ORIGINAL ARTICLE

Dolutegravir or Darunavir in Combination with Zidovudine or Tenofovir to Treat HIV

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ABSTRACT

BACKGROUND

The World Health Organization recommends dolutegravir with two nucleoside reverse-transcriptase inhibitors (NRTIs) for second-line treatment of human immunodeficiency virus type 1 (HIV-1) infection. Evidence is limited for the efficacy of this regimen when NRTIs are predicted to lack activity because of drug resistance, as well as for the recommended switch of an NRTI from tenofovir to zidovudine.

METHODS

In a two-by-two factorial, open-label, noninferiority trial, we randomly assigned patients for whom first-line therapy was failing (HIV-1 viral load, ≥1000 copies per milliliter) to receive dolutegravir or ritonavir-boosted darunavir and to receive tenofovir or zidovudine; all patients received lamivudine. The primary outcome was a week 48 viral load of less than 400 copies per milliliter, assessed with the Food and Drug Administration snapshot algorithm (noninferiority margin for the between-group difference in the percentage of patients with the primary outcome, 12 percentage points).

RESULTS

We enrolled 464 patients at seven sub-Saharan African sites. A week 48 viral load of less than 400 copies per milliliter was observed in 90.2% of the patients in the dolutegravir group (212 of 235) and in 91.7% of those in the darunavir group (210 of 229) (difference, −1.5 percentage points; 95% confidence interval [CI], −6.7 to 3.7; P=0.58; indicating noninferiority of dolutegravir, without superiority) and in 92.3% of the patients in the tenofovir group (215 of 233) and in 89.6% of those in the zidovudine group (207 of 231) (difference, 2.7 percentage points; 95% CI, −2.6 to 7.9; P=0.32; indicating noninferiority of tenofovir, without superiority). In the subgroup of patients with no NRTIs that were predicted to have activity, a viral load of less than 400 copies per milliliter was observed in more than 90% of the patients in the dolutegravir group and the darunavir group. The incidence of adverse events did not differ substantially between the groups in either factorial comparison.

CONCLUSIONS

Dolutegravir in combination with NRTIs was effective in treating patients with HIV-1 infection, including those with extensive NRTI resistance in whom no NRTIs were predicted to have activity. Tenofovir was noninferior to zidovudine as second-line therapy. (Funded by Janssen; NADIA ClinicalTrials.gov number, NCT03988452.)

Antiretroviral therapy for human immunodeficiency virus (HIV) infection is delivered globally mainly with the use of the public health approach recommended by the World Health Organization (WHO), comprising a small number of standardized regimens and simplified monitoring and care.[1] Dolutegravir, an integrase strand-transfer inhibitor, taken with tenofovir and lamivudine (both of which belong to the nucleoside reverse-transcriptase inhibitor [NRTI] drug class) is the WHO-recommended first-line regimen. It is also recommended as second-line therapy in patients for whom non–dolutegravir-containing first-line regimens have failed, although the efficacy is uncertain when dolutegravir is given with NRTIs that are predicted to be compromised by cross-resistance.[2,3] Darunavir (or other drugs from the protease inhibitor class) with two NRTIs is currently recommended as an alternative second-line regimen and is known to have good efficacy even with NRTIs that have extensive cross-resistance.

WHO guidelines also recommend changing one of the NRTIs from tenofovir to zidovudine when switching to second-line therapy (both drugs are given with lamivudine).[2,3] However, because of its side effects, zidovudine is more likely to be discontinued than tenofovir, and it requires twice-daily dosing. Observational data suggest that this switch may not be essential, but data from randomized trials are needed.[4,5]

We conducted a trial under the conditions of monitoring and care recommended within the WHO public health approach to determine whether dolutegravir would be noninferior to darunavir in a population of patients switching to second-line therapy, including patients for whom NRTIs are predicted to have little or no activity. We also assessed whether maintaining tenofovir treatment would be noninferior to switching to zidovudine.

Methods

Trial Design and Oversight

The Nucleosides and Darunavir/Dolutegravir in Africa (NADIA) Trial is a prospective, multicenter, two-by-two factorial, randomized, open-label, noninferiority, 96-week trial comparing dolutegravir with darunavir and comparing tenofovir with zidovudine in patients for whom a nonnucleoside reverse-transcriptase inhibitor (NNRTI)–based first-line regimen had failed. In the trial, we used a monitoring approach that is generalizable to sub-Saharan Africa. Data on the primary outcome (48-week viral suppression, defined as a week 48 viral load of <400 copies per milliliter) are reported here along with safety data.

A Quick Take is available at NEJM.org

The trial was designed by academic investigators from the NADIA trial team; the Infectious Diseases Institute, Uganda, served as the coordinating center and led the conduct of the trial. An independent trial steering committee provided trial oversight, and an independent data and safety monitoring committee reviewed safety data. The trial was approved by local ethics committees and national regulatory agencies. All the patients provided written informed consent. The manuscript that was submitted for publication was written by the first author. The authors vouch for the accuracy and completeness of the data and for the adherence of the trial to the protocol, available with the full text of this article at NEJM.org. Janssen provided funding but was not involved in trial conduct, data analysis, or the decision to publish the results.

