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Initial HIV Therapy for Adults and Treatment-Associated Weight Gain
The Opti-DOR Randomized Clinical Trial

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IMPORTANCE Antiretroviral therapy (ART), particularly regimens containing tenofovir alafenamide with dolutegravir or bictegravir, is associated with substantial weight gain, potentially exacerbating cardiometabolic risk in people with HIV.

OBJECTIVE To determine whether a regimen with doravirine, lamivudine, and tenofovir disoproxil fumarate results in less weight gain than a regimen with dolutegravir, emtricitabine, and tenofovir alafenamide while maintaining noninferior viral suppression.

DESIGN, SETTING, AND PARTICIPANTS Open-label, noninferiority randomized clinical trial including ART-naive adults (≥18 years of age) with an HIV RNA level greater than 500 copies/mL and no detectable baseline, high-level doravirine resistance. The study was conducted at 2 South African sites and individuals were recruited between October 2023 and March 2025. The final participant visit occurred in February 2026.

INTERVENTIONS A once-daily regimen with 100 mg of doravirine, 300 mg of lamivudine, and 300 mg of tenofovir disoproxil fumarate (n = 299) or 50 mg of dolutegravir, 200 mg of emtricitabine, and 25 mg of tenofovir alafenamide (n = 301).

MAIN OUTCOMES AND MEASURES The primary outcome was viral suppression (HIV RNA level <50 copies/mL) at week 48 (prespecified noninferiority margin of −10 percentage points). The key secondary outcomes included changes in body weight, treatment-associated effects on body composition, and safety and adverse events.

RESULTS Among 600 participants, 597 (99.5%) were Black African, 413 (68.8%) were assigned female at birth, and the median age was 34 years (IQR, 28-41). At week 48, 266 participants (89.0%) in the doravirine, lamivudine, and tenofovir disoproxil fumarate group achieved viral suppression (HIV RNA level <50 copies/mL) vs 273 participants (90.7%) in the dolutegravir, emtricitabine, and tenofovir alafenamide group (between-group difference, −1.7 percentage points [95% CI, −6.6 to 3.1], meeting the prespecified noninferiority margin of −10 percentage points). The median weight gain was 3.0 kg in the doravirine, lamivudine, and tenofovir disoproxil fumarate group vs 5.0 kg in the dolutegravir, emtricitabine, and tenofovir alafenamide group (between-group difference, −2.0 kg [95% CI, −3.0 to −1.0 kg]; $P < .001$). Among participants in the doravirine, lamivudine, and tenofovir disoproxil fumarate group, the median change in hip bone mineral density (BMD) was −2.1% (IQR, −4.1% to −0.5%) and was −3.2% (IQR, −5.4% to −0.8%) for spine BMD vs −0.5% (IQR, −1.9% to 1.2%) for hip BMD and −1.3% (IQR, −3.2% to 0.8%) for spine BMD with dolutegravir, emtricitabine, and tenofovir alafenamide ($P < .001$ for each between-group comparison). Resistance to doravirine emerged among 7 of 9 participants experiencing virologic failure in the doravirine, lamivudine, and tenofovir disoproxil fumarate group. Of these 7 participants, 5 of 6 achieved viral suppression after switching to dolutegravir-based therapy and 1 was lost to follow-up. Serious adverse events and deaths (n = 2) were infrequent and not considered treatment-related.

CONCLUSIONS AND RELEVANCE Among predominantly Black African adults initiating ART, a regimen with doravirine, lamivudine, and tenofovir disoproxil fumarate was noninferior to a regimen with dolutegravir, emtricitabine, and tenofovir alafenamide for 48-week viral suppression and was associated with less weight gain.

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Second-generation integrase strand transfer inhibitor (InSTI)-based regimens, particularly dolutegravir and bictegravir, are the global standard for first-line HIV treatment because of their high potency, tolerability, and high barrier to treatment resistance.[1-5] In low- and middle-income countries, more than 23 million people receive dolutegravir-containing regimens, largely as tenofovir disoproxil fumarate-based fixed-dose combinations, whereas bictegravir, emtricitabine, and tenofovir alafenamide is now the predominant regimen in high-income countries.[2,3,6] However, data from randomized clinical trials, observational cohorts, and meta-analyses show that InSTI-based regimens, particularly when combined with tenofovir alafenamide, are associated with substantial weight gain that is most pronounced during the first 1 to 2 years of treatment that disproportionately affects women, Black populations, and people with advanced HIV disease.[7-10]

Weight gain associated with InSTI-based regimens including tenofovir alafenamide has been linked to diabetes, hypertension, and elevated cardiovascular risk.[7,11-16] Critically, once established, this weight gain appears largely irreversible. Studies of therapy switches to protease inhibitor-based or doravirine-based regimens have not demonstrated meaningful weight loss, indicating prevention of weight gain after initiation of antiretroviral therapy (ART) may be more achievable than weight loss later in treatment.[17-19] To our knowledge, no head-to-head randomized clinical trial has evaluated regimen selection specifically to mitigate treatment-associated weight gain after initiation of ART.[20]

Doravirine is a second-generation nonnucleoside reverse transcriptase inhibitor (NNRTI). Use of doravirine as a single agent or in a fixed-dose combination (regimen with doravirine, lamivudine, and tenofovir disoproxil fumarate) has demonstrated robust virologic efficacy and favorable lipid and metabolic profiles in registration trials.[21] Across comparative ART studies, regimens without an InSTI and tenofovir alafenamide, including doravirine-based combinations, have generally been associated with less weight gain. African surveillance data show low baseline doravirine resistance despite high background first-generation NNRTI resistance.[7,22,23]

The replacement of tenofovir disoproxil fumarate by tenofovir alafenamide was driven by improvements in markers of kidney function and bone density demonstrated in randomized clinical trials, supporting guideline recommendations across high-income settings and, increasingly, low-income settings, advantages most relevant in individuals with preexisting risk of chronic kidney disease or low bone density; these clinical benefits have not been demonstrated in general ART-naive populations.[24] However, tenofovir alafenamide is associated with greater weight gain and less favorable lipid profiles than tenofovir disoproxil fumarate, which are differences that are often amplified when combined with an InSTI.[25]

The current trial was designed to determine whether a regimen with doravirine, lamivudine, and tenofovir disoproxil fumarate is noninferior to a regimen with dolutegravir, emtricitabine, and tenofovir alafenamide for virologic suppression while attenuating treatment-associated weight gain and improving metabolic profiles in adults with HIV at risk of weight gain. The prespecified 48-week virologic, weight, and metabolic outcomes are reported here.

