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## ORIGINAL ARTICLE

# Dolutegravir-Based or Low-Dose Efavirenz-Based Regimen for the Treatment of HIV-1

The NAMSAL ANRS 12313 Study Group\*

## ABSTRACT

**BACKGROUND**

The members of the writing committee (Charles Kouanfack, M.D., Ph.D., Mireille Mpoudi-Etame, M.D., M.P.H., Pierrette Omgba Bassega, M.D., Sabrina Eymard-Duvernay, M.Sc., Sandrine Leroy, M.D., Ph.D., Sylvie Boyer, Ph.D., Martine Peeters, Ph.D., Alexandra Calmy, M.D., Ph.D., and Eric Delaporte, M.D., Ph.D.) assume responsibility for the overall content and integrity of this manuscript. The affiliations of the members of the writing committee are listed in the Appendix. Address reprint requests to Dr. Delaporte at TransVIHMI, University of Montpellier—IRD—INSERM, 911 Ave. Agropolis, 34394 Montpellier, France, or at [eric.delaporte@umontpellier.fr](mailto:eric.delaporte@umontpellier.fr).

An efavirenz-based regimen (with a 600-mg dose of efavirenz, known as EFV600) was the World Health Organization preferred first-line treatment for human immunodeficiency virus type 1 (HIV-1) infection until June 2018. Given concerns about side effects, dolutegravir-based and low-dose efavirenz-based combinations have been considered as first-line treatments for HIV-1 in resource-limited settings.

**METHODS**

We conducted an open-label, multicenter, randomized, phase 3 noninferiority trial in Cameroon. Adults with HIV-1 infection who had not received antiretroviral therapy and had an HIV-1 RNA level (viral load) of at least 1000 copies per milliliter were randomly assigned to receive either dolutegravir or the reference treatment of low-dose efavirenz (a 400-mg dose, known as EFV400), combined with tenofovir and lamivudine. The primary end point was the proportion of participants with a viral load of less than 50 copies per milliliter at week 48, on the basis of the Food and Drug Administration snapshot algorithm. The difference between treatment groups was calculated, and noninferiority was tested with a margin of 10 percentage points.

**RESULTS**

A total of 613 participants received at least one dose of the assigned regimen. At week 48, a viral load of less than 50 copies per milliliter was observed in 231 of 310 participants (74.5%) in the dolutegravir group and in 209 of 303 participants (69.0%) in the EFV400 group, with a difference of 5.5 percentage points (95% confidence interval [CI], -1.6 to 12.7;  $P < 0.001$  for noninferiority). Among those with a baseline viral load of at least 100,000 copies per milliliter, a viral load of less than 50 copies per milliliter was observed in 137 of 207 participants (66.2%) in the dolutegravir group and in 123 of 200 participants (61.5%) in the EFV400 group, with a difference of 4.7 percentage points (95% CI, -4.6 to 14.0). Virologic failure (a viral load of  $>1000$  copies per milliliter) was observed in 3 participants in the dolutegravir group (with none acquiring drug-resistance mutations) and in 16 participants in the EFV400 group. More weight gain was observed in the dolutegravir group than in the EFV400 group (median weight gain, 5.0 kg vs. 3.0 kg; incidence of obesity, 12.3% vs. 5.4%).

**CONCLUSIONS**

In HIV-1-infected adults in Cameroon, a dolutegravir-based regimen was noninferior to an EFV400-based reference regimen with regard to viral suppression at week 48. Among participants who had a viral load of at least 100,000 copies per milliliter when antiretroviral therapy was initiated, fewer participants than expected had viral suppression. (Funded by Unitaid and the French National Agency for AIDS Research; NAMSAL ANRS 12313 ClinicalTrials.gov number, NCT02777229.)

\*A complete list of members of the NAMSAL ANRS 12313 Study Group is provided in the Supplementary Appendix, available at [NEJM.org](http://NEJM.org).

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UNTIL MID-2018, THE PREFERRED INITIAL antiretroviral therapy (ART) recommended in the World Health Organization (WHO) guidelines for human immunodeficiency virus type 1 (HIV-1) infection consisted of two nucleoside reverse-transcriptase inhibitors (NRTIs) combined with a nonnucleoside reverse-transcriptase inhibitor (NNRTI), namely efavirenz at a dose of 600 mg daily (known as EFV600).<sup>1</sup> The EFV600-based reference regimen was then challenged by the landmark Study ING114467 (SINGLE) trial,<sup>2</sup> which showed that a dolutegravir-based regimen (dolutegravir is an integrase inhibitor) had a more favorable profile with regard to sustained viral suppression and immunologic recovery than did the EFV600-based regimen. Because dolutegravir has a high genetic barrier to resistance and is available in a fixed-dose combination and at low cost,<sup>3</sup> it appears to be an ideal candidate for a universal first-line ART regimen and was introduced as a WHO preferred first-line treatment in 2018, but this recommendation was conditional.<sup>1</sup> Warnings have been issued that exposure to dolutegravir at the time of conception may be associated with neural-tube defects in infants.<sup>4</sup> Risks of insomnia and a significant increase in body weight have also been associated with dolutegravir use.<sup>5,6</sup>