Trial Population

We enrolled patients at seven sites in Uganda, Kenya, and Zimbabwe between July 30, 2019, and December 18, 2019. To be eligible for participation, patients needed to be at least 12 years of age; to have received tenofovir, lamivudine (or emtricitabine), and an NNRTI for at least 6 months continuously before screening; to have missed no more than 3 days of treatment in the month before screening; and to have had a viral load of at least 1000 copies per milliliter within 6 months before screening that was confirmed at screening or to meet that viral load threshold on two tests performed during screening. The main exclusion criteria were previous use of protease or integrase inhibitor drugs, current pregnancy, severe hepatic impairment, or an estimated glomerular filtration rate (eGFR) below 50 ml per minute per 1.73 m^2 (details are provided in the Supplementary Appendix, available at NEJM.org).[6]

Treatment

Patients were randomly assigned (in a 1:1:1:1 ratio, following the two-by-two factorial design) to a regimen containing either dolutegravir (50 mg) once daily or ritonavir-boosted darunavir (800 mg of darunavir plus 100 mg of ritonavir) once daily, given in combination with either tenofovir (300 mg) plus lamivudine (300 mg) once daily or zidovudine (300 mg) plus lamivu-

dine (150 mg) twice daily. The randomly assigned NRTIs were given in a fixed-dose combination pill; other drugs were given as separate pills.

Randomization was stratified according to site and viral load at screening (<100,000 copies per milliliter or ≥100,000 copies per milliliter). Randomization was performed with a secure Web-based system that was preprogrammed with a computer-generated randomization list with the use of random permuted blocks.

Patients in the zidovudine group who had hepatitis B virus coinfection had tenofovir added to their regimen. The protocol permitted NRTI substitution for toxic effects and switching from dolutegravir to darunavir for pregnancy. Patients with tuberculosis took dolutegravir twice daily or rifabutin-based tuberculosis treatment with darunavir–ritonavir.

ASSESSMENTS AND OUTCOMES

Visits were scheduled at weeks 4, 8, 12, 24, 36, and 48 and were mostly nurse-led. Adherence was assessed at each visit with standard questions, and adverse events were graded with the use of standard criteria.[7] A complete blood count was obtained and alanine aminotransferase and creatinine levels were measured at weeks 12 and 48, and a CD4+ cell count was obtained at weeks 24 and 48. Viral load was measured with the standard site assay in samples obtained at week 12 (stored for later batched testing, with results seen only by the independent data and safety monitoring committee) and at weeks 24 and 48 (with testing performed after each visit and results returned to the clinician). Patients with a viral load of at least 1000 copies per milliliter received intensive adherence counseling, and viral load measurement was repeated after 12 weeks; if the viral load was confirmed to be 1000 copies per milliliter or higher, the patient underwent evaluation for a switch to third-line treatment. If adherence remained suboptimal, a further period of adherence counseling and repeat viral load measurement was allowed, at the clinician's discretion, before a decision was made to switch treatment. Genotypic resistance testing was performed with the use of a plasma sample stored at baseline for later batched testing (with results not returned to the clinician) and at the time of a confirmed viral load rebound of at least 1000 copies per milliliter. Resistance testing was performed at a WHO-accredited central laboratory (Joint Clinical Research Centre, Kampala, Uganda), and drug-susceptibility prediction was performed with the Stanford algorithm.[8]

The primary outcome for both factorial comparisons was a viral load of less than 400 copies per milliliter at week 48, determined with the use of a modified Food and Drug Administration snapshot algorithm.[9] The main secondary outcomes were a viral load of less than 1000 copies per milliliter at week 48, confirmed viral load rebound (≥1000 copies per milliliter) by week 48, confirmed viral load rebound with at least one major mutation conferring resistance to dolutegravir or darunavir, and the change in CD4+ cell count.

STATISTICAL ANALYSIS

Analysis of the primary outcome was performed in the intention-to-treat population, which excluded only patients who underwent randomization in error and were withdrawn before receiving any trial drug. Noninferiority could be concluded if the lower limit of the two-sided 95% confidence interval (unadjusted, calculated with binomial methods) for the difference between the groups in the percentage of patients with a viral load of less than 400 copies per milliliter was above –12 percentage points. This margin reflects the clinical consensus and is within the range used in previous second-line treatment trials.[4,10-13] Sensitivity analyses were performed with a per-protocol population (defined in the Supplementary Appendix), with the use of an adjusted model, with imputation of missing viral load values, and with the use of complete cases. Superiority testing was planned only if noninferiority was shown in the primary intention-to-treat analysis and in the per-protocol population. Noninferiority of dolutegravir as compared with darunavir was prespecified as the main hypothesis to be tested; a test for interaction was performed to determine whether the comparison of zidovudine and tenofovir could be analyzed independently of the main comparison. No adjustment for multiple comparisons was required for the primary outcome, given the prespecified hierarchical testing approaches. There was no correction for multiple comparisons for tests of secondary and other outcomes, so results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiple comparisons, and the intervals should therefore not be used to infer definitive treatment effects.

