ORIGINAL ARTICLE

Long-Acting Cabotegravir and Rilpivirine for Maintenance of HIV-1 Suppression

S. Swindells, J.-F. Andrade-Villanueva, G.J. Richmond, G. Rizzardini, A. Baumgarten, M. Masiá, G. Latiff, V. Pokrovsky, F. Bredeek, G. Smith, P. Cahn, Y.-S. Kim, S.L. Ford, C.L. Talarico, P. Patel, V. Chounta, H. Crauwels, W. Parys, S. Vanveggel, J. Mrus, J. Huang, C.M. Harrington, K.J. Hudson, D.A. Margolis, K.Y. Smith, P.E. Williams, and W.R. Spreen

ABSTRACT

BACKGROUND

Simplified regimens for the treatment of human immunodeficiency virus type 1 (HIV-1) infection may increase patient satisfaction and facilitate adherence.

METHODS

In this phase 3, open-label, multicenter, noninferiority trial involving patients who had had plasma HIV-1 RNA levels of less than 50 copies per milliliter for at least 6 months while taking standard oral antiretroviral therapy, we randomly assigned participants (1:1) to either continue their oral therapy or switch to monthly intramuscular injections of long-acting cabotegravir, an HIV-1 integrase strand-transfer inhibitor, and long-acting rilpivirine, a nonnucleoside reverse-transcriptase inhibitor. The primary end point was the percentage of participants with an HIV-1 RNA level of 50 copies per milliliter or higher at week 48, determined with the use of the Food and Drug Administration snapshot algorithm.

RESULTS

Treatment was initiated in 308 participants per group. At week 48, HIV-1 RNA levels of 50 copies per milliliter or higher were found in 5 participants (1.6%) receiving long-acting therapy and in 3 (1.0%) receiving oral therapy (adjusted difference, 0.6 percentage points; 95% confidence interval [CI], –1.2 to 2.5), a result that met the criterion for noninferiority for the primary end point (noninferiority margin, 6 percentage points). An HIV-1 RNA level of less than 50 copies per milliliter at week 48 was found in 92.5% of participants receiving long-acting therapy and in 95.5% of those receiving oral therapy (adjusted difference, –3.0 percentage points; 95% CI, –6.7 to 0.7), a result that met the criterion for noninferiority for this end point (noninferiority margin, –10 percentage points). Virologic failure was confirmed in 3 participants who received long-acting therapy and 4 participants who received oral therapy. Adverse events were more common in the long-acting–therapy group and included injection-site pain, which occurred in 231 recipients (75%) of long-acting therapy and was mild or moderate in most cases; 1% withdrew because of this event. Serious adverse events were reported in no more than 5% of participants in each group.

CONCLUSIONS

Monthly injections of long-acting cabotegravir and rilpivirine were noninferior to standard oral therapy for maintaining HIV-1 suppression. Injection-related adverse events were common but only infrequently led to medication withdrawal. (Funded by ViiV Healthcare and Janssen; ATLAS ClinicalTrials.gov number, NCT02951052.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Swindells at the Department of Internal Medicine, University of Nebraska Medical Center, 988106 Nebraska Medical Center, Omaha, NE 68198-8106, or at sswindells@unmc.edu.

This article was published on March 4, 2020, at NEJM.org.

N Engl J Med 2020;382:1112-23.
DOI: 10.1056/NEJMoa1904398

Combination antiretroviral therapy for human immunodeficiency virus type 1 (HIV-1) infection provides durable viral suppression, which is associated with improved immunologic function and extended survival.[1] Current guideline-recommended first-line regimens require lifelong daily oral therapy that can be burdensome, potentially affecting adherence and risking treatment failure.[2-4] Surveys suggest that there is substantial interest among persons living with HIV for less frequent dosing options.[5,6] Consequently, ongoing therapeutic research, including development of longer-acting injectable regimens, has been directed at simplifying antiretroviral therapy to improve satisfaction and facilitate adherence.[6-8]

Integrase strand-transfer inhibitors (INSTIs) or nonnucleoside reverse-transcriptase inhibitors (NNRTIs) are included in most guideline-recommended treatment regimens.[1] Cabotegravir is structurally related to the approved INSTI dolutegravir and has a higher barrier to resistance than first-generation INSTIs.[8,9] Rilpivirine is an approved second-generation NNRTI.[10,11]

Long-acting formulations of cabotegravir and rilpivirine can maintain exposure at plasma concentrations exceeding in vitro 90% inhibitory concentrations with monthly intramuscular injections.[8] In LATTE-2 (Long-Acting Antiretroviral Treatment Enabling Trial 2), the percentage of participants with HIV-1 RNA suppression through 96 weeks was similar among those who switched to long-acting cabotegravir plus long-acting rilpivirine and those who continued oral cabotegravir-based therapy.[12] Participants reported general satisfaction with injectable dosing and greater convenience than with previous oral therapy.[13]

Here we report the 48-week (primary end point) results of the phase 3 Antiretroviral Therapy as Long Acting Suppression (ATLAS) trial, the purpose of which was to establish whether switching to long-acting cabotegravir plus rilpivirine (long-acting therapy) is noninferior to continuation of current oral therapy among adults with virologically suppressed HIV-1 infection.

METHODS

TRIAL DESIGN

For this randomized, multicenter, parallel-group, open-label trial, we enrolled HIV-1–infected patients who were 18 years of age or older and had been receiving antiretroviral drugs in an uninterrupted regimen without virologic failure and without a change in medication for at least 6 months before screening. A single regimen switch was permitted 6 months or more before screening. A plasma HIV-1 RNA level of less than 50 copies per milliliter had to have been documented at screening and within 6 and 12 months before screening. Acceptable current antiretroviral regimens included two nucleoside or nucleotide reverse-transcriptase inhibitors (NRTIs) plus one of the following drugs: an INSTI, an NNRTI, a boosted protease inhibitor (PI), or unboosted atazanavir. To maximize generalizability, patients who were taking abacavir plus dolutegravir and lamivudine were excluded, because a large number of participants received this regimen in the related First Long-Acting Injectable Regimen (FLAIR) trial, which involved patients who had never received treatment.[14]

Participants were excluded if they had evidence of active hepatitis B virus infection, previous virologic failure, INSTI or NNRTI resistance mutations (except K103N in reverse transcriptase), or interruption of the current antiretroviral regimen within 6 months before screening or any interruption exceeding 1 month in duration. A complete list of the eligibility criteria is provided in the Supplementary Appendix and protocol, available with the full text of this article at NEJM.org.