EFV600 has now been downgraded in the latest international recommendations because of adverse neurosensory effects.<sup>7</sup> Moreover, the low genetic barrier of efavirenz, especially in the context of frequent drug shortages and limited access to routine HIV-1 RNA monitoring, can result in the accumulation of drug-resistance mutations with persistent use of the drug. In turn, this contributes to increased mortality,<sup>8</sup> the spread of HIV-1 with drug-resistance mutations, and an increased prevalence of primary drug resistance.<sup>9</sup> However, the ENCORE1 trial<sup>10</sup> showed that a reduced dose of efavirenz (a dose of 400 mg daily, known as EFV400) was noninferior to EFV600 with regard to efficacy; in addition, EFV400 was associated with a better safety profile among adults who had not received ART and with a lower rate of discontinuation, while remaining efficient in pregnant patients and in patients who have tuberculosis without adjustment of the dose.<sup>11,12</sup>

The SINGLE and ENCORE1 trials<sup>2,10</sup> were conducted in high-income countries and involved mainly white men with low viral loads. In low-

and middle-income countries, where the vast majority of the 36.9 million people who have HIV are living, the characteristics of the patients are notably different; the patients are predominantly women, have higher baseline viral loads with limited access to viral-load monitoring, and are infected with HIV-1 non-B subtypes.<sup>13</sup> To interpret results in a context that is close to a real-life resource-limited setting, we conducted a randomized trial in Cameroon, an African country known for HIV-1 with a high level of genetic diversity and an increasing rate of primary drug resistance,<sup>9</sup> in which we compared the efficacy and safety of a dolutegravir-based regimen with those of an EFV400-based regimen, with viral-load monitoring performed according to WHO recommendations. EFV400 was chosen as the reference treatment on the basis of the ENCORE1 trial results in the context of WHO recommendations at that time (before 2018).<sup>1</sup>

## METHODS

### TRIAL OVERSIGHT

The New Antiretroviral and Monitoring Strategies in HIV-Infected Adults in Low-Income Countries (NAMSAL) ANRS 12313 trial was a 48-week, open-label, randomized, phase 3 trial to evaluate dolutegravir as compared with EFV400, both combined with tenofovir disoproxil fumarate and lamivudine, as first-line ART for HIV-1-infected adults in low- and middle-income countries. The trial was a noninferiority trial performed as a gatekeeping procedure before testing for superiority. Participants were enrolled in three hospitals in Yaoundé, Cameroon, between July 2016 and August 2017. Approval from the Cameroon National Ethics Committee was obtained in November 2015. All the participants provided written informed consent before any trial-specific procedures were performed. An independent data and safety monitoring committee performed separate reviews of unblinded efficacy and safety data during the trial. Participants and investigators were unaware of the results of these interim analyses. The members of the writing committee vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol, available with the full text of this article at NEJM.org. The trial drugs were paid for by Unitaid; no commercial support for drugs or tests was provided.

**PARTICIPANTS**

Eligible participants were 18 years of age or older, had not received ART, and had HIV-1 group M infection with a viral load of at least 1000 copies per milliliter. Women of childbearing potential had to agree to use effective contraceptive methods. Exclusion criteria were pregnancy, breast-feeding, severe hepatic impairment, renal failure, severe psychiatric illness, and unstable tuberculosis coinfection (Table S1 in the Supplementary Appendix, available at NEJM.org). Randomization was stratified according to baseline viral load (<100,000 copies per milliliter vs. ≥100,000 copies per milliliter) and trial site. Participants were randomly assigned, in a 1:1 ratio, to receive dolutegravir or EFV400 in a central procedure performed before the start of the trial (Table S2 in the Supplementary Appendix).

**END POINTS**

The primary end point was the proportion of participants with a viral load of less than 50 copies per milliliter at week 48, on the basis of the Food and Drug Administration (FDA) snapshot algorithm (Table S2 in the Supplementary Appendix).<sup>2,14-18</sup> Secondary end points included the viral load with other thresholds (a viral load of <200 copies per milliliter on the basis of the FDA snapshot algorithm; and virologic failure, defined by the WHO as a viral load of >1000 copies per milliliter after reinforcement of adherence) at weeks 24 and 48, as well as drug resistance. We analyzed the change from baseline in the CD4+ T-cell count at weeks 24 and 48, morbidity (WHO stage), survival, adherence to treatment, safety, and patient-reported outcomes (depression, anxiety, and stress; HIV-treatment symptoms, including efavirenz-related symptoms; and quality of life).<sup>19-22</sup> Details regarding the conduct of the trial are provided in the protocol, including the statistical analysis plan.

