ORIGINAL ARTICLE

Cabotegravir plus Rilpivirine for Persons with HIV and Adherence Challenges

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ABSTRACT

BACKGROUND

Randomized trials of long-acting injectable antiretroviral therapy (ART) in persons with human immunodeficiency virus (HIV) who face challenges with adherence to oral medication are lacking.

METHODS

We conducted an open-label, randomized trial involving persons with HIV who had inadequate adherence to ART (a persistent HIV-1 RNA level of >200 copies per milliliter or loss to follow-up). Participants received up to 24 weeks of adherence support, conditional economic incentives, and standard care with oral ART (step 1). Participants who had an HIV-1 RNA level of 200 copies per milliliter or lower in step 1 were randomly assigned in a 1:1 ratio to either continue standard care or switch to monthly injections of long-acting cabotegravir plus rilpivirine with or without oral lead-in therapy (step 2). The primary outcome was regimen failure, defined as confirmed virologic failure (two consecutive HIV-1 RNA measurements of >200 copies per milliliter) or treatment discontinuation during step 2.

RESULTS

In step 1 of the trial, we enrolled 453 participants; the median age was 40 years, 63% were Black, and 29% had been assigned female sex at birth. In step 2, a total of 306 participants underwent randomization; 152 were assigned to receive cabotegravir–rilpivirine and 154 to receive standard care. Step 2 randomization was stopped early on the basis of the superiority of cabotegravir–rilpivirine to standard care in secondary outcomes at a prespecified analysis performed after a median follow-up of 48 weeks. The cumulative incidence of regimen failure by week 48 was 22.8% in the cabotegravir–rilpivirine group and 41.2% in the standard-care group (difference, –18.4 percentage points; 98.4% confidence interval [CI], –32.4 to –4.3; P=0.002). The cumulative incidence of an adverse event was 43.5% in the cabotegravir–rilpivirine group and 42.4% in the standard-care group (difference, 1.1 percentage points; 95% CI, –12.7 to 15.0). Resistance-associated mutations developed in 2 participants with confirmed virologic failure in each group.

CONCLUSIONS

Monthly injections of long-acting cabotegravir–rilpivirine were superior to standard oral ART in reducing the risk of regimen failure among persons with HIV who had adherence challenges. (Funded by the National Institute of Allergy and Infectious Diseases; LATITUDE ClinicalTrials.gov number, NCT03635788.)

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Antiretroviral therapy (ART) lowers mortality and slows the progression of disease among persons with human immunodeficiency virus (HIV) and prevents the transmission of HIV.[1] Although modern ART is composed mostly of fixed-dose, combination daily oral tablets, which have an established safety profile, the estimated percentage of viral suppression among persons with HIV is only 67% in the United States.[2,3] Many persons with HIV face challenges in adhering to ART, such as social and structural barriers, side effects, stigma, and competing priorities. Long-acting injectable ART offers a less-frequent dosing alternative that is directly observed by health care providers, which could facilitate durable virologic suppression in this population.

In 2021, the Food and Drug Administration approved the combination of long-acting injectable cabotegravir plus rilpivirine (cabotegravir–rilpivirine) for the treatment of virologically suppressed HIV-1 infection in persons receiving oral ART, which is administered once a month or once every 2 months.[4-6] However, phase 3 trials of cabotegravir–rilpivirine generally excluded persons with HIV who had viremia and challenges with adherence to oral ART. Emerging data from observational studies and case series suggest that durable viral suppression can be achieved with long-acting injectable therapy in this population.[7-9] These observations prompted recent changes to treatment guidelines in the United States, which now recommend the consideration of long-acting injectable cabotegravir–rilpivirine in persons with HIV who have inadequate adherence to ART, advanced disease, and limited treatment options; however, treatment with cabotegravir–rilpivirine is a CIII recommendation (expert opinion).[10,11] To date, randomized clinical trials evaluating this treatment strategy in this population are lacking.

Here, we report the primary results of the Advancing Clinical Therapeutics Globally for HIV/AIDS and Other Infections (ACTG) A5359 LATITUDE (Long-Acting Therapy to Improve Treatment Success in Daily Life) trial, a phase 3, prospective, multicenter, open-label, randomized trial. We compared the safety and efficacy of monthly injections of long-acting cabotegravir–rilpivirine with daily oral ART (standard care) in persons in the United States with a history of adherence challenges.

Methods

Trial Oversight and Participants

Eligible participants were 18 years of age or older, had HIV without hepatitis B coinfection, and had previously received ART. In addition, participants had no clinically relevant mutations associated with resistance to rilpivirine or integrase strand-transfer inhibitors (INSTIs) and had evidence of nonadherence. Nonadherence was defined as a poor virologic response in patients with an active prescription for ART, loss to clinical follow-up with nonadherence to ART, or both, each lasting for at least 6 consecutive months and occurring within 18 months before trial entry. Full eligibility criteria and details of the trial design are provided in the protocol, available with the full text of this article at NEJM.org. Additional details about the design of the trial are provided in the Supplementary Appendix (available at NEJM.org).

