ORIGINAL ARTICLE

Second-Line Antiretroviral Therapy for Children Living with HIV in Africa

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ABSTRACT

BACKGROUND

Children living with human immunodeficiency virus (HIV) have limited options for second-line antiretroviral therapy (ART).

METHODS

In this open-label trial with a 2-by-4 factorial design, we randomly assigned children with HIV who had first-line treatment failure to receive second-line therapy with tenofovir alafenamide fumarate (TAF)–emtricitabine or standard care (abacavir or zidovudine, plus lamivudine) as the backbone and dolutegravir or ritonavir-boosted darunavir, atazanavir, or lopinavir as the anchor drug. The primary outcome was a viral load of less than 400 copies per milliliter at 96 weeks. We hypothesized that TAF–emtricitabine would be noninferior to standard care, that dolutegravir and ritonavir-boosted darunavir would each be superior to ritonavir-boosted lopinavir and atazanavir analyzed in combination, and that ritonavir-boosted atazanavir would be noninferior to ritonavir-boosted lopinavir. Safety was also assessed.

RESULTS

A total of 919 children underwent randomization; 458 were assigned to receive TAF–emtricitabine, and 461 to receive standard care. Assigned anchor drugs were dolutegravir (229 participants), ritonavir-boosted darunavir (232), ritonavir-boosted atazanavir (231), and ritonavir-boosted lopinavir (227). The median age of participants was 10 years, and 497 (54.1%) were male. The median viral load at baseline was 17,573 copies per milliliter. At week 96, TAF–emtricitabine was superior to standard care: the adjusted difference in the percentage of participants with a viral load of less than 400 copies per milliliter was 6.3 percentage points (95% confidence interval [CI], 2.0 to 10.6; P=0.004). Dolutegravir was superior to ritonavir-boosted lopinavir and atazanavir analyzed in combination (adjusted difference, 9.7 percentage points; 95% CI, 4.8 to 14.5; P<0.001), but ritonavir-boosted darunavir was not (adjusted difference, 5.6 percentage points; 95% CI, 0.3 to 11.0; P=0.04 [prespecified threshold, P=0.03]). Ritonavir-boosted atazanavir was noninferior to ritonavir-boosted lopinavir. One child died, and 29 (3.2%) had serious adverse events, with no significant between-group differences.

CONCLUSIONS

Second-line ART regimens including TAF–emtricitabine and dolutegravir were effective for children, with no evidence of safety concerns. Ritonavir-boosted darunavir was also effective. (Funded by the European and Developing Countries Clinical Trials Partnership and others; CHAPAS-4 ISRCTN Registry number, ISRCTN22964075.)

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Globally, the number of children living with human immunodeficiency virus (HIV) who are receiving first-line antiretroviral therapy (ART) is increasing. This increase in access to ART, coupled with increased monitoring of HIV viral load, is in turn increasing the number of children in need of second- or subsequent-line ART after virologic failure.[1-3] Most children with HIV live in Africa, where until recently first-line nonnucleoside reverse-transcriptase inhibitor (NNRTI)–based regimens were widely used. After the failure of first-line NNRTI-based ART, guidelines recommend an anchor drug from a new class (a ritonavir-boosted protease inhibitor or integrase inhibitor), plus a backbone of two nucleoside (or nucleotide) reverse-transcriptase inhibitors (NRTIs). Maximizing effectiveness and acceptability to patients while minimizing side effects is particularly important for children in need of lifelong ART.[4] Which backbone and anchor drugs are safest and most effective for pediatric second-line ART remains unclear.

A tenofovir disoproxil fumarate–based backbone is recommended for first- and second-line ART for adolescents weighing more than 30 kg; integrase inhibitor–based regimens including tenofovir have shown robust efficacy as compared with ritonavir-boosted protease inhibitor–based regimens including zidovudine in trials of second-line ART regimens in adults.[5-7] However, concerns about negative effects on bone and kidney health and the lack of pediatric formulations limit pediatric use of tenofovir disoproxil fumarate.[8]

Tenofovir alafenamide fumarate (TAF), a tenofovir prodrug, can be used at lower doses and has better safety profiles with respect to kidney and bone health than tenofovir disoproxil fumarate,[9,10] and a new pediatric fixed-dose combination of TAF at a dose of 15 mg and emtricitabine at a dose of 120 mg has been developed, although it is not currently widely available. There are minimal data on the use of TAF in African children; early pediatric pharmacokinetic data showed tenofovir concentrations equivalent to those considered to be safe and effective in adults.[11] Dolutegravir is available in child-friendly formulations. Ritonavir-boosted protease inhibitors provide sustained suppression of viral load and a high barrier to resistance,[6,7] but current formulations present challenges.[12] Lopinavir is the only pediatric protease inhibitor coformulated with a ritonavir booster, but it requires twice-daily administration and is unpalatable; ritonavir-boosted darunavir and atazanavir can be administered once daily, but pediatric fixed-dose combinations are unavailable and ritonavir-boosted darunavir is relatively costly. To further explore ART options for children with HIV, the CHAPAS-4 trial compared the efficacy and safety of different second-line anchor drugs in combination with TAF-based or standard-care backbone therapy in African children 3 to 15 years of age.

METHODS

TRIAL DESIGN AND OVERSIGHT

We conducted this open-label, randomized trial with a 2-by-4 factorial design. The trial was approved by the Joint Clinical Research Centre research ethics committee in Uganda, the University of Zambia biomedical research ethics committee in Zambia, the joint research ethics committee of the University of Zimbabwe College of Health Sciences and the Medical Research Council of Zimbabwe in Zimbabwe, the University of Cape Town human research ethics committee in South Africa, and the University College London research ethics committee in the United Kingdom. University College London was the trial sponsor (a role that involved oversight of the trial but no funding), with central management by the Medical Research Council Clinical Trials Unit at University College London. Participants were recruited at six centers in three African countries: in Uganda, the Joint Clinical Research Centres in Kampala and Mbarara; in Zambia, the University Teaching Hospital, Lusaka, and Arthur Davison Children's Hospital, Ndola; and in Zimbabwe, the University of Zimbabwe Clinical Research Center, Harare, and Mpilo Central Hospital, Bulawayo.

The main funder (the European and Developing Countries Clinical Trials Partnership) and pharmaceutical companies that provided additional funding (Johnson & Johnson and Gilead Sciences) and drugs (Johnson & Johnson, Gilead Sciences, ViiV Healthcare, and Cipla) did not participate in designing or conducting the trial or analyzing the data. Contributions of individual authors are listed in the Supplementary Appendix, available with the full text of this article at NEJM.org. The authors had the opportunity to comment on drafts of the manuscript, and all

agreed to submit the manuscript for publication. The third and third-to-last authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, available at NEJM.org.

PARTICIPANTS

Participants were children with HIV who were 3 to 15 years of age, weighed at least 14 kg, were receiving first-line NNRTI-based ART, had treatment failure according to World Health Organization (WHO) criteria (a confirmed viral load of >1000 copies per milliliter after receiving counseling about adherence to the treatment regimen, or immunologic or clinical criteria for failure), and had a viral load above 400 copies per milliliter at the screening visit. Postmenarchal girls were required to have a pregnancy test with negative results. Guardians provided written informed consent, with additional assent obtained from children as appropriate according to age, knowledge of HIV status, and national guidelines. Children were excluded if they had severe hepatic impairment (defined as an alanine aminotransferase level at least five times the upper limit of the normal range, an alanine aminotransferase level at least three times the upper limit of the normal range and a bilirubin level at least two times the upper limit of the normal range, or clinical liver disease). Full details of the criteria for inclusion and exclusion are provided in the protocol.