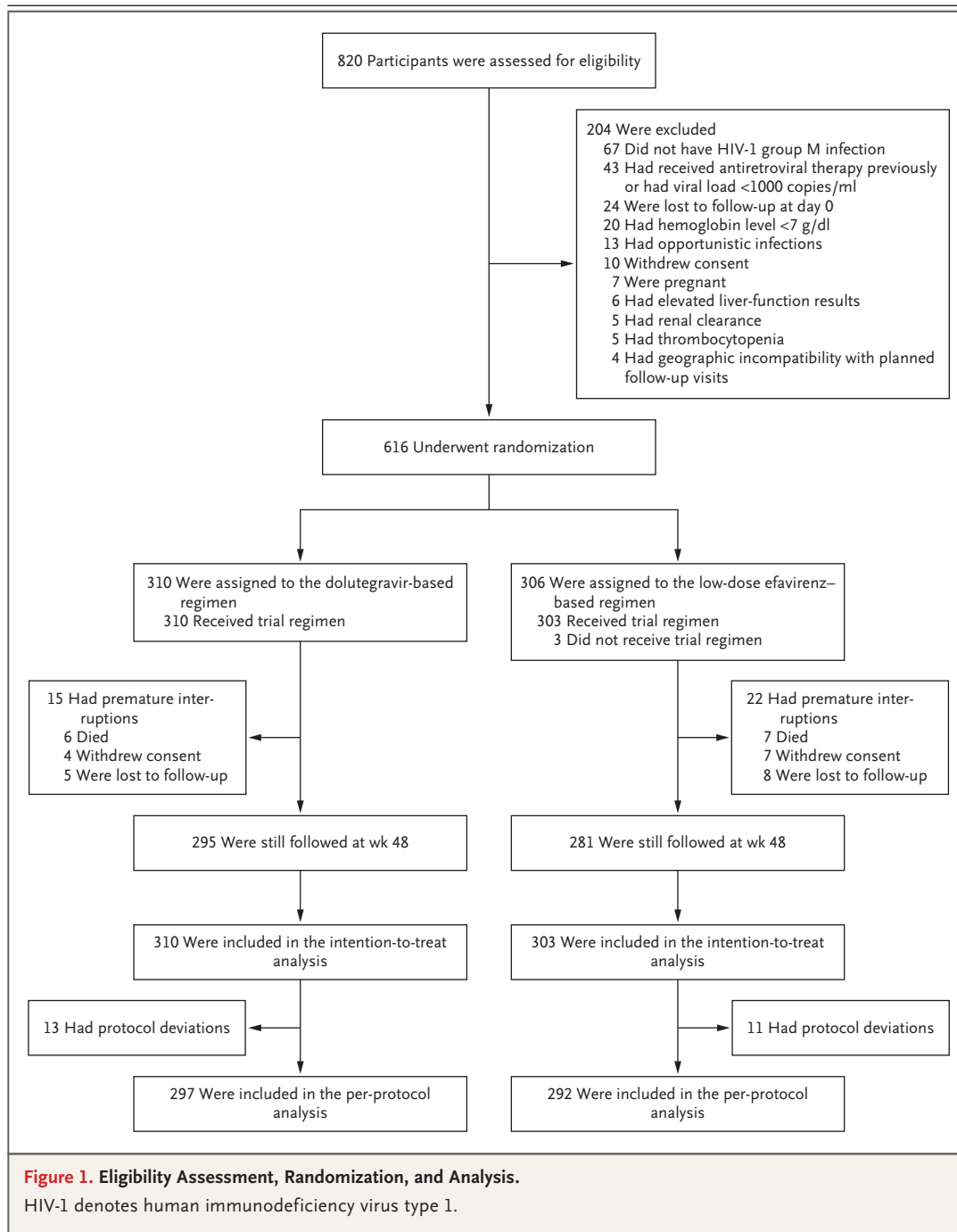
**ASSESSMENTS**

Trial visits were scheduled at baseline and on a regular basis until week 48 (Table S3 in the Supplementary Appendix). After the week 48 visit, participants continued follow-up until week 96. The plasma HIV-1 RNA level (viral load) was measured with the use of the m2000rt RealTime HIV-1 Viral Load assay (Abbott Molecular). These measurements were obtained at weeks 24 and 48 in order to be close to viral-load monitoring

conditions in low- and middle-income countries. Viral load measurements for the week 4 and week 12 visits were obtained retrospectively. The CD4+ T-cell count was assessed by means of flow cytometry performed at the CREMER laboratory (Yaoundé, Cameroon). Genotypic drug-resistance testing was performed retrospectively at baseline and at the time of virologic failure at the TransVIHMI laboratory (Montpellier, France). Drug-susceptibility predictions were made with the use of the Stanford algorithm.<sup>23</sup> Patient-reported outcomes were evaluated with the use of the 12-Item Short-Form General Health Survey (SF-12),<sup>20</sup> the short-form version of the Depression, Anxiety, and Stress Scales,<sup>21</sup> and HIV-treatment and efavirenz-related symptom questionnaires.<sup>21,22</sup>

**STATISTICAL ANALYSIS**

The primary analysis examined the difference between treatment groups in the proportion of participants with a viral load of less than 50 copies per milliliter at week 48, which was to be first tested for noninferiority in the intention-to-treat and per-protocol populations and then tested for superiority at a two-sided significance level of 0.05 if noninferiority was shown<sup>24</sup> (Table S2 in the Supplementary Appendix). The noninferiority of dolutegravir to EFV400 could be concluded if the lower limit of the two-sided 95% confidence interval for the difference between the two groups in the proportion of participants with a viral load of less than 50 copies per milliliter was above -10 percentage points. This margin was chosen for its consistency across other trials<sup>2,10</sup> and European and FDA recommendations.<sup>25,26</sup> A sample of 606 participants (303 per group) would provide the trial with 90% power to show noninferiority in the intention-to-treat analysis with the use of a one-sided significance level of 0.025, as recommended, and a noninferiority margin of 10 percentage points; a 10% increase in the sample size would maintain the same power in the per-protocol analysis (with the assumption that 10% of the participants might be excluded). Subsequent testing for superiority was to be performed if noninferiority was shown without the need to adapt the type I error rate. Analyses of efficacy, safety, and patient-reported outcomes were performed in the intention-to-treat population, since the efficacy and safety populations were identical in the trial.