The trial protocol was approved by a central institutional review board and by local institutional review boards. All the participants provided written informed consent. The Division of AIDS of the National Institute of Allergy and Infectious Diseases provided regulatory sponsorship and was responsible for clinical monitoring of the trial. ViiV Healthcare and Johnson & Johnson donated cabotegravir–rilpivirine and oral ART, contributed to the design of the trial, and reviewed an earlier version of the manuscript; they had no role in the analysis of the data. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Trial Design and Randomization

The trial was designed with two steps for the evaluation of the primary outcome. On completion of the first two steps, participants either enrolled in an extension phase (step 3) and continued to receive treatment with cabotegravir–rilpivirine or entered an observation phase (step 4) and discontinued treatment with cabotegravir–rilpivirine (Fig. 1A). This article focuses on the results of the primary outcome. In step 1, participants started receiving standard care — an oral ART regimen consisting of at least three drugs (two or more of which were predicted to be fully active), which included a boosted protease inhibitor, an INSTI, or both for up to 24 weeks.

In step 1, participants received adherence support and were eligible to receive conditional economic incentives at each visit (maximum total incentive, $675) on the basis of meeting benchmarks for visit completion, decreased viral load, or both (see the Supplementary Appendix).[12,13] The participants in whom virologic suppression was achieved during step 1 were randomly assigned in a 1:1 ratio to either continue standard care or switch to injections of long-acting cabotegravir–rilpivirine for 52 weeks (step 2).

Participants who underwent randomization and were assigned to the cabotegravir–rilpivirine group received optional oral lead-in therapy with 30 mg of cabotegravir and 25 mg of rilpivirine once daily for approximately 4 weeks, followed by loading injections of 600 mg (3 ml) of cabotegravir and 900 mg (3 ml) of rilpivirine. Subsequent injections of cabotegravir, at a dose of 400 mg (2 ml), and rilpivirine, at a dose of 600 mg (2 ml), were administered within 24 to 32 days after the previous injection for the second and third injections and within 21 to 35 days thereafter. During step 2, participants received continued adherence support without conditional economic incentives.

Randomization was stratified with the use of permuted blocks and was balanced according to site. Three versions of the protocol were implemented before this primary analysis (see the Supplementary Appendix). The protocol revisions included the following major changes: modifying the viral load threshold needed to advance to step 2 (from <50 copies per milliliter in version 1 to <200 copies per milliliter in version 2), shortening the required time in step 1 before randomization in step 2 (from 20 weeks in version 1 to 12 weeks in version 2 and 4 weeks in version 3), allowing enrollment of participants who had viral suppression at screening but had an HIV viral load that was greater than 200 copies per milliliter within 12 months before trial entry (in version 3), and making oral lead-in therapy optional in step 2 (in versions 2 and 3).

