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ORIGINAL ARTICLE

Long-Acting Cabotegravir and Rilpivirine after Oral Induction for HIV-1 Infection

C. Orkin, K. Arasteh, M.G. Hernández-Mora, V. Pokrovsky, E.T. Overton, P.-M. Girard, S. Oka, S. Walmsley, C. Bettacchi, C. Brinson, P. Philibert, J. Lombaard, M. St. Clair, H. Crauwels, S.L. Ford, P. Patel, V. Chounta, R. D'Amico, S. Vanveggel, D. Dorey, A. Cutrell, S. Griffith, D.A. Margolis, P.E. Williams, W. Parys, K.Y. Smith, and W.R. Spreen

ABSTRACT

BACKGROUND

Long-acting injectable regimens may simplify therapy for patients with human immunodeficiency virus type 1 (HIV-1) infection.

METHODS

We conducted a phase 3, randomized, open-label trial in which adults with HIV-1 infection who had not previously received antiretroviral therapy were given 20 weeks of daily oral induction therapy with dolutegravir–abacavir–lamivudine. Participants who had an HIV-1 RNA level of less than 50 copies per milliliter after 16 weeks were randomly assigned (1:1) to continue the current oral therapy or switch to oral cabotegravir plus rilpivirine for 1 month followed by monthly injections of long-acting cabotegravir plus rilpivirine. The primary end point was the percentage of participants who had an HIV-1 RNA level of 50 copies per milliliter or higher at week 48 (Food and Drug Administration snapshot algorithm).

RESULTS

At week 48, an HIV-1 RNA level of 50 copies per milliliter or higher was found in 6 of 283 participants (2.1%) who received long-acting therapy and in 7 of 283 (2.5%) who received oral therapy (adjusted difference, −0.4 percentage points; 95% confidence interval [CI], −2.8 to 2.1), a result that met the criterion for noninferiority for the primary end point (margin, 6 percentage points). An HIV-1 RNA level of less than 50 copies per milliliter at week 48 was found in 93.6% who received long-acting therapy and in 93.3% who received oral therapy (adjusted difference, 0.4 percentage points; 95% CI, −3.7 to 4.5), a result that met the criterion for noninferiority for this end point (margin, −10 percentage points). Of the participants who received long-acting therapy, 86% reported injection-site reactions (median duration, 3 days; mild or moderate severity, 99% of cases); 4 participants withdrew from the trial for injection-related reasons. Grade 3 or higher adverse events and events that met liver-related stopping criteria occurred in 11% and 2%, respectively, who received long-acting therapy and in 4% and 1% who received oral therapy. Treatment satisfaction increased after participants switched to long-acting therapy; 91% preferred long-acting therapy at week 48.

CONCLUSIONS

Therapy with long-acting cabotegravir plus rilpivirine was noninferior to oral therapy with dolutegravir–abacavir–lamivudine with regard to maintaining HIV-1 suppression. Injection-site reactions were common. (Funded by ViiV Healthcare and Janssen; FLAIR ClinicalTrials.gov number, NCT02938520.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Orkin at Queen Mary University of London, Department of Infection and Immunity, Royal London Hospital, Barts Health NHS Trust, London E1 1BB, United Kingdom, or at c.m.orkin@qmul.ac.uk.

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Combination antiretroviral therapy can significantly prolong the life expectancy of people living with human immunodeficiency virus (HIV), but HIV infection remains a chronic condition that requires lifelong daily oral treatment.[1,2] Current antiretroviral regimens are highly effective, and one focus of ongoing drug development is improvement of the side-effect profile and convenience to reduce disengagement from care. Prolonged daily regimens can engender dissatisfaction, contribute to stigma, and increase the risk of nonadherence to treatment and treatment failure.[3,4] Surveys indicate that many patients would prefer therapeutic alternatives.[5,6] Two-drug regimens have been developed as an option[7,8]; long-acting injectable regimens are another alternative that can free patients from the burden of daily regimens and potentially provide a more acceptable therapeutic approach.

Long-acting injectable formulations are being developed for cabotegravir, which is an integrase strand-transfer inhibitor (INSTI), and rilpivirine, which is a nonnucleoside reverse-transcriptase inhibitor (NNRTI) with an approved oral formulation.[9-11] In the Long-Acting Antiretroviral Treatment Enabling Trial 2 (LATTE-2), participants who had not previously received antiretroviral therapy were given oral cabotegravir-based treatment; those who had viral suppression were randomly assigned to continue oral treatment or switch to monthly intramuscular injections of long-acting cabotegravir plus rilpivirine. Viral suppression was maintained through week 96 in 87% of the participants who switched to monthly long-acting therapy, as compared with 84% of the participants who continued oral therapy[12]; viral suppression was maintained through week 160 in 83% of the recipients of long-acting therapy.[13]

The First Long-Acting Injectable Regimen (FLAIR) trial evaluated a potential pathway to long-acting injectable therapy for patients who had not previously received antiretroviral therapy. We assessed whether switching to monthly injections of long-acting cabotegravir plus rilpivirine would be noninferior to continuing oral therapy in patients with HIV type 1 (HIV-1) who had viral suppression in response to oral induction therapy.

Methods

Trial Design and Participants

We designed this phase 3, randomized, multicenter, open-label, noninferiority trial to have screening, induction, maintenance, extension, and long-term follow-up phases (Fig. 1A). Eligible participants were 18 years of age or older, had not previously received antiretroviral therapy, and had a plasma HIV-1 RNA level of 1000 copies per milliliter or higher at screening. The complete eligibility criteria are provided in the Supplementary Appendix and the protocol, available with the full text of this article at NEJM.org.

