the Supplementary Appendix). (Weight gain was not reported as an adverse event.) There were minor between-group differences in alkaline phosphatase levels (higher in the standard-care group than in the other two groups) and creatinine clearance (lower in the TDF-based group than in the TAF-based group) (Table S9 in the Supplementary Appendix). There were 15 cases of tuberculosis (4 in the TAF-based group, 3 in the TDF-based group, and 8 in the standard-care group), 10 within 3 months after the initiation of ART, and 4 possible cases of

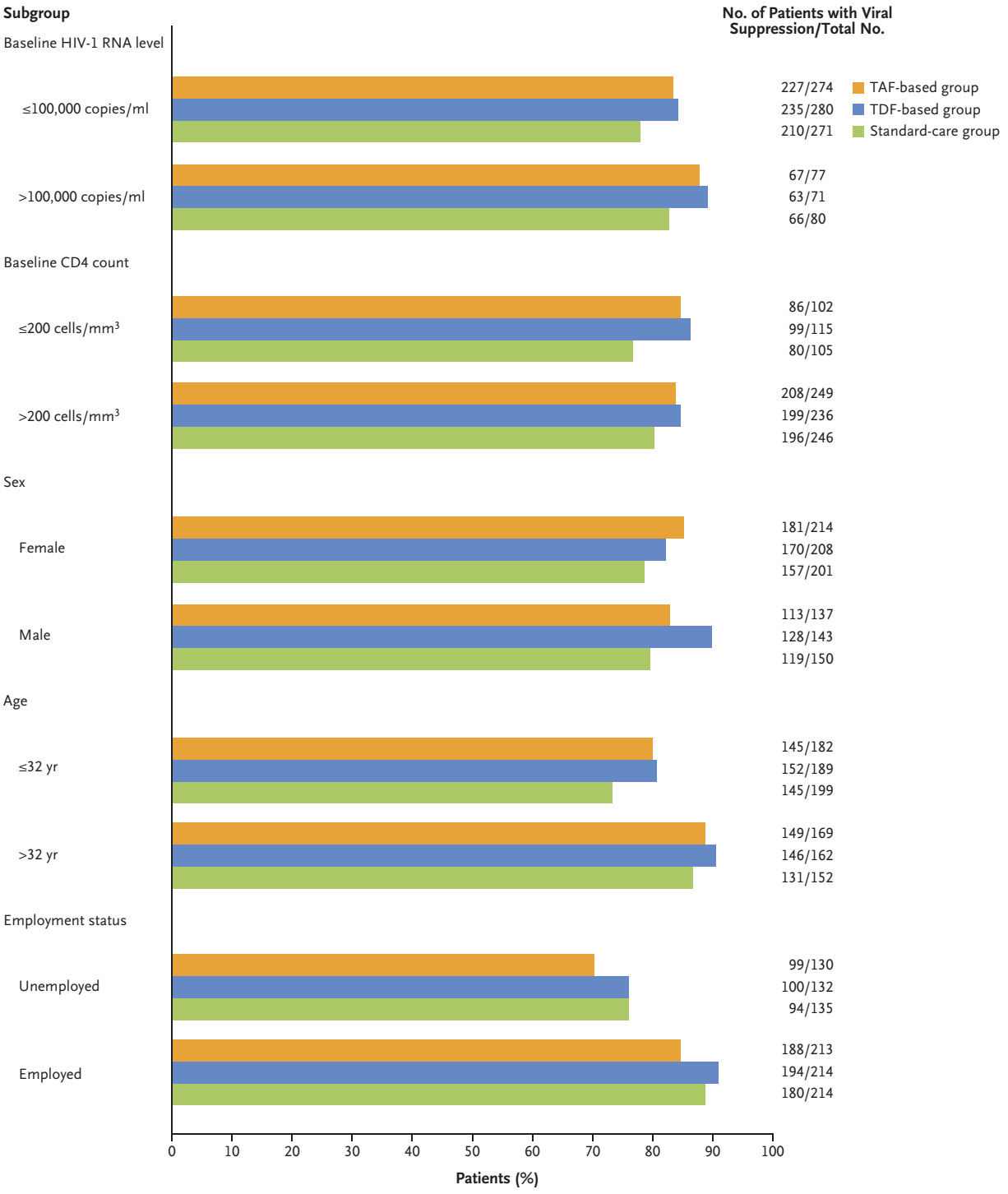


Figure 2. Subgroup Analysis.