Eligible participants were randomly assigned (in a 1:1 ratio) to either continue their current oral therapy or switch to the long-acting therapy regimen (Fig. 1A). Randomization was stratified according to the class of the third agent in the baseline antiretroviral regimen (PI, INSTI, or NNRTI) and sex at birth. Participants in the long-acting–therapy group received 30 mg of oral cabotegravir plus 25 mg of rilpivirine once daily with food for the first 4 weeks (oral lead-in period) to assess safety and side effects. After their eligibility for injectable therapy had been confirmed, participants received initial doses of 600 mg of cabotegravir and 900 mg of rilpivirine (a 3-ml injection of each drug) by injection into the gluteus muscle, followed by injections of 400 mg of cabotegravir and 600 mg of rilpivirine (a 2-ml injection of each drug) every 4 weeks through week 52 of the maintenance phase. Bridging therapy with oral cabotegravir and rilpivirine was available for participants who were unable to attend a clinic visit within the permitted window (21 to 28 days after the previous

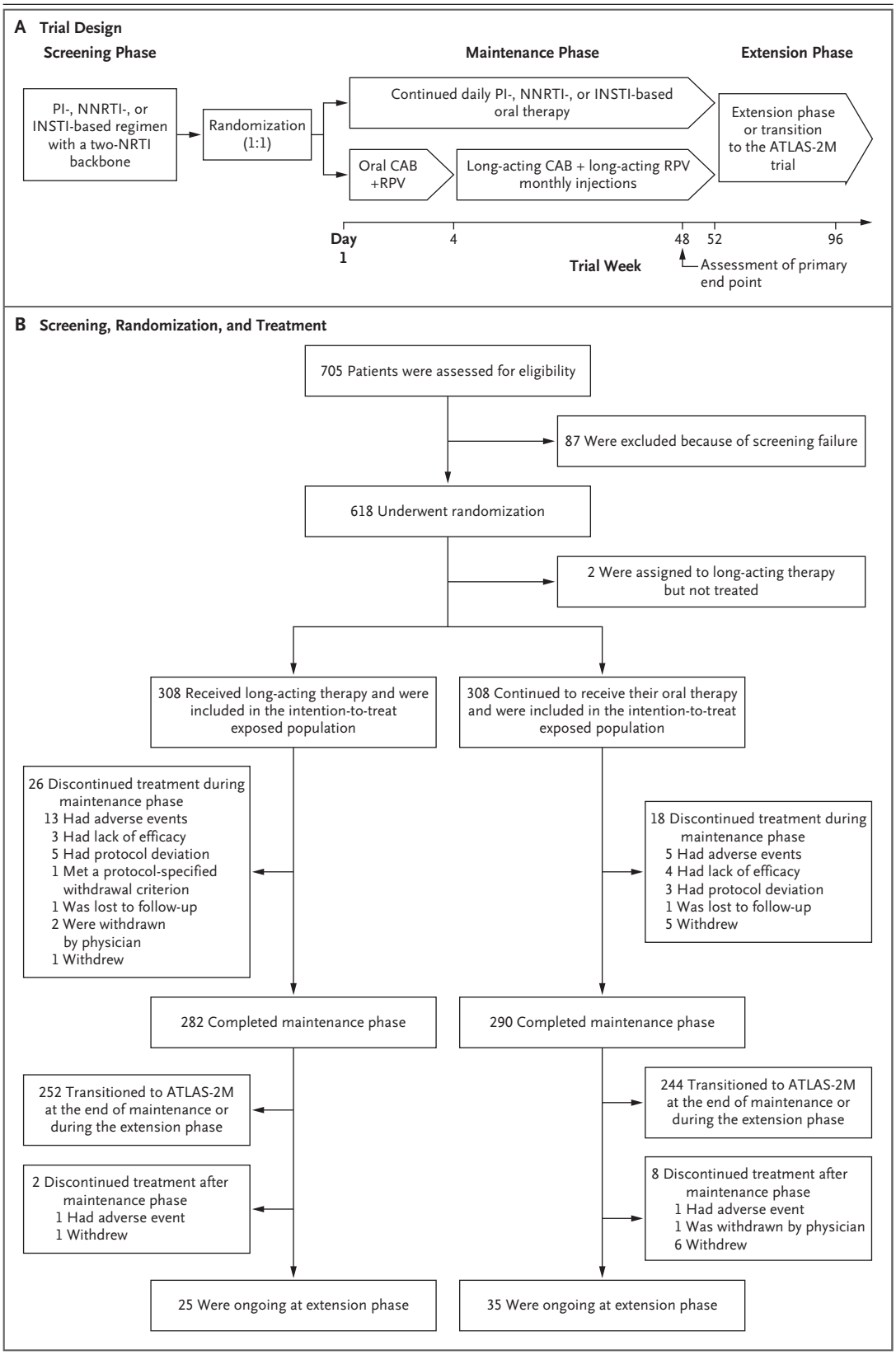

Figure 1 (facing page). Trial Design, Screening, Randomization, and Treatment.