## RESULTS

### TRIAL POPULATION

Of the 616 participants who underwent randomization, 613 received at least one dose of the assigned regimen (Fig. 1). Overall, 24 participants were excluded from the per-protocol analy-

sis owing to deviations from the protocol (Table S4 in the Supplementary Appendix). Demographic and disease characteristics at baseline were well balanced between the two treatment groups (Table 1). The median age was 37 years; 65.9% of the participants were women. The median baseline viral load was 5.3 log<sub>10</sub> copies per

**Table 1. Characteristics of the Participants at Baseline.\***

Characteristic	Dolutegravir Group (N = 310)	EFV400 Group (N = 303)	Intention-to-Treat Population (N = 613)
Trial site — no. (%)			
Central Hospital	172 (55.5)	169 (55.8)	341 (55.6)
Military Hospital	67 (21.6)	64 (21.1)	131 (21.4)
Cité Verte Hospital	71 (22.9)	70 (23.1)	141 (23.0)
Female sex — no. (%)	197 (63.5)	207 (68.3)	404 (65.9)
Median age (IQR) — yr	38 (31–46)	36 (29–43)	37 (29–44)
Median weight (IQR) — kg	64 (58–73)	64 (56–71)	64 (57–72)
Median body-mass index (IQR)†‡	23 (21–26)	23 (21–26)	23 (21–26)
WHO stage — no. (%)§¶			
1	179 (57.9)	184 (60.7)	363 (59.3)
2	41 (13.3)	40 (13.2)	81 (13.2)
3	84 (27.2)	75 (24.8)	159 (26.0)
4	5 (1.6)	4 (1.3)	9 (1.5)
Positive for hepatitis B virus surface antigen — no. (%)	25 (8.1)	34 (11.2)	59 (9.6)
HIV-1 viral load			
Median (IQR) — log <sub>10</sub> copies/ml	5.3 (4.8–5.8)	5.3 (4.7–5.8)	5.3 (4.8–5.8)
≥100,000 copies/ml — no. (%)	207 (66.8)	200 (66.0)	407 (66.4)
≥500,000 copies/ml — no. (%)	93 (30.0)	95 (31.4)	188 (30.7)
CD4+ T-cell count			
Median (IQR) — per mm <sup>3</sup>	289 (157–452)	271 (147–427)	281 (154–444)
<200 per mm <sup>3</sup> — no. (%)	97 (31.3)	107 (35.3)	204 (33.3)
200 to 349 per mm <sup>3</sup> — no. (%)	89 (28.7)	88 (29.0)	177 (28.9)
350 to 499 per mm <sup>3</sup> — no. (%)	63 (20.3)	56 (18.5)	119 (19.4)
≥500 per mm <sup>3</sup> — no. (%)	61 (19.7)	52 (17.2)	113 (18.4)
Hematologic measurements			
Median hemoglobin level (IQR) — g/dl	12 (11–13)	12 (10–13)	12 (10–13)
Median neutrophil count (IQR) — 10 <sup>9</sup> /liter	1.7 (1.3–2.3)	1.8 (1.4–2.2)	1.8 (1.3–2.2)
Renal-function measurements			
Median creatinine level (IQR) — mg/liter	8.0 (6.9–9.0)	7.6 (6.4–9.0)	7.7 (6.6–9.0)
Median renal clearance according to MDRD equation (IQR) — ml/min	122 (105–143)	123 (105–146)	122 (105–145)
Other laboratory measurements			
Median alanine aminotransferase level (IQR) — IU/liter	28 (19–39)	28 (21–38)	28 (20–38)
Median glucose level (IQR) — g/liter¶	0.82 (0.74–0.89)	0.81 (0.75–0.88)	0.81 (0.75–0.88)
Lipid measurements‡			
Median cholesterol level (IQR) — g/liter	1.5 (1.3–1.7)	1.5 (1.3–1.8)	1.5 (1.3–1.8)
Median triglyceride level (IQR) — g/liter	0.84 (0.61–1.08)	0.81 (0.61–1.08)	0.82 (0.61–1.08)

\* The trial regimen consisted of dolutegravir (dolutegravir group) or efavirenz at a dose of 400 mg daily (EFV400 group) combined with tenofovir disoproxil fumarate and lamivudine. There were no significant differences between the two groups with regard to baseline characteristics. IQR denotes interquartile range, and MDRD Modification of Diet in Renal Disease.

† Body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Data were available for 611 participants.

§ World Health Organization (WHO) stage 1 indicates asymptomatic infection, stage 2 mildly symptomatic infection, stage 3 moderately symptomatic infection, and stage 4 severely symptomatic infection or acquired immunodeficiency syndrome-defining illness.

¶ Data were available for 612 participants.

milliliter, and 66.4% of the participants had a baseline viral load of at least 100,000 copies per milliliter. The median CD4+ T-cell count was 281 per cubic millimeter. Adherence to treatment was similar in the two groups (Table S5 in the Supplementary Appendix).