Key Points

Question Among adults with HIV at risk of treatment-associated weight gain, does an alternative first-line regimen produce less weight gain than treatment combinations containing an integrase strand transfer inhibitor (eg, dolutegravir or bictegravir) along with tenofovir alafenamide?

Findings In this noninferiority randomized clinical trial including 600 adults with HIV, initiating a regimen with doravirine, lamivudine, and tenofovir disoproxil fumarate was noninferior to a regimen with dolutegravir, emtricitabine, and tenofovir alafenamide for viral suppression (HIV RNA level <50 copies/mL) at 48 weeks (89.0% vs 90.7%, respectively, meeting the prespecified noninferiority margin of −10 percentage points), and was associated with less weight gain.

Meaning Among adults initiating antiretroviral therapy, a regimen with doravirine, lamivudine, and tenofovir disoproxil fumarate was noninferior to a regimen with dolutegravir, emtricitabine, and tenofovir alafenamide for viral suppression at 48 weeks and was associated with less weight gain.

Methods

Study Design

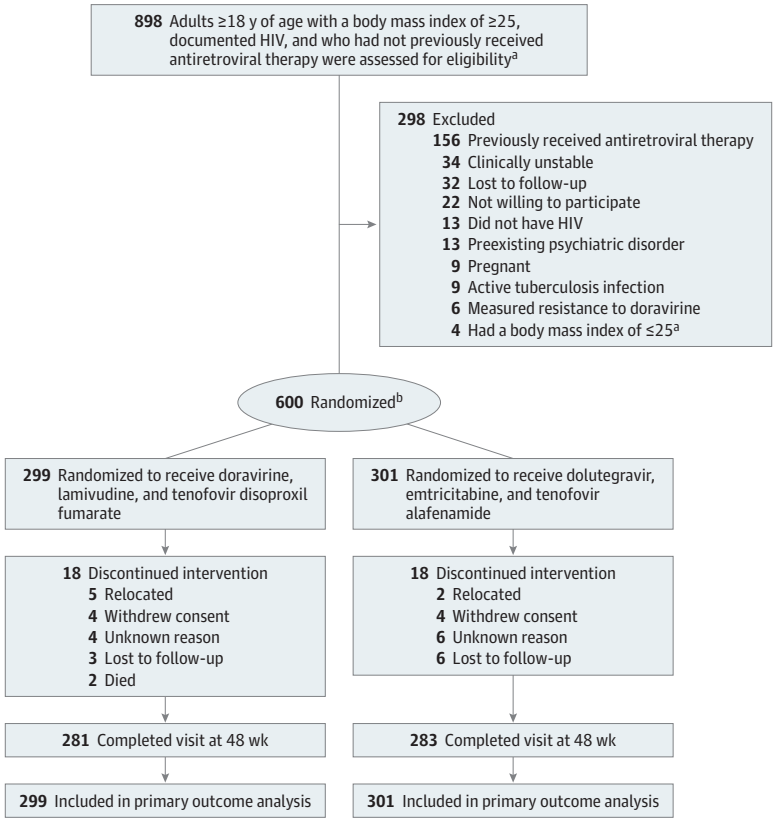
The investigator-initiated, open-label, noninferiority, Opti-DOR randomized clinical trial compares once-daily doravirine, lamivudine, and tenofovir disoproxil fumarate with once-daily dolutegravir, emtricitabine, and tenofovir alafenamide as initial ART for adults with HIV. The trial was conducted at the Ezintsha Research Centre in Johannesburg, South Africa (urban site), and at the Africa Health Research Institute in Somkhele, South Africa (rural site), and included 96 weeks of planned follow-up and a prespecified primary outcome analysis at week 48.

The trial protocol (appears in Supplement 1) was approved by the human research ethics committee of the University of the Witwatersrand. All participants provided written informed consent. This randomized clinical trial was conducted in accordance with the Declaration of Helsinki[26] and the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Participants

Participants were identified at surrounding HIV testing sites. Eligible participants were adults (≥18 years of age) with documented HIV infection, without prior exposure to ART, who had a screening HIV RNA level greater than 500 copies/mL, and who had no detectable resistance to doravirine (Stanford University HIV drug resistance score ≥60). Key exclusion criteria included active tuberculosis, estimated creatinine clearance less than 60 mL/min/1.73 m^2, clinically significant liver disease, use of contraindicated concomitant medications, and being pregnant or breastfeeding. Women of childbearing potential

Figure 1. Flow Diagram Depicting the Inclusion, Exclusion, and Randomization Process of the Trial



[a]Body mass index calculated as weight in kilograms divided by height in meters squared.

[b]Randomization was stratified by site. Allocation was concealed until completion of baseline assessments.

were required to use highly effective contraception throughout the trial.

Race was self-reported by participants using fixed categories to assess the representativeness and generalizability of the trial findings in a South African context. Race also has had a correlation with weight gain in prior HIV clinical trials. The initial body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) threshold (≥25) was removed by protocol amendment in August 2024 after 326 participants were enrolled. At that point, the weight end points were sufficiently powered; therefore, the threshold was relaxed to reflect the full BMI distribution of adults presenting for ART initiation in South Africa.

Randomization and Masking

Participants were randomly assigned 1:1 using a centralized computer-generated schedule stratified by site, with allocation concealed until completion of the baseline assessments (**Figure 1**). The randomization process used randomly varying permuted block sizes of 2, 4, 6, and 8 to maintain allocation concealment while preserving treatment balance within each site. This was an open-label trial.

Interventions

Each ART regimen was taken orally once daily. Participants received (1) 100 mg of doravirine, 300 mg of lamivudine, and 300 mg of tenofovir disoproxil fumarate (Delstrigo; Merck Sharp & Dohme) or (2) 50 mg of dolutegravir, 200 mg of emtricitabine, and 25 mg of tenofovir alafenamide (Viatris). At each visit, treatment adherence and use of concomitant medications were assessed and lifestyle counseling was provided. The management of regimen changes followed protocol-specified algorithms (additional information appears in Supplement 1).