Eligible patients were randomly assigned (in a 1:1 ratio) to continue their current oral antiretroviral therapy or to switch to the long-acting therapy regimen. Participants assigned to long-acting therapy initially received 4 weeks of treatment with oral cabotegravir plus rilpivirine once daily, after which they transitioned to the injectable regimen. After their eligibility for injectable therapy had been confirmed, these participants received initial doses of 600 mg of cabotegravir and 900 mg of rilpivirine by injection into the gluteus muscle, followed by injections of 400 mg of cabotegravir and 600 mg of rilpivirine every 4 weeks through week 52 of the maintenance phase. Participants who discontinue or complete long-acting therapy enter a 52-week long-term follow-up phase. Overall, 618 patients underwent randomization; 87 were screened but did not undergo randomization. Treatment was initiated in 308 participants in each treatment group, who made up the intention-to-treat exposed population; 2 participants who underwent randomization withdrew before starting treatment. The safety and intention-to-treat exposed populations were identical. On completion of the maintenance phase, participants had the option of continuing to participate in the extension phase, transitioning to ATLAS-2M, or leaving the trial (with no withdrawal visit required); 3 participants in each group fell into the last category and were not included in the extension phase or considered to have withdrawn from the trial. CAB denotes cabotegravir, INSTI integrase strand-transfer inhibitor, NNRTI nonnucleoside reverse-transcriptase inhibitor, NRTI nucleoside or nucleotide reverse-transcriptase inhibitor, PI protease inhibitor, and RPV rilpivirine.

injection for injections 2 and 3; 21 to 35 days subsequently). At week 52, participants receiving long-acting therapy continued their assigned therapy within the trial extension phase. Participants who had continued to take their oral antiretrovirals could either complete trial participation or switch to the long-acting therapy regimen. Alternatively, eligible participants in either group were offered entry into the ATLAS-2M randomized trial (ClinicalTrials.gov number, NCT03299049) to receive the long-acting therapy every 4 or 8 weeks.

The trial was conducted in accordance with the Declaration of Helsinki.[15] All participants provided written informed consent, and the protocol was approved by an institutional review board or ethics committee from each study site. Clinical data were collected by the academic authors; authors who are employees of ViiV Healthcare or GlaxoSmithKline performed the resistance analyses, pharmacokinetic studies, analyses of patient-reported outcomes, and statistical analyses. All the authors participated in the interpretation of the data and the writing of the manuscript that was submitted for publication. The authors vouch for the adherence of the trial to the protocol and for the accuracy and completeness of the data presented.

ASSESSMENTS AND END POINTS

Monthly clinic visits included physical examinations; assessments of adverse events[16]; collection of blood samples for clinical chemical and hematologic testing, HIV-1 RNA determinations, and pharmacokinetic analyses; and injection of long-acting cabotegravir and rilpivirine for participants assigned to that regimen (see the Supplementary Appendix). Blood samples for possible future genotypic testing of HIV-1 DNA were obtained at baseline. Patient-reported outcomes were assessed at selected visits.

The primary end point was the percentage of participants with plasma HIV-1 RNA levels of 50 copies per milliliter or higher at week 48, determined with the use of the Food and Drug Administration (FDA) snapshot algorithm in the intention-to-treat exposed population (i.e., all participants who received at least one dose of their assigned treatment).[17] The key secondary efficacy end point was the percentage of participants with plasma HIV-1 RNA levels of less than 50 copies per milliliter at week 48 (FDA snapshot algorithm). Other end points included virologic outcomes according to randomization strata and other baseline characteristics, confirmed virologic failure (two consecutive plasma HIV-1 RNA measurements of ≥200 copies per milliliter), genotypic and phenotypic resistance coincident with virologic failure, CD4+ lymphocyte counts, graded adverse events and laboratory abnormalities[16] and associated discontinuations, and plasma concentrations of cabotegravir and rilpivirine. Satisfaction with patients' current antiretroviral therapy was assessed at baseline and at weeks 24 and 44 with the 12-item HIV Treatment Satisfaction Questionnaire, status version (HIVTSQs), which adds assessments of pain and discomfort and of ease and difficulty to the original 10-item version. The 12-item HIVTSQs total score ranges from 0 (very dissatisfied) to 66 (very satisfied) (additional details are provided in the protocol). A single-item question regarding preference for long-acting or oral therapy was assessed in the long-acting–therapy group at week 48.

STATISTICAL ANALYSIS

The primary efficacy analysis included all participants who received at least one dose of their assigned treatment (intention-to-treat exposed population). The primary and key secondary efficacy analyses were based on a stratified Cochran–Mantel–Haenszel analysis, with adjustment for the class of the third agent in the baseline antiretroviral regimen and for sex at birth. The 95% confidence intervals for subgroup differences were calculated with an unconditional exact method with two inverted one-sided tests. Key efficacy end points were also assessed in the per-protocol population, which excluded participants with protocol deviations that were likely to affect efficacy assessments or lead to discontinuation of treatment. HIVTSQs outcomes in each treatment group at weeks 24 and 44 were compared by analysis of covariance.

In the analysis of the primary end point, noninferiority of long-acting therapy was concluded if the upper limit of the 95% confidence interval for the difference between long-acting therapy and oral therapy in the percentage of participants with an HIV-1 RNA level of 50 copies per milliliter or higher at week 48 was less than 6 percentage points. Assuming that 3% and 2% of participants in the long-acting–therapy group and the oral-therapy group, respectively, would have HIV-1 RNA levels of 50 copies per milliliter or higher at week 48, and with the noninferiority margin of 6 percentage points and a 2.5% one-sided significance level, we calculated that a sample of 285 participants in each treatment group would provide approximately 97% power to show noninferiority for the primary end point. This sample size would also provide at least 94% power to show noninferiority with regard to the key secondary end point, under assumptions of 87% of participants in each treatment group having a response, a –10-percentage-point noninferiority margin, and a 2.5% one-sided significance level.