RANDOMIZATION AND PROCEDURES

Participants were randomly assigned to receive one of two backbone drug combinations — TAF–emtricitabine or standard care (abacavir–lamivudine or zidovudine–lamivudine, whichever was not used in first-line ART) — and were simultaneously randomly assigned to receive one of four anchor drugs (dolutegravir, ritonavir-boosted darunavir, ritonavir-boosted atazanavir, or ritonavir-boosted lopinavir). Drugs that were not donated to the trial were purchased from Emcure Pharmaceuticals. Randomization was stratified according to site and first-line NRTI (abacavir or zidovudine). A computer-generated sequential randomization list with variably sized permuted blocks was prepared by the trial statistician and incorporated securely into an online database. Allocation was concealed until eligibility was confirmed by local center staff, who then assigned participants to the treatment regimens.

Participants were seen at screening; at the time when the assigned ART regimen was initiated, designated week 0; at 2, 6, and 12 weeks; and every 12 weeks thereafter until at least week 96 (when the primary outcome was assessed). Extended follow-up continued until February 2, 2023. Children with tuberculosis at enrollment or during follow-up underwent regimen modification to account for drug interactions with rifampicin. Additional measures ensured participant follow-up during the coronavirus disease 2019 (Covid-19) pandemic (details are provided in the Supplementary Appendix).

OUTCOMES

The primary outcome was a viral load of less than 400 copies per milliliter at 96 weeks; death before week 96 was considered to be treatment failure. Secondary efficacy outcomes were viral loads of less than 60 copies per milliliter (the lower limit of detection at one site) and less than 1000 copies per milliliter at 96 weeks, death, a clinical stage 3 or 4 event according to WHO criteria (stages range from 1 [no symptoms] to 4 [severe symptoms]), changes from baseline in the CD4 cell count and CD4 cell percentage, and HIV genotypic drug resistance. Safety outcomes were grade 3 and 4 adverse events, serious adverse events, adverse events that led to ART modification, and changes in levels of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, bilirubin, and creatinine clearance. Other exploratory outcomes included changes in weight-for-age, height-for-age, and body-mass index (BMI)–for-age z scores and bone mineral density. An economic analysis considered costs, which were estimated from the health-system perspective and included expenses for ART, clinic visits, and hospital stays in 2022 U.S. dollars, discounted at 3% per annum (Supplementary Appendix).

STATISTICAL ANALYSIS

For the randomization to different backbone drug combinations, we calculated that a sample size of 920 participants would provide the trial with at least 95% power at a two-sided alpha level of 0.05 to show that TAF was noninferior to standard care, with a noninferiority margin of 10 percentage points, under the assumptions that

80.0 to 87.5% of participants assigned to receive standard care would have a viral load of less than 400 copies per milliliter at week 96 and that 2.5% of participants would be lost to follow-up (an estimate that was reduced from 10% in the original protocol). For the randomization to different anchor drugs, we calculated that a sample size of 920 participants would provide the trial with 88% power at a two-sided alpha level of 0.05 to show that ritonavir-boosted atazanavir was noninferior to ritonavir-boosted lopinavir, with a noninferiority margin of 12 percentage points, under the assumption that 80% of participants would have a viral load of less than 400 copies per milliliter at week 96; we calculated that the trial would have 89% power at a two-sided alpha level of 0.03 (for multiple comparisons) to detect a difference of 10 percentage points in the percentage of participants with a viral load of less than 400 copies per milliliter at 96 weeks with dolutegravir and with ritonavir-boosted darunavir considered individually as compared with ritonavir-boosted lopinavir and ritonavir-boosted atazanavir analyzed in combination, with a loss to follow-up of 2.5%. Margins reflect the clinical consensus and are within the range used in previous trials of second-line treatment in adults (Supplementary Appendix). An independent data monitoring committee reviewed interim data four times with the use of the Haybittle–Peto criterion (with a 99.9% confidence interval).

Analyses were performed according to the intention-to-treat principle with the use of Stata software (version 17.0). Primary-outcome analyses were performed with the use of logistic regression (with adjustment for stratification factors), followed by marginal estimation of risk differences. For noninferiority comparisons, secondary per-protocol analyses included all participants who received the assigned backbone or anchor for more than 90% of the follow-up period. For analyses of outcome events including death, WHO clinical stage 3 or 4 events, grade 3 or 4 adverse events, serious adverse events, or adverse events leading to modification of ART, groups were compared with the use of Cox regression (unadjusted). Changes in continuous outcomes were analyzed with the use of normal generalized estimating equations with adjustment for the individual visit, stratification factors, and baseline values (and interactions between these factors and values and the individual visit), for an overall analysis of difference between groups over all visits (independent correlation); mean differences are reported. The 95% confidence intervals were not adjusted for multiple tests (Supplementary Appendix).

RESULTS

PARTICIPANTS

A total of 919 children underwent randomization between December 17, 2018, and April 1, 2021 (Fig. 1); 458 were assigned to receive TAF–emtricitabine as the backbone, and 461 to receive standard care. In the randomization to anchor drugs, 227 participants were assigned to receive ritonavir-boosted lopinavir, 231 to receive ritonavir-boosted atazanavir, 232 to receive ritonavir-boosted darunavir, and 229 to receive dolutegravir. Baseline characteristics were similar across groups (Table 1 and Table S3 in the Supplementary Appendix). The median age was 10 years (interquartile range, 8 to 13); 497 participants (54.1%) were male, and 777 (84.5%) had WHO clinical stage 1 or 2 infection. Median weight-for-age, height-for-age, and BMI-for-age z scores were between –1.0 and –1.6. The median viral load was 17,573 copies per milliliter (interquartile range, 5549 to 55,700); the median CD4 cell count was 669 cells per cubic millimeter (interquartile range, 413 to 971), and the median CD4 cell percentage was 28.0% (interquartile range, 19.2 to 36.0). The median time on first-line ART was 5.6 years (44.1% of participants had received nevirapine, and 55.9% had received efavirenz). Over a period of 96 weeks, 98.9% of visits were attended. Eleven children (1.2%; 4 assigned to receive TAF–emtricitabine and 7 assigned to receive standard care in the backbone randomization; 4 assigned to receive ritonavir-boosted lopinavir, 2 assigned to receive ritonavir-boosted atazanavir, 2 assigned to receive ritonavir-boosted darunavir, and 3 assigned to receive dolutegravir in the anchor drug randomization) were lost to follow-up; these participants were excluded from efficacy analyses. A total of 674 participants (73.3%) entered the extended follow-up period, in which the median additional follow-up was 60 weeks (interquartile range, 30 to 75).

BACKBONE RANDOMIZATION

Among 461 participants assigned to receive standard care, 217 (47.1%) received abacavir–lamivudine and 244 (52.9%) received zidovudine–lamivudine. Participants received the assigned treatment for 99.1% of the time from randomization through week 96 (99.5% among those assigned to receive TAF–emtricitabine and 98.8% among those assigned to receive standard care), and 5 participants (0.5%; 2 [0.4%] in the TAF–emtricitabine group and 3 [0.7%] in the standard-care group) were switched to third-line ART. During the extended follow-up, participants received the assigned treatment for 93.5% of the time (95.6% among those receiving TAF–emtricitabine and 91.4% among those receiving standard care) (Fig. S1).