#### EFFICACY

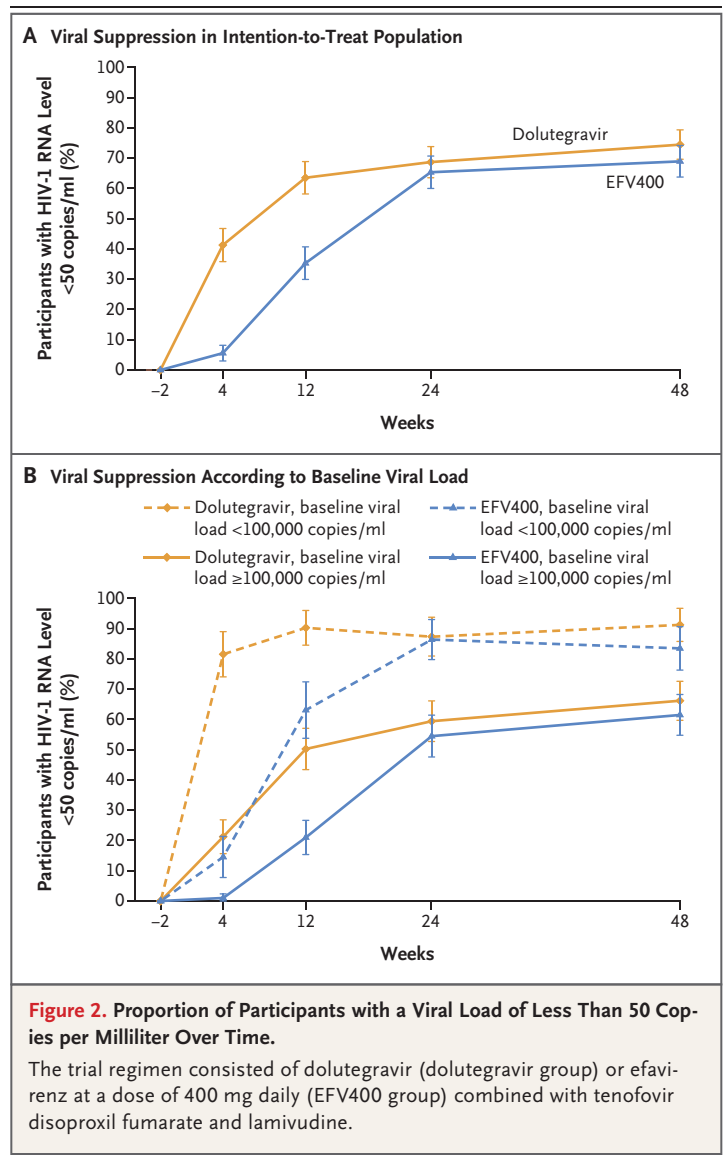
At week 48, a total of 231 of 310 participants (74.5%) in the dolutegravir group and 209 of 303 participants (69.0%) in the EFV400 group had a viral load of less than 50 copies per milliliter (Fig. 2). The difference between treatment groups was 5.5 percentage points (95% confidence interval [CI], -1.6 to 12.7), thus meeting the criterion for noninferiority ( $P < 0.001$ ) but not for superiority ( $P = 0.13$ ) (Fig. 3, and Table S6 in the Supplementary Appendix). Among those with a baseline viral load of at least 100,000 copies per milliliter, a total of 137 of 207 participants (66.2%) in the dolutegravir group and 123 of 200 participants (61.5%) in the EFV400 group had a viral load of less than 50 copies per milliliter, with a difference of 4.7 percentage points (95% CI, -4.6 to 14.0), thus showing noninferiority. Among those with the highest baseline viral load ( $\geq 500,000$  copies per milliliter), less than 60% of the participants reached a viral load of less than 50 copies per milliliter in the two groups (Fig. 3). More women had viral suppression in the dolutegravir group than in the EFV400 group (157 of 197 [79.7%] vs. 147 of 207 [71.0%]; difference, 8.7 percentage points; 95% CI, 0.3 to 17.0).

Results obtained with the use of a viral load threshold of less than 200 copies per milliliter showed that 276 of 310 participants (89.0%) in the dolutegravir group and 253 of 303 participants (83.5%) in the EFV400 group had viral suppression. The difference was 5.5 percentage points (95% CI, 0.1 to 11.0), thus meeting the criteria for noninferiority and superiority (Table S7 in the Supplementary Appendix). Results at week 24 showed that the proportion of participants who had viral suppression for each viral load threshold ( $< 50$  copies per milliliter and  $< 200$  copies per milliliter) was similar to the proportion at week 48 (Fig. 2, and Tables S6 and S7 in the Supplementary Appendix). Fewer participants had virologic failure (a viral load of  $> 1000$  copies per milliliter) in the dolutegravir group than in the EFV400 group (3 vs. 16). The median change from baseline in the CD4+ T-cell

count at week 48 was slightly but not significantly greater in the dolutegravir group than in the EFV400 group (increase of 178 per cubic millimeter [interquartile range, 103 to 275] vs. 150 per cubic millimeter [interquartile range, 77 to 239]) (Fig. S2 and Table S8 in the Supplementary Appendix).

#### HIV DRUG RESISTANCE AND VIROLOGIC OUTCOMES

HIV-1 genotypic analysis was performed at baseline, with analyses of reverse-transcriptase and integrase genes performed in 309 and 308 participants, respectively, in the dolutegravir group and in 302 and 301 participants in the EFV400