If the criterion for noninferiority was met for the primary end point, a superiority test was planned,[18] but it was not included in the prespecified hierarchical testing procedure for key secondary end points (see section 5.5.2 of the statistical analysis plan, available with the protocol at NEJM.org). The 6-percentage-point margin balanced potential clinical advantages of long-acting therapy (e.g., improved adherence and satisfaction) against a low failure rate; if a 2% observed failure rate was assumed for the oral-therapy group, then noninferiority would be shown if the observed between-group difference was less than 3 percentage points. Furthermore, the sample size supports the noninferiority assessment with a stringent 4-percentage-point margin with 90% power in an analysis of pooled phase 3 data from the FLAIR trial.[14]

RESULTS

PARTICIPANTS

Screening began on October 28, 2016, and the last participant completed week 48 on May 29, 2018. A total of 705 people were screened at 115 sites in 13 countries (see the Supplementary Appendix), and 618 underwent randomization (Fig. 1B). In each treatment group, 308 participants started investigational treatment (intention-to-treat exposed population); 2 participants who had been assigned to the long-acting therapy regimen withdrew before starting treatment. Overall, the trial population was 33% female, 32% nonwhite, and a median of 42 years of age; 74% had CD4+ lymphocyte counts of 500 per cubic millimeter or higher (Table 1). The antiretroviral regimens at baseline included a two-NRTI backbone plus an NNRTI in 50% of participants, an INSTI in 33%, or a PI in 17% (Table S1 in the Supplementary Appendix). At trial entry, participants had been receiving their current antiretroviral regimen for a median of 4.3 years.

A total of 93% of participants completed maintenance-phase treatment through week 52, and 26 participants (8%) in the long-acting–therapy group and 18 (6%) in the oral-therapy group withdrew from the trial (Fig. 1). Adverse events were the most frequent cause for withdrawal, occurring in 14 participants (5%) in the long-acting–therapy group and 5 (2%) in the oral-therapy group; 1% of participants in each group withdrew for lack of efficacy (Tables 2 and 3). In the long-acting–therapy group, 98% of injections were administered within the permitted visit window (Fig. S1); 7 participants (2%) used oral bridging therapy (4 to 29 days) to cover missed or delayed injection visits.

EFFICACY

In the intention-to-treat exposed population, HIV-1 RNA levels of 50 copies per milliliter or

Table 1. Baseline Characteristics of Participants in the Intention-to-Treat Exposed Population.*

Characteristic	Long-Acting Therapy (N=308)	Oral Therapy (N=308)	Overall (N=616)
Median age (range) — yr	40 (21–74)	43 (18–82)	42 (18–82)
Age group — no. (%)			
<35 yr	80 (26)	80 (26)	160 (26)
35–49 yr	162 (53)	132 (43)	294 (48)
≥50 yr	66 (21)	96 (31)	162 (26)
Female sex — no. (%)	99 (32)	104 (34)	203 (33)
Median body-mass index (range)†	26 (15–51)	26 (18–58)	26 (15–58)
Race — no. (%)‡			
White	214 (69)	207 (67)	421 (68)
Black	62 (20)	77 (25)	139 (23)
Asian	22 (7)	13 (4)	35 (6)
Other	10 (3)	11 (4)	21 (3)
CD4+ lymphocyte count — no. (%)			
<350/mm^3	23 (7)	27 (9)	50 (8)
350–499/mm^3	56 (18)	57 (19)	113 (18)
≥500/mm^3	229 (74)	224 (73)	453 (74)
Median time since first ART (range) — mo	52 (7–222)	52 (7–257)	52 (7–257)
Third ART agent class — no. (%)			
NNRTI	155 (50)	155 (50)	310 (50)
INSTI	102 (33)	99 (32)	201 (33)
PI	51 (17)	54 (18)	105 (17)

* The intention-to-treat exposed population included all participants who received at least one dose of their assigned treatment. Percentages may not total 100 because of rounding. ART denotes antiretroviral therapy, INSTI integrase strand-transfer inhibitor, NNRTI nonnucleoside reverse-transcriptase inhibitor, and PI protease inhibitor.
† Body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Race was reported by the participant.

higher at week 48 were found in 5 participants (1.6%) in the long-acting–therapy group and 3 (1.0%) in the oral-therapy group (adjusted difference, 0.6 percentage points; 95% confidence interval [CI], –1.2 to 2.5); these results met the prespecified noninferiority criterion for the primary end point (Table 2). Similarly, the long-acting therapy was noninferior to oral therapy with respect to the key secondary end point of an HIV-1 RNA level of less than 50 copies per milliliter at week 48 (92.5% and 95.5%, respectively; adjusted difference, –3.0 percentage points; 95% CI, –6.7 to 0.7). No evidence of heterogeneity in these between-group differences was found across randomization strata or according to other baseline characteristics (Fig. S2). Results were consistent in the per-protocol population (Table 2), which excluded 30 participants for protocol deviations (Table S2). Results were also consistent with those of other secondary efficacy analyses (Table 2 and Table S3).

RESISTANCE ANALYSES

Three participants in the long-acting–therapy group had confirmed virologic failure — two with HIV-1 subtype A/A1 (failure occurred at week 8 in one participant and at week 20 in the other) and one with subtype AG (in whom failure occurred at week 12). Rilpivirine resistance–associated reverse-transcriptase mutations were detected in HIV-1 RNA samples from all three participants at the time of virologic failure, including E138A in one participant and E138K plus V108I in another (in both these participants, the same E138 mutations were present in HIV-1 DNA at baseline) and E138E/K plus the