Participants received oral induction therapy with a fixed-dose combination of 50 mg of dolutegravir, 600 mg of abacavir, and 300 mg of lamivudine once daily for 20 weeks; those who had side effects in association with this therapy or were positive for HLA-B*5701 received dolutegravir plus two nucleoside reverse-transcriptase inhibitors other than abacavir. Participants who had a plasma HIV-1 RNA level of less than 50 copies per milliliter after 16 weeks of oral induction therapy were randomly assigned, in a 1:1 ratio, to either continue the current oral therapy during the maintenance phase or switch to long-acting therapy for at least 100 weeks. Participants in the long-acting–therapy group received oral lead-in therapy with 30 mg of cabotegravir and 25 mg of rilpivirine once daily for approximately 4 weeks so that the safety and side-effect profile of the drugs could be confirmed before long-acting injectable therapy was begun. At week 4, the participants received loading injections of 600 mg of cabotegravir and 900 mg of rilpivirine (3 ml each), administered into the gluteus muscle. Subsequent injections of 400 mg of cabotegravir and 600 mg of rilpivirine (2 ml each) were administered within a window of 21 to 28 days after the previous injection for the second and third injections and a window of 21 to 35 days thereafter. Oral bridging therapy with cabotegravir and rilpivirine was available for participants who were unable to attend a visit for injections.

Participants who had confirmed virologic failure (two consecutive plasma HIV-1 RNA levels ≥200 copies per milliliter) discontinued the assigned treatment. Participants who started long-acting therapy and then discontinued the treatment for any reason entered the 52-week follow-up phase and started an alternative, investigator-selected antiretroviral regimen.

The trial was conducted in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consent, and institutional review boards at all sites ap-

proved the protocol. The trial funders (ViiV Healthcare and Janssen Research and Development) participated in the design of the trial and in the gathering, analysis, and interpretation of the data. All the authors vouch for the accuracy and completeness of the data and the fidelity of the trial to the protocol.

RANDOMIZATION AND MASKING

A randomization sequence generated by GlaxoSmithKline-verified randomization software (RandAll NG, version 1.3.3) was used for treatment assignments, with stratification according to the baseline (preinduction) HIV-1 RNA level (<100,000 or ≥100,000 copies per milliliter) and sex at birth. Central randomization, performed with blocks shared across sites, concealed the treatment schedule to prevent selection bias.

PROCEDURES AND END POINTS

Details regarding the trial assessments are provided in the Supplementary Appendix. The primary end point was the percentage of participants who had a plasma HIV-1 RNA level of 50 copies per milliliter or higher at week 48 of the maintenance phase, determined with the use of the Food and Drug Administration (FDA) snapshot algorithm.[14] The key secondary end point was the percentage of participants who had a plasma HIV-1 RNA level of less than 50 copies per milliliter at week 48 (FDA snapshot algorithm). Other secondary end points included confirmed virologic failure, genotypic and phenotypic resistance coincident with virologic failure, CD4+ lymphocyte counts, graded adverse events,[15] laboratory abnormalities, plasma pharmacokinetics of cabotegravir and rilpivirine, treatment satisfaction scores, adherence to treatment, and virologic outcomes according to randomization strata and baseline subgroups. The baseline subgroups included post hoc subgroups defined according to the presence or absence of the L74I integrase polymorphism and the HIV-1 subtype distribution in each country.[16] Treatment satisfaction was measured with the use of the HIV Treatment Satisfaction Questionnaire, change version (HIVTSQc), at week 48.[17] The HIVTSQc evaluates participants' satisfaction with current antiretroviral therapy as compared with induction therapy; total scores range from −33 (much less satisfied now) to 33 (much more satisfied now). In an exploratory analysis, a single-item question regarding preference for long-acting or oral therapy at week 48 was evaluated in the long-acting–therapy group (Table S6 in the Supplementary Appendix). A complete list of trial end points is provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

The primary efficacy analysis included all participants who received at least one dose of the assigned trial drugs during the maintenance phase (intention-to-treat exposed population). For the primary and key secondary efficacy end points, the adjusted difference between treatment groups in the percentage of participants and corresponding 95% confidence intervals were calculated on the basis of a stratified Cochran–Mantel–Haenszel analysis, with adjustment for randomization stratification factors. The primary and key secondary efficacy end points were also assessed in the per-protocol population, which excluded participants who had protocol deviations that were likely to affect efficacy assessments or lead to discontinuation of the trial drugs.

For the primary end point, noninferiority was concluded if the upper limit of a two-sided 95% confidence interval for the difference between the long-acting–therapy group and the oral-therapy group in the percentage of participants who had an HIV-1 RNA level of 50 copies per milliliter or higher at week 48 was less than 6 percentage points. The noninferiority margin of 6 percentage points was based on clinical considerations that balanced the potential advantages of long-acting therapy over daily oral therapy (e.g., treatment satisfaction and direct observation of treatment administration) with a clinically acceptable virologic failure rate: assuming an observed virologic failure rate in the oral-therapy group of 2%, we determined that noninferiority of long-acting therapy would be shown if the observed difference between treatment groups was less than 3 percentage points. Furthermore, the sample size allows 90% power to assess noninferiority with a more stringent margin of 4 percentage points with the use of pooled data from this trial and the Antiretroviral Therapy as Long Acting Suppression (ATLAS) trial, which involved patients who had previously received antiretroviral therapy.[18]