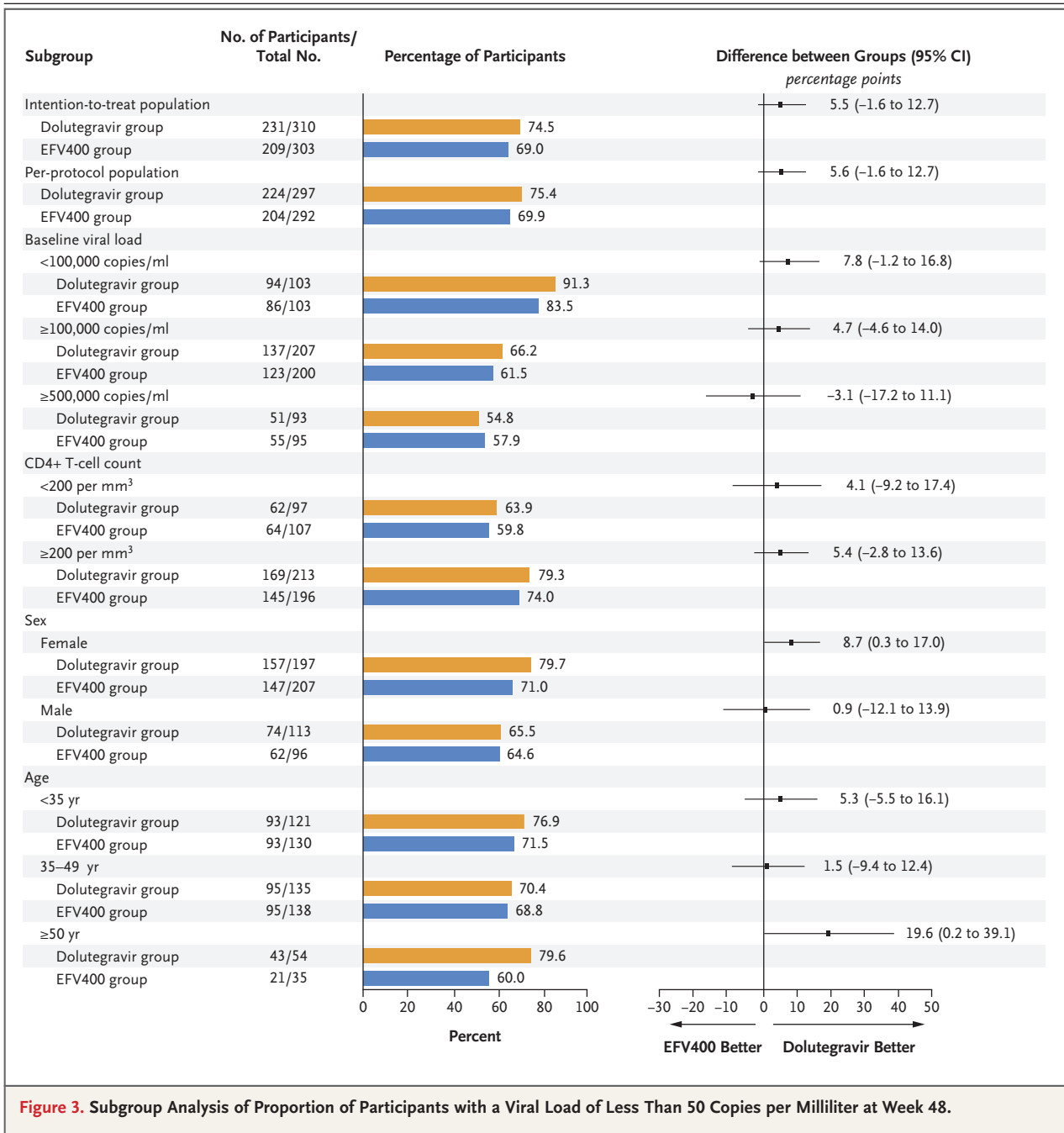


Figure 3. Subgroup Analysis of Proportion of Participants with a Viral Load of Less Than 50 Copies per Milliliter at Week 48.

group. The analysis showed a high level of genetic diversity (including eight subtypes, 12 circulating recombinant forms, and numerous unique recombinant forms), with a predominance of circulating recombinant form CRF02 (present in 176 of 309 participants [57.0%] in the dolutegravir group and 190 of 301 participants [63.1%] in the EFV400 group), and showed that the preva-

lence of drug-resistance mutations was well balanced between the two groups. The prevalence of primary resistance to NRTIs was low (1.3%; 8 participants), whereas the prevalence of primary resistance to NNRTIs was 6.1% (37 participants, including 35 with a mutation conferring resistance to efavirenz). A high level of genetic integrase polymorphism was observed, with 51



participants (8.4%) having E157Q mutations. Multivariate analyses performed separately in the dolutegravir and EFV400 groups showed that the presence of primary drug resistance (including a mutation conferring resistance to efavirenz) was not associated with an absence of viral suppression to a viral load of less than 50 copies per milliliter; the main factor associated with drug resistance was a baseline viral load of at least 100,000 copies per milliliter.

Among those with virologic failure according to the WHO definition, none of 3 participants in the dolutegravir group had drug-resistance mutations at baseline or acquired them during the trial, whereas 6 of 16 participants in the EFV400 group had drug-resistance mutations at baseline (5 had mutations conferring resistance to efavirenz, and 1 to lamivudine, tenofovir, and efavirenz). Of the 10 remaining participants in the EFV400 group who did not have drug-resistance mutations at baseline, 8 acquired them (2 acquired mutations conferring resistance to efavirenz, 3 to lamivudine and efavirenz, and 3 to lamivudine, tenofovir, and efavirenz). In the EFV400 group, virologic failure was significantly associated with primary resistance to efavirenz, a baseline viral load of at least 100,000 copies per milliliter, and adherence to treatment after adjustment by means of multivariate modeling. Details regarding the results of the genotypic analysis are provided in Tables S9 through S14 in the Supplementary Appendix.