Table 2. Efficacy Outcomes at Week 48.*

Outcome	Long-Acting Therapy (N=308)	Oral Therapy (N=308)	Difference (95% CI)	Adjusted Difference (95% CI)†
			percentage points	
Intention-to-treat exposed population				
HIV-1 RNA level — no. (%)				
<50 copies/ml	285 (92.5)	294 (95.5)	−2.9 (−6.7 to 0.8)	−3.0 (−6.7 to 0.7)
≥50 copies/ml‡	5 (1.6)	3 (1.0)	0.6 (−1.1 to 2.4)	0.6 (−1.2 to 2.5)
Level not below threshold — no. (%)	1 (0.3)	1 (0.3)	—	—
Discontinued treatment for lack of efficacy — no. (%)	3 (1.0)	2 (0.6)	—	—
Discontinued treatment for other reason — no. (%)	1 (0.3)	0	—	—
No virologic data — no. (%)	18 (5.8)	11 (3.6)	—	—
Withdrew from trial because of adverse event or death§	11 (3.6)	5 (1.6)	—	—
Withdrew from trial for other reasons	7 (2.3)	6 (1.9)	—	—
HIV-1 RNA level <200 copies/ml — no. (%)	286 (92.9)	295 (95.8)	—	—
Subgroup analysis of HIV-1 RNA level ≥50 copies/ml — no./total no. (%)				
Sex at birth				
Female	2/99 (2.0)	0/104	2.0 (−1.7 to 7.1)	—
Male	3/209 (1.4)	3/204 (1.5)	0.0 (−3.0 to 2.9)	—
Baseline third-agent class				—
PI	1/51 (2.0)	0/54	2.0 (−5.0 to 10.6)	—
INSTI	0/102	2/99 (2.0)	−2.0 (−7.1 to 1.8)	—
NNRTI	4/155 (2.6)	1/155 (0.6)	1.9 (−1.3 to 5.9)	—
Median change from baseline in CD4+ lymphocyte count (range) — per mm^3	4.0 (−536 to 801)	13.5 (−1043 to 521)	—	—
Per-protocol population¶				
HIV-1 RNA level — no./total no. (%)				
<50 copies/ml	276/294 (93.9)	280/292 (95.9)	−2.0 (−5.6 to 1.6)	−2.0 (−5.6 to 1.5)
≥50 copies/ml	4/294 (1.4)	3/292 (1.0)	0.3 (−1.4 to 2.1)	0.3 (−1.4 to 2.1)

* HIV-1 denotes human immunodeficiency virus type 1.
† Values are from a Cochran–Mantel–Haenszel stratified analysis with adjustment for sex at birth and class of the third agent at baseline (PI, NNRTI, or INSTI).
‡ 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.
§ There was one death in the oral-therapy group due to a methamphetamine overdose.
¶ The per-protocol population excluded participants with protocol deviations that were likely to affect efficacy assessments or lead to discontinuation of treatment.

integrase mutation N155H in the third. These mutations reduced susceptibility to rilpivirine by a factor of 6.5, and cabotegravir susceptibility was reduced by a factor of 2.7 in the participant with N155H (Table S4). Two participants also had an L74I integrase polymorphism at baseline and at virologic failure, although this accessory mutation by itself does not decrease susceptibility to INSTIs.[19] No participant with virologic failure missed an injection or received injections outside the permitted window. Four participants in the oral-therapy group had confirmed virologic failure, and reverse-transcriptase mutations were detected in three of these participants: one had the M184I mutation, one had M184V plus G190S, and one had M230M/I.

Table 3. Postbaseline Adverse Events.

Event Category	All Adverse Events		Adverse Events Related to Trial Regimen*	
	Long-Acting Therapy (N=308)	Oral Therapy (N=308)	Long-Acting Therapy (N=308)	Oral Therapy (N=308)
	number of participants (percent)			
Any event	294 (95)	220 (71)	255 (83)	8 (3)
Any event, excluding injection-site reactions	264 (86)	220 (71)	88 (29)	8 (3)
Grade 3 or 4 events	35 (11)	23 (7)	14 (5)	1 (<1)
Grade 3 or 4 events, excluding injection-site reactions	25 (8)	23 (7)	4 (1)	1 (<1)
Events leading to withdrawal†	14 (5)‡	5 (2)	10 (3)	1 (<1)
Any serious adverse events	13 (4)	14 (5)	0	1 (<1)§
Fatal serious adverse events	0	1 (<1)¶	0	0
Any injection-site reaction	250 (81)	—	198 (64)	—
Any injection-site pain	231 (75)	—	186 (60)	—
Grade 3 injection-site pain‖	10 (3)	—	8 (3)	—
Injection-site pain leading to withdrawal	4 (1)	—	4 (1)	—
Injection-site nodule	37 (12)	—	22 (7)	—
Injection-site induration	30 (10)	—	20 (6)	—
Injection-site swelling	23 (7)	—	19 (6)	—
Events, excluding injection-site reactions, reported in ≥5% of participants in either group				
Nasopharyngitis	52 (17)	42 (14)	0	1 (<1)
Upper respiratory tract infection	32 (10)	25 (8)	0	0
Headache	34 (11)	17 (6)	11 (4)	0
Diarrhea	22 (7)	15 (5)	2 (1)	0
Back pain	21 (7)	10 (3)	2 (1)	0
Influenza-like illness	17 (6)	14 (5)	5 (2)	0
Cough	16 (5)	14 (5)	0	0
Pyrexia	21 (7)	9 (3)	11 (4)	0
Fatigue	22 (7)	6 (2)	11 (4)	0
Viral respiratory tract infection	11 (4)	17 (6)	0	0

* The relationship of an adverse event to the trial drug was determined by the investigator reporting the event. In some cases, injection-site reactions may have been considered to be caused by the injection, as distinct from the drug delivered by the injection, and reported as not related to the trial drug.

† The most frequent events leading to withdrawal in the long-acting–therapy group were injection-site pain (4 participants), viral hepatitis (3), and headache (2). All other events in both groups were reported in 1 participant each.

‡ The numbers in this category do not necessarily align with the numbers of participants who were classified in the efficacy analysis as having withdrawn from the trial because of adverse events or death. For example, if a participant withdrew from the trial at week 44 because of adverse events but had a viral load of less than 50 copies per milliliter within the week 48 snapshot window (week 42 through week 54), data for this participant would be assigned to the category of an HIV-1 RNA level of less than 50 copies per milliliter, per the Food and Drug Administration snapshot algorithm, rather than to the "withdrew from trial because of adverse event or death" subcategory of "no virologic data."

§ The serious adverse event in this participant was suicidal ideation.

¶ This death was due to a methamphetamine overdose.