Assuming that the percentage of participants who had an HIV-1 RNA level of 50 copies per milliliter or higher at week 48 (FDA snapshot algorithm) would be 3% in the long-acting–

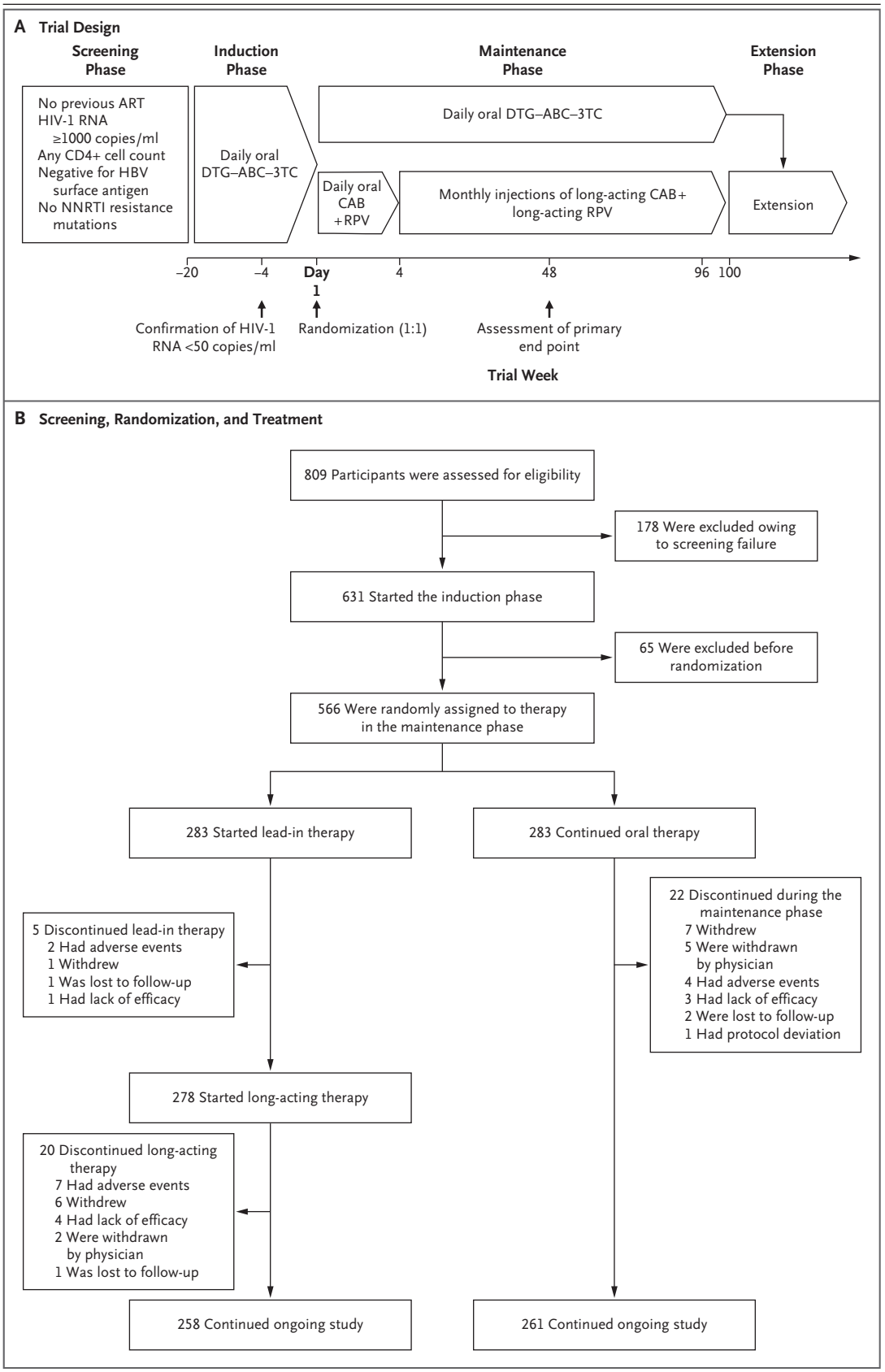
A Trial Design
Screening Phase
Induction Phase
Maintenance Phase
Extension Phase
No previous ART
HIV-1 RNA ≥1000 copies/ml
Any CD4+ cell count
Negative for HBV surface antigen
No NNRTI resistance mutations
Daily oral DTG–ABC–3TC
Daily oral DTG–ABC–3TC
Daily oral CAB +RPV
Monthly injections of long-acting CAB+ long-acting RPV
Extension
–20
–4
Day 1
4
48
96
100
Confirmation of HIV-1 RNA <50 copies/ml
Randomization (1:1)
Assessment of primary end point
Trial Week
B Screening, Randomization, and Treatment
809 Participants were assessed for eligibility
178 Were excluded owing to screening failure
631 Started the induction phase
65 Were excluded before randomization
566 Were randomly assigned to therapy in the maintenance phase
283 Started lead-in therapy
283 Continued oral therapy
5 Discontinued lead-in therapy
2 Had adverse events
1 Withdrew
1 Was lost to follow-up
1 Had lack of efficacy
22 Discontinued during the maintenance phase
7 Withdrew
5 Were withdrawn by physician
4 Had adverse events
3 Had lack of efficacy
2 Were lost to follow-up
1 Had protocol deviation
278 Started long-acting therapy
20 Discontinued long-acting therapy
7 Had adverse events
6 Withdrew
4 Had lack of efficacy
2 Were withdrawn by physician
1 Was lost to follow-up
258 Continued ongoing study
261 Continued ongoing study

Figure 1 (facing page). Trial Design, Screening, Randomization, and Treatment.