Shown is the percentage of patients with an HIV-1 RNA level of less than 50 copies per milliliter at week 48, according to randomized treatment group and subgroup. In a multivariate analysis of response, younger age (≤32 years) and unemployment were significant predictors of treatment failure at week 48 ($P<0.01$ for both comparisons). Baseline HIV-1 RNA level, baseline CD4 count, and sex were not significant predictors of response in this analysis.

Table 2. Selected Adverse Events and Laboratory Abnormalities That Emerged during Treatment.*

Adverse Event	TAF-Based Group (N=351)	TDF-Based Group (N=351)	Standard-Care Group (N=351)
Adverse event leading to discontinuation of trial regimen — no. of patients†	1	0	10
Elevated liver enzymes	1	0	5
Neuropsychiatric disorders, including dizziness	0	0	1
Rash	0	0	2
Renal disorder	0	0	2
Adverse event of grade 2–4 — no. of patients	21	19	26
Hypertension‡	11	13	4
Dizziness	0	0	12
Neutropenia	4	4	9
Insomnia	6	2	1
Most common grade 3 or 4 laboratory abnormalities — no. of patients§	26	37	83
Elevated γ-glutamyltransferase	4	6	35
Elevated alanine aminotransferase	10	7	18
Elevated aspartate aminotransferase	6	6	14
Abnormal creatinine clearance	3	11	6
Low hemoglobin	3	7	10
DXA of bone			
New osteopenia — no./total no. (%)			
Whole body	4/279 (1)	6/295 (2)	2/262 (1)
Spine	37/203 (18)	50/220 (23)	45/202 (22)
Hip	15/227 (7)	38/234 (16)	40/225 (18)
New osteoporosis — no./total no. (%)			
Spine	9/200 (4)	15/213 (7)	15/196 (8)
Hip	3/223 (1)	2/229 (1)	10/216 (5)
DXA of body composition — kg¶			
Mean change in truncal fat			
Male patients	0.6	0.1	−0.4
Female patients	1.7	0.7	0.1
Mean change in truncal lean mass			
Male patients	1.8	1.2	0.7
Female patients	1.1	1.0	0.6
Mean change in limb fat			
Male patients	0.5	0.1	−0.4
Female patients	1.9	0.6	0.2
Mean change in limb lean mass			
Male patients	2.2	1.5	0.7
Female patients	1.8	1.2	0.7
New obesity — no./total no. (%)‖			
Male patients	8/113 (7)	4/127 (3)	4/116 (3)
Female patients	26/133 (20)	13/123 (11)	9/104 (9)

Table 2. (Continued.)

Adverse Event	TAF-Based Group (N=351)	TDF-Based Group (N=351)	Standard-Care Group (N=351)
New underweight — no./total no. (%)**			
Male patients	2/91 (2)	1/115 (1)	9/105 (9)
Female patients	1/149 (1)	1/144 (1)	0/125 (0)

* DXA denotes dual-energy x-ray absorptiometry.
† All discontinuations were for presumed DTG or efavirenz toxicity, except for two discontinuations due to renal disorders, both of which involved clinical conditions that resulted in discontinuation of TDF.
‡ Despite the higher number of patients reporting hypertension in the groups receiving the DTG-containing regimens than in the standard-care group, there were no substantial differences among the three groups with regard to systolic or diastolic blood pressure.
§ Shown are grade 3 or 4 laboratory abnormalities that occurred in at least 5% of the patients. Grading of laboratory abnormalities was done according to criteria of the Division of AIDS, National Institute of Allergy and Infectious Diseases.
¶ Shown is the mean change from baseline to week 48.
‖ New obesity was measured from baseline to week 48. All patients with paired data were included in the analysis, except for patients who were obese at baseline.
** New underweight was measured from baseline to week 48. All patients with paired data were included in the analysis, except for patients who were underweight at baseline and female patients who were pregnant.

immune reconstitution inflammatory syndrome (IRIS) that were not associated with tuberculosis.