We assumed that 82% of the patients in each group would have viral load suppression to less than 400 copies per milliliter (on the basis of pre-

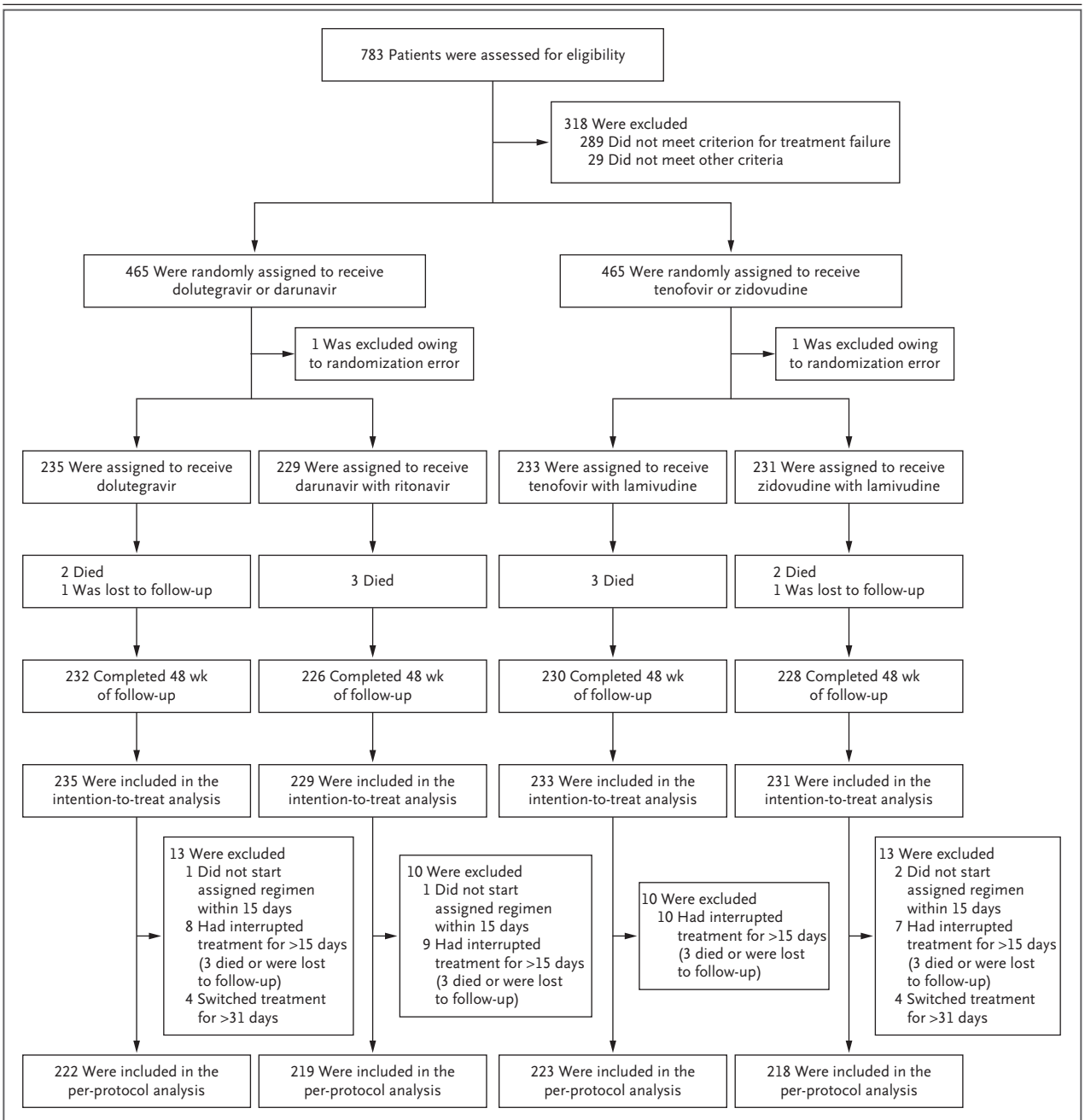

Figure 1. Eligibility Assessment, Randomization, Treatment, and Follow-up.

vious data).[4] With a noninferiority margin of 12 percentage points and a 2.5% one-sided significance level, we calculated that 440 patients (220 per group) would provide 90% power to show noninferiority.

Secondary and other analyses are described in the statistical analysis plan (available with the protocol). All analyses were performed with the use of Stata software, version 15.1 (StataCorp).

RESULTS

PATIENTS

Of the 465 patients who underwent randomization, 1 had undergone randomization in error and was immediately withdrawn, 5 died, and 1 was lost to follow-up before week 48 (Fig. 1). The baseline characteristics of the patients were well balanced between the groups in each factorial

Table 1. Baseline Characteristics of the Patients (Intention-to-Treat Population).*