Panel A shows the trial design scheme, which includes screening, induction, maintenance, and extension phases. During the screening phase, adults who met the inclusion criteria were enrolled in the trial; key exclusion criteria were previous use of antiretroviral therapy (ART), detection of hepatitis B virus (HBV) surface antigen, and the presence of nonnucleoside reverse-transcriptase inhibitor (NNRTI) resistance mutations other than the K103N mutation. During the induction phase, a single-tablet regimen of dolutegravir, abacavir, and lamivudine (DTG–ABC–3TC) was administered once daily for 20 weeks; those who had side effects in association with this therapy or were positive for HLA-B*5701 received dolutegravir plus two nucleoside reverse-transcriptase inhibitors other than abacavir. During randomization, participants were randomly assigned to continue the current oral therapy or switch to long-acting therapy during the maintenance phase. Participants in the long-acting–therapy group received oral lead-in therapy with cabotegravir (CAB) plus rilpivirine (RPV), followed by injections of long-acting formulations: initial loading injections of 600 mg of cabotegravir and 900 mg of rilpivirine were administered at week 4, and subsequent injections of 400 mg of cabotegravir and 600 mg of rilpivirine were administered every 4 weeks beginning at week 8. In this ongoing trial, participants who discontinue or complete long-acting therapy enter a 52-week long-term follow-up phase. Participants in the oral-therapy group who maintain viral suppression have the option to switch to long-acting therapy during the extension phase. Panel B shows participants who underwent screening, randomization, and treatment. Overall, 566 adults were randomly assigned to treatment; 180 adults who underwent screening were not assigned to treatment, primarily because they did not meet the eligibility requirements (149 participants). Of those 180 participants, 65 were excluded from the trial before randomization, primarily because they did not meet the viral suppression criterion while receiving oral induction therapy; 2 withdrew before receiving induction therapy. Treatment was initiated in 283 participants in each treatment group (intention-to-treat exposed population). The safety and intention-to-treat exposed populations were identical.

therapy group and 2% in the oral-therapy group, with a noninferiority margin of 6 percentage points and a one-sided significance level of 2.5%, we calculated that a sample of 285 participants per treatment group would give the trial approximately 97% power to show noninferiority of long-acting therapy to oral therapy with regard to the primary end point. This sample size would also provide more than 94% power to show noninferiority with regard to the key secondary end point, with the assumption of a response rate of 87% with each treatment, a noninferiority margin of –10 percentage points, and a one-sided significance level of 2.5%.

RESULTS

PARTICIPANTS

A total of 809 adults were screened at 108 sites in 11 countries beginning on October 27, 2016 (Fig. 1B); the last participant completed week 48 on August 30, 2018. Oral induction therapy was initiated in 629 participants; 63 of those participants withdrew from the trial before randomization, primarily because of a lack of efficacy, and the remaining 566 were randomly assigned to treatment in the maintenance phase (283 to each treatment group). During the maintenance phase, 25 participants (9%) in the long-acting–therapy group and 22 participants (8%) in the oral-therapy group withdrew from the trial; withdrawals were most frequently due to adverse events in the long-acting–therapy group (in 9 participants) and participant decision to withdraw in the oral-therapy group (in 7). In the long-acting–therapy group, 98% of the 3577 expected injection visits (12 per participant by week 48, with additional visits beyond week 48) occurred within a window of 21 to 35 days after the previous injection; four of five missed injections were covered with oral bridging therapy (Fig. S1). In the oral-therapy group, adherence to treatment was more than 90% on the basis of patient-reported treatment interruptions of 3 or more consecutive days.

Across the two treatment groups, participants were a median of 34 years of age, 22% were female, and 74% were white; approximately 20% had an HIV-1 RNA level of 100,000 copies per milliliter or higher at baseline (Table 1). Before the induction phase, 69% of the participants had a CD4+ lymphocyte count of 350 per microliter or higher, and this percentage increased to 90% by the start of maintenance therapy.

EFFICACY

At week 48, an HIV-1 RNA level of 50 copies per milliliter or higher was found in 6 participants (2.1%) who received long-acting therapy and in 7 participants (2.5%) who received oral therapy (adjusted difference, –0.4 percentage points; 95% confidence interval [CI], –2.8 to 2.1), a result that met the prespecified noninferiority criterion for the primary end point (Table 2). For this end point, there was no meaningful esti-

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline, Intention-to-Treat Exposed Population.*

Characteristic	Long-Acting Therapy (N=283)	Oral Therapy (N=283)	Total (N=566)
Median age (range) — yr	34 (19–68)	34 (18–68)	34 (18–68)
Age group — no. (%)			
<35 yr	143 (51)	145 (51)	288 (51)
35 to <50 yr	107 (38)	109 (39)	216 (38)
≥50 yr	33 (12)	29 (10)	62 (11)
Female sex — no. (%)	63 (22)	64 (23)	127 (22)
Race — no. (%)†			
White	216 (76)	201 (71)	417 (74)
Black	47 (17)	56 (20)	103 (18)
Other	20 (7)	24 (8)	44 (8)
Missing	0	2 (1)	2 (<1)
Median body-mass index (range)‡	24 (17–45)	24 (13–47)	24 (13–47)
HIV-1 RNA level — no. (%)			
<1000 copies/ml	9 (3)	5 (2)	14 (2)
1000 to <10,000 copies/ml	64 (23)	71 (25)	135 (24)
10,000 to <50,000 copies/ml	95 (34)	113 (40)	208 (37)
50,000 to <100,000 copies/ml	59 (21)	38 (13)	97 (17)
100,000 to <200,000 copies/ml	30 (11)	33 (12)	63 (11)
≥200,000 copies/ml	26 (9)	23 (8)	49 (9)
CD4+ lymphocyte count — no. (%)			
<200 per μl	16 (6)	23 (8)	39 (7)
200 to <350 per μl	71 (25)	64 (23)	135 (24)
350 to <500 per μl	88 (31)	88 (31)	176 (31)
≥500 per μl	108 (38)	108 (38)	216 (38)