At 96 weeks, 406 of 454 participants (89.4%) assigned to receive TAF–emtricitabine had a viral load of less than 400 copies per milliliter as compared with 378 of 454 participants (83.3%) assigned to receive standard care (adjusted difference, 6.3 percentage points; 95% confidence interval [CI], 2.0 to 10.6; P=0.004) (Fig. 2). Therefore, TAF–emtricitabine was noninferior (and superior) to standard care according to the prespecified noninferiority margin of 10 percentage points. There was no evidence of heterogeneity in the effect of TAF–emtricitabine as compared with standard care in any of 11 prespecified subgroups (Fig. S2), including those defined according to first-line NRTI, assigned anchor drug, country, and baseline viral load. Results of per-protocol analyses were similar; 403 of 449 participants (89.8%) receiving TAF–emtricitabine had a viral load of less than 400 copies per milliliter, as compared with 370 of 445 participants (83.1%) receiving standard care (adjusted difference, 6.8 percentage points; 95% CI, 2.4 to 11.1; P=0.002). Differences between groups in the suppression of viral load to less than 60 copies per milliliter and to less than 1000 copies per milliliter were similar, as were results at weeks 48 and 144 (Table S4).

Over a period of 96 weeks, a total of 176 grade 3 or 4 adverse events occurred in 127 of 919 participants (13.8%): 63 of 458 participants (13.8%) assigned to receive TAF–emtricitabine and 64 of 461 (13.9%) assigned to receive standard care (P=0.93 by Cox regression) (Table 2 and Table S6). These adverse events included 8 infections, all in the standard-care group (4 cases of malaria, 3 cases of tuberculosis, and 1 case of herpes zoster). A total of 31 serious adverse events occurred in 29 participants (3.2%): 15 participants (3.3%) assigned to receive TAF–emtricitabine and 14 (3.0%) assigned to receive standard care (P=0.84) (Table 2 and Table S7); most were hospitalizations for infection. One child receiving TAF–emtricitabine plus dolutegravir died from hypotension, toxic shock, and severe malnutrition; this death was judged by the investigators to be unrelated to ART. A total of 41 adverse events of any grade leading to ART modification occurred in 24 participants (2.6%): 11 (2.4%) assigned to receive TAF–emtricitabine and 13 (2.8%) assigned to receive standard care (P=0.68); 33 of these events were related to tuberculosis, and modifications to ART were made as prespecified by the protocol (Table 2).

Over a period of 96 weeks, weight-for-age, height-for-age, and BMI-for-age z scores increased more with TAF–emtricitabine than with standard care; the mean between-group difference, averaged over all visits to week 96, was 0.09 (95% CI, 0.04 to 0.13) for the weight-for-age z score, 0.04 (95% CI, 0.01 to 0.07) for the height-for-age z score, and 0.10 (95% CI, 0.04 to 0.16) for the BMI-for-age z score. In the extended follow-up, increases were maintained, and differences between groups were similar to those at week 96 (Fig. 3 and Fig. S6). At 96 weeks, the mean weight increase from baseline was 7.0 kg with TAF–emtricitabine and 6.2 kg with standard care; the mean height increase was 10.2 cm and 9.8 cm, respectively. There was a small reduction in mean creatinine clearance in both groups at week 96, with greater reduction in the TAF–emtricitabine group than in the standard-care group (mean reduction, –16 ml per minute vs. –11 ml per minute), which persisted into the extended follow-up period (Fig. S4). Phosphate excretion was similar in the two groups (Fig. S5), and no participant discontinued TAF owing to kidney dysfunction.

ANCHOR DRUG RANDOMIZATION

At randomization, 910 of 919 participants (99.0%) began receiving their assigned anchor drug; 8 participants with tuberculosis coinfection who were assigned to receive ritonavir-boosted atazanavir or ritonavir-boosted darunavir received ritonavir-boosted lopinavir or dolutegravir instead because of protocol-specified modifications, and

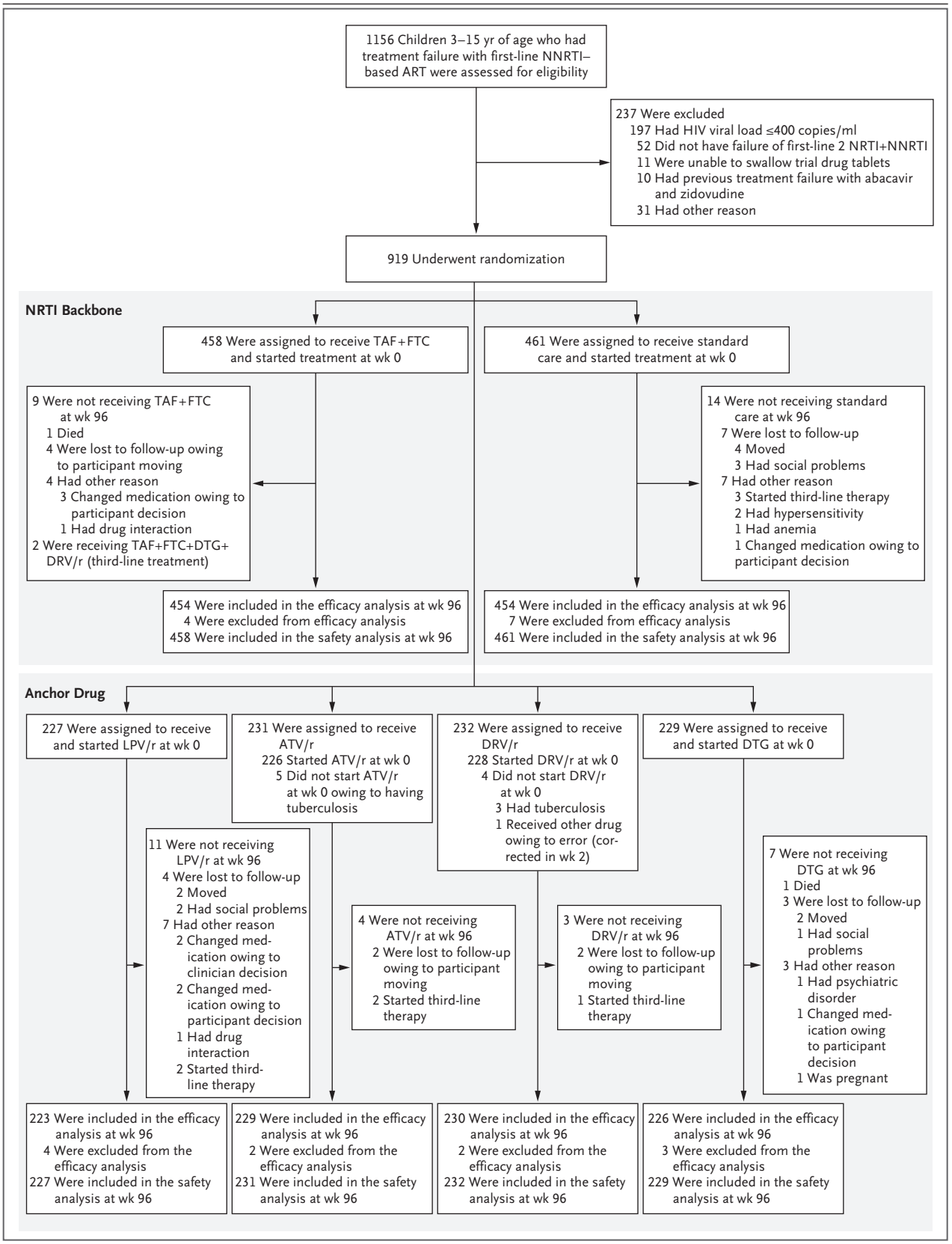

Figure 1 (facing page). Screening, Randomization, and Follow-up.