Procedures and Assessments

At enrollment and prespecified follow-up visits through week 48, participants underwent standardized anthropometric measurements, whole-body dual-energy x-ray absorptiometry scanning at baseline and week 48, and fasting laboratory assessment of lipids, glycemic markers, kidney and liver function, CD4 cell count, and HIV RNA level. The full visit schedules, assay methods, and patient-reported outcome instruments appear in Supplement 1.

Virologic Management Algorithm

Virologic failure was defined as 2 consecutive HIV RNA level measurements that were 1000 copies/mL or greater from week 24 onward or 2 consecutive HIV RNA level measurements that were 200 copies/mL or greater at week 48. Participants with confirmed virologic failure underwent genotypic resistance testing. Doravirine resistance was assessed using Stanford University HIV drug resistance scoring and prespecified doravirine-associated variations.[5,27] The participants with

significant doravirine resistance were switched to the dolutegravir-based regimen. Participants without detectable doravirine resistance received intensified adherence support. The full management algorithms appear in Supplement 1.

Pregnancy

Women of childbearing potential underwent pregnancy testing at each follow-up visit and were counseled to avoid pregnancy, with contraception offered per local guidelines. Participants who chose to continue pregnancy were followed up per the protocol-specified maternal and infant assessments. Pregnant participants receiving the doravirine-containing regimen were offered a switch to the dolutegravir-containing regimen due to limited data on safety for doravirine during pregnancy.

Outcomes

The primary outcome was the proportion of participants with viral suppression (HIV RNA level <50 copies/mL) at week 48 by randomization group using a modified US Food and Drug Administration (FDA) snapshot approach that counted missing data as treatment failures and applied a noninferiority margin of −10 percentage points.[28] The secondary virologic outcomes included viral suppression at baseline (HIV RNA level <50 copies/mL) and at week 48 (<200 copies/mL at week 48), time to virologic failure, and emergent treatment resistance.

Other prespecified secondary outcomes were mean change from baseline to week 48 in CD4 cell count, body weight, body composition, hematologic measures, fasting lipid and glycemic measures, and kidney and liver function. Prespecified safety outcomes included adverse events, serious adverse events, grade 3 or 4 laboratory abnormalities, treatment discontinuations due to adverse events, and deaths. The post hoc outcomes were the proportions of participants with greater than 5% or 10% weight gain; weight loss; incidence of new-onset diabetes, hypertension, obesity, or the metabolic syndrome; laboratory parameters of special interest; and adverse events of clinical interest.

Statistical Analysis

Assuming a 90% rate of virologic suppression in each group at week 48 and a noninferiority margin of −10 percentage points, a sample of 600 participants (300 per group) provided 90% or greater power at a 1-sided α level of .025, allowing for a rate of 10% or less for lost to follow-up. The percentage-point margin of −10 was selected because it is within the 10% to 12% noninferiority margin recommended in FDA guidance for treatment-naive HIV trials (considered clinically acceptable because it preserves a substantial proportion of the established treatment effect of active ART).[28]

The primary outcome (the proportion with viral suppression [HIV RNA level <50 copies/mL] at week 48) was analyzed in the randomized population using the modified FDA snapshot algorithm, which classifies all participants without a valid measurement of HIV RNA level at week 48 (whether due to missing data, early discontinuation, or treatment change) as having virologic failure.[28] This approach is often used in regulatory submissions for approval of ART and helps prevent differential dropout from artificially inflating response rates in either group. Between-group differences and 95% CIs were estimated using the unstratified Miettinen-Nurminen method. The per-protocol analyses were prespecified as sensitivity analyses.

Multivariable logistic regression for virologic suppression included treatment group, age, sex assigned at birth, study site, baseline BMI category, baseline CD4 cell count category, and baseline HIV RNA level as covariates. Multivariable linear regression for weight change included treatment group, baseline weight, sex assigned at birth, study site, baseline visceral adipose tissue area, baseline total lean mass, baseline CD4 cell count, and baseline HIV RNA level as covariates (full model outputs appear in eTables 1-2 in Supplement 2).

Weight and most other continuous measures were not normally distributed with influential outliers at week 48, so the original mixed-effects models for repeated measures could not be used. These outcome measures were summarized as medians with IQRs and compared using the Wilcoxon rank sum test. These comparisons were not prespecified; thus, they are exploratory. No adjustment for multiple testing was applied. Binary secondary outcomes were compared using absolute risk differences with 95% CIs (Miettinen-Nurminen method). Time-to-event outcomes were analyzed using Kaplan-Meier methods with log-rank tests.

Type I error was controlled at a 1-sided α level of .025 for the primary outcome and, separately, for the superiority analysis of weight gain via a prespecified, hierarchically gated testing strategy (Section 9.8 in Supplement 1). No correction was applied across these 2 independent analytic domains, which is consistent with standard practice for multidomain trials. Prespecified subgroup analyses evaluated virologic and weight outcomes by sex assigned at birth, baseline BMI category, baseline CD4 cell count category, and baseline HIV RNA level. All analyses were conducted using Stata version 18 (StataCorp). Further information on the statistical methods used can be found in the trial protocol (Supplement 1).

Results

Between October 2023 and March 2025, 898 individuals were assessed for eligibility. Among screened participants with resistance testing (n = 717), 159 (22.2%) had NNRTI resistance variations (Stanford University HIV drug resistance score ≥30), most commonly K103N. High-level resistance to doravirine was rare (0.8%) and these 6 individuals were not enrolled in the trial (Figure 1). Of the 737 HIV subtype results, 733 (99.5%) were clade C and there was a single case each of clade A1, A2, G, and J. Of the 600 participants randomized (299 in the doravirine, lamivudine, and tenofovir disoproxil fumarate group vs 301 in the dolutegravir, emtricitabine, and tenofovir alafenamide group), 564 (94.0%) completed the week 48 visit (Figure 1). The final participant visit occurred in February 2026.