At week 48, absolute weight gain and the percentage of patients in whom obesity emerged during treatment were highest in the TAF-based group (6 kg, 14% new obesity), but the values in the TDF-based group (3 kg, 7% new obesity) were also higher than those in the standard-care group (1 kg, 6% new obesity) (Table 2, and Fig. S3 in the Supplementary Appendix). Weight gain was significantly higher in female patients than in male patients across all three groups, with no clear plateau in the increase (Fig. 3). The percentage of patients in whom underweight emerged during treatment was higher in the standard-care group (4%) than in the other two groups (1% in each group) (Table 2). There were increases in DXA-assessed lean and fat mass in the limbs and trunk, with significant differences according to treatment group and sex (Table 2, and Fig. S2 in the Supplementary Appendix). Regression analysis showed that obesity that emerged during treatment at week 48 was associated with a lower CD4 count, a higher viral load, and older age. There was no substantial between-group difference in mean systolic or diastolic blood pressure, and there were small differences in lipid and glucose levels (Table S9 in the Supplementary Appendix).

The TDF-containing regimens had a greater effect on lumbar and hip DXA-assessed bone density and renal tubular markers than the TAF-based regimen (Table 2, and Table S10 in the Supplementary Appendix). Changes in creatinine clearance were minor. There were three fractures, all associated with major trauma.

Sleep questionnaires showed that sleep quantity and quality changed little over time, with no significant difference according to group. There were slightly more reported cases of grade 3 or 4 insomnia in the TAF-based group than in the other groups but no discontinuations of the trial regimen due to insomnia (Table 2, and Tables S12 and S13 in the Supplementary Appendix).

Current known pregnancy outcomes, including beyond 48 weeks, are provided in Table S11 in the Supplementary Appendix. There were 78 pregnancies, two thirds (50 of 78) in female patients receiving DTG-containing regimens. There were 34 live births (44%), 15 spontaneous abortions (19%), and 19 elective terminations (24%); 8 pregnancies (10%) are ongoing with no neural-tube defects identified. There was 1 neonatal death (1%) and 1 stillbirth (1.3%) in the TAF-based group and standard-care group, respectively. Four female patients who became pregnant and presented before 8 weeks elected to move from DTG to EFV, after counseling and revised informed-consent procedures over concern about neural-tube defects. (Detailed safety data are provided in Tables S4 through S13 in the Supplementary Appendix.)