‖ No pain worse than grade 3 was reported.

SAFETY AND SIDE EFFECTS

Adverse events were infrequent during the 4-week lead-in period with oral cabotegravir plus rilpivirine; three participants withdrew during this period. In the maintenance phase, 95% of participants in the long-acting–therapy group and 71% of participants in the oral-therapy group reported at least one adverse event (Table 3 and

Table S5). Differences between the treatment groups were largely attributable to injection-site reactions, which occurred in 83% of participants in the long-acting–therapy group. Other drug-related adverse events, which were primarily of mild or moderate severity (grade 1 or 2), were more frequent with long-acting therapy (29%) than with oral therapy (3%). Grade 3 or 4 adverse events (primarily injection-site reactions) were more frequent in the long-acting–therapy group. Other than injection-site reactions, the most severe events reported as being related to the long-acting therapy were grade 3 pyrexia (one participant), nausea (one), diarrhea (one), and headache (two) and grade 4 lipase increase (one). At week 48, the median weight gains were 1.80 kg (interquartile range, −0.30 to 4.90) in the long-acting–therapy group and 0.30 kg (interquartile range, −1.60 to 2.50) in the oral-therapy group.

The incidence of serious adverse events was similar in the two groups (Table S6); one event (suicidal ideation in the oral-therapy group) was considered by the investigators to be related to the trial regimen. In each group, eight participants (3%) had disease progression to Centers for Disease Control and Prevention stage 3 or death (Table S3). Four participants in the long-acting–therapy group (1%) withdrew because of injection-site reactions; all four reported injection-site pain, and two also reported a nodule or swelling (Table S7). Other than injection-site reactions, no specific type of adverse event led to withdrawal in more than two participants in either group.

Among the participants who received long-acting therapy, 99% of injection-site reactions (Table 3) were of mild or moderate severity; no life-threatening or fatal (grade 4 or 5) reactions were reported, and 88% of reactions resolved within 7 days (median, 3 days). The most common injection-site reaction was pain (75% of participants); nodule (12%), induration (10%), and swelling (7%) were less common. Injection-site reactions were reported in 69% of participants after the initial 3-ml injections at week 4; frequencies of such reactions declined progressively after the subsequent 2-ml injections, reaching 11% at week 48 (Fig. S3).

Five participants in the long-acting–therapy group and one in the oral-therapy group had alanine aminotransferase elevations to at least 3 times the upper limit of the normal range (Table S8). Five of these events met protocol-defined liver-related stopping criteria. Among the participants who had these events, hepatitis A was diagnosed in three, hepatitis B in one, and hepatitis C in one. The trial treatment was stopped in all five participants and was restarted subsequently in one (in the oral-therapy group).

PHARMACOKINETICS

The concentrations of cabotegravir and rilpivirine in plasma during long-acting therapy were similar to those reported during oral therapy (Fig. 2).[20,21] Both drugs showed accumulation by a factor of approximately 2.3 from the first trough at week 8 to the trough at week 48, approximating steady-state drug concentrations. Geometric mean concentrations of cabotegravir and rilpivirine in plasma at week 48 (2.84 μg per milliliter and 90.3 ng per milliliter, respectively) were 17 times and 7.5 times as high as their respective protein-adjusted concentrations required for 90% viral inhibition, similar to outcomes after monthly dosing in a phase 2 study.[12] All three participants in the long-acting–therapy group who had confirmed virologic failure received all injections on schedule; however, plasma concentrations of cabotegravir and rilpivirine at the time of failure were in the lower quartiles of the ranges of observed concentrations (Table S9).

PATIENT-REPORTED OUTCOMES

After 44 weeks, participants in the long-acting–therapy group reported substantially greater improvement from baseline in treatment satisfaction than participants in the oral-therapy group, as assessed with the HIVTSQs; the adjusted mean increase in score from baseline was 5.68 points higher (95% CI, 4.37 to 6.98) in the long-acting–therapy group than in the oral-therapy group (Table S10). This difference meets the threshold for the minimal clinically important difference according to the distribution-based approach. In a within-group comparison conducted at week 48 in the long-acting–therapy group, 97% of participants who responded to the questionnaire (266 of 273) and 86% of participants in the intention-to-treat exposed population (266 of 308) selected the injectable regimen over daily oral therapy as their preferred HIV treatment.

DISCUSSION

Treatment simplification has been a focus of recent HIV-1 research to improve adherence, side effects, and quality of life. This trial shows successful treatment of HIV-1 infection with an all-injectable regimen as an alternative to daily oral treatment. Monthly dosing with longer-acting formulations of the INSTI cabotegravir and the NNRTI rilpivirine provided plasma concentrations of the drugs that were similar to those observed during daily oral therapy with cabotegravir and rilpivirine in combination with NRTIs.[20,21] HIV-1 suppression through 48 weeks was maintained in similarly high percentages of participants with the injectable long-acting regimen and conventional three-drug oral regimens. In subgroup analyses, no meaningful differences in virologic outcomes were observed according to sex, third-agent class (INSTI, NNRTI, or PI) in previous oral regimens, or baseline disease or demographic characteristics.

Participants who received the long-acting therapy reported greater satisfaction and preferred the regimen over previous oral therapy. Although agreement to enroll in the trial implies willingness to try injectable therapy, most participants maintained a favorable view of the regimen even after 12 monthly injections.

Frequencies of serious adverse events were similar in the two treatment groups; no treatment-related serious adverse events were reported in the long-acting–therapy group. Injection-site reactions, primarily pain, were common after the first injection but became less frequent subsequently; 1% of participants discontinued long-acting therapy as a result of these events. As has occurred in previous switch studies, participants who switched to the long-acting therapy reported more adverse events than those who continued their familiar oral regimens, potentially contributing to the greater frequency of drug-related adverse events other than injection-site reactions in the long-acting–therapy group.[22,23]

All confirmed virologic failures in the long-acting therapy group occurred in participants with HIV-1 subtype A or AG, a finding that warrants further investigation. Low trough concentrations of the trial drugs may have contributed to virologic failure in recipients of long-acting therapy; however, all injections in participants with virologic failure were received within the prescribed visit window, and a clear relationship between drug concentrations and infrequent virologic failure could not be established.