* Percentages may not total 100 because of rounding.
† Race was reported by the participant.
‡ Body-mass index is the weight in kilograms divided by the square of the height in meters.

mated difference between treatments across subgroups (Fig. S2). Similarly, long-acting therapy was noninferior to oral therapy with regard to the key secondary end point of the percentage of participants with an HIV-1 RNA level of less than 50 copies per milliliter at week 48 (93.6% and 93.3%, respectively; adjusted difference, 0.4 percentage points; 95% CI, −3.7 to 4.5). On tests for evidence against homogeneity in the differences between treatments across randomization strata, results were not significant. All these results were similar in the per-protocol population (Table 2).

In the long-acting–therapy group, 4 participants had confirmed virologic failure. In 1 of those participants (who had HIV-1 subtype AG), oral lead-in therapy was suspended owing to a false-positive pregnancy test; on reinitiation of oral therapy, criteria for confirmed virologic failure were met and the participant was withdrawn from the trial before long-acting therapy was initiated, with no resistance mutations detected. The other 3 participants had NNRTI and INSTI resistance mutations (Table S1) that developed during long-acting therapy; these mutations reduced susceptibility to rilpivirine in 2 participants by a factor of more than 2 and reduced susceptibility to cabotegravir in all 3 participants by a factor of more than 5. These 3 participants had HIV-1 subtype A1 with the L74I integrase polymorphism at baseline. However, 51 of the 54 participants in the long-acting–therapy group

Table 2. Efficacy Outcomes at Week 48.

Outcome	Long-Acting Therapy (N=283)	Oral Therapy (N=283)	Difference (95% CI)	Adjusted Difference (95% CI)*
			percentage points	
Intention-to-treat exposed population				
HIV-1 RNA level — no. (%)				
<50 copies/ml	265 (93.6)	264 (93.3)	0.4 (–3.7 to 4.4)	0.4 (–3.7 to 4.5)
≥50 copies/ml†	6 (2.1)	7 (2.5)	–0.4 (–2.8 to 2.1)	–0.4 (–2.8 to 2.1)
Level not below threshold	2 (0.7)	2 (0.7)	—	—
Discontinued treatment for lack of efficacy	4 (1.4)	3 (1.1)	—	—
Discontinued treatment for other reasons	0	2 (0.7)	—	—
No virologic data	12 (4.2)	12 (4.2)	—	—
Withdrew from trial owing to adverse event or death	8 (2.8)	2 (0.7)	—	—
Withdrew from trial for other reasons	4 (1.4)	10 (3.5)	—	—
Subgroup analysis of HIV-1 RNA level ≥50 copies/ml — no./total no. (%)‡				
Sex at birth				
Female	3/63 (4.8)	1/64 (1.6)	3.2 (–4.3 to 12.0)	—
Male	3/220 (1.4)	6/219 (2.7)	–1.4 (–4.7 to 1.6)	—
Baseline HIV-1 RNA level				
<100,000 copies/ml	4/227 (1.8)	5/227 (2.2)	–0.4 (–3.6 to 2.5)	—
≥100,000 copies/ml	2/56 (3.6)	2/56 (3.6)	0.0 (–9.2 to 9.2)	—
Per-protocol population§				
HIV-1 RNA level — no./total no. (%)				
<50 copies/ml	260/278 (93.5)	263/282 (93.3)	0.3 (–3.9 to 4.4)	0.3 (–3.8 to 4.4)
≥50 copies/ml	6/278 (2.2)	7/282 (2.5)	–0.3 (–2.8 to 2.2)	–0.3 (–2.8 to 2.2)

* Values are based on a stratified Cochran–Mantel–Haenszel analysis, with adjustment for sex at birth and baseline (preinduction) human immunodeficiency virus type 1 (HIV-1) RNA level.

† A level of 50 copies per milliliter or higher was observed at week 48 (level not below threshold) or at the time of treatment discontinuation before week 48.

‡ Separate tests of homogeneity in the differences between treatments across randomization strata were conducted with the use of a weighted least-squares chi-square statistic and a 10% one-sided significance level. The 95% confidence intervals for differences across subgroups were calculated with the use of an unconditional exact method with two inverted one-sided tests.

§ The per-protocol population excluded 5 participants in the long-acting–therapy group (2 who received treatment outside the permitted window, 2 who had HIV-1 RNA samples that were compromised at the central laboratory, and 1 who received a prohibited HIV-1 medication before the baseline visit) and 1 participant in the oral-therapy group (who received prohibited medications).

who had HIV-1 with the L74I integrase polymorphism at baseline did not have virologic failure (Table S2). In subgroup analyses of the primary end point, no significant difference between treatments was observed in subgroups defined according to the presence or absence of the L74I integrase polymorphism or according to HIV-1 subtype (Fig. S2). In the oral-therapy group, 3 participants had confirmed virologic failure without the development of resistance mutations or phenotypic changes during treatment. In the primary analysis, 2 participants who received long-acting therapy and 4 participants who received oral therapy had an HIV-1 RNA level of 50 copies per milliliter or higher without confirmed virologic failure; neither of the participants who received long-acting therapy had HIV-1 resistance mutations.