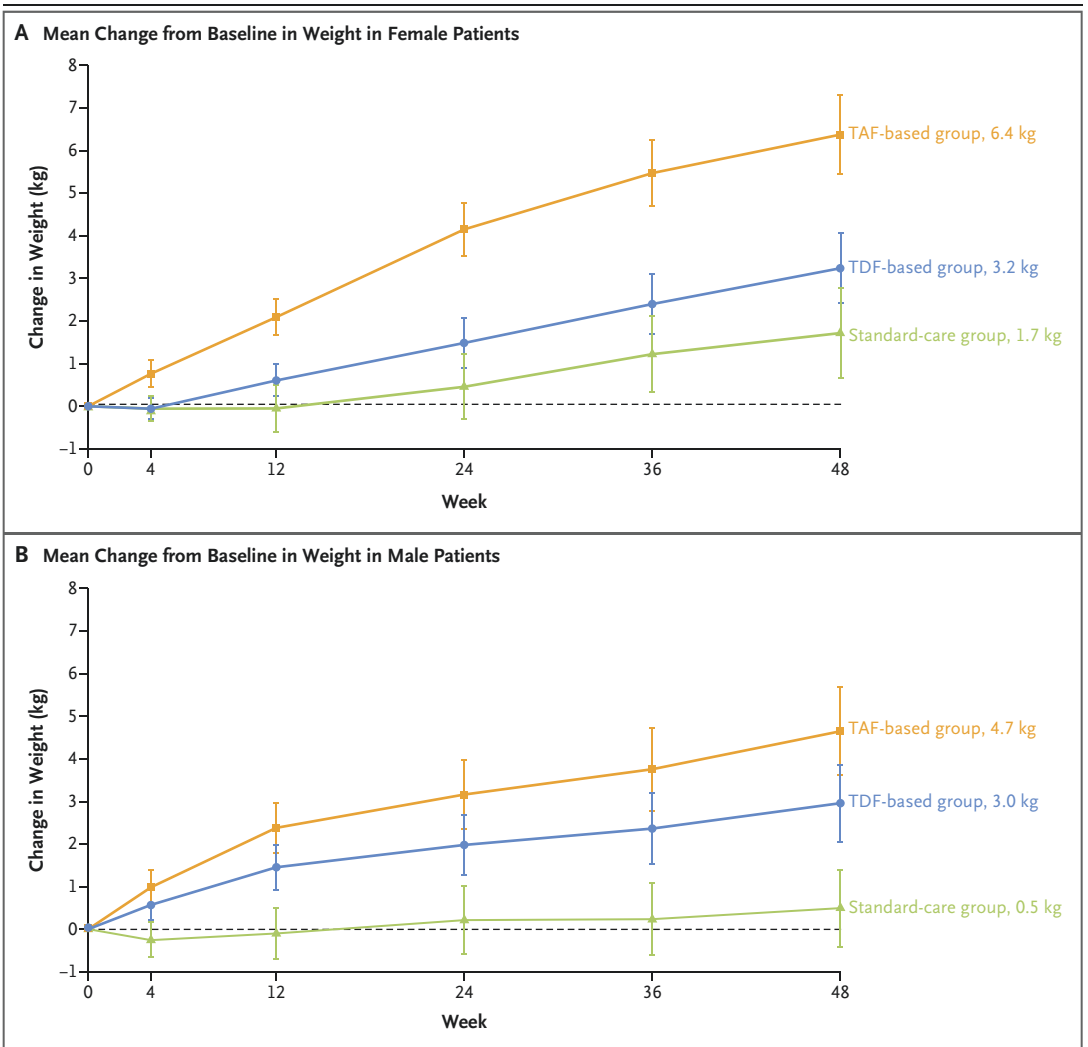


Figure 3. Change in Body Weight over Time.

Shown is the mean change from baseline in weight in female patients (excluding those who were pregnant) (Panel A) and in male patients (Panel B).

DISCUSSION

In the ADVANCE trial, treatment with DTG combined with either of two tenofovir prodrugs (TAF and TDF) was noninferior to the standard-of-care regimen with respect to the percentage of patients with HIV-1 RNA suppression at week 48. The standard-care group had more discontinuations because of adverse events and a higher incidence of loss to follow-up than the other two groups. There was significantly more weight gain with the DTG-containing regimens, especially in combination with TAF, than with the standard-care regimen.

All three regimens had virologic efficacy, similar to the results of other large, randomized trials comparing DTG and EFV, but without baseline drug-resistance testing to guide this choice.[10,23] There was similar efficacy for the TAF-based regimen and the TDF-based regimen, findings that are consistent with the results of previous studies comparing the two combination regimens.[16,17] In the per-protocol analysis, the percentage of patients with viral suppression at an HIV-1 RNA level of less than 50 copies per milliliter was similar in the three treatment groups after week 24 (Fig. 1B). Despite no baseline resistance testing and high reported back-

ground NNRTI resistance in this trial population, 90% of the patients in the standard-care group had viral suppression at an HIV-1 RNA level of less than 1000 copies per milliliter at the week 4 visit; a threshold of 1000 copies per milliliter is commonly used to assess transmission risk and, in many programs in low- and middle-income countries, to choose a treatment regimen. Interventions to improve adherence led to resuppression in most cases of viremia.[24,25] The WHO currently recommends DTG in place of EFV for first-line initiation of ART in countries such as South Africa with background EFV resistance of more than 10%.[8,25,26] EFV-based therapy may be more effective than is generally thought, if coupled with effective counseling regarding adherence, even in the presence of increasing NNRTI resistance.[27]