Baseline Characteristics

The baseline characteristics were well balanced (**Table 1**). Of the 600 participants, 597 (99.5%) were Black African, 413

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	Doravirine, lamivudine, and tenofovir disoproxil fumarate (n = 299)	Dolutegravir, emtricitabine, and tenofovir alafenamide (n = 301)
Age, median (IQR), y	34 (28-40)	34 (28-41)
Age group, No. (%), y		
18-29	97 (32.4)	93 (30.9)
30-39	120 (40.1)	115 (38.2)
40-49	57 (19.1)	68 (22.6)
≥50	25 (8.4)	25 (8.3)
Sex assigned at birth, No. (%)		
Female	207 (69.2)	206 (68.4)
Male	92 (30.8)	95 (31.6)
Race, No. (%)[a]		
Black African	297 (99.3)	300 (99.7)
Other[b]	2 (0.7)	1 (0.3)
Country of birth was South Africa, No. (%)	242 (80.9)	226 (75.1)
Study site, No. (%)		
Johannesburg (urban)	211 (70.6)	211 (70.1)
Somkhele (rural)	88 (29.4)	90 (29.9)
Plasma HIV RNA level, median (IQR), $\log_{10}$ copies/mL	4.3 (3.7-4.8)	4.4 (3.9-4.8)
HIV RNA level >100 000 copies/mL, No. (%)	52 (17.4)	57 (18.9)
CD4 cell count, median (IQR), cells/μL	322 (177-486)	324 (199-523)
CD4 cell count, No. (%), cells/μL		
<200	88 (29.4)	76 (25.2)
200-350	79 (26.4)	81 (26.9)
>350	132 (44.2)	144 (47.8)
Preexisting conditions, No. (%)		
Type 2 diabetes	3 (1.0)	8 (2.7)
Hypertension	29 (9.7)	40 (13.3)
Body mass index, No. (%)[c]		
Underweight (<18.5)	4 (1.3)	7 (2.3)
Normal weight (18.5-24.9)	62 (20.8)	67 (22.3)
Overweight (25.0-29.9)	131 (43.8)	125 (41.5)
Class 1 obesity (30.0-34.9)	61 (20.4)	60 (19.9)
Class 2 or 3 obesity (≥35.0)	41 (13.7)	42 (14.0)

[a] Self-reported by participants using fixed categories.

[b] Included "Colored," which is a term used for a South African population group.

[c] Calculated as weight in kilograms divided by height in meters squared.

(68.8%) were assigned female at birth, and the median age was 34 years (IQR, 28-41 years). The median body weight was 74.9 kg (IQR, 66.1-85.0 kg), the median BMI was 27.7 (IQR, 25.1-31.7), and 34.0% of participants had a BMI of 30 or greater (obesity). The median CD4 cell count was 324 cells/μL (IQR, 191-505 cells/μL) and 27.3% of participants had a CD4 cell count less than 200 cells/μL. In the doravirine, lamivudine, and tenofovir disoproxil fumarate group, the median HIV RNA level was 4.3 $\log_{10}$ copies/mL (IQR, 3.7-4.8 $\log_{10}$ copies/mL) compared with 4.4 $\log_{10}$ copies/mL (IQR, 3.9-4.8 $\log_{10}$ copies/mL) in the dolutegravir, emtricitabine, and tenofovir alafenamide group. There were 109 participants (18.2%) who had an HIV RNA level greater than 100 000 copies/mL.

Virologic Failure and Treatment Resistance

At week 48, 266 participants (89.0%) in the doravirine, lamivudine, and tenofovir disoproxil fumarate group achieved viral suppression (HIV RNA level <50 copies/mL) vs 273 participants (90.7%) in the dolutegravir, emtricitabine, and tenofovir alafenamide group (between-group difference, −1.7 percentage points [95% CI, −6.6 to 3.1 percentage points]), meeting the prespecified noninferiority margin of −10 percentage points (**Table 2** and **Figure 2**). In the multivariable analysis, older participants were significantly more likely to demonstrate viral suppression (adjusted odds ratio per 10-year increase was 1.58 (95% CI, 1.12 to 2.24). From baseline to week 48, the CD4 cell count increased by a mean of 180 cells/μL in the doravirine, lamivudine, and tenofovir disoproxil fumarate group vs 185 cells/μL in the dolutegravir, emtricitabine, and tenofovir alafenamide group (between-group difference, −4.8 [95% CI, −31.3 to 21.7]; P = .72).

Protocol-defined virologic failure occurred in 9 participants receiving doravirine, lamivudine, and tenofovir disoproxil fumarate and in 6 participants receiving dolutegravir,

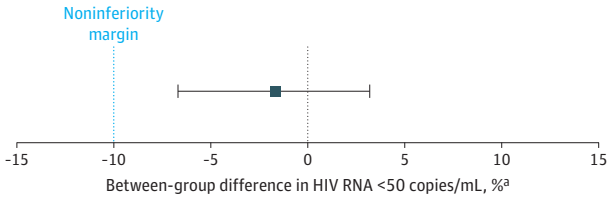
Table 2. Primary and Secondary Outcomes Through Week 48

	No. (%)[a]		
	Doravirine, lamivudine, and tenofovir disoproxil fumarate (n = 299)	Dolutegravir, emtricitabine, and tenofovir alafenamide (n = 301)	Between-group difference (95% CI), percentage points[a]
Primary outcome at 48 wk			
Viral suppression (HIV RNA level <50 copies/mL)	266 (89.0)	273 (90.7)	−1.7 (−6.6 to 3.1)[b]
Secondary outcomes at 48 wk[a]			
Viral suppression (HIV RNA level <200 copies/mL)	270 (90.3)	276 (91.7)	−1.3 (−5.8 to 3.2)
Confirmed viremia			
HIV RNA level >1000 copies/mL at 24 wk	8 (2.7)	4 (1.3)	
HIV RNA level >200 copies/mL	3 (1.0)	2 (0.7)	
Protocol-defined virologic failure	9 (3.0)	6 (2.0)	
Time to virologic failure, median (IQR), wk	24.9 (24.0 to 36.1)	25.1 (25.0 to 45.0)	
Switched to alternative regimen	6 (66.7) [n = 9]	0	
Achieved virologic suppression after regimen switch	5 (83.3) [n = 6]	0	
Virologic failure with viremia continuing at 48 wk	2 (22.2) [n = 9]	2 (33.3) [n = 6]	
Immunologic response (change in CD4 cell count), mean (SD), cells/μL	180 (143.2) [n = 280]	185 (177.1) [n = 283]	−4.8 (−31.3 to 21.7)

[a] Unless otherwise indicated.