Characteristic	Dolutegravir (N=235)	Darunavir (N=229)	Tenofovir (N=233)	Zidovudine (N=231)	Overall (N=464)
Female sex — no (%)	140 (59.6)	142 (62.0)	140 (60.1)	142 (61.5)	282 (60.8)
Median age (IQR) — yr	33 (28–40)	35 (28–42)	34 (28–43)	35 (28–40)	34 (28–41)
Age group — no (%)					
12–17 yr	1 (0.4)	2 (0.9)	0	3 (1.3)	3 (0.6)
18–34 yr	138 (58.7)	121 (52.8)	128 (54.9)	131 (56.7)	259 (55.8)
35–49 yr	82 (34.9)	82 (35.8)	87 (37.3)	77 (33.3)	164 (35.3)
≥50 yr	14 (6.0)	24 (10.5)	18 (7.7)	20 (8.7)	38 (8.2)
Country of birth — no (%)					
Uganda	181 (77.0)	170 (74.2)	176 (75.5)	175 (75.8)	351 (75.6)
Kenya	25 (10.6)	26 (11.4)	25 (10.7)	26 (11.3)	51 (11.0)
Zimbabwe	29 (12.3)	30 (13.1)	29 (12.4)	30 (13.0)	59 (12.7)
Other†	0	3 (1.3)	3 (1.3)	0	3 (0.6)
Median body-mass index (IQR)‡	21.2 (19.3–23.9)	21.6 (20.0–24.7)	21.8 (19.8–24.4)	21.1 (19.5–24.1)	21.4 (19.7–24.3)
HBV surface antigen positive — no./total no. (%)§	9/234 (3.8)	13/229 (5.7)	9/233 (3.9)	13/230 (5.7)	22/463 (4.8)
Median CD4+ cell count (IQR) — per mm^3	189 (58–388)	202 (84–357)	200 (77–388)	191 (58–340)	194 (68–367)
CD4+ cell-count group — no. (%)					
<50 per mm^3	54 (23.0)	39 (17.0)	45 (19.3)	48 (20.8)	93 (20.0)
50–199 per mm^3	71 (30.2)	74 (32.3)	70 (30.0)	75 (32.5)	145 (31.2)
200–349 per mm^3	43 (18.3)	56 (24.5)	47 (20.2)	52 (22.5)	99 (21.3)
≥350 per mm^3	67 (28.5)	60 (26.2)	71 (30.5)	56 (24.2)	127 (27.4)
Median HIV-1 viral load (IQR) — log_{10} copies/ml	4.5 (3.9–5.1)	4.4 (3.8–5.1)	4.4 (3.9–5.1)	4.4 (3.9–5.1)	4.4 (3.9–5.1)
HIV-1 viral load group — no. (%)					
<100,000 copies/ml	169 (71.9)	167 (72.9)	171 (73.4)	165 (71.4)	336 (72.4)
≥100,000 copies/ml	66 (28.1)	62 (27.1)	62 (26.6)	66 (28.6)	128 (27.6)
Median time receiving first-line ART (IQR) — yr	3.6 (1.4–6.3)	3.7 (1.7–5.9)	3.7 (1.6–6.1)	3.7 (1.7–6.4)	3.7 (1.6–6.2)
Previously received zidovudine — no. (%)	14 (6.0)	14 (6.1)	15 (6.4)	13 (5.6)	28 (6.0)

K65R/N present at baseline — no./total no. (%)¶‖	120/228 (52.6)	106/225 (47.1)	116/230 (50.4)	110/223 (49.3)	226/453 (49.9)
M184V/I present at baseline — no./total no. (%)¶	196/228 (86.0)	195/225 (86.7)	201/230 (87.4)	190/223 (85.2)	391/453 (86.3)
Intermediate- or high-level resistance present — no./total no. (%)¶**					
Tenofovir	139/228 (61.0)	126/225 (56.0)	133/230 (57.8)	132/223 (59.2)	265/453 (58.5)
Zidovudine	45/228 (19.7)	38/225 (16.9)	41/230 (17.8)	42/223 (18.8)	83/453 (18.3)
Lamivudine	213/228 (93.4)	203/225 (90.2)	213/230 (92.6)	203/223 (91.0)	416/453 (91.8)

* The intention-to-treat population included 464 patients and excluded the 1 patient who had undergone randomization in error and was immediately withdrawn. Percentages may not total 100 because of rounding. ART denotes antiretroviral therapy, HIV-1 human immunodeficiency virus type 1, and IQR interquartile range.
† Other countries of birth were Rwanda (2 patients) and Mozambique (1 patient).
‡ Body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Testing for hepatitis B virus (HBV) was not performed for 1 patient assigned to receive dolutegravir and zidovudine.
¶ Denominators indicate the numbers of patients with available viral sequences.
‖ Of the 226 patients with a K65R/N mutation, 223 had K65R and 3 had K65N.
** Intermediate- or high-level resistance was determined with the Stanford algorithm.

comparison (Table 1). Overall, 58.5% of the patients had viral mutations that were associated with intermediate- or high-level resistance to tenofovir at baseline; 57.8% of those who were randomly assigned to the tenofovir group had no NRTIs that were predicted to have activity in their prescribed regimen (Table S1 in the Supplementary Appendix). Patients received their randomly assigned drugs for 96% of follow-up time (Table S2), attended more than 99% of scheduled visits, and reported complete adherence at 80% of visits.

EFFICACY

In the intention-to-treat population, a viral load of less than 400 copies per milliliter was found in 212 patients (90.2%) in the dolutegravir group and in 210 patients (91.7%) in the darunavir group (difference, −1.5 percentage points; 95% confidence interval [CI], −6.7 to 3.7), which met the prespecified noninferiority criterion for the primary outcome (Table 2 and Fig. S1A). The noninferiority criterion was also met in the per-protocol population, which excluded 26 patients who interrupted or switched treatment; there was no evidence of superiority of dolutegravir ($P=0.58$ for superiority) (Table 2). Results were consistent in sensitivity analyses of the primary outcome and of viral load thresholds of 1000 copies per milliliter and 50 copies per milliliter (Table 2). Responses were similar across prespecified subgroups (Fig. 2). More than 90% of the patients who were taking either dolutegravir or darunavir and had no NRTIs that were predicted to have activity had a viral load of less than 400 copies per milliliter (Fig. 2).