SAFETY AND SIDE EFFECTS

During the maintenance phase, the most common adverse events in the long-acting–therapy

group, excluding injection-site reactions, were nasopharyngitis, headache, upper respiratory tract infection, and diarrhea (Table 3 and Table S3). Serious adverse events occurred in 18 participants (6%) who received long-acting therapy and in 12 participants (4%) who received oral therapy (Table S4); each type of event occurred in 1 participant (except hepatitis A, which occurred in 3 participants who received long-acting therapy), with no deaths. Adverse events that led to withdrawal from the trial occurred in 9 participants (3%) who received long-acting therapy and in 4 participants (1%) who received oral therapy. In the long-acting–therapy group, the only events that led to withdrawal in more than 1 participant were viral hepatitis and injection-site pain (in 5 and 2 participants, respectively) (Table S5). During the maintenance phase, events that met liver-related stopping criteria occurred in 7 participants (2%) who received long-acting therapy and in 2 participants (1%) who received oral therapy, including eight cases of acute viral hepatitis and one case of inorganic solvent toxicity. One participant in the oral-therapy group was pregnant and had a healthy baby. At week 48, the median weight gain from baseline was 1.3 kg (interquartile range, –1.0 to 5.0) in the long-acting–therapy group and 1.5 kg (interquartile range, –1.0 to 3.9) in the oral-therapy group.

Of the participants who received long-acting therapy, 86% had at least one injection-site reaction. The most common injection-site reaction was pain, which was reported by 227 of the 278 participants (82%) who received at least one injection (Table S3). Most of the 1879 pain events were of mild or moderate severity (86% and 13%, respectively); 12 events (<1%) in 11 participants were severe (grade 3), and there were no grade 4 events. The incidence of injection-site reactions was highest (71%) after the initial 3-ml injections at week 4 and subsequently decreased to 20% at week 48 (Fig. S3). The median duration of injection-site reactions was 3 days; 88% of cases resolved within 7 days. Injection-site reactions led to withdrawal from the trial in 2 participants, and another 2 participants withdrew consent for other injection-related reasons. Other adverse events that were considered by investigators to be drug-related were more common with long-acting therapy than with oral therapy (occurring in 28% vs. 10% of the participants). There was no discernible pattern to these events; other than injection-site reactions, the most common drug-related events (occurring in ≥5% of the participants) in the long-acting–therapy group were headache and pyrexia.

PHARMACOKINETICS

Plasma concentrations of cabotegravir and rilpivirine during long-acting therapy (Fig. 2) were similar to the concentrations reported during oral therapy.[19,20] The geometric mean cabotegravir trough concentration was 1.56 μg per milliliter at week 8 and 3.13 μg per milliliter at week 48; these concentrations are 9.4 times and 18.9 times, respectively, as high as the in vitro protein-adjusted 90% inhibitory concentration ($PA\text{-}IC_{90}$) for the drug. The geometric mean rilpivirine trough concentration was 41.2 ng per milliliter at week 8 and 82.4 ng per milliliter at week 48; these concentrations are 3.4 times and 6.9 times as high as the $PA\text{-}IC_{90}$. The three participants who received long-acting therapy and had confirmed virologic failure had cabotegravir and rilpivirine concentrations in the lowest quartile, with one having drug concentrations below the fifth percentile (Fig. S4); all three had a body-mass index (the weight in kilograms divided by the square of the height in meters) of more than 30 at baseline, but none missed an injection or received injections outside the permitted window.

PATIENT-REPORTED OUTCOMES

At week 48, the HIVTSQc total score for satisfaction with current treatment as compared with induction treatment was higher in the long-acting–therapy group than in the oral-therapy group (adjusted mean difference, 4.1 points; 95% CI, 2.8 to 5.5) (Table S7). An exploratory analysis of a single-item question regarding therapy preference at week 48 indicated that 257 of 283 participants (91%) who received long-acting therapy in the intention-to-treat exposed population and 257 of 259 participants (99%) who responded to the survey preferred the long-acting regimen over the previous oral therapy.

DISCUSSION

The results of this trial show a pathway for patients who have not previously received antiretroviral therapy to reach and maintain HIV-1

Table 3. Adverse Events during the Maintenance Phase.*

Event Category	Long-Acting Therapy (N=283)	Oral Therapy (N=283)
	number of participants (percent)	
Any adverse event	267 (94)	225 (80)
Any adverse event, excluding injection-site reactions	246 (87)	225 (80)
Grade ≥3 adverse events	31 (11)	11 (4)
Grade ≥3 adverse events, excluding injection-site reactions	22 (8)	11 (4)
Adverse events that led to withdrawal from the trial†	9 (3)	4 (1)
Serious adverse events‡	18 (6)	12 (4)
Adverse events that led to death	0	0
Drug-related adverse events		
Any	236 (83)	28 (10)
Any, excluding injection-site reactions§	79 (28)	28 (10)
Grade ≥3	14 (5)	0
Grade ≥3, excluding injection-site reactions¶	4 (1)	0
Injection-site pain		
Any	227 (80)	NA
Grade ≥3	11 (4)	NA
Adverse events reported in ≥5% of participants in either treatment group, excluding injection-site reactions		
Nasopharyngitis	56 (20)	48 (17)
Headache	39 (14)	21 (7)
Upper respiratory tract infection	38 (13)	28 (10)
Diarrhea	32 (11)	25 (9)
Influenza	25 (9)	20 (7)
Vitamin D deficiency	23 (8)	13 (5)
Back pain	22 (8)	13 (5)
Pyrexia	22 (8)	4 (1)
Hemorrhoids	16 (6)	3 (1)
Nausea	16 (6)	11 (4)
Dizziness	15 (5)	3 (1)
Gastroenteritis	15 (5)	11 (4)
Pharyngitis	15 (5)	9 (3)