[b] Noninferiority was established because the lower bound (−6.6 percentage points) exceeded the prespecified noninferiority margin of −10 percentage points (per guidance from the US Food and Drug Administration and the International Conference on Harmonization).

Figure 2. Noninferiority Diagram Showing the Difference in Overall HIV-RNA Suppression Between the Treatment Groups



The 95% CI does not cross the noninferiority margin; therefore, noninferiority is demonstrated.

[a]The difference is defined as the doravirine, lamivudine, and tenofovir disoproxil fumarate group minus the dolutegravir, emtricitabine, and tenofovir alafenamide group.

emtricitabine, and tenofovir alafenamide; the probability of remaining free of virologic failure at week 48 was 96.8% vs 97.9%, respectively, with similar median time to virologic failure (24.9 [IQR, 24.0-36.1] weeks vs 25.1 [IQR, 25.0-45.0] weeks) (eFigure in Supplement 2). During follow-up, 7 participants in the doravirine, lamivudine, and tenofovir disoproxil fumarate group developed high-level resistance to doravirine; V106M was detected in 6 typically alongside NNRTI variations (eTable 3 in Supplement 2). These participants generally had advanced HIV at baseline (mean CD4 cell count, 35.3 cells/μL; mean HIV RNA level, 4.9 $\log_{10}$ copies/mL). By week 48, 2 of 9 participants (22.2%) with protocol-defined virologic failure in the doravirine, lamivudine, and tenofovir disoproxil fumarate group continued to have viremia. Of the 6 participants who were switched to dolutegravir-based therapy after resistance to doravirine was detected, 5 (83.3%) achieved viral suppression and 1 was lost to follow-up. No emergent treatment resistance to InSTIs was detected in the dolutegravir, emtricitabine, and tenofovir alafenamide group.

Weight and Body Composition

Both ART regimens were associated with weight gain, but increases were greater with dolutegravir, emtricitabine, and tenofovir alafenamide (**Table 3**). By week 48, the median weight gain was 3.0 kg (IQR, −0.2 to 6.1 kg) with doravirine, lamivudine, and tenofovir disoproxil fumarate vs 5.0 kg (IQR, 1.5 to 8.0 kg) with dolutegravir, emtricitabine, and tenofovir alafenamide (between-group difference −2.0 kg [95% CI, −3.0 to −1.0 kg]; $P < .001$). Dual-energy x-ray absorptiometry was used to assess body composition. Participants in the doravirine, lamivudine, and tenofovir disoproxil fumarate group had lower increases in total body fat percentage (median, 1.5% [IQR, −0.2% to 3.2%]) compared with the dolutegravir, emtricitabine, and tenofovir alafenamide group (median, 2.2% [IQR, 0.7% to 3.9%]; $P < .001$) and in trunk fat (median, 1.3 kg [IQR, 0.1 to 2.5 kg] vs 2.0 kg [IQR, 0.8 to 3.2 kg], respectively; $P < .001$). The site-specific dual-energy x-ray absorptiometry measures appear in eTable 4 in Supplement 2. Visceral adipose tissue area increased by a median of 8.4 cm^2 (IQR, −1.9 to 24.2 cm^2) with doravirine, lamivudine, and tenofovir disoproxil fumarate compared with 11.6 cm^2 (IQR, 0 to 30.0 cm^2) with dolutegravir, emtricitabine, and tenofovir alafenamide ($P = .04$).

Metabolic, Kidney, and Hepatic Outcomes

There were minimal changes in either group for fasting glucose level, hemoglobin A_{1c} level, fasting insulin level, and homeostatic model assessment of insulin resistance over time (Table 3). Incident diabetes and hypertension were uncommon and occurred similarly in each group. Lipid changes were more favorable with doravirine, lamivudine, and tenofovir disoproxil fumarate (Table 3).

A decline of 25% or greater in creatinine clearance occurred in 23.9% of participants receiving dolutegravir, emtricitabine, and tenofovir alafenamide vs 10.7% receiving doravirine, lamivudine, and tenofovir disoproxil fumarate ($P < .001$).