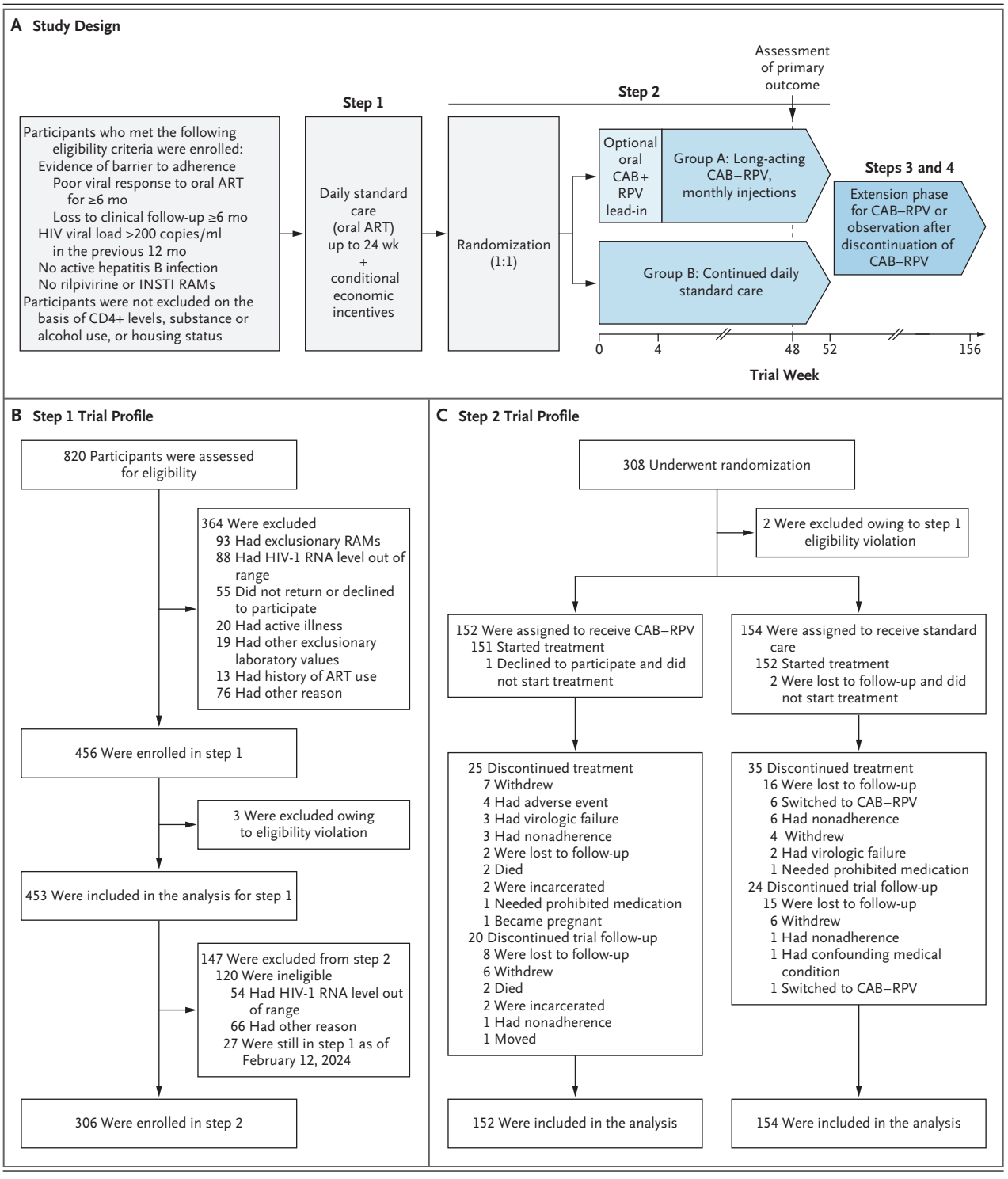
TRIAL PROCEDURES AND OUTCOMES

After enrollment, participants were asked to complete a trial visit every 4 weeks to assess their eligibility for conditional economic incentives (in step 1) or receive injections of cabotegravir–rilpivirine (in step 2). Participants who were assigned to continue standard care in step 2 had less-frequent visits (every 8 weeks starting at week 12 and every 12 weeks starting at week 24) to more closely mimic the standard care of persons with HIV who have adherence challenges in the United States. The primary outcome was regimen failure in step 2, which was defined as the earliest occurrence of either confirmed virologic failure (two consecutive HIV-1 RNA measurements of >200 copies per milliliter after randomization) or permanent discontinuation (which included participants who died, never started treatment, or both) of the trial treatment. The secondary outcomes reported here include virologic failure, treatment-related failure (defined as the earliest occurrence of virologic failure or premature treatment discontinuation due to treatment-related adverse events), genotypic resistance with virologic failure, adverse events, and plasma pharmacokinetics of cabotegravir and rilpivirine in participants with confirmed virologic failure. Additional participant-reported outcomes are described in the Supplementary Appendix.

STATISTICAL ANALYSIS

We calculated that a sample size of 320 participants in step 2 would provide the trial with approximately 80% power to detect a difference of 16 percentage points in the cumulative incidence of regimen failure between the cabotegravir–rilpivirine group and the standard-care group, with a two-sided type I error of 5%. The primary analysis was performed according to the intention-to-treat principle. We used the Kaplan–Meier method to estimate the the cumulative incidence of regimen failure at week 48. The same approach was used for the analysis of the virologic failure, treatment-related failure, and premature treatment discontinuation (secondary efficacy outcomes). For the analysis of virologic failure, data from the participants who prematurely discontinued the trial during the follow-up period or from those who died were censored. The effects of treatment on the primary and secondary efficacy outcomes were evaluated in prespecified subgroups. Details of other secondary outcome measures, supportive analyses, and statistical analysis methods are provided in the Supplementary Appendix.

Interim efficacy analyses were conducted with the use of the Lan–DeMets spending function analogue of the O'Brien–Fleming boundaries.[14] At the second planned efficacy review on February 12, 2024, which included trial data through



January 3, 2024, the data and safety monitoring board recommended stopping randomization in step 2 on the basis of the efficacy results for virologic failure and treatment-related failure (see the Supplementary Appendix). The analyses in this article include data collected up to the date of the efficacy review (February 12, 2024), with an information fraction of 76.6%, which provided a type I error of 0.0161. Two-sided 98.4% confidence intervals were provided for the primary and

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

Active hepatitis B infection was defined as a positive test for hepatitis B virus surface antigen or any detectable hepatitis B DNA in participants with isolated hepatitis B core antibody and hepatitis B DNA. Conditional economic incentives were distributed during step 1 for visit attendance ($75 at week 2) and every 4 weeks thereafter for human immunodeficiency virus type 1 (HIV-1) RNA benchmark completion ($75 at weeks 4 and 8, $150 at weeks 12, 16, and 20) for a total $675 (see details in the Supplementary Appendix). In versions 2 and 3 of the protocol, participants could receive the full $675 once they had an HIV-1 RNA level of less than 200 copies per milliliter after week 12 (in version 2) and week 4 (in version 3). Virologic failure was defined by two consecutive HIV-1 RNA measurements of greater than 200 copies per milliliter after randomization. ART denotes antiretroviral therapy, CAB cabotegravir, INSTI integrase strand-transfer inhibitor, RAM resistance-associated mutation, and RPV rilpivirine.

secondary efficacy outcomes. Other outcomes were summarized with point estimates and two-sided 95% confidence intervals. The widths of the confidence intervals were not adjusted for multiplicity and should not be used to infer definitive treatment effects for secondary outcomes and subgroup analyses. All statistical analyses were performed with the use of SAS software, version 9.4M7 for Linux (SAS Institute).

RESULTS

PARTICIPANTS

Between March 28, 2019, and February 12, 2024, a total of 820 adults were screened at 33 sites across the United States, and 453 eligible participants were enrolled in step 1 of the trial (Fig. 1B). The median age of the participants in step 1 was 40 years (interquartile range, 32 to 51), 29% had been assigned a female sex at birth, 63% were Black, 17% were Hispanic or Latinx, and 14% reported either ongoing or previous use of injection drugs (Table 1). We assessed social determinants of health that affect outcomes among persons with HIV,[15,16] including household income and housing status (Table 1), employment status, health care coverage, and education level (see the Supplementary Appendix). Screening for alcohol use and urine drug testing were performed at baseline and throughout the trial (Table 1), in addition to assessments of depression and anxiety (see the Supplementary Appendix).