Confirmed virologic rebound occurred in 14 patients (6.0%) in the dolutegravir group and in 13 patients (5.7%) in the darunavir group (Table 2). Dolutegravir resistance–associated viral mutations were detected in 4 patients in the dolutegravir group (conferring high-level resistance in 3 and intermediate-level resistance in 1); no darunavir resistance–associated mutations were detected in the darunavir group (Table 2). The CD4+ cell count increased similarly in the dolutegravir group and the darunavir group (Table 2).

No interaction was detected between the zidovudine–tenofovir and darunavir–dolutegravir randomization factors for the primary outcome ($P=0.99$), and therefore the results for

Table 2. Efficacy Outcomes at Week 48.*

Outcome	Dolutegravir (N=235)	Darunavir (N=229)	Difference (95% CI)	P Value†	Tenofovir (N=233)	Zidovudine (N=231)	Difference (95% CI)	P Value†
Primary outcome: HIV-1 RNA level, intention-to-treat population — no. (%)‡								
<400 copies/ml	212 (90.2)	210 (91.7)	−1.5 (−6.7 to 3.7)	0.58	215 (92.3)	207 (89.6)	2.7 (−2.6 to 7.9)	0.32
≥400 copies/ml§	20 (8.5)	16 (7.0)	—	—	15 (6.4)	21 (9.1)	—	—
No virologic data	3 (1.3)	3 (1.3)	—	—	3 (1.3)	3 (1.3)	—	—
Withdrew because of adverse event or death	2 (0.9)	3 (1.3)	—	—	3 (1.3)	2 (0.9)	—	—
Withdrew for other reasons	1 (0.4)	0	—	—	0	1 (0.4)	—	—
HIV-1 RNA level, sensitivity analyses								
<400 copies/ml, adjusted — %¶	88.2	89.8	−1.6 (−6.9 to 3.6)	—	88.2	85.4	2.8 (−2.5 to 8.0)	—
<400 copies/ml, per protocol — no./total no. (%)‖	205/222 (92.3)	204/219 (93.2)	−0.8 (−5.6 to 4.0)	—	209/223 (93.7)	200/218 (91.7)	2.0 (−2.9 to 6.8)	—
<400 copies/ml, imputed — %	91.4	93.0	−1.6 (−6.5 to 3.3)	—	93.6	90.8	2.7 (−2.2 to 7.6)	—
<400 copies/ml, complete case — no./total no. (%)	212/232 (91.4)	210/226 (92.9)	−1.5 (−6.5 to 3.4)	—	215/230 (93.5)	207/228 (90.8)	2.7 (−2.2 to 7.6)	—
Secondary and other efficacy outcomes								
Viral load <1000 copies/ml — no. (%)	217 (92.3)	213 (93.0)	−0.7 (−5.4 to 4.1)	—	219 (94.0)	211 (91.3)	2.6 (−2.1 to 7.4)	—
Viral load <50 copies/ml — no. (%)	190 (80.9)	182 (79.5)	1.4 (−5.9 to 8.6)	—	188 (80.7)	184 (79.7)	1.0 (−6.2 to 8.3)	—
Confirmed viral load rebound to ≥1000 copies/ml — no. (%)**	14 (6.0)	13 (5.7)	0.3 (−4.0 to 4.5)	—	11 (4.7)	16 (6.9)	−2.2 (−6.5 to 2.1)	—
Confirmed viral load rebound to ≥1000 copies/ml with ≥1 dolutegravir or darunavir major resistance mutation — no.††	4	0	—	—	1	3	—	—
Change from baseline in CD4+ cell count — cells/mm^3‡‡	148±172	150±199	−2 (−36 to 32)	—	157±182	142±189	15 (−19 to 49)	—

* Plus–minus values are means ±SD. All analyses of viral load suppression above or below the threshold were conducted with the use of the Food and Drug Administration snapshot algorithm and involved the intention-to-treat population, except where stated for sensitivity analyses. Analyses of viral load rebound and changes in CD4+ cell count were conducted with the use of complete-case analyses. The widths of the confidence intervals have not been adjusted for multiple comparisons, and therefore the intervals cannot be used to infer treatment effects with respect to secondary and other efficacy outcomes.

the comparison of zidovudine and tenofovir are presented according to randomly assigned group. In the intention-to-treat population, a viral load of less than 400 copies per milliliter was found in 215 patients (92.3%) in the tenofovir group and in 207 patients (89.6%) in the zidovudine group (difference, 2.7 percentage points; 95% CI, −2.6 to 7.9), which met the prespecified noninferiority criterion (Table 2 and Fig. S1B). The noninferiority criterion was also met in the per-protocol population (Table 2); there was no evidence of superiority of tenofovir (P=0.32 for superiority). Results were consistent in sensitivity analyses and in analyses of viral suppression at other viral load thresholds (Table 2). Responses were similar across subgroups, including those with a K65R viral mutation or intermediate- or high-level tenofovir resistance at baseline (Fig. 3).

Confirmed virologic rebound occurred in 11 patients (4.7%) in the tenofovir group and in 16 patients (6.9%) in the zidovudine group. Three of the four cases of dolutegravir resistance occurred in the zidovudine group (Table 2).