Table 3. Secondary Outcomes of Weight, Body Composition, and Metabolic Health

Secondary outcomes	Median (IQR)[a]						Between-group difference (95% CI)	*P* value[b]
	Doravirine, lamivudine, and tenofovir disoproxil fumarate (n = 299)			Dolutegravir, emtricitabine, and tenofovir alafenamide (n = 301)				
	At baseline	At 48 wk	Change	At baseline	At 48 wk	Change		
Body weight								
Body weight, kg	75.0 (66.2 to 83.9)	78.4 (69.2 to 88.3)	3.0 (−0.2 to 6.1)	74.8 (66.0 to 85.5)	80.0 (71.3 to 89.8)	5.0 (1.5 to 8.0)	−2.0 (−3.0 to −1.0)	<.001
Weight gain, No. (%)								
≥5%		123 (41.1)			171 (56.8)		−15.7 (−23.6 to −7.8)	<.001
≥10%		49 (16.4)			79 (26.2)		−9.9 (−16.4 to −3.4)	.003
Weight loss, No./total (%)		75/282 (26.6)			40/283 (14.1)		12.5 (5.9 to 19.0)	<.001
Body mass index[c]	27.7 (25.2 to 31.8)	29.0 (25.8 to 33.3)	1.1 (−0.1 to 2.3)	27.8 (25.0 to 31.7)	29.4 (26.6 to 34.0)	1.9 (0.6 to 3.0)	−0.7 (−1.2 to −0.4)	<.001
Body composition (measured with DXA)[d]								
Total body fat, %	39.8 (30.1 to 45.1)	42.1 (30.2 to 46.6) [n = 272]	1.5 (−0.2 to 3.2)	39.0 (29.8 to 44.1)	41.9 (31.9 to 46.2) [n = 275]	2.2 (0.7 to 3.9)	−0.6 (−1.1 to −0.2)	<.001
Total body fat, kg	27.7 (19.6 to 35.3)	30.5 (21.3 to 38.0) [n = 272]	2.4 (0.1 to 4.6)	27.0 (20.3 to 34.2)	30.7 (22.7 to 38.9) [n = 275]	3.7 (1.2 to 6.0)	−1.3 (−1.9 to −0.7)	<.001
Lean body mass, kg	44.3 (39.8 to 50.6)	45.3 (40.0 to 51.5) [n = 272]	0.9 (−0.5 to 2.2)	44.6 (39.5 to 50.5)	46.1 (40.8 to 51.9) [n = 275]	1.0 (−0.04 to 2.6)	0.2 (−0.6 to 0.3)	.01
Trunk fat, kg	11.6 (8.1 to 15.8)	13.3 (9.4 to 17.4) [n = 272]	1.3 (0.1 to 2.5)	11.6 (8.4 to 15.3)	14.0 (10.2 to 18.1) [n = 275]	2.0 (0.8 to 3.2)	−0.6 (−1.0 to −0.2)	<.001
Adipose tissue area, cm^2								
Visceral	83.8 (57.4 to 122.5)	96.2 (65.5 to 137.7) [n = 266]	8.4 (−1.9 to 24.2)	92.2 (57.0 to 126.7)	109.0 (74.2 to 144.7) [n = 268]	11.6 (0 to 30.0)	−3.2 (−7.8 to 1.4)	.04
Subcutaneous	305.7 (174.0 to 430.0)	339.8 (212.0 to 454.4) [n = 268]	22.0 (−2.5 to 53.0)	295.3 (179.5 to 413.4)	340.9 (215.9 to 472.8) [n = 268]	39.6 (13.0 to 69.0)	−17.6 (−25.2 to −9.8)	<.001
Bone mineral density, %								
Hip			−2.1 (−4.1 to −0.5)			−0.5 (−1.9 to 1.2)	−1.5 (−2.1 to −1.0)	<.001
Spine			−3.2 (−5.4 to −0.8)			−1.3 (−3.2 to 0.8)	−1.9 (−2.6 to −1.2)	<.001
Anthropometric indices								
Waist circumference, cm	88 (80 to 96)	92 (84 to 100) [n = 280]	4.0 (−1.0 to 8.0)	88 (81 to 96)	92 (85 to 101) [n = 282]	4.0 (−1.0 to 8.0)	0.6 (−1.1 to 1.1)	.39
Hip circumference, cm	108 (99 to 117)	110 (102 to 118) [n = 280]	2.0 (−2.0 to 5.0)	108 (100 to 115)	110 (102 to 118) [n = 282]	3.0 (0 to 6.0)	−1.0 (−2.5 to 0.5)	.008
Waist-to-hip ratio	0.8 (0.8 to 0.9)	0.8 (0.8 to 0.9) [n = 280]	0 (0 to 0.1)	0.8 (0.7 to 0.8)	0.8 (0.8 to 0.9) [n = 282]	0 (0 to 0.01)	0 (0 to 0.01)	.45
Glucose metabolism								
Fasting glucose level, mmol/L	4.3 (4.0 to 4.6)	4.5 (4.2 to 4.8) [n = 275]	0.2 (−0.1 to 0.6)	4.3 (4.0 to 4.6)	4.5 (4.2 to 4.9) [n = 274]	0.2 (−0.1 to 0.6)	0 (−0.1 to 0.2)	.65
Hemoglobin A_{1c} level, %	5.3 (5.0 to 5.7)	5.1 (4.9 to 5.4) [n = 274]	−0.1 (−0.4 to 0.1)	5.3 (5.0 to 5.7)	5.1 (4.9 to 5.5) [n = 275]	−0.1 (−0.4 to 0.1)	0 (−0.1 to 0.1)	.49
Fasting insulin level, μIU/mL	5.2 (3.1 to 8.0)	6.7 (4.4 to 10.5) [n = 275]	1.5 (−0.6 to 3.9)	5.4 (3.4 to 8.2)	7.2 (5.1 to 11.0) [n = 275]	1.8 (−0.4 to 4.3)	−0.4 (−1.1 to 0.3)	.58

(continued)

Table 3. Secondary Outcomes of Weight, Body Composition, and Metabolic Health (continued)

Secondary outcomes	Median (IQR)[a]						Between-group difference (95% CI)	*P* value[b]
	Doravirine, lamivudine, and tenofovir disoproxil fumarate (n = 299)			Dolutegravir, emtricitabine, and tenofovir alafenamide (n = 301)				
	At baseline	At 48 wk	Change	At baseline	At 48 wk	Change		
Homeostatic model assessment of insulin resistance	1.0 (0.5 to 1.6)	1.3 (0.8 to 2.2) [n = 275]	0.3 (−0.4 to 1.0)	1.1 (0.6 to 1.7)	1.5 (1.0 to 2.4) [n = 273]	0.4 (−0.4 to 1.0)	−0.1 (−0.3 to 0.1)	.52
Fasting lipid levels								
Total cholesterol, mmol/L	3.8 (3.3 to 4.3)	3.6 (3.2 to 4.2) [n = 274]	−0.1 (−0.5 to 0.3)	3.9 (3.3 to 4.4)	4.0 (3.5 to 4.6) [n = 274]	0.2 (−0.3 to 0.5)	−0.3 (−0.5 to −0.2)	<.001
LDL cholesterol, mmol/L	2.3 (1.7 to 2.7)	2.1 (1.7 to 2.6) [n = 274]	−0.1 (−0.5 to 0.2)	2.3 (1.0 to 2.7)	2.4 (1.9 to 2.9) [n = 274]	0.1 (−0.2 to 0.4)	−0.2 (−0.3 to −0.1)	<.001
HDL cholesterol, mmol/L	1.0 (0.9 to 1.2)	1.1 (0.9 to 1.3) [n = 274]	0.1 (−0.1 to 0.2)	1.0 (0.9 to 1.2)	1.1 (1.0 to 1.4) [n = 274]	0.2 (0 to 0.3)	−0.1 (−0.1 to 0)	.01
Triglycerides, mmol/L	0.9 (0.7 to 1.1)	0.7 (0.6 to 1.0) [n = 274]	−0.1 (−0.3 to 0.1)	0.9 (0.7 to 1.3)	0.9 (0.7 to 1.3) [n = 274]	−0.1 (−0.3 to 0.2)	−0.1 (−0.1 to −0.1)	.004
Ratio of total cholesterol to HDL cholesterol	3.7 (3.0 to 4.5) [n = 290]	3.3 (2.7 to 4.0) [n = 272]	−0.4 (−0.8 to −0.1)	3.9 (3.1 to 4.6) [n = 291]	3.4 (2.9 to 4.3) [n = 272]	−0.2 (−0.7 to 0.1)	−0.10 (−0.25 to −0.03)	.01
Post hoc outcomes								
Blood pressure level, mm Hg								
Systolic	120 (111 to 130)	119 (112 to 128) [n = 280]	−0.5 (−11.0 to 7.0)	120 (111 to 130)	120 (112 to 128) [n = 282]	0 (−9.0 to 8.0)	−0.5 (−3.5 to 2.5)	.34
Diastolic	79 (73 to 86)	79 (73 to 86) [n = 280]	0 (−6.0 to 5.0)	80 (73 to 85)	80 (73 to 85) [n = 282]	0 (−5.0 to 5.0)	0 (−1.0 to 2.0)	.77
New-onset disease or syndrome, No./total (%)								
Hypertension		3/270 (1.1)			7/261 (2.6)		−1.6 (−3.9 to 4.6)	.22
Diabetes		3/290 (1.0)			1/291 (0.3)		0.7 (−0.7 to 2.0)	.37
Clinical obesity[e]		36/197 (18.3)			44/301 (14.6)		−3.8 (−11.7 to 4.1)	.38
Metabolic syndrome[f]		17/272 (6.3)			29/301 (9.6)		−4.9 (−9.7 to −0.2)	.04