This trial has several limitations. The trial population had stably suppressed HIV-1 infection and substantial treatment histories but no previous virologic failure, which may limit generalizability. In this regard, the FLAIR trial is evaluat-

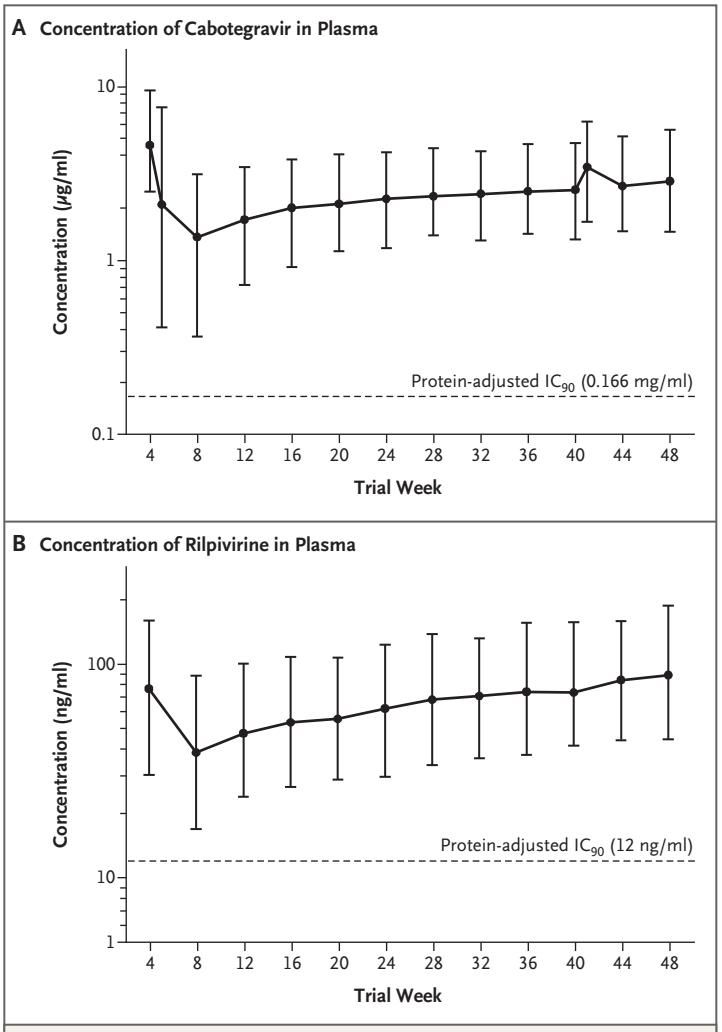

Figure 2. Plasma Concentration–Time Profiles.

The median plasma concentration–time profiles in participants receiving monthly intramuscular injections of the long-acting therapy are shown. I bars indicate the 5th and 95th percentiles. The dashed horizontal line indicates the in vitro protein-adjusted 90% inhibitory concentration (IC_{90}). Predose plasma concentrations are shown, with the exception of the week 5 and week 41 visits in Panel A, for which 1-week-postdose plasma concentrations are shown.

ing patients who had not previously received antiretroviral therapy and who switched to the long-acting regimen after having viral suppression with oral dolutegravir–abacavir–lamivudine, and the ongoing ATLAS-2M trial is comparing long-acting treatment intervals of 4 and 8 weeks. Both trials include extension phases to evaluate longer-term outcomes. Studies involving populations that may derive benefit from the long-acting regimen, such as patients with adherence challenges or gastrointestinal absorption issues, would provide additional useful information.

In this trial, the monthly injectable long-acting regimen was noninferior to standard once-daily oral therapy for maintaining HIV-1 suppression. Injection-site reactions were common but generally were of mild or moderate severity and transient, and participant satisfaction was higher with the injectable regimen. This regimen may provide a new treatment option for patients living with HIV.

Supported by ViiV Healthcare and Janssen.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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

We thank all the trial participants and their families, the ATLAS clinical investigators and their staff, and trial team members at ViiV Healthcare, GlaxoSmithKline, and Janssen. Editorial assistance with a previous version of the manuscript was provided by Richard Boehme, Ph.D., of Articulate Science and was funded by ViiV Healthcare.

APPENDIX

The authors' full names and academic degrees are as follows: Susan Swindells, M.B., B.S., Jaime-Federico Andrade-Villanueva, M.D., Gary J. Richmond, M.D., Giuliano Rizzardini, M.D., Axel Baumgarten, M.D., Mar Masiá, M.D., Gulam Latiff, M.D., Vadim Pokrovsky, M.D., Fritz Bredeek, M.D., Graham Smith, M.D., Pedro Cahn, M.D., Yeon-Sook Kim, M.D., Ph.D., Susan L. Ford, Pharm.D., Christine L. Talarico, M.S., Parul Patel, Pharm.D., Vasiliki Chounta, M.S., Herta Crauwels, Ph.D., Wim Parys, M.D., Simon Vanveggel, M.S., Joseph Mrus, M.D., Jenny Huang, M.S., Conn M. Harrington, B.A., Krischan J. Hudson, Ph.D., David A. Margolis, M.D., Kimberly Y. Smith, M.D., Peter E. Williams, Ph.D., and William R. Spreen, Pharm.D.