Children with multiple reasons for exclusion from the trial are counted in all applicable categories, so numbers given for individual reasons do not add up to the total number excluded from randomization. Among other reasons for exclusion were a choice not to participate (7 children), failure to return for enrollment within the specified time (4 children), age outside the specified range of 3 to 15 years (4 children), biochemical data (3 children), previous treatment failure with ritonavir-boosted lopinavir (2 children), lack of use of contraception (1 child), contraindications to the proposed therapy (1 child), coexisting conditions (1 child), and death (1 child). Details of social problems were not specified. ATV/r denotes ritonavir-boosted atazanavir, DRV/r ritonavir-boosted darunavir, DTG dolutegravir, FTC emtricitabine, LPV/r ritonavir-boosted lopinavir, NNRTI nonnucleoside reverse-transcriptase inhibitor, NRTI nucleoside (or nucleotide) reverse-transcriptase inhibitor, and TAF tenofovir alafenamide fumarate.

1 participant received a different anchor drug than the one assigned (ritonavir-boosted atazanavir instead of ritonavir-boosted darunavir) owing to an error. Participants received the assigned anchor drug for 98.6% of the time from randomization through week 96 (99.1% among participants assigned to receive dolutegravir, 98.5% among those assigned to receive ritonavir-boosted darunavir, 98.6% among those assigned to receive ritonavir-boosted atazanavir, and 98.4% among those assigned to receive ritonavir-boosted lopinavir). Five participants (0.5%; 1 receiving ritonavir-boosted darunavir, 2 receiving ritonavir-boosted atazanavir, and 2 receiving ritonavir-boosted lopinavir) were switched to third-line ART. During the extended follow-up period, participants received the assigned treatment for 86.2% of the time (99.1% among those assigned to receive dolutegravir, 95.6% among those assigned to receive ritonavir-boosted darunavir, 93.7% among those assigned to receive ritonavir-boosted atazanavir, and 54.9% among those assigned to receive ritonavir-boosted lopinavir).

At week 96, a viral load of less than 400 copies per milliliter was observed in 92.0% of participants receiving dolutegravir, 88.3% of those receiving ritonavir-boosted darunavir, 84.3% of those receiving ritonavir-boosted atazanavir, and 80.7% of those receiving ritonavir-boosted lopinavir (Fig. 2). Dolutegravir was superior to ritonavir-boosted lopinavir and ritonavir-boosted atazanavir analyzed in combination with respect to the primary outcome (adjusted difference in the percentage of participants with a viral load of <400 copies per milliliter, 9.7 percentage points; 95% CI, 4.8 to 14.5; P<0.001) (Table S5). Ritonavir-boosted darunavir was not superior to ritonavir-boosted lopinavir and ritonavir-boosted atazanavir analyzed in combination, because the comparison did not meet the prespecified significance level (adjusted difference, 5.6 percentage points; 95% CI, 0.3 to 11.0; P=0.04, which is greater than the prespecified threshold of P=0.03 from multiple comparisons). Ritonavir-boosted atazanavir was noninferior to ritonavir-boosted lopinavir (adjusted difference, 3.4 percentage points; 95% CI, −3.4 to 10.2; P=0.33). Results of the per-protocol analysis were similar (Supplementary Appendix).

For each comparison, there was no evidence of heterogeneity among 11 prespecified subgroups, including those defined according to first-line NRTI, assigned backbone, country, and baseline viral load, apart from a marginally greater difference in the response with dolutegravir as compared with ritonavir-boosted lopinavir and ritonavir-boosted atazanavir analyzed in combination when nevirapine rather than efavirenz was used as first-line treatment. In a post hoc analysis, the percentage of participants with viral load suppression was higher by 4.0 percentage points (95% CI, −1.3 to 9.4) with dolutegravir than with ritonavir-boosted darunavir. For each comparison, results with respect to viral loads of less than 60 copies per milliliter and less than 1000 copies per milliliter were similar, as was suppression at weeks 48 and 144 (Fig. 2).

Over a period of 96 weeks, 127 of 919 participants (13.8%) had grade 3 or 4 adverse events (Table 2), most commonly hyperbilirubinemia, which, predictably, was associated almost exclusively with ritonavir-boosted atazanavir (Fig. S7). Fewer children had grade 3 or 4 adverse events with dolutegravir (5.2%) than with ritonavir-boosted lopinavir (11.5%) (P=0.02); there was no evidence of a significant difference in the incidence of grade 3 or 4 adverse events with ritonavir-boosted darunavir (8.6%) as compared with ritonavir-boosted lopinavir (11.5%) (P=0.31). Serious adverse events occurred in 29 participants (3.2%) — 6 receiving dolutegravir, 8 receiving ritonavir-boosted darunavir, 5 receiving ritonavir-boosted atazanavir, and 10 receiving ritonavir-boosted lopinavir (P>0.1 for all comparisons).

Table 1. Clinical and Demographic Characteristics of the Participants at Baseline.*