Of the 453 participants enrolled in step 1, a total of 306 (68%) successfully completed step 1 and were enrolled in step 2; 54 participants (12%) did not meet the criteria for virologic suppression needed for randomization, 66 (15%) discontinued step 1 prematurely, and 27 (6%) remained in step 1 as of February 12, 2024. In step 2, of the 306 eligible participants enrolled, 152 were randomly assigned to receive cabotegravir–rilpivirine and 154 to receive standard care (Fig. 1C). Three participants (1 in the cabotegravir–rilpivirine group and 2 in the standard-care group) did not start their assigned treatment. The characteristics of the participants at baseline were similar among those who entered step 2 and those who did not, except for the CD4+ T-cell count and HIV-1 RNA level (see the Supplementary Appendix). At the time of enrollment into step 2, the participants who were not enrolled had a lower CD4+ T-cell count (median of 206 per cubic millimeter) and a higher level of HIV-1 RNA (4.23 $\log_{10}$ copies per milliliter) than those who were enrolled (median of 300 per cubic millimeter and 2.91 $\log_{10}$ copies per milliliter, respectively). Although participants were required to have an HIV-1 RNA level of 200 copies per milliliter or less at or after week 4 of step 1 in order to be eligible for randomization, at the step 2 randomization visit itself, 24 participants (16%) in the cabotegravir–rilpivirine group and 10 participants (7%) in the standard-care group had an HIV-1 RNA level that was greater than 200 copies per milliliter; 8 participants (5%) in the cabotegravir–rilpivirine group had an HIV-1 RNA level that was greater than 10,000 copies per milliliter. These participants remained eligible to participate in step 2.

The median duration of follow-up was 48 weeks (interquartile range, 20 to 52). Treatment was discontinued prematurely in 25 participants (16%) in the cabotegravir–rilpivirine group and in 35 participants (23%) in the standard-care group. Premature discontinuation of follow-up occurred in 20 participants (13%) in the cabotegravir–rilpivirine group and in 24 participants (16%) in the standard-care group. Of the 152 eligible participants who were assigned to receive cabotegravir–rilpivirine, 87 received oral lead-in therapy, and 11 did not begin injection administration (6 completed oral lead-in therapy, 2 prematurely discontinued oral lead-in therapy, 2 were still receiving oral lead-in therapy at the time of data

cutoff, and 1 never started oral lead-in therapy). The remaining 141 participants received a total of 1359 injections during step 2. After administration of the loading doses of cabotegravir and rilpivirine, 94% of the cabotegravir–rilpivirine injections were administered on time. Across the step 2 visits, only 34 to 46% of participants in the standard-care group reported no missed doses in the 30 days before their trial visit. Fifteen participants (11%) had at least one missed injection. Four participants in the cabotegravir–rilpivirine group received bridging therapy with oral ART owing to an anticipated delay in injection administration.

OUTCOMES

Regimen failure (the primary outcome) was observed in 29 participants (19%) in the cabotegravir–rilpivirine group and in 55 participants (36%) in the standard-care group. In the cabotegravir–rilpivirine group, the first primary-outcome event was virologic failure in 5 participants and permanent treatment discontinuation in 24. In the standard-care group, the first primary-outcome event was virologic failure in 32 participants and permanent treatment discontinuation in 23. The cumulative incidence of regimen failure at week 48 was 22.8% in the cabotegravir–rilpivirine group and 41.2% in the standard-care group, for a between-group difference of −18.4 percentage points (98.4% confidence interval [CI], −32.4 to −4.3; P=0.002), a finding that showed the superiority of cabotegravir–rilpivirine over standard care (Fig. 2A and 2B). The results of subgroup analyses and supportive analyses are provided in the Supplementary Appendix.

Virologic failure occurred in 6 participants in the cabotegravir–rilpivirine group and in 34 participants in the standard-care group. At week 48, the between-group difference in the cumulative incidence of virologic failure at week 48 was −21.4 percentage points (98.4% CI, −33.5 to −9.3). Treatment-related failure occurred in 9 participants in the cabotegravir–rilpivirine group and in 34 participants in the standard-care group. At week 48, the between-group difference in the cumulative incidence of treatment-related failure was −19.2 percentage points (98.4% CI, −31.6 to −6.9). Permanent discontinuation occurred in 26 participants in the cabotegravir–rilpivirine group and in 37 participants in the standard-care group. At week 48, the between-group difference in the cumulative incidence of permanent treatment dis-