#### CLINICAL AND PATIENT-REPORTED OUTCOMES

The number of participants who had new HIV-related, WHO stage 3 or higher events was similar in the two groups (16 of 310 participants [5.2%] in the dolutegravir group and 18 of 303 participants [5.9%] in the EFV400 group). Of the 13 participants (2.1%) who died, 12 died from HIV-related illnesses, including 2 participants (in the EFV400 group) who died from an immune reconstitution inflammatory syndrome in the context of pulmonary tuberculosis or Kaposi's sarcoma. Of the 404 women who were exposed to trial drugs, 25 (6.2%) became pregnant during the trial (13 in the dolutegravir group and 12 in the EFV400 group). All the children who were delivered from mothers with such exposures were born alive, without any reported congenital abnormalities.

No major safety concerns were reported or

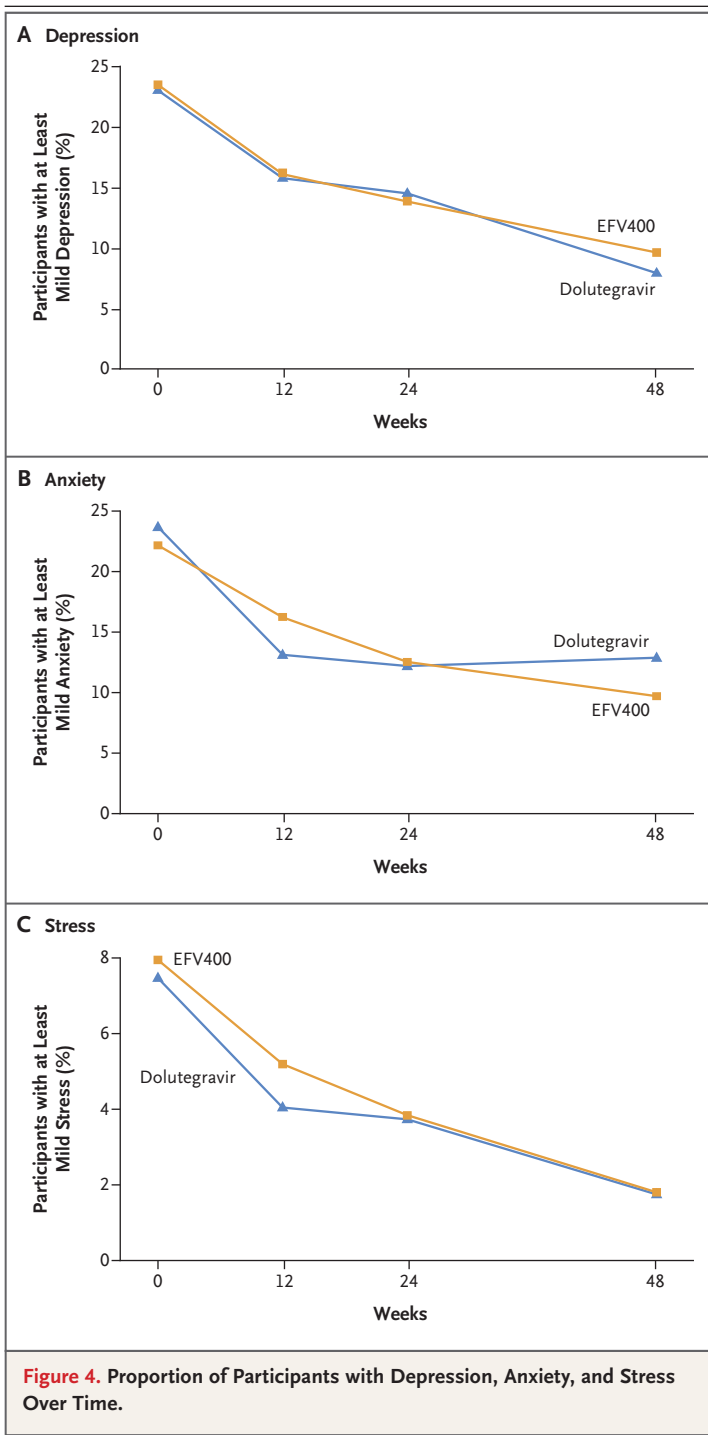
led to treatment discontinuation. A significantly greater median increase in body weight was observed in the dolutegravir group than in the EFV400 group (5.0 kg [interquartile range, 1.0 to 8.0] vs. 3.0 kg [interquartile range, 0.0 to 7.0],  $P < 0.001$ ). Weight gain of at least 10% was observed in more women than men (147 of 379 [38.8%] vs. 44 of 192 [22.9%],  $P < 0.001$ ) and in more participants who had a low body-mass index (BMI) at baseline than participants who were in other BMI categories at baseline. A significantly greater increase in the cholesterol level in both groups, as well as a greater increase in the glucose level in the dolutegravir group, was observed in participants who had weight gain of at least 10% than in participants who did not. Obesity occurred in significantly more participants in the dolutegravir group than in the EFV400 group (36 of 293 participants [12.3%] vs. 15 of 278 participants [5.4%],  $P = 0.004$ ). Details regarding safety and clinical outcomes are provided in Tables S15 through S22 in the Supplementary Appendix.