Weight gain has emerged as a major concern with respect to the integrase inhibitor class in the past year, which has resulted in a postmarketing change to package inserts, with some concern relating to ethnic group, sex, and CD4 count at initiation.[28-31] In our trial, weight gain was associated with DTG, was less severe with TDF, and was significantly more severe in female patients and patients with lower CD4 counts and higher viral loads. Thus, such weight gain is unlikely to be simply a "return to health" effect, because viral suppression, CD4 recovery, and clinical events were similar across the groups. The weight gain in our trial among black male patients receiving the TAF-based regimen was similar to that seen in predominantly white men in registration studies comparing DTG with bictegravir.[17,29,32] It is worrying that weight gain includes increases in truncal fat, which has been associated with known cardiovascular outcomes in other studies.[33-35] Use of TDF has been associated with smaller increases in weight than TAF or other NRTI combinations[29]; however, it is unclear whether TAF amplifies or TDF mitigates the weight-gain effect of DTG.

TDF was associated with a small but significant decrease in bone mineral density, reduced creatinine clearance, and more effect on tubular markers than TAF. DTG was associated with a small decrease in creatinine clearance, presumably due to its effect on tubular secretion. Neuropsychiatric and sleep-related side effects have been a recurring concern with both DTG and EFV.[2,4,36,37] It is reassuring that there was a very small number of neuropsychiatric-linked discontinuations of EFV that justified stopping randomized treatment (and none in the groups that received DTG-containing regimens) and that there was no effect on sleep across the groups.

In our trial, no safety issues were reported in female patients who were pregnant or in their infants, but numbers are too small to draw meaningful conclusions. The VESTED trial involving HIV-1–infected pregnant women and their infants (ClinicalTrials.gov number, NCT03048422) includes the same randomized treatment regimens as the ADVANCE trial.

A low incidence of tuberculosis was presumably due to the use of isoniazid preventive therapy. Drug interactions between TAF and rifampin and between DTG and rifampin are an ongoing concern; current recommendations with respect to adjusting the dose of DTG during receipt of tuberculosis treatment add considerable supply-line complexities in low- and middle-income countries.[7] The administration of TAF with rifampin is still being studied. IRIS was uncommon, and previous concern about an association between integrase inhibitors and an increased risk of IRIS[37,38] was not confirmed.

Limitations of the trial include the open-label design and lack of standardized pill quantity per group. The trial was conducted in inner-city Johannesburg, with patients from across the region (almost 40% of patients were from outside South Africa, since Johannesburg is a major hub for economic migrants from both within and outside South Africa) and recruited from routine patient care, factors that strengthen generalizability. We were unable to recruit adequate numbers of adolescents to analyze separately and thus were unable to specifically study outcomes in this important group.

The concern around the potential teratogenicity of DTG and a dearth of pregnancy safety data with TAF pose complex challenges for practitioners in low- and middle-income countries that rely on health systems with limited options, especially for women. The increased risk of weight gain with both DTG-containing regimens and the limited knowledge base regarding TAF in pregnancy need to be evaluated against improvements in side-effect profile and adherence, slight reductions in time to virologic control, and effect on bone mineral density and renal function.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

Presented in part at the 10th International AIDS Society Conference on HIV Science, Mexico City, July 21–24, 2019.

Supported by the U.S. Agency for International Development, Unitaid, and the South African Medical Research Council. Investigational drugs were donated by Gilead Sciences and ViiV Healthcare.

Dr. Venter reports receiving lecture fees and travel support from Roche, grant support, advisory board fees, and provision of drugs from Gilead Sciences, advisory board fees from ViiV Healthcare, lecture fees from Merck and Adcock Ingram, and lecture fees and advisory board fees from Johnson & Johnson and Mylan; Dr. Moorhouse, receiving honoraria and conference attendance support from Johnson & Johnson, Cipla, and ViiV Healthcare, honoraria, advisory board fees, and conference attendance sponsorship from Gilead Sciences, advisory board fees from AbbVie, and conference attendance sponsorship from Merck; and Dr. Abrams, receiving advisory committee fees from ViiV Healthcare. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the trial participants, the staff of the South African Department of Health, the trial staff members, and the members of the oversight committees, to which many senior professionals donated their time.

APPENDIX

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