Characteristic	NRTI Backbone Randomization		Anchor Drug Randomization				All (N = 919)
	Standard Care (N = 461)	TAF (N = 458)	Ritonavir-Boosted Lopinavir (N = 227)	Ritonavir-Boosted Atazanavir (N = 231)	Ritonavir-Boosted Darunavir (N = 232)	Dolutegravir (N = 229)	
Male sex — no. (%)	256 (55.5)	241 (52.6)	120 (52.9)	129 (55.8)	121 (52.2)	127 (55.5)	497 (54.1)
Age							
Median (IQR) — yr	10 (7–13)	10 (8–13)	10 (7–12)	10 (8–13)	10 (8–12)	11 (8–13)	10 (8–13)
Distribution — no. (%)							
3–4 yr	21 (4.6)	18 (3.9)	12 (5.3)	14 (6.1)	7 (3.0)	6 (2.6)	39 (4.2)
5–9 yr	178 (38.6)	180 (39.3)	95 (41.9)	83 (35.9)	96 (41.4)	84 (36.7)	358 (39.0)
10–15 yr	262 (56.8)	260 (56.8)	120 (52.9)	134 (58.0)	129 (55.6)	139 (60.7)	522 (56.8)
WHO clinical stage — no. (%)†							
1	244 (52.9)	239 (52.2)	114 (50.2)	121 (52.4)	130 (56.0)	118 (51.5)	483 (52.6)
2	140 (30.4)	154 (33.6)	79 (34.8)	74 (32.0)	65 (28.0)	76 (33.2)	294 (32.0)
3	63 (13.7)	50 (10.9)	30 (13.2)	29 (12.6)	27 (11.6)	27 (11.8)	113 (12.3)
4	14 (3.0)	15 (3.3)	4 (1.8)	7 (3.0)	10 (4.3)	8 (3.5)	29 (3.2)
Median CD4 cell count (IQR) — cells/mm^3‡	667 (405 to 963)	673 (434 to 982)	692 (432 to 1035)	685 (446 to 943)	682 (416 to 1000)	625 (349 to 891)	669 (413 to 971)
Median CD4 cell percentage (IQR)§	27.5 (19.0 to 35.4)	28.3 (20.3 to 37.0)	28.7 (19.2 to 36.0)	28.0 (20.5 to 35.2)	28.0 (19.4 to 37.1)	27.0 (18.0 to 36.0)	28.0 (19.2 to 36.0)
Median viral load (IQR) — copies/ml	17,909 (5417 to 58,359)	17,265 (5764 to 50,655)	16,885 (6333 to 59,994)	16,784 (5070 to 56,600)	18,675 (6673 to 49,668)	19,409 (4992 to 57,076)	17,573 (5549 to 55,700)
Median weight (IQR) — kg	26.1 (20.2 to 33.5)	25.8 (21.0 to 32.8)	25.1 (20.0 to 33.4)	25.2 (20.3 to 32.1)	26.0 (21.0 to 32.3)	27.0 (21.3 to 34.0)	25.9 (20.5 to 33.1)
Median weight-for-age z score (IQR)¶	−1.6 (−2.4 to −0.9)	−1.6 (−2.4 to −0.9)	−1.5 (−2.3 to −0.8)	−1.6 (−2.5 to −0.9)	−1.7 (−2.4 to −0.9)	−1.6 (−2.5 to −0.9)	−1.6 (−2.4 to −0.9)
Median height (IQR) — cm	130.9 (118.0 to 142.5)	130.1 (120.7 to 141.6)	130.0 (118.2 to 142.0)	129.5 (119.0 to 140.8)	131.6 (118.7 to 142.3)	133.0 (120.6 to 143.5)	130.5 (119.4 to 142.0)
Median height-for-age z score (IQR)¶	−1.5 (−2.3 to −0.9)	−1.6 (−2.4 to −0.8)	−1.5 (−2.3 to −0.6)	−1.7 (−2.4 to −1.0)	−1.6 (−2.3 to −0.8)	−1.5 (−2.5 to −0.9)	−1.6 (−2.3 to −0.8)
Median BMI (IQR)‖	15.4 (14.4 to 16.5)	15.5 (14.3 to 16.8)	15.5 (14.4 to 16.8)	15.5 (14.3 to 16.7)	15.4 (14.1 to 16.5)	15.5 (14.5 to 16.8)	15.5 (14.3 to 16.7)
Median BMI-for-age z score (IQR)¶	−1.0 (−1.6 to −0.4)	−0.9 (−1.8 to −0.3)	−0.8 (−1.6 to −0.3)	−1.0 (−1.8 to −0.3)	−1.0 (−1.7 to −0.5)	−1.0 (−1.7 to −0.3)	−1.0 (−1.7 to −0.4)

Median duration of first-line ART (IQR) — yr	5.6 (3.2 to 7.8)	5.5 (3.3 to 7.7)	5.2 (3.2 to 7.5)	5.4 (3.0 to 7.6)	6.0 (3.3 to 7.8)	5.7 (3.5 to 8.1)	5.6 (3.3 to 7.8)
First-line NRTI — no. (%)							
Abacavir	244 (52.9)	246 (53.7)	121 (53.3)	124 (53.7)	123 (53.0)	122 (53.3)	490 (53.3)
Zidovudine	217 (47.1)	212 (46.3)	106 (46.7)	107 (46.3)	109 (47.0)	107 (46.7)	429 (46.7)
First-line NNRTI — no. (%)							
Efavirenz	247 (53.6)	267 (58.3)	131 (57.7)	128 (55.4)	124 (53.4)	131 (57.2)	514 (55.9)
Nevirapine	214 (46.4)	191 (41.7)	96 (42.3)	103 (44.6)	108 (46.6)	98 (42.8)	405 (44.1)
Assigned NRTI backbone therapy — no. (%)							
Standard care	461 (100)	0	115 (50.7)	115 (49.8)	114 (49.1)	117 (51.1)	461 (50.2)
TAF	0	458 (100)	112 (49.3)	116 (50.2)	118 (50.9)	112 (48.9)	458 (49.8)
Assigned anchor drug — no. (%)							
Ritonavir-boosted lopinavir	115 (24.9)	112 (24.5)	227 (100)	0	0	0	227 (24.7)
Ritonavir-boosted atazanavir	115 (24.9)	116 (25.3)	0	231 (100)	0	0	231 (25.1)
Ritonavir-boosted darunavir	114 (24.7)	118 (25.8)	0	0	232 (100)	0	232 (25.2)
Dolutegravir	117 (25.4)	112 (24.5)	0	0	0	229 (100)	229 (24.9)

* ART denotes antiretroviral therapy, IQR interquartile range, NNRTI nonnucleoside reverse-transcriptase inhibitor, NRTI nucleoside (or nucleotide) reverse-transcriptase inhibitor, and TAF tenofovir alafenamide fumarate.
† Disease severity was assessed according to the World Health Organization (WHO) criteria for clinical staging of human immunodeficiency virus infection; stages range from 1 (no symptoms) to 4 (severe symptoms).
‡ Data are missing for 13 participants (9 assigned to receive TAF–emtricitabine and 4 assigned to receive standard care in the backbone randomization; 3 assigned to receive ritonavir-boosted lopinavir, 5 assigned to receive ritonavir-boosted atazanavir, 2 assigned to receive ritonavir-boosted darunavir, and 3 assigned to receive dolutegravir in the anchor drug randomization).
§ Data are missing for 14 participants (10 assigned to receive TAF–emtricitabine and 4 assigned to receive standard care in the backbone randomization; 3 assigned to receive ritonavir-boosted lopinavir, 5 assigned to receive ritonavir-boosted atazanavir, 3 assigned to receive ritonavir-boosted darunavir, and 3 assigned to receive dolutegravir in the anchor drug randomization).
¶ The z scores were determined with the use of British 1990 reference data, which cover the full age range of children in the trial.
‖ Body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