Table 1. Demographic Characteristics of the Participants in Step 1 and Step 2.*

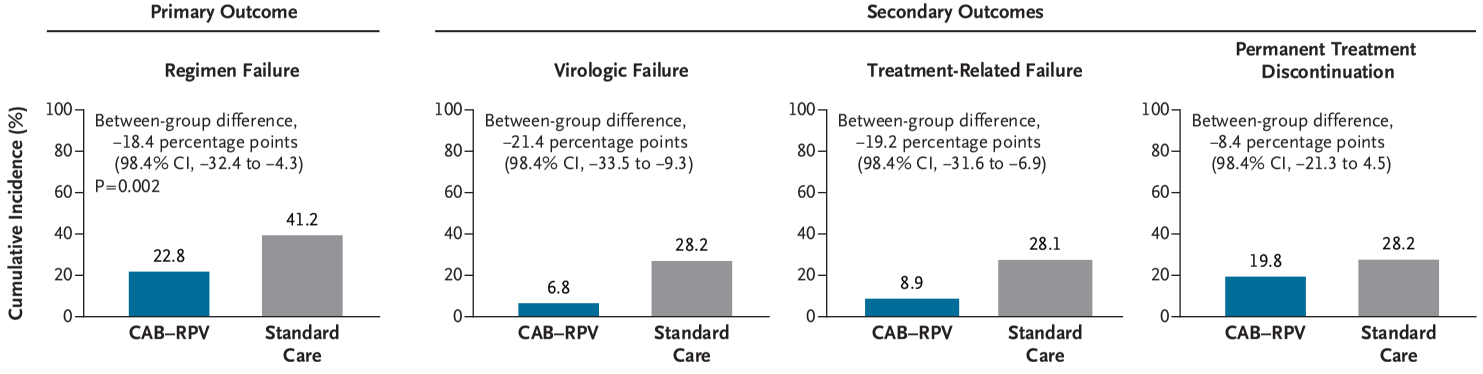
Characteristic	Step 1	Step 2		
	Overall (N=453)	Cabotegravir–Rilpivirine Group (N=152)	Standard-Care Group (N=154)	Overall (N=306)
Age				
Median (IQR) — yr	40 (32 to 51)	41 (32 to 53)	42 (33 to 52)	42 (32 to 52)
Distribution — no. (%)				
18 to 24 yr	29 (6)	8 (5)	7 (5)	15 (5)
25 to 30 yr	64 (14)	21 (14)	20 (13)	41 (13)
31 to 40 yr	142 (31)	46 (30)	40 (26)	86 (28)
41 to 50 yr	102 (23)	27 (18)	45 (29)	72 (24)
≥51 yr	116 (26)	50 (33)	42 (27)	92 (30)
Sex assigned at birth — no. (%)				
Female	133 (29)	43 (28)	41 (27)	84 (27)
Male	320 (71)	109 (72)	113 (73)	222 (73)
Race — no. (%)†				
Black	286 (63)	94 (62)	103 (67)	197 (64)
White	125 (28)	44 (29)	36 (23)	80 (26)
Other, multiple races, or unknown	42 (9)	14 (9)	15 (10)	29 (9)

Table 1. (Continued.)

Characteristic	Step 1	Step 2		
	Overall (N=453)	Cabotegravir–Rilpivirine Group (N=152)	Standard-Care Group (N=154)	Overall (N=306)
Hispanic or Latinx ethnic group — no. (%)†	79 (17)	29 (19)	26 (17)	55 (18)
Nonadherence at enrollment — no. (%)‡				
Lost to follow-up	93 (21)	33 (22)	37 (24)	70 (23)
Poor virologic response	294 (65)	99 (65)	95 (62)	194 (63)
Both	66 (15)	20 (13)	22 (14)	42 (14)
Median duration of ART use before trial entry (IQR) — yr	7 (3–13)	9 (3–15)	7 (4–13)	8 (3–14)
Baseline HIV-1 RNA level — no./total no. (%)				
≤200 copies/ml	154/453 (34)	126/150 (84)	142/152 (93)	268/302 (89)
201–10,000 copies/ml	114/453 (25)	16/150 (11)	9/152 (6)	25/302 (8)
>10,000 copies/ml	185/453 (41)	8/150 (5)	1/152 (1)	9/302 (3)
Median CD4+ T-cell count at baseline (IQR) — per mm^3	273 (119–511)	417 (198–703)	379 (202–611)	389 (199–638)
Median time since HIV diagnosis (IQR) — yr	13 (7–21)	13 (7–22)	12 (7–19)	13 (7–20)
Median body-mass index at baseline (IQR)	26 (22–30)	27 (23–31)	26 (23–31)	26 (23–31)
Annual household income — no./total no. (%)				
<$5,000	128/439 (29)	42/149 (28)	47/151 (31)	89/300 (30)
$5,000–9,999	59/439 (13)	24/149 (16)	22/151 (15)	46/300 (15)
$10,000–19,999	99/439 (23)	32/149 (21)	31/151 (21)	63/300 (21)
>$20,000	153/439 (35)	51/149 (34)	51/151 (34)	102/300 (34)
Housing status — no./total no. (%)				
Residing in own house or apartment	270/444 (61)	101/150 (67)	99/152 (65)	200/302 (66)
Residing in parents' house	64/444 (14)	15/150 (10)	21/152 (14)	36/302 (12)
Residing in someone else's housing	57/444 (13)	25/150 (17)	16/152 (11)	41/302 (14)
Unstable housing or homeless	42/444 (9)	7/150 (5)	14/152 (9)	21/302 (7)
Other	11/444 (2)	2/150 (1)	2/152 (1)	4/302 (1)
Hazardous alcohol use, according to AUDIT-C score — no./total no. (%)§	144/452 (32)	44/152 (29)	53/154 (34)	97/306 (32)
Positive urine drug screen at any time during step — no./ total no. (%)				
Cocaine	98/405 (24)	41/148 (28)	47/147 (32)	88/295 (30)
Amphetamine or methamphetamine	113/405 (28)	46/148 (31)	42/147 (29)	88/295 (30)
Opiate or methadone	45/400 (11)	26/147 (18)	13/147 (9)	39/294 (13)
Marijuana	239/405 (59)	98/147 (67)	86/147 (59)	184/294 (63)
Benzodiazepine, barbiturate, or phencyclidine	45/405 (11)	19/147 (13)	16/147 (11)	35/294 (12)
≥2 Drugs	186/405 (46)	75/148 (51)	71/147 (48)	146/295 (49)