SAFETY

In total, 30 grade 3 or 4 adverse events, 2 events that led to drug cessation (both events were anemia, leading to discontinuation of zidovudine), 22 serious adverse events, 5 deaths (from cryptococcal meningitis in 1 patient and from unknown causes in 4 patients), and 4 new WHO stage 4 events (all cryptococcal meningitis) occurred, with a generally balanced distribution between the groups in each factorial comparison (Tables S3–S5). Two patients (both of whom were taking tenofovir and darunavir) had an eGFR of less than 60 ml per minute per 1.73 m^2, and 6 patients (4 of whom were taking zidovudine) had a hemoglobin level of less than 9 g per deciliter. Changes in weight and body-mass index and the incidence of obesity (25 cases, all in female participants) were similar in the two groups in each factorial comparison (Table S6).

DISCUSSION

In this trial, we found that dolutegravir with two NRTIs was noninferior to ritonavir-boosted darunavir with two NRTIs for second-line therapy. Treatment was delivered with the use of the WHO-recommended public health approach, with nurse-led care, an emphasis on adherence coun-

† P values for the primary outcome are for superiority (not noninferiority).
‡ P=0.99 for the interaction between the two factorial comparisons.
§ All patients with a viral load of 400 copies per milliliter or greater had this value measured at week 48 (none were due to switches for lack of efficacy or withdrawal).
¶ Estimates were from a binomial linear regression with adjustment for the other factorial comparison, site, baseline viral load, CD4+ cell count, and sex.
‖ The per-protocol population excludes 26 patients who died, were lost to follow-up, or interrupted or switched treatment for reasons not permitted by the protocol.
** One additional patient (assigned to receive dolutegravir and tenofovir) had a viral load of at least 1000 copies per milliliter at week 48 that could not be confirmed. (The patient had not taken any ART drugs for >3 months and withdrew from the trial after the visit.)
†† Data are based on available viral sequences for 23 of 27 patients. The mutations in the 4 patients who had at least one major viral mutation associated with dolutegravir resistance were T66TA, G118R, E138K, G149GA, and G163GR in 1 patient (high-level resistance according to Stanford criteria); E138K, G140A, and Q148R in 1 patient (high-level resistance); T66I, G118R, E138K, and G149GA in 1 patient (high-level resistance); and R263K and M50I in 1 patient (intermediate-level resistance). No patients had viral mutations associated with darunavir resistance.
‡‡ CD4+ cell-count data were available for 458 patients; missing values were due to death (5 patients [2 who received dolutegravir, 3 who received darunavir, 3 who received tenofovir, and 2 who received zidovudine]) or loss to follow-up (1 patient who received dolutegravir and zidovudine).

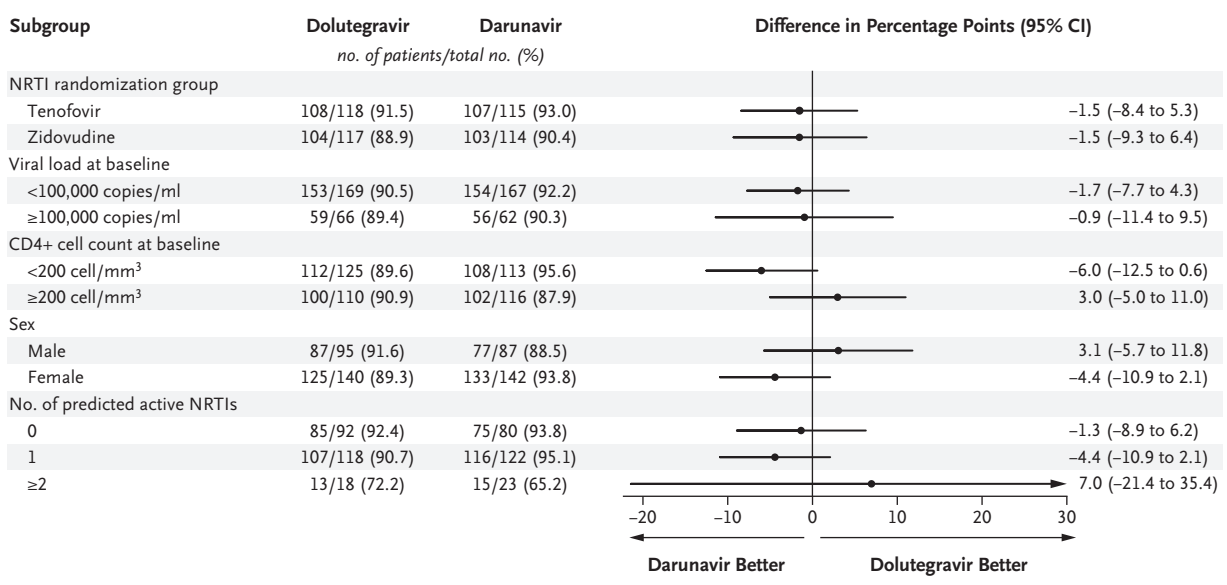

Figure 2. Subgroup Analysis of Viral Suppression in the Dolutegravir and Darunavir Groups.

Shown is the percentage of patients with a viral load of less than 400 copies per milliliter at week 48, according to randomly assigned treatment group and prespecified subgroups. The first subgroups shown are the other factorial randomization groups (i.e., the nucleoside reverse-transcriptase inhibitor [NRTI] treatment groups). The percentage of patients with viral suppression is based on the Food and Drug Administration (FDA) snapshot algorithm and includes all patients with data available for subgroup classification. The widths of the confidence intervals have not been adjusted for multiple comparisons and cannot be used to infer treatment effects.

seling, and infrequent viral load and safety monitoring and without baseline genotypic resistance testing to guide the selection of NRTIs. The results are therefore generalizable to most patients worldwide who receive treatment for HIV infection in this way.