Abbreviations: DXA, dual-energy x-ray absorptiometry; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

SI conversion factors: To convert HDL, LDL, and total cholesterol to mg/dL, divide by 0.0259; glucose to mg/dL, divide by 0.0555; insulin to pmol/L, multiply by 6.945; triglycerides to mg/dL, divide by 0.0113.

[a] Unless otherwise indicated.

[b] The Wilcoxon rank sum test was used to calculate the *P* values, which should be interpreted as exploratory because the study was not powered for assessment of the secondary outcomes and no adjustment was made for multiple testing.

[c] Calculated as weight in kilograms divided by height in meters squared.

[d] The DXA scans were performed at baseline and at week 48. Whole-body DXA was performed at 2 study sites using site-specific DXA systems (Hologic at one site and GE Lunar at the other). The analyses focused on within-participant change from baseline rather than direct comparison of absolute values across scanners.

[e] Defined as a body mass index of 30 or greater.

[f] Defined as the presence of at least 3 of the following: elevated waist circumference (>102 cm in men or >88 cm in women); triglycerides level of 1.7 mmol/L or greater; reduced HDL cholesterol level (<1.03 mmol/L in men or <1.29 mmol/L in women); systolic/diastolic blood pressure of 140/90 mm Hg or greater; or fasting plasma glucose level of 5.6 mmol/L or greater.

Table 4. Safety and Adverse Events Through Week 48

	No. (%)	
	Doravirine, lamivudine, and tenofovir disoproxil fumarate (n = 299)	Dolutegravir, emtricitabine, and tenofovir alafenamide (n = 301)
Any adverse event	273 (91.3)	270 (89.7)
Any grade 3 or 4 adverse event	25 (8.4)	37 (12.3)
Any drug-related adverse event	3 (1.0)	5 (1.7)
Any serious adverse event	11 (3.7)	7 (2.3)
Death	2 (0.7)	0
Adverse event leading to treatment discontinuation	0	1 (0.3)
Grade 3 or 4 laboratory abnormalities		
Any	16 (5.4)	30 (10.0)
Creatinine level increase of >1.5 × baseline	5 (1.7)	22 (7.3)
Hemoglobin level <8.0 g/dL	5 (1.7)	4 (1.3)
Alanine aminotransferase level >5 × upper limit of normal	3 (1.0)	3 (1.0)
Alkaline phosphatase level >3 × upper limit of normal	1 (0.3)	1 (0.3)
Laboratory parameters of special interest		
Creatinine clearance		
Decrease from baseline	241 (80.6)	275 (91.4)
Decrease ≥25% from baseline	32 (10.7)	72 (23.9)
Level was <50 mL/min/1.73 m^2 at any visit	0	0
Cystatin C level increase of ≥25% from baseline	14 (4.7)	13 (4.3)
Alanine aminotransferase level increase of ≥1.25 × upper limit of normal	67 (22.3)	61 (20.3)
Alkaline phosphatase level increase of ≥1.25 × upper limit of normal	39 (13.0)	25 (8.3)
Adverse events of clinical interest		
Transaminase elevation (any grade)	113 (37.8)	105 (34.9)
Headache	25 (8.4)	18 (6.0)
Nausea	11 (3.7)	7 (2.3)
Rash (any grade)	9 (3.0)	14 (4.7)
Pregnancy-related adverse events	3 (1.0)	3 (1.0)
Dizziness	2 (0.7)	0
Tuberculosis	1 (0.3)	0
Immune reconstitution inflammatory syndrome	1 (0.3)	0
Autoimmune hepatitis	0	1 (0.3)

However, cystatin C increases of 25% or greater were comparable between groups (4.3% in the dolutegravir, emtricitabine, and tenofovir alafenamide group vs 4.7% in the doravirine, lamivudine, and tenofovir disoproxil fumarate group).

At week 48, the median decreases in bone mineral density (BMD) in the doravirine, lamivudine, and tenofovir disoproxil fumarate group were −2.1% (IQR, −4.1% to −0.5%) for hip BMD and −3.2% (IQR, −5.4% to −0.8%) for spine BMD vs −0.5% (IQR, −1.9% to 1.2%) for hip BMD and −1.3% (IQR, −3.2% to 0.8%) for spine BMD in the dolutegravir, emtricitabine, and tenofovir alafenamide group (Table 3). The median decrease in BMD was −1.2% (IQR, −2.6% to 0.02%) in the doravirine, lamivudine, and tenofovir disoproxil fumarate group compared with −0.1% (IQR, −1.3% to 1.2%) in the dolutegravir, emtricitabine, and tenofovir alafenamide group ($P < .001$).