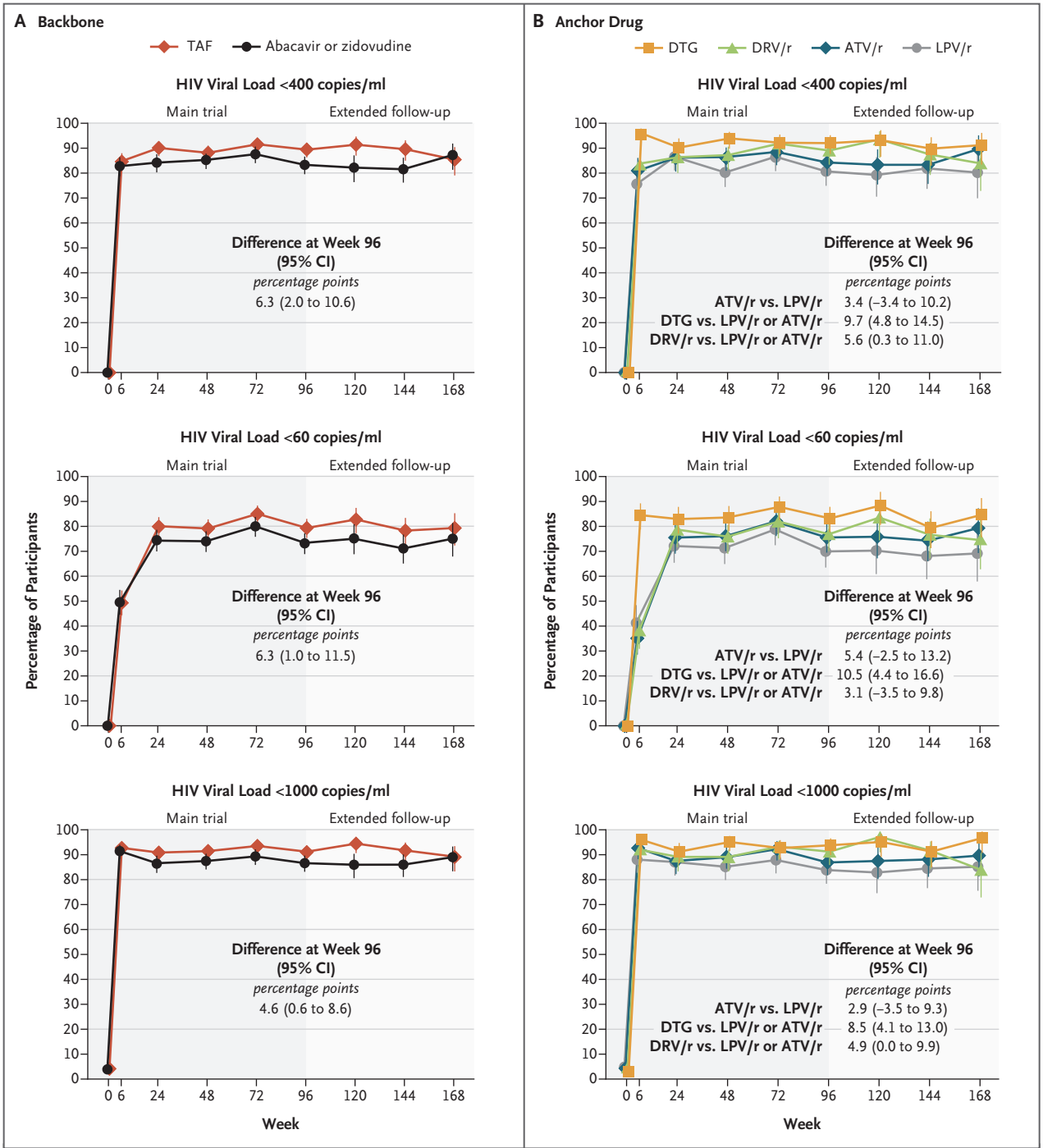

Figure 2. HIV Viral Load According to Assigned Treatment.

Shown are percentages of participants with a human immunodeficiency virus (HIV) viral load of less than 400 copies per milliliter, less than 60 copies per milliliter, and less than 1000 copies per milliliter over time during the main trial and during the extended follow-up period according to the assigned backbone (Panel A) or anchor drug (Panel B).

Adverse events of any grade leading to ART modification occurred in 24 participants (2.6%) — 7 receiving dolutegravir, 5 receiving ritonavir-boosted darunavir, 5 receiving ritonavir-boosted atazanavir, and 7 receiving ritonavir-boosted lopinavir — with no significant between-group differences (P>0.5 for all comparisons).

Weight-for-age and BMI-for-age z scores in-

creased more with ritonavir-boosted atazanavir, ritonavir-boosted darunavir, and dolutegravir than with ritonavir-boosted lopinavir (Fig. 3 and Table S8). There was no evidence that the effects of anchor drugs on weight-for-age z scores differed according to the backbone drug combination. The CD4 cell count improved in all groups, with no evidence of differences among groups over a period of 96 weeks or during the extended follow-up. Results of additional secondary-outcome analyses (including comparisons of CD4 cell counts and percentages [Fig. S8], lipid profiles [Fig. S9], and bone health [Fig. S10]) are reported in the Supplementary Appendix.

HEALTH ECONOMIC ANALYSIS

Over the 96-week trial period, the mean cost per patient of treatment with TAF–emtricitabine was lower than that with standard care (by $37.68), a finding that indicates a high probability of treatment with TAF–emtricitabine being cost-saving. Dolutegravir was the least costly anchor drug, saving $190.77 as compared with ritonavir-boosted atazanavir; ritonavir-boosted darunavir was the most expensive (see the Supplementary Appendix).

DISCUSSION

TAF–emtricitabine provided superior virologic suppression as compared with abacavir–lamivudine or zidovudine–lamivudine. Dolutegravir-based regimens were virologically superior to ritonavir-boosted lopinavir and ritonavir-boosted atazanavir analyzed in combination; ritonavir-boosted darunavir–based regimens achieved greater virologic suppression than ritonavir-boosted lopinavir and ritonavir-boosted atazanavir analyzed in combination but did not meet criteria for superiority (although the significance of the difference was close to the threshold adjusted for multiple comparisons). Ritonavir-boosted lopinavir was associated with the poorest virologic outcomes, growth, lipid profiles, and bone health. These comparisons between treatment with TAF–emtricitabine (including a new pediatric formulation with 120 mg of TAF and 15 mg of emtricitabine) and standard care and among the four main second-line anchor drugs currently available for children provide much-needed robust evidence to inform future development of drug formulations and pediatric guidelines.

Among the participants, hospitalization and disease progression were infrequent, and only one death (due to advanced disease) occurred over a period of 96 weeks. These favorable clinical outcomes are in part attributable to relatively high baseline CD4 cell counts, an observation that supports the principle of switching to second-line treatment before evidence of clinically significant immune compromise.

The percentage of participants who had virologic suppression at 96 weeks with TAF–emtricitabine — 89.4% — is similar to the 93 to 100% reported in four small, single-group pediatric studies of TAF.[13] More than 85% of participants in those studies had virologic suppression at baseline, whereas all children in the present trial had a baseline viral load of more than 400 copies per milliliter. Our results are also similar to the percentages of patients with virologic suppression (86 to 92%) with tenofovir disoproxil fumarate or TAF in the NADIA (Nucleosides and Darunavir/Dolutegravir in Africa) and VISEND second-line trials involving African adults[5-7] and the percentages with virologic suppression at 96 weeks (84 to 86%) in a pooled analysis of tenofovir disoproxil fumarate and TAF in seven trials of initial treatment in adults.[14]

Weight-for-age, height-for-age, and BMI-for-age z scores all increased more with TAF–emtricitabine than with standard care, a result that suggests overall better growth, which is potentially a consequence of improved virologic suppression. There was no evidence of negative effects on bone health with TAF, which was associated with greater increases in bone mineral density than standard care as assessed by total-body-less-head dual-energy x-ray absorptiometry, irrespective of the anchor drug. These findings, along with the additional benefits of smaller pill size, once-daily administration, lower cost, and lower risk of hypersensitivity, make TAF a valuable second-line option. Although mean creatinine clearance decreased slightly more over a period of 96 weeks with TAF–emtricitabine than with standard care, values remained within normal limits, with no grade 3 or 4 adverse events considered by the clinician to be associated with the treatment; no child discontinued medication owing to kidney impairment, and there was no evidence of tubulopathy.