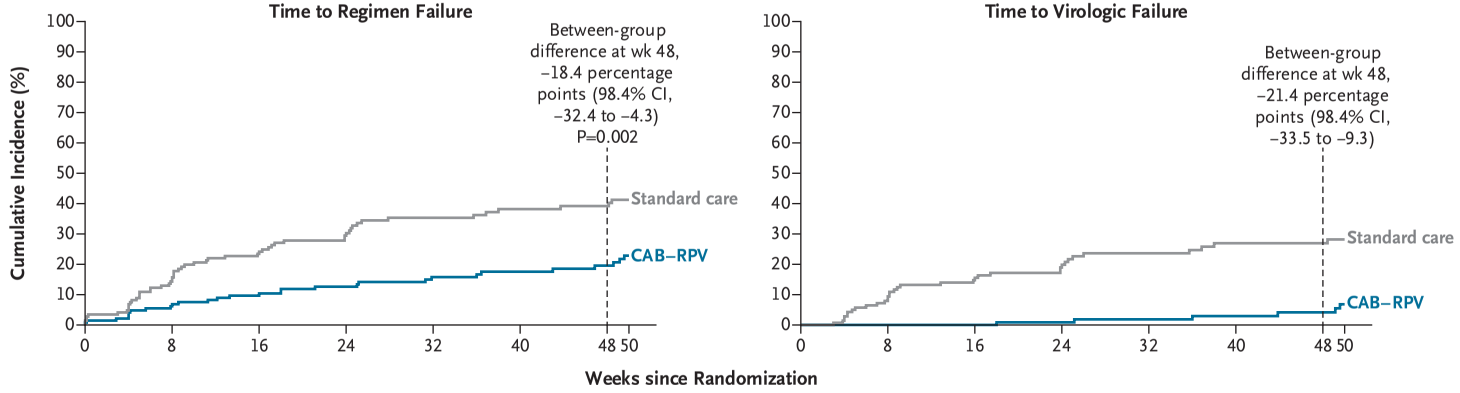
* ART denotes antiretroviral therapy, HIV-1 human immunodeficiency virus type 1, and IQR interquartile range. Percentages may not total 100% because of rounding.
† Race and ethnic group were reported by the participants.
‡ Nonadherence was defined as a poor virologic response in patients with an active prescription for ART, loss to clinical follow-up with nonadherence to ART, or both, each lasting for at least 6 consecutive months and occurring within 18 months before trial entry.
§ AUDIT-C (Alcohol Use Disorders Identification Test–Consumption) scores range from 0 to 12, with higher scores indicating greater alcohol use. Hazardous drinking was defined as a total score of at least 4 for men or at 3 for women.

A Primary Outcome and Key Secondary Outcomes



	Regimen Failure		Virologic Failure		Treatment-Related Failure		Permanent Treatment Discontinuation	
No. of Participants	**29**	**55**	**6**	**34**	**9**	**34**	**26**	**37**
Virologic failure	5	32			6	34		
Treatment discontinuation	24	23						
Treatment discontinuation owing to adverse events					3	0		

B Time to Event for Cumulative Incidence of Regimen Failure and Virologic Failure in Step 2



Cumulative Incidence — %														
Standard care	1	16	24	30	35	38	39 41	0	9	16	20	24	27	27 28
CAB–RPV	1	7	10	13	16	18	20 23	0	0	0	1	2	3	4 7
No. at Risk														
Standard care	154	125	107	86	75	63	60 57	154	124	109	90	77	65	62 58
CAB–RPV	152	137	124	116	104	87	78 70	152	133	122	107	96	80	76 70

Figure 2 (facing page). Primary and Secondary Outcomes.

Panel A shows the cumulative incidence of regimen failure (the primary outcome), which was defined as the earliest occurrence of either virologic failure or permanent discontinuation of the trial treatment. Also shown is the cumulative incidence of virologic failure, treatment-related failure (defined as the earliest occurrence of virologic failure or premature treatment discontinuation due to treatment-related adverse events), and permanent discontinuation (key secondary outcomes). Panel B shows the times to regimen failure and virologic failure in step 2. The week 48 visit was performed within a prespecified window (>42 to 50 weeks after randomization). CI denotes confidence interval.

continuation was −8.4 percentage points (98.4% CI, −21.3 to 4.5).

A total of 60 participants (25 in the cabotegravir–rilpivirine group and 35 in the standard-care group) discontinued treatment in step 2. The most common reasons for treatment discontinuation in the standard-care group were loss to follow-up or participant withdrawal (in 20 participants [57%]) and nonadherence to the trial regimen (in 6 [17%]). In the cabotegravir–rilpivirine group, the reasons for treatment discontinuation were more varied and included loss to follow-up or participant withdrawal (in 9 participants [36%]), adverse events (in 4 [16%]), death that was deemed by the site investigator to be unrelated to the trial drug (in 2 [8%]), and incarceration (in 2 [8%]). Among the participants who had virologic failure and had available resistance data, mutations associated with resistance to INSTIs developed in 2 of 5 (40%) participants in the cabotegravir–rilpivirine group and in 2 of 22 (9%) in the standard-care group (Fig. 3).