* NA denotes not applicable.
† The most common events that led to withdrawal in the long-acting–therapy group were acute hepatitis B (in 2 participants), hepatitis A (2), and injection-site pain (2); 1 of the participants with hepatitis B had inadequate antibody titers after vaccination. All other adverse events that led to withdrawal were reported in 1 participant each.
‡ The most common serious adverse event in the long-acting–therapy group was hepatitis A, which was reported in 3 participants, 2 of whom withdrew from the trial. All other serious adverse events were reported in 1 participant each.
§ Other than injection-site reactions, the most common adverse events that were considered by investigators to be possibly or probably related to long-acting therapy were headache (in 14 participants), pyrexia (13), increased body temperature (8), asthenia (7), and malaise (5). The most common drug-related events in the oral-therapy group were nausea (in 6 participants) and fatigue (5).
¶ In the long-acting–therapy group, 3 participants had grade 3 events of night sweats, right knee monoarthritis, and poor-quality sleep; 1 participant had a grade 4 elevated lipase level.

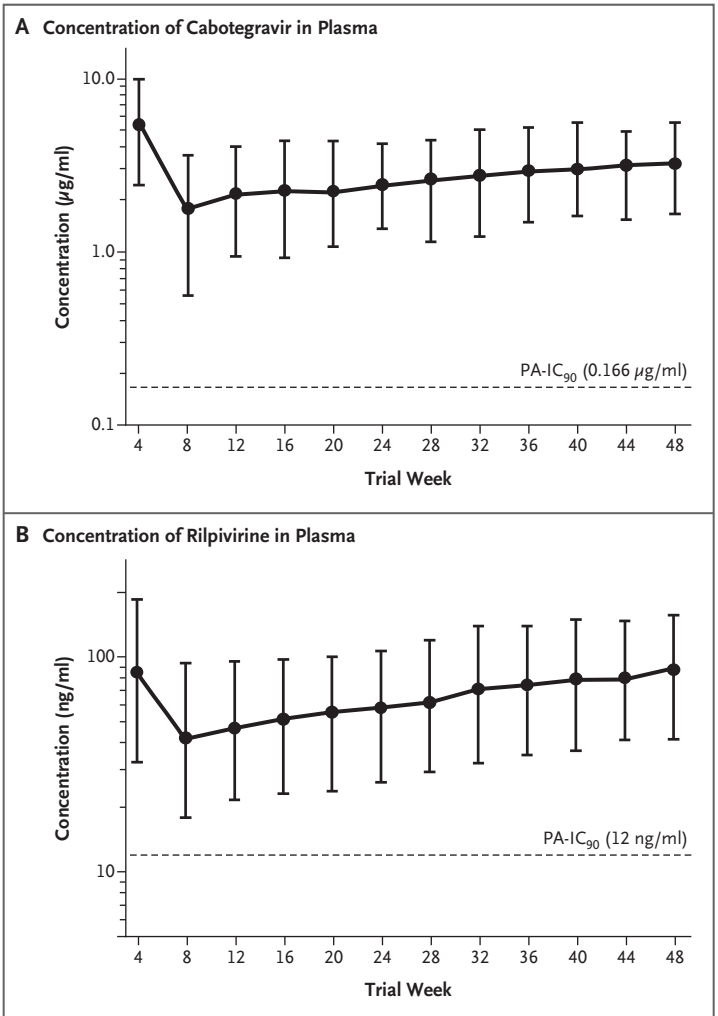

Figure 2. Plasma Concentration–Time Profiles.

Shown are the median plasma concentration–time profiles for cabotegravir (Panel A) and rilpivirine (Panel B) in 278 participants who received monthly injections of long-acting therapy. I bars indicate the 5th and 95th percentiles. Dashed lines indicate the in vitro protein-adjusted 90% inhibitory concentration ($PA\text{-}IC_{90}$). Predose plasma concentrations are shown.

suppression with oral induction therapy and a subsequent transition to monthly injectable therapy. After viral suppression was achieved with a standard oral INSTI-based regimen, the simplified injectable regimen, which consisted of long-acting formulations of cabotegravir and rilpivirine, was noninferior to continued oral therapy with regard to maintaining suppression through week 48.

Baseline viral load had no significant effect on the results for the primary end point; this finding suggests that if the viral load is suppressed without evidence of cabotegravir or rilpivirine resistance mutations, a transition to long-acting therapy is feasible. At baseline, HIV-1 subtype A1 was present in 8 participants in the long-acting–therapy group, 5 of whom maintained viral suppression and 3 of whom had virologic failure. All 3 of the participants who had virologic failure during long-acting therapy also had a body-mass index of more than 30, plasma drug levels in the lowest quartile, and HIV-1 with the L74I integrase polymorphism. However, the L74I integrase polymorphism does not confer resistance to cabotegravir by itself: 51 of 54 participants in the long-acting–therapy group who had the L74I integrase polymorphism did not have virologic failure at week 48.[21,22] No dosing complications that may have contributed to virologic failure were reported. With virologic failure occurring in only 4 participants in the long-acting–therapy group (and occurring before the initiation of long-acting therapy in 1 of those participants), the potential contributions of virologic, pharmacokinetic, demographic, and other factors to virologic outcomes remain uncertain; future analyses of pooled study data may provide clarification.