The superior virologic suppression with dolutegravir as compared with ritonavir-boosted atazanavir and ritonavir-boosted lopinavir analyzed in combination extends findings from the ODYSSEY (Once-Daily Dolutegravir in Young People

Table 2. Grade 3 and 4 Adverse Events, Serious Adverse Events, and Adverse Events Leading to Modification of ART during 96 Weeks of Follow-up.*

Event	NRTI Backbone Randomization		Anchor Drug Randomization				All (N=919)
	Standard Care (N=461)	TAF (N=458)	Ritonavir-Boosted Lopinavir (N=227)	Ritonavir-Boosted Atazanavir (N=231)	Ritonavir-Boosted Darunavir (N=232)	Dolutegravir (N=229)	
Grade 3 or 4 adverse events							
Any grade 3 or 4 adverse event							
No. of participants (%)	64 (13.9)	63 (13.8)	26 (11.5)	69 (29.9)	20 (8.6)	12 (5.2)	127 (13.8)
No. of events	93	83	36	92	28	20	176
Elevated bilirubin							
No. of participants (%)	25 (5.4)	34 (7.4)	1 (0.4)	57 (24.7)	1 (0.4)	0	59 (6.4)
No. of events	32	36	1	66	1	0	68
Serious adverse events							
Any serious adverse event							
No. of participants (%)	14 (3.0)	15 (3.3)	10 (4.4)	5 (2.2)	8 (3.4)	6 (2.6)	29 (3.2)
No. of events	14	17	10	6	9	6	31
Death†							
No. of participants (%)	0	1 (0.2)	0	0	0	1 (0.4)	1 (0.1)
No. of events	0	1	0	0	0	1	1
Any life-threatening event							
No. of participants (%)	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.4)	0	0	2 (0.2)
No. of events	1	2	1	2	0	0	3
Any event leading to or prolonging hospitalization							
No. of participants (%)	13 (2.8)	14 (3.1)	9 (4.0)	5 (2.2)	8 (3.4)	5 (2.2)	27 (2.9)
No. of events	13	16	9	6	9	5	29
Any important medical condition emerging during the trial‡							
No. of participants (%)	1 (0.2)	1 (0.2)	2 (0.9)	0	0	0	2 (0.2)
No. of events	1	1	2	0	0	0	2
Events leading to ART modification							
Any event leading to ART modification							
No. of participants (%)	13 (2.8)	11 (2.4)	7 (3.1)	5 (2.2)	5 (2.2)	7 (3.1)	24 (2.6)
No. of events	22	19	11	11	9	10	41
Psychiatric disorder							
No. of participants (%)	0	1 (0.2)	0	0	0	1 (0.4)	1 (0.1)
No. of events	0	1	0	0	0	1	1
Acute hepatitis							
No. of participants (%)	1 (0.2)	0	1 (0.4)	0	0	0	1 (0.1)
No. of events	1	0	1	0	0	0	1

Table 2. (Continued.)

Event	NRTI Backbone Randomization		Anchor Drug Randomization				All (N=919)
	Standard Care (N=461)	TAF (N=458)	Ritonavir-Boosted Lopinavir (N=227)	Ritonavir-Boosted Atazanavir (N=231)	Ritonavir-Boosted Darunavir (N=232)	Dolutegravir (N=229)	
Hypersensitivity reaction							
No. of participants (%)	2 (0.4)	0	2 (0.9)	0	0	0	2 (0.2)
No. of events	4	0	4	0	0	0	4
Tuberculosis							
No. of participants (%)	9 (2.0)	9 (2.0)	4 (1.8)	5 (2.2)	4 (1.7)	5 (2.2)	18 (2.0)
No. of events	16	17	6	11	8	8	33
Pregnancy							
No. of participants (%)	0	1 (0.2)	0	0	0	1 (0.4)	1 (0.1)
No. of events	0	1	0	0	0	1	1
Anemia							
No. of participants (%)	1 (0.2)	0	0	0	1 (0.4)	0	1 (0.1)
No. of events	1	0	0	0	1	0	1

* Data are shown for events that occurred within 96 weeks after randomization. Events that occurred during the extended follow-up beyond 96 weeks are not included.
† Causes of death included hypotension, shock, and toxic shock, with severe malnutrition and esophageal, tracheal, bronchial, or pulmonary candidiasis as secondary causes.
‡ Important medical conditions included adverse events that were not immediately life-threatening or did not result in death or hospitalization but may have jeopardized the participant and may have led to medical intervention to prevent progression to life-threatening status, hospitalization, or death.

versus Standard Therapy) trial, which showed superiority of dolutegravir to standard care for both first- and second-line ART (in the ODYSSEY trial, second-line standard care was treatment with ritonavir-boosted lopinavir for 72% of participants, ritonavir-boosted atazanavir for 24%, and ritonavir-boosted darunavir for 1%).[15] Our trial provides additional evidence through direct randomized comparisons of dolutegravir and ritonavir-boosted darunavir with ritonavir-boosted atazanavir or ritonavir-boosted lopinavir. Given the cost-effectiveness of dolutegravir, the small milligram doses available, and the authorization for use in children younger than 3 years of age, these results further support dolutegravir as a second-line anchor drug of choice in WHO guidelines (when it is not used as a first-line drug).[8] The WHO also recommends dolutegravir combined with a new NRTI backbone drug combination selected according to the previously received first-line backbone for adults in whom NNRTI-based ART has failed,[8] a recommendation based in part on the superiority of dolutegravir to ritonavir-boosted lopinavir in DAWNING (Comparative Efficacy and Safety Study of Dolutegravir and Lopinavir/Ritonavir in Second-Line Treatment)[16] and the noninferiority of dolutegravir to ritonavir-boosted darunavir (with tenofovir disoproxil fumarate or zidovudine) in the NADIA trial.[6,7]

Our trial showed immune reconstitution with all drugs, particularly during the first 24 weeks after the initiation of second-line ART. Age-appropriate weight gain was observed with all anchor drugs except ritonavir-boosted lopinavir, which was associated with minimal increases in weight-for-age z scores in a population with low z scores at randomization (Fig. 3). A systematic review and meta-analysis that evaluated weight gain among adults showed greater weight gain when dolutegravir was combined with TAF than when it was combined with other NRTIs,[17] but we observed no excessive weight gain with any backbone–anchor combination, including dolutegravir plus TAF–emtricitabine. Excess weight gain in adults has been associated with advanced