The percentages of patients who had viral suppression while taking either dolutegravir-based or darunavir-based second-line treatment were similar to those among patients taking dolutegravir-based first-line treatment in trials performed in sub-Saharan Africa.[14,15] Responses were good in subgroups of patients with a high viral load, those with a low CD4+ cell count, and, crucially, those for whom NRTIs that had no predicted activity had been prescribed. The marked contribution of NRTIs to the efficacy of regimens despite high levels of cross-resistance has been described with protease inhibitor–based regimens,[4,5,10,11,16-18] but such evaluations of NRTIs with dolutegravir have been lacking; current WHO guidelines include caveats about the use of dolutegravir in this important subpopulation.[2,3] The reason for preserved NRTI activity is uncertain, but it may be due to impairment of viral replicative capacity by NRTI resistance mutations.[4,5,19,20] The paradoxical worse outcome in the subgroup of patients who were treated with at least two NRTIs that were predicted to have activity (i.e., patients who did not have viral mutations associated with NRTI resistance at baseline) may have arisen from an overrepresentation of patients with particularly poor adherence combined with an absence of beneficial effects of mutations on viral replicative capacity.[5]

Our results are relevant to millions of patients worldwide who are switching to dolutegravir-based regimens either for identified treatment failure or electively because programs are shifting to universal dolutegravir-based treatment for anticipated population health gains.[21] Programmatic switches between regimens are often implemented without viral load testing and inevitably involve some patients with occult viral replication and accumulated NRTI resistance.[22] Our trial provides evidence that such patients, even if they have extensive NRTI resistance, are likely to have viral suppression after a

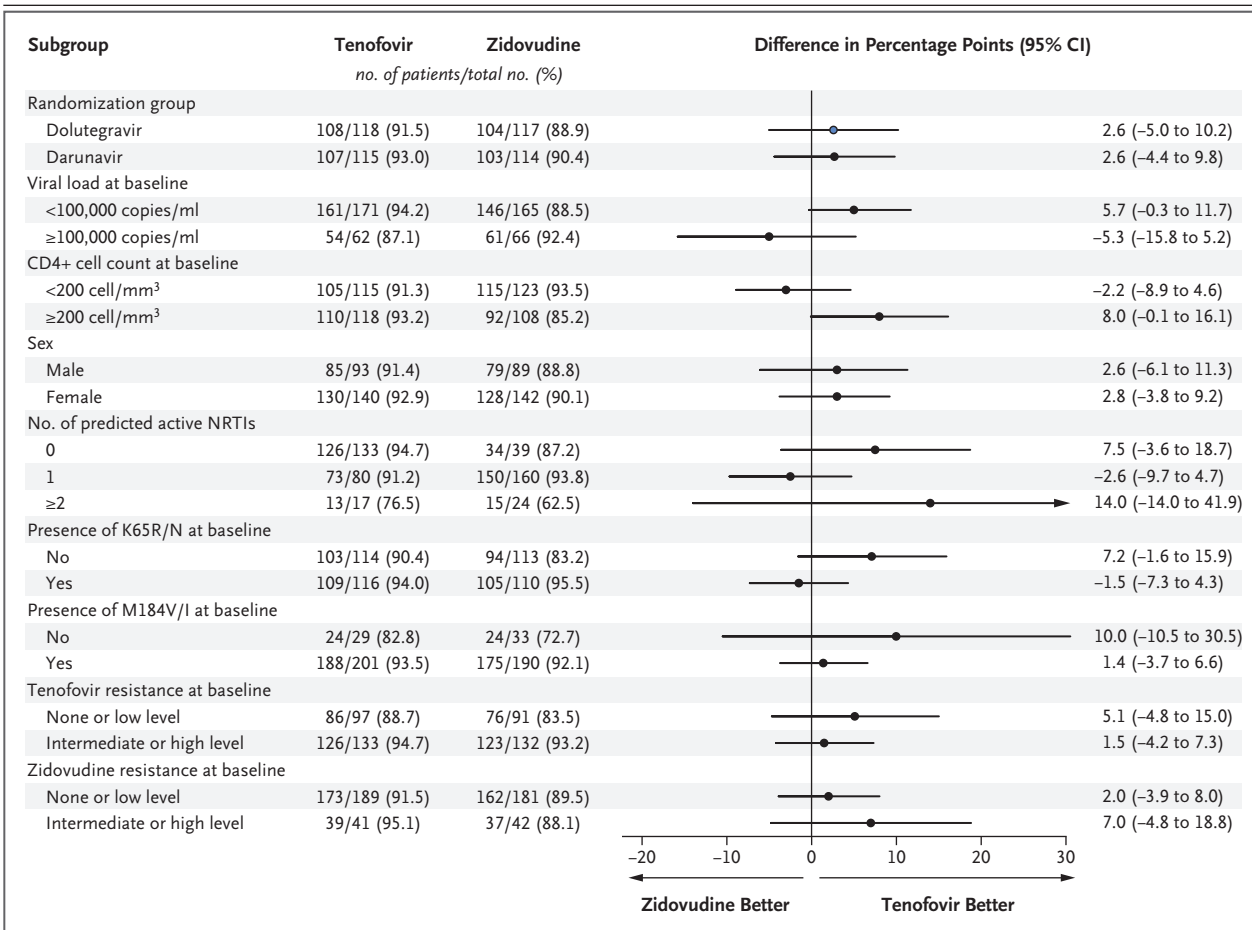

Figure 3. Subgroup Analysis of Viral Suppression in the Tenofovir and Zidovudine Groups.