Safety, Adverse Events, and Pregnancy Outcomes

Overall safety profiles were similar between groups (**Table 4**). Adverse events of any grade occurred in 273 of 299 participants (91.3%) in the doravirine, lamivudine, and tenofovir disoproxil fumarate group compared with 270 of 301 participants (89.7%) in the dolutegravir, emtricitabine, and tenofovir alafenamide group; grade 3 or 4 adverse events occurred in 8.4% vs 12.3%, respectively; and grade 3 or 4 laboratory abnormalities in 5.4% vs 10.0%. Treatment discontinuation due to adverse events was rare (only occurred in 1 participant in the dolutegravir, emtricitabine, and tenofovir alafenamide group). Serious adverse events occurred in 3.7% of participants in the doravirine, lamivudine, and tenofovir disoproxil fumarate group vs 2.3% of participants in the dolutegravir, emtricitabine, and tenofovir alafenamide group ($P = .35$); none were considered related to study treatment. There were 2 deaths in the doravirine, lamivudine, and tenofovir disoproxil fumarate group; both were adjudicated as being unrelated to the study regimen.

Through week 48, 4 pregnancies occurred among participants in the doravirine, lamivudine, and tenofovir disoproxil fumarate group compared with 5 pregnancies in the dolutegravir, emtricitabine, and tenofovir alafenamide group. Three of the

participants who became pregnant in the doravirine, lamivudine, and tenofovir disoproxil fumarate accepted a switch early during gestation to the dolutegravir-containing regimen; one participant did not accept the regimen switch. Four pregnancies resulted in live births (2 per group), including 1 preterm infant with transient jaundice in the dolutegravir, emtricitabine, and tenofovir alafenamide group. Two spontaneous abortions occurred in participants assigned to doravirine, lamivudine, and tenofovir disoproxil fumarate. No major congenital anomalies or other notable neonatal events were reported.

Discussion

Doravirine, lamivudine, and tenofovir disoproxil fumarate achieved noninferior virologic suppression with less weight gain than dolutegravir, emtricitabine, and tenofovir alafenamide, making it a potential treatment option for individuals beginning ART, particularly those at risk of treatment-associated weight gain.

To our knowledge, the current study is the first head-to-head randomized clinical trial comparing doravirine, lamivudine, and tenofovir disoproxil fumarate with a contemporary InSTI regimen with tenofovir alafenamide at ART initiation. The regimen of doravirine, lamivudine, and tenofovir disoproxil fumarate is one of few currently available fixed-dose combinations that pair a non-InSTI anchor with a tenofovir disoproxil fumarate backbone, offering a biologically plausible strategy to attenuate ART-associated weight gain, avoiding both the effects of InSTI class and tenofovir alafenamide while retaining a once-daily, single-tablet regimen.[7,8,29] The ART regimen of dolutegravir, emtricitabine, and tenofovir alafenamide was chosen as the comparator because it is a relevant proxy for current InSTI regimens with tenofovir alafenamide, which are standard in high-income countries, and are increasingly being considered elsewhere.[2-4,30]

High-level resistance to doravirine at baseline was rare (0.8%) despite the background first-generation NNRTI resistance among more than 20% of the participants in this population predominantly with HIV subtype clade C.[31] Virologic suppression was high and similar between regimens. Doravirine resistance emerged in a small number of participants in the doravirine, lamivudine, and tenofovir disoproxil fumarate group. All participants with doravirine resistance had advanced HIV infection at baseline and most had the V106M variation; however, virologic suppression was achieved with dolutegravir-based therapy in the majority of these participants. The feasibility of doravirine, lamivudine, and tenofovir disoproxil fumarate as first-line ART therapy hinges on the ability to rapidly detect virologic failure and switch promptly to an InSTI-based regimen.

This trial had several strengths including a randomized design, recruitment from both urban and rural sites, high retention rates, detailed longitudinal assessment of body composition, metabolic and treatment resistance data, and a high proportion of Black women, enhancing generalizability to populations at greatest risk of ART-associated weight gain.

Limitations

There were also several limitations. First, the trial had an open-label design and only a 48-week follow-up, limiting the ability to link early weight gain to longer-term cardiovascular and metabolic events.

Second, the regimen-level comparison cannot disentangle contributions of the anchor drug (doravirine vs dolutegravir) from the backbone drug (tenofovir disoproxil fumarate vs tenofovir alafenamide) to the observed weight and metabolic differences. A recent phase 3 trial comparing doravirine and islatravir vs bictegravir, emtricitabine, and tenofovir alafenamide reported similar 48-week weight gain between the 2 regimens, suggesting that the excess weight gain seen with combinations of an InSTI and tenofovir alafenamide is not unique to dolutegravir and reinforcing the rationale for evaluating tenofovir disoproxil fumarate–based combinations as alternatives.[32] An international, ongoing trial (NCT06203132) of a common backbone with tenofovir disoproxil fumarate and lamivudine will directly compare dolutegravir vs doravirine.[33]

Third, few pregnancies occurred, which limits inference regarding pregnancy safety. Fourth, cost differences were not assessed. Bilateral voluntary licenses have been issued to manufacturers of generic drugs to support the manufacture of doravirine and the fixed-dose ART combination in 86 countries, covering all of sub-Saharan Africa and some other low- and lower-middle-income settings, but the economic aspects of using doravirine, lamivudine, and tenofovir disoproxil fumarate represents a priority for future work to inform regulatory and formulary decisions.[34]

Fifth, individuals were excluded if high-level resistance to doravirine was detected at baseline. In settings without pretreatment genotyping, some individuals could be at risk of early virologic failure due to transmitted doravirine resistance, though population-level surveillance data suggest this risk is low.

Conclusions

Among predominantly Black African adults initiating ART, a regimen with doravirine, lamivudine, and tenofovir disoproxil fumarate was noninferior to a regimen with dolutegravir, emtricitabine, and tenofovir alafenamide for 48-week viral suppression and was associated with less weight gain.

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