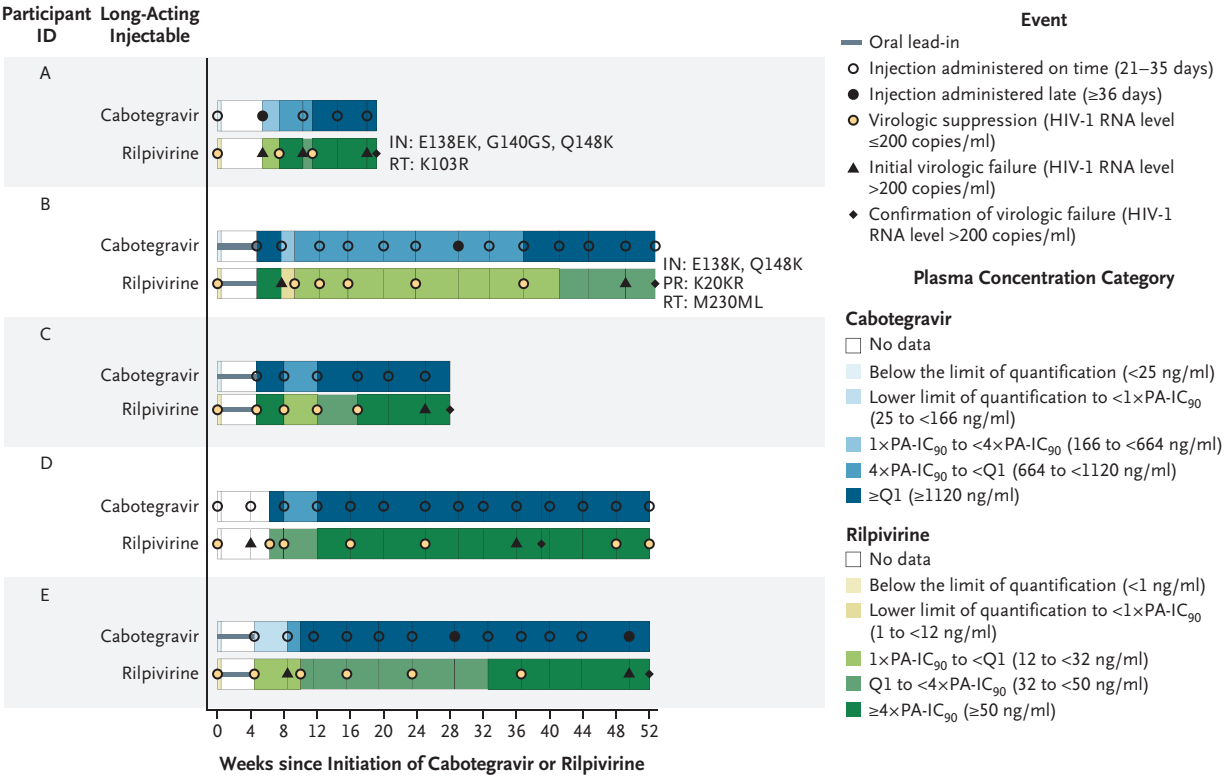
VIROLOGIC FAILURE IN THE CABOTEGRAVIR–RILPIVIRINE GROUP

Six participants in the cabotegravir–rilpivirine group had virologic failure. One of these participants had started oral lead-in therapy but discontinued treatment before injection administration (which met the criteria for regimen failure). This patient continued to be observed in the trial and had subsequent virologic failure. The other five participants had no detectable level of HIV-1 RNA at the time treatment with cabotegravir–rilpivirine was initiated and had no missed injections (Fig. 3). In three participants, administration of injections was delayed at least once; however, all these injections were delayed by less than 5 days. Although guidelines suggest that persons with a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of more than 30 should receive injections with 2-in. (50-mm) needle lengths,[10] the four participants who had virologic failure and a BMI greater than 30 received injections with a needle length of 1.6 in. (40 mm) or less. Virologic failure occurred in all but one of these participants after week 24 in step 2. All four of these participants with virologic failure were determined to have the viral subtype clade B. Subsequent viral suppression was achieved with the use of oral ART in all the participants with virologic failure, with the exception of one participant who was lost to follow-up (no resistance-associated mutations were identified at the visit in which virologic failure was confirmed).

Plasma concentrations of cabotegravir and rilpivirine were all above the lowest quartile at the time of initial and confirmed virologic failure, findings that are consistent with previously reported adequate exposure (Fig. 3).[17,18] However, laboratory testing in each participant showed trends in trough concentrations below the lowest quartile for at least one of the agents soon after starting treatment with cabotegravir–rilpivirine, some of which were also accompanied by a single detectable viral load that was suppressed again by the subsequent visit.