Shown is the percentage of patients with a viral load of less than 400 copies per milliliter at week 48, according to randomly assigned treatment group and prespecified subgroups. The first subgroups shown are the other factorial randomization groups (i.e., the dolutegravir group and darunavir group). The percentage of patients with suppression is based on the FDA snapshot algorithm and includes all patients with data available for subgroup classification. The widths of the confidence intervals have not been adjusted for multiple comparisons and cannot be used to infer treatment effects.

switch to dolutegravir. Models that have estimated a substantial negative effect of NRTI resistance on the efficacy of dolutegravir regimens may have, on the basis of this assumption, underestimated the population health benefits arising from universal dolutegravir treatment.[21]

We did not find evidence of the superiority of dolutegravir that was seen in three previous trials in which dolutegravir was compared with a protease inhibitor, each given with NRTIs, in first-line or second-line therapy.[13,23,24] The absence of superiority may reflect a better side-effect profile or a greater potency of darunavir as compared with those of the alternative protease inhibitors that were used in some earlier trials, the effect of the NRTI resistance milieu (as discussed above), or differences among trials in their approach to the detection and management of nonsuppressed viral loads. Our trial has also strengthened the evidence base for using darunavir with NRTIs in the public health approach. Given the absence of a negative effect of NRTI cross-resistance on its observed activity, the darunavir-based regimen should provide good viral suppression whether it is used after failure of an NNRTI-based or a dolutegravir-based regimen.

Although viral load suppression at 48 weeks is the standard trial efficacy outcome, other

outcomes may be as important for evaluating regimens used in the public health approach. Evolution of drug resistance is of particular concern. Existing high-quality evidence shows the durability of regimens consisting of protease inhibitors with NRTIs in the public health approach, even in the context of NRTI resistance.[4,25] Dolutegravir resistance is rare when the drug is used with fully active NRTIs in first-line therapy, but trials of monotherapy have shown vulnerability to the development of resistance[26]; resistance has also been reported in patients who begin treatment with dolutegravir and NRTIs after previous NRTI exposure.[13,27] Our finding of four cases of intermediate- or high-level dolutegravir resistance within 48 weeks (as compared with no cases in the darunavir group) underlines this concern. A finding of substantial increases in resistance with longer-term follow-up could represent a problem for the use of this regimen in the public health approach, because frequent monitoring of viral load is not feasible and provision of integrase resistance testing for clinical management in patients with viral rebound will be challenging. Surveillance for emerging dolutegravir resistance after large-scale programmatic treatment switches also appears to be an important safeguard. We observed incident obesity in 10% of female participants, but this did not differ between the groups in each factorial comparison. Our trial continues follow-up to assess the longer-term durability of viral load suppression, emergence of resistance, and drug toxicity.

Our trial was performed with a second, factorial randomization to provide an answer to another question of public health importance. WHO guidelines have consistently recommended algorithmic NRTI switching at the transition from first-line to second-line therapy, in accordance with a long-established principle in the treatment of infectious diseases to avoid changing a single drug in a failing combination regimen (in order to minimize the risk of the development of resistance).[28,29] Worldwide, most patients take tenofovir-based first-line therapy and switch to zidovudine for second-line therapy. Our finding of noninferiority for tenofovir indicates that the WHO guidelines could be simplified to recommend maintaining tenofovir and lamivudine at the time of a switch to second-line treatment. This would be appealing for patients, because zidovudine requires twice-daily administration and generally has a less acceptable side-effect profile than tenofovir (although adverse events associated with the two drugs were similar in this trial); it is also appealing for programs, because maintaining tenofovir would enable greater drug standardization. Further simplification with the use of darunavir plus lamivudine alone may be possible, even in the context of lamivudine resistance.[18] However, the cases of high-level dolutegravir resistance and the low incidence of serious tenofovir-related toxic effects we observed suggest that the risks may outweigh the benefits of dolutegravir with lamivudine alone for second-line therapy in the public health approach. Our findings strengthen the evidence indicating that resistance-testing algorithms for predicting NRTI activity may need revision,[5] given the limited relationship between predicted NRTI activity and outcomes, whether NRTIs are combined with dolutegravir or darunavir.

The main strengths of the trial are its small number of exclusion criteria, its high proportion of female participants, the generalizability of its treatment delivery to the public health approach, and its factorial design, which allowed investigation of the contribution of individual drugs to different treatment combinations. The main limitation of the trial is the use of open-label treatment, but blinding would have required multiple placebos and twice-daily dosing for all the patients, thereby diminishing the relevance of our results for public health programs. Negligible patient attrition and the use of laboratory-based outcomes reduced the likelihood of substantial bias.

Our trial provides evidence to support broad use of dolutegravir in the public health approach and provides confidence that the use of this drug leads to high levels of virologic suppression even when used with NRTIs that are predicted to have no activity. Our results also support maintaining tenofovir in second-line therapy rather than switching to zidovudine.

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