The authors' affiliations are as follows: the University of Nebraska Medical Center, Omaha (S.S.); Centro Universitario de Ciencias de la Salud, University of Guadalajara, Guadalajara, Mexico (J.-F.A.-V.); Broward Health Medical Center, Broward Health Imperial Point, Fort Lauderdale, FL (G.J.R.); Fatebenefratelli Sacco Hospital, Milan (G.R.); the Center for Infectious Diseases, Berlin (A.B.); Hospital de Elche, Elche, Spain (M.M.); Maxwell Centre, Durban, South Africa (G.L.); the Central Research Institute of Epidemiology, Moscow (V.P.); Metropolis Medical Group, San Francisco (F.B.); Maple Leaf Research, Toronto (G.S.), and GlaxoSmithKline, Mississauga (J.H.) — both in Ontario, Canada; Fundación Huésped, Buenos Aires (P.C.); Chungnam National University School of Medicine, Daejeon, South Korea (Y.-S.K.); GlaxoSmithKline (S.L.F.) and ViiV Healthcare (C.L.T., P.P., J.M., C.M.H., K.J.H., D.A.M., K.Y.S., W.R.S.) — both in Research Triangle Park, NC; ViiV Healthcare, Brentford, United Kingdom (V.C.); and Janssen Research and Development, Beerse, Belgium (H.C., W.P., S.V., P.E.W.).

REFERENCES

1. AIDSinfo. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Bethesda, MD: Department of Health and Human Services, 2018 (https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf).
2. Ortego C, Huedo-Medina TB, Llorca J, et al. Adherence to highly active antiretroviral therapy (HAART): a meta-analysis. AIDS Behav 2011;15:1381-96.
3. Gardner EM, Sharma S, Peng G, et al. Differential adherence to combination antiretroviral therapy is associated with virological failure with resistance. AIDS 2008;22:75-82.
4. Bangsberg DR, Perry S, Charlebois ED, et al. Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. AIDS 2001;15:1181-3.
5. Weld ED, Rana MS, Dallas RH, et al. Interest of youth living with HIV in long-acting antiretrovirals. J Acquir Immune Defic Syndr 2019;80:190-7.
6. Williams J, Sayles HR, Meza JL, et al. Long-acting parenteral nanoformulated antiretroviral therapy: interest and attitudes of HIV-infected patients. Nanomedicine (Lond) 2013;8:1807-13.
7. Flexner C, Thomas DL, Swindells S. Creating demand for long-acting formulations for the treatment and prevention of HIV, tuberculosis, and viral hepatitis. Curr Opin HIV AIDS 2019;14:13-20.
8. Spreen WR, Margolis DA, Pottage JC Jr. Long-acting injectable antiretrovirals for HIV treatment and prevention. Curr Opin HIV AIDS 2013;8:565-71.
9. Oliveira M, Ibanescu R-I, Anstett K, et al. Selective resistance profiles emerging in patient-derived clinical isolates with cabotegravir, bictegravir, dolutegravir, and elvitegravir. Retrovirology 2018;15:56.
10. Edurant (rilpivirine) prescribing information. Titusville, NJ: Janssen Therapeutics, 2019 (http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/EDURANT-pi.pdf).
11. Cohen CJ, Molina J-M, Cahn P, et al. Efficacy and safety of rilpivirine (TMC278) versus efavirenz at 48 weeks in treatment-naive HIV-1-infected patients: pooled results from the phase 3 double-blind randomized ECHO and THRIVE Trials. J Acquir Immune Defic Syndr 2012;60:33-42.
12. Margolis DA, Gonzalez-Garcia J, Stellbrink H-J, et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. Lancet 2017;390:1499-510.
13. Kerrigan D, Mantsios A, Gorgolas M, et al. Experiences with long acting injectable ART: a qualitative study among PLHIV participating in a phase II study of cabotegravir + rilpivirine (LATTE-2) in the United States and Spain. PLoS One 2018;13(1):e0190487.
14. Orkin C, Arasteh K, Górgolas Hernández-Mora M, et al. Long-acting cabotegravir and rilpivirine after oral induction for HIV-1 infection. N Engl J Med 2020;382:1124-35.
15. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013;310:2191-4.

16. Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 1.0. Bethesda, MD: National Institute of Allergy and Infectious Diseases, Division of AIDS, 2009 (https://rsc.niaid.nih.gov/sites/default/files/table-for-grading-severity-of-adult-pediatric-adverse-events.pdf).
17. FDA Center for Drug Evaluation and Research. Human immunodeficiency virus-1 infection: developing antiretroviral drugs for treatment. Guidance for industry. 2015 (https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm355128.pdf).
18. Points to consider on switching between superiority and noninferiority. London: European Medicines Agency, 2000 (https://www.ema.europa.eu/en/documents/scientific-guideline/points-consider-switching-between-superiority-non-inferiority_en.pdf).
19. Wensing AM, Calvez V, Günthard HF, et al. 2017 Update of the drug resistance mutations in HIV-1. Top Antivir Med 2016;24:132-3.
20. Margolis DA, Brinson CC, Smith GHR, et al. Cabotegravir plus rilpivirine, once a day, after induction with cabotegravir plus nucleoside reverse transcriptase inhibitors in antiretroviral-naive adults with HIV-1 infection (LATTE): a randomised, phase 2b, dose-ranging trial. Lancet Infect Dis 2015;15:1145-55.
21. Crauwels HM, van Schaick E, van Heeswijk RPG, Vanveggel S, Boven K, Vis P. Effect of intrinsic and extrinsic factors on the pharmacokinetics of TMC278 in antiretroviral-naive, HIV-1-infected patients in ECHO and THRIVE. J Int AIDS Soc 2010;13:Suppl 4:P186. abstract.
22. Singh S, Loke YK. Drug safety assessment in clinical trials: methodological challenges and opportunities. Trials 2012;13:138.
23. Llibre JM, Hung C-C, Brinson C, et al. Efficacy, safety, and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomised, non-inferiority SWORD-1 and SWORD-2 studies. Lancet 2018;391:839-49.

CLINICAL TRIAL REGISTRATION

The *Journal* requires investigators to register their clinical trials in a public trials registry. The members of the International Committee of Medical Journal Editors (ICMJE) will consider most reports of clinical trials for publication only if the trials have been registered. Current information on requirements and appropriate registries is available at www.icmje.org/about-icmje/faqs/.