The three-drug combination of dolutegravir, abacavir, and lamivudine that was used for induction therapy and as the control regimen during the maintenance phase is a recommended first-line regimen for patients who have not previously received antiretroviral therapy.[23] Efficacy results with long-acting therapy in this trial were similar to those seen in the ATLAS trial, which had a similar switch design but enrolled participants who had longer-term viral suppression, which had been achieved with the use of other standard three-drug oral therapies.[18] Together, the FLAIR and ATLAS trials show that the long-acting regimen effectively maintained viral suppression that had initially been achieved with the use of oral regimens, both in adults new to treatment and in those who had received prolonged previous treatment.

Other than injection-site reactions, no patterns of adverse events with the long-acting regimen were evident, a finding consistent with the reported safety profiles of oral cabotegravir and rilpivirine.[12,20] Injection-site reactions, primarily pain, were common, but the incidence decreased from 71% to 20% during the trial. Injection-site

reactions were generally of mild or moderate severity and transient; 4 of the 283 participants in the long-acting–therapy group withdrew from the trial owing to injection-site reactions or other injection-related reasons. The incidences of some adverse events other than injection-site reactions were higher in the long-acting–therapy group than in the oral-therapy group; however, effects associated with starting a new treatment (as opposed to continuing the same treatment) may have contributed to the observed differences — a possibility consistent with observations in previous switch studies.[8,24]

The long-acting regimen was preferred over the previous oral therapy by 91% of recipients, even after 12 monthly injections. Conclusions derived from this finding are limited to patients who are willing to consider injectable therapy, reflecting the enrolled trial population. Similarly, in clinical practice, the long-acting regimen is a therapeutic option that patients can select according to their preference. For patients who choose long-acting therapy, the data regarding treatment preference suggest that their expectations of regimen benefits will be met.

The potential clinical role of the long-acting regimen remains to be fully defined for the spectrum of patients with HIV-1 infection, particularly those who have adherence challenges, in different practice settings. In this regard, additional randomized efficacy and safety trials of the long-acting regimen include the ATLAS trial,[18] which enrolled participants who had previously received antiretroviral therapy, and the LATITUDE trial (ClinicalTrials.gov number, NCT03635788), which enrolled participants who had adherence difficulties. Ongoing follow-up of the FLAIR and ATLAS trials will assess outcomes of long-acting therapy extended beyond 48 weeks. Several additional ongoing or planned studies (e.g., the Cabotegravir plus Rilpivirine in the U.S. to Optimize and Measure Implementation and Experience [CUSTOMIZE] trial; NCT04001803) are focused on implementation of the long-acting regimen in various settings, including university hospitals and private and public health clinics.

In conclusion, monthly two-drug long-acting therapy was noninferior to standard three-drug oral therapy with regard to maintaining viral suppression for 48 weeks in adults with HIV-1 infection who had not previously received antiretroviral therapy, with greater reported treatment satisfaction.

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

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APPENDIX

The authors' full names and academic degrees are as follows: Chloe Orkin, M.D., Keikawus Arasteh, M.D., M. Górgolas Hernández-Mora, M.D., Vadim Pokrovsky, M.D., Edgar T. Overton, M.D., Pierre-Marie Girard, M.D., Ph.D., Shinichi Oka, M.D., Ph.D., Sharon Walmsley, M.D., Chris Bettacchi, M.D., Cynthia Brinson, M.D., Patrick Philibert, M.D., Johan Lombaard, M.D., Marty St. Clair, Ph.D., Herta Crauwels, Ph.D., Susan L. Ford, Pharm.D., Parul Patel, Pharm.D., Vasiliki Chounta, M.S., Ronald D'Amico, D.O., Simon Vanveggel, M.S., David Dorey, M.Math., Amy Cutrell, M.S., Sandy Griffith, Pharm.D., David A. Margolis, M.D., Peter E. Williams, Ph.D., Wim Parys, M.D., Kimberly Y. Smith, M.D., and William R. Spreen, Pharm.D.

The authors' affiliations are as follows: Queen Mary University of London, London (C.O.), and ViiV Healthcare, Brentford (V.C.) — both in the United Kingdom; EPIMED, Berlin (K.A.); Fundación Jiménez Díaz, Madrid (M.G.H.-M.); Central Research Institute of Epidemiology, Moscow (V.P.); the University of Alabama at Birmingham, Birmingham (E.T.O.); Hôpital Saint Antoine, Paris (P.-M.G.), and Hôpital Européen, Marseille (P. Philibert) — both in France; the National Center for Global Health and Medicine, Tokyo (S.O.); the University Health Network, University of Toronto, Toronto (S.W.), and GlaxoSmithKline, Mississauga (S.L.F., D.D.) — both in Ontario, Canada; North Texas Infectious Disease Consultants, Dallas (C. Bettacchi), and Central Texas Clinical Research, Austin (C. Brinson); Josha Research, Bloemfontein, South Africa (J.L.); ViiV Healthcare, Research Triangle Park, NC (M.S.C., P. Patel, R.D., A.C., S.G., D.A.M., K.Y.S., W.R.S.); and Janssen Research and Development, Beerse, Belgium (H.C., S.V., P.E.W., W.P.).

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