There were no significant differences between the two groups with regard to the following outcomes: the proportion of participants who had depression, anxiety, or stress over time (Fig. 4); the mean number of symptoms, regardless of symptom severity; and the mean number of efavirenz-related symptoms during follow-up. Mean scores on the SF-12 physical and mental component summaries at baseline and over time did not differ significantly between the two groups, except at week 48, when the mean score on the mental component summary was significantly lower in the dolutegravir group than in the EFV400 group. Details regarding patient-reported outcomes are provided in Figures S3 and S4 and Table S23 in the Supplementary Appendix.

#### DISCUSSION

In the NAMSAL ANRS 12313 trial, we compared a dolutegravir-based regimen with a low-dose efavirenz-based regimen for the treatment of HIV-1 infection in a resource-limited setting. The results of this randomized, phase 3 trial showed the noninferiority of dolutegravir to EFV400 with regard to the primary end point of viral suppression at week 48.

The trial was conducted in Cameroon and



had few eligibility restrictions, thus allowing the inclusion of participants who had high baseline HIV-1 viral loads and had characteristics that largely differed from those of people living in high-income countries, where registrational trials

were conducted. The participants in our trial were mainly women of childbearing potential, had high baseline viral loads (66.4% had a viral load of  $\geq 100,000$  copies per milliliter, and 30.7% had a viral load of  $\geq 500,000$  copies per milliliter), and often had coexisting conditions, whereas the participants included in the SINGLE and ENCORE1 trials were predominantly men, and one third had a baseline viral load of at least 100,000 copies per milliliter.<sup>2,10</sup>

In addition, WHO recommendations for the diagnosis and management of virologic failure were followed closely. In this real-life context, the noninferiority of dolutegravir to EFV400 was shown, but superiority was not shown, even though approximately 6% of the participants in the EFV400 group had primary resistance to efavirenz at baseline; in contrast, the superiority of dolutegravir to efavirenz was shown in the SINGLE trial.<sup>2</sup> Of note, in the EFV400 group, participants who had primary drug resistance were at an increased risk for virologic failure. The occurrence of drug-resistance mutations in those who did not have primary drug resistance was frequently observed, a finding that shows the well-known low genetic barrier of efavirenz and the limitation of the WHO definition for virologic failure in this context.

Efficacy (measured as the proportion of participants with a viral load of  $< 50$  copies per milliliter at week 48) in the dolutegravir group was lower in our trial than in reference trials: 74.5% in our trial, as compared with 88% in the group that received dolutegravir, abacavir, and lamivudine in the SINGLE trial<sup>2</sup> and 90% in the group that received dolutegravir and two NRTIs in the FLAMINGO trial.<sup>27</sup> Similarly, viral suppression in the EFV400 group was observed in 69.0% of participants in our trial, as compared with 82% in the ENCORE1 trial.<sup>10</sup> Among those in our trial with the highest baseline viral load ( $\geq 500,000$  copies per milliliter), decreased efficacy was observed, with viral suppression occurring in less than 60% in both groups. These participants represented one third of our trial population and were rarely represented in registrational trials, a factor that probably contributed to the observed differences in efficacy.

In contrast, efficacy results were much better with the use of a viral load threshold of less than 200 copies per milliliter, with viral suppression occurring in 89.0% and 83.5% of the partici-

pants in the dolutegravir and EFV400 groups, respectively; these results indicate that participants had a low persistent viremia. Apart from the high baseline viral loads, the lower efficacy in the primary analysis may be explained by lower-than-expected adherence to treatment or by drug resistance at baseline. Adherence to treatment was high on the basis of scores on a validated questionnaire (Table S5 in the Supplementary Appendix), but this measure has limitations. The retrospective analysis of drug-resistance mutations at baseline showed a low prevalence of primary resistance to NRTIs, and the presence of a mutation conferring resistance to efavirenz at baseline was not associated with an absence of viral suppression to a viral load of less than 50 copies per milliliter, a finding that was also observed in the ENCORE1 trial.<sup>10</sup> The prevalence of primary resistance to tenofovir, lamivudine, or both was too low to evaluate the effect, particularly on the risk of functional dolutegravir monotherapy. A high level of integrase polymorphism with mainly E157Q and T97A mutations (in 8% and 6%, respectively) was observed. Although these mutations have been suspected to decrease the efficacy of integrase inhibitors,<sup>28-30</sup> no effect on viral suppression was identified in the dolutegravir group. However, long-term follow-up studies would help to further evaluate the effect of these mutations, especially those associated with the persistent low viremia observed in a subgroup of our trial population.

Increased body weight and an increased incidence of obesity (12.3% and 5.4% in the dolutegravir and EFV400 groups, respectively) were

observed in this typical African population. Follow-up of these participants will be critical, given the potentially important public health consequences that may jeopardize the large-scale use of dolutegravir. Pregnancy occurred in 25 women while they were receiving trial drugs, with no adverse outcomes in live births. Of note, the WHO alert regarding the teratogenicity of dolutegravir was issued in May 2018,<sup>4</sup> after most of the participants had reached week 48.

In conclusion, this phase 3 trial showed the noninferiority of a dolutegravir-based regimen, which is associated with a low risk of acquiring drug-resistance mutations, to a low-dose efavirenz-based regimen with regard to viral suppression at week 48 in a typical population of adults with HIV-1 infection in Cameroon, supporting the current WHO recommendations to initiate ART with a dolutegravir-based regimen. We also found that viral suppression was impaired in participants with a high baseline viral load, thus supporting the worldwide effort for early diagnosis and treatment of HIV-1. We recognize the concerns related to dolutegravir use in women of childbearing potential, and the risk of obesity needs to be explored further.

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#### APPENDIX

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