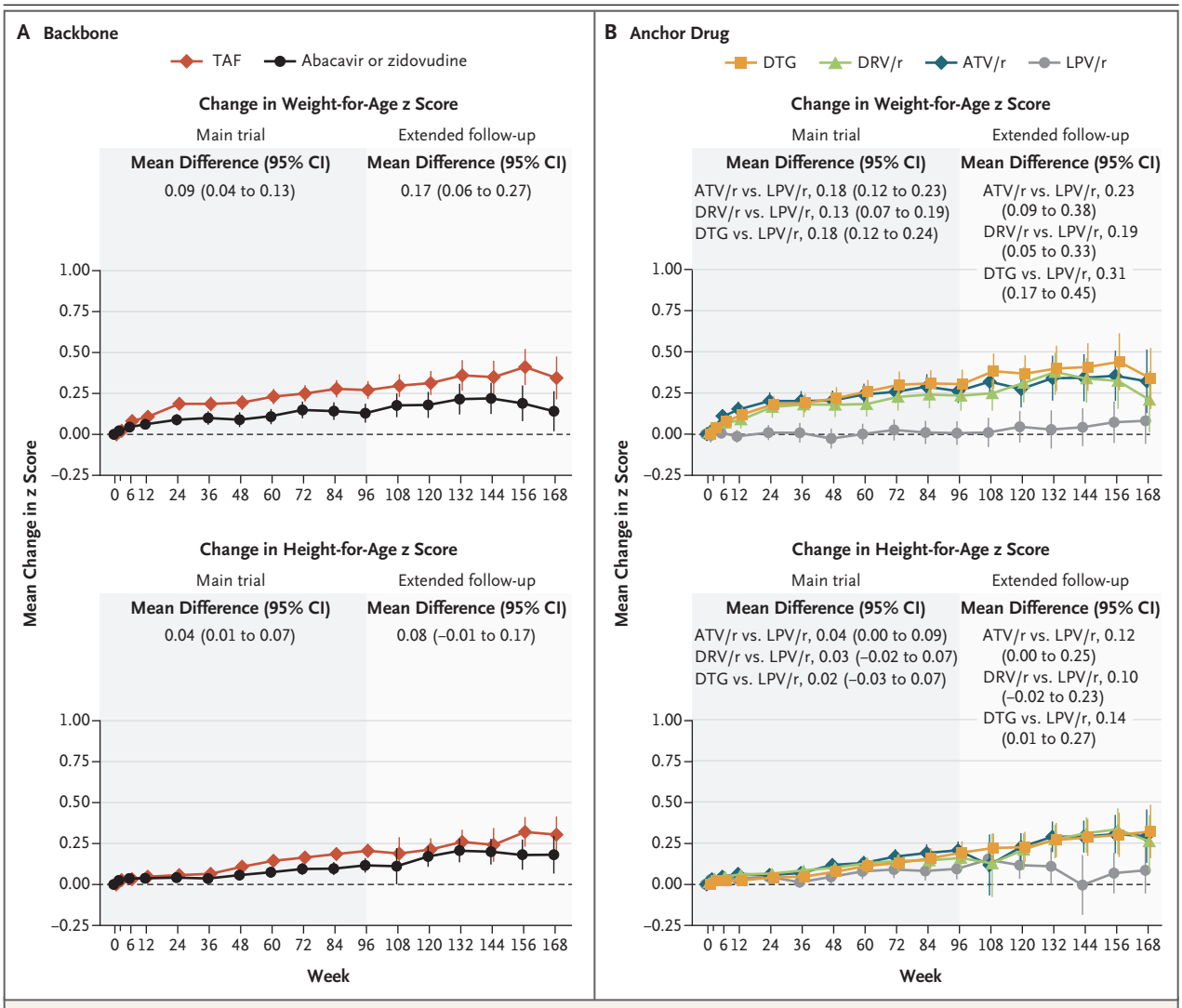

Figure 3. Changes in Weight-for-Age and Height-for-Age z Scores.
Changes are shown according to the assigned backbone (Panel A) or anchor drug (Panel B).

immunosuppression at ART initiation, high viral load, female sex, and Black race and occurs primarily in the first 2 years of therapy.[18] This phenomenon has been described as "return to health" — resting energy expenditure returns to normal as HIV viremia and inflammation are controlled.[19] Participants in our trial were either normal weight or underweight at baseline (Table 1), and none had evidence of obesity. Results may therefore not be generalizable to pediatric populations with a greater prevalence of overweight and obesity. As expected, lipid profiles were less favorable with ritonavir-boosted lopinavir than with other anchor drugs, and hyperbilirubinemia was predictably seen with ritonavir-boosted atazanavir.

Our findings also show that ritonavir-boosted darunavir and ritonavir-boosted atazanavir are effective once-daily treatment options and could be considered if dolutegravir cannot be used in second-line ART. Previous small studies have shown ritonavir-boosted atazanavir to be effective in children, and it may be a preferred second-line option with fewer side effects than ritonavir-boosted lopinavir,[20] as long as hyperbilirubinemia is not associated with discontinuation. The use of ritonavir-boosted lopinavir in children is complicated by the challenges of unpalatability and

twice-daily dose administration. The additional data showing poorer growth, abnormal lipid profiles, and lower virologic suppression with ritonavir-boosted lopinavir than with other anchor drugs in our trial emphasize that ritonavir-boosted lopinavir may not be a preferred option.

The strengths of our trial include its power to compare both dolutegravir and ritonavir-boosted darunavir with ritonavir-boosted atazanavir and ritonavir-boosted lopinavir while using a factorial design to compare TAF–based backbone treatment with standard care. The trial was conducted at locations in three African countries, including three centers outside capital cities, which increases the generalizability of results across sub-Saharan Africa, where the majority of children with HIV live. Although the findings can inform guidelines on second-line regimens after NNRTI-based first-line ART, children currently beginning first-line treatment with dolutegravir will also need effective second-line options. Our trial does not provide direct evidence to inform the choice of backbone–anchor combinations in this situation, which is a limitation of the trial; however, safety and efficacy could be inferred (given the lack of evidence of interaction), and the combinations shown to be efficacious in this trial will undoubtedly remain important future options. The relatively high CD4 cell counts among participants at enrollment may also limit the generalizability of our results to severely immunocompromised children.

One factor that may have affected the efficacy of ritonavir-boosted atazanavir and ritonavir-boosted darunavir in our trial was the lack of coformulated tablets, which resulted in a relatively high pill burden (although a small, 25-mg generic ritonavir pill was used). Overcoming this barrier through the manufacture of fixed-drug combinations may further enhance the effectiveness of ritonavir-boosted protease inhibitors for children in the future. The open-label design of the trial may have introduced bias; however, the primary outcome (viral load) was objective. Table S1 provides further review of the representativeness of the trial population and the generalizability of results.

The effects of HIV genotypic resistance to NRTIs at baseline on the risk of virologic failure, as well as the development of acquired resistance mutations during second-line ART, are important considerations in the prioritization of products and formulations. Retrospective analyses of drug resistance in all participants at baseline and in those with a viral load of more than 400 copies per milliliter at week 48, week 96, or both are ongoing.

Overall, our results provide data on the efficacy and safety of TAF–emtricitabine and dolutegravir for pediatric second-line ART. If scaled up, the use of TAF–emtricitabine could also result in cost savings (Supplementary Appendix). Ritonavir-boosted darunavir offers several benefits over ritonavir-boosted atazanavir (e.g., a higher barrier to resistance and ongoing development of fixed-dose combinations) but cannot be used in children younger than 3 years of age and is relatively costly, so alternative ritonavir-boosted protease inhibitor or non–integrase inhibitor anchor options for young children remain important.[21] Our results support further development of child-friendly fixed-dose combinations of TAF–emtricitabine, with or without anchor drugs, and the inclusion of such combinations on the priority list of the WHO Paediatric Drug Optimization program,[22] which in turn should inform future guidelines and prioritization of the most effective pediatric drugs and formulations for rollout in Africa and around the world.

The views and opinions of the authors expressed herein do not necessarily state or reflect those of the European and Developing Countries Clinical Trials Partnership.

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

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