SAFETY

At least one adverse event occurred during step 2 in 52 participants (34%) in the cabotegravir–rilpivirine group and in 46 participants (30%) in the standard-care group (Table 2). At week 48, the cumulative incidence of an adverse event was 43.5% in the cabotegravir–rilpivirine group and 42.4% in the standard-care group (between-group difference, 1.1 percentage points; 95% CI, −12.7 to 15.0). At least one serious adverse event was reported during step 2 in 21 participants (14%) in the cabotegravir–rilpivirine group and 16 participants (10%) in the standard-care group. At week 48, the cumulative incidence of a serious adverse event was 19.3% in the cabotegravir–rilpivirine group and 14.5% in the standard-care group (between-group difference, 4.8%; 95% CI, −5.6 to 15.2). Treatment discontinuation due to adverse events occurred in 4 participants in the cabote-



Participant ID	Baseline HIV-1 RNA Level	Initial Virologic Failure		Confirmation of Virologic Failure		BMI at Time of Virologic Failure	Subsequent Suppression with Oral ART
		Study wk	HIV-1 RNA level	Study wk	HIV-1 RNA level		
	copies/ml		*copies/ml*		*copies/ml*		
A	36	18	997	19	984	59.6	Yes
B	<20	49	2,112	53	570	32.9	Yes
C	29	25	31,625	28	74,473	32.4	Yes
D	30	36	500	39	289	19.0	Yes
E	<20	50	450	52	798	34.9	No

Figure 3. Characteristics of Participants with Confirmed Virologic Failure after Initiation of Step 2.

The top of the figure shows the cabotegravir and rilpivirine plasma concentrations overlaid with the timing of injections and viral loads for each participant who had confirmed virologic failure after initiation of step 2. One additional participant had confirmed virologic failure after randomization in step 2 but never received long-acting cabotegravir–rilpivirine and thus is not included in this figure. Also shown are the resistance-associated mutations that were detected at the time of confirmed virologic failure (in Participants A and B). The bottom of the figure summarizes additional data, including the HIV-1 RNA level at baseline, details on initial virologic failure and confirmed virologic failure, body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) at the time of virologic failure, and whether subsequent suppression occurred with oral ART. IN denotes integrase gene, $PA\text{-}IC_{90}$ protein-adjusted concentration at which 90% inhibition of viral replication is achieved, PR protease gene, Q1 first quartile (25th percentile) trough concentrations from phase 3 trials, and RT reverse transcriptase gene.

gravir–rilpivirine group (with 2 due to low-grade injection-site pain or pain and nodule, 1 due to seizure, and 1 due to cerebrovascular accident and hemiparesis treated with anticoagulation that was deemed by the site investigator to be unrelated to the trial treatment). Only 1 participant in the standard-care group discontinued treatment because of adverse events (ischemic cerebral infarction and encephalopathy). Two deaths were reported in step 2, both of which occurred in the cabotegravir–rilpivirine group (one from fentanyl overdose at week 43 and one from coronary ar-

Table 2. Adverse Events in Step 2.*

Event	All Adverse Events		Adverse Events Related to Trial Regimen†	
	Cabotegravir–Rilpivirine Group (N=152)	Standard-Care Group (N=154)	Cabotegravir–Rilpivirine Group (N=152)	Standard-Care Group (N=154)
Any event — no. (%)	52 (34)	46 (30)	8 (5)	1 (1)
Any event, excluding injection-site reactions — no. (%)	50 (33)	46 (30)	3 (2)	1 (1)
Grade 3 or 4 events — no. (%)	45 (30)	35 (23)	6 (4)	1 (1)
Grade 3 or 4 events, excluding injection-site reactions — no. (%)	43 (28)	35 (23)	3 (2)	1 (1)
Events leading to treatment discontinuation — no. (%)	4 (3)	1 (1)	3 (2)	1 (1)
Any serious adverse events — no. (%)	21 (14)	16 (10)	0	0
Fatal serious adverse events — no. (%)	2 (1)	0	0	0
Any injection-site reaction — no./total no. (%)‡	84/141 (60)	NA	5/141 (4)	NA
Any injection-site pain — no./total no. (%)	55/141 (39)	NA	5/141 (4)	NA
Grade 3 injection-site pain — no./total no. (%)	3/141 (2)	NA	3/141 (2)	NA
Any injection-site nodule — no./total no. (%)	31/141 (22)	NA	2/141 (1)	NA
Any injection-site swelling — no./total no. (%)	5/141 (4)	NA	2/141 (1)	NA
Injection-site pain or nodule leading to treatment discontinuation — no./total no. (%) ‡	2/141 (1)	NA	2/141 (1)	NA
Median duration of injection-site reaction (IQR) — days	3 (2–6)	NA	14 (6–43)	NA
Events, excluding injection-site reactions, reported in ≥5% of participants in either group — no. (%)				
Coronavirus disease 2019	4 (3)	9 (6)	0	0
Creatinine clearance decreased	3 (2)	8 (5)	0	0

* NA denotes not applicable.
† The relationship of an adverse event to the trial regimen was determined by the investigator. Adverse events of grade 3 or higher or those of any grade that led to treatment discontinuation are shown. Injection-site reactions that led to treatment discontinuation were pain and nodule (grade 1, in one participant) and pain (grade 2, in one participant).
‡ Among the participants who were randomly assigned to the cabotegravir–rilpivirine group, 11 had not started injection administration at the time of data analysis. Of the 11 participants who did not start injection administration, 1 never started oral lead-in therapy, 2 prematurely discontinued oral lead-in therapy, 2 were still receiving oral lead-in therapy as of February 12, 2024, and 6 completed oral lead-in therapy but never started treatment with cabotegravir–rilpivirine.

tery disease at week 44); neither death was considered by the site investigator to be related to the trial drug.

INJECTION-SITE REACTIONS

Among the 141 participants who received treatment with cabotegravir–rilpivirine, 84 (60%) had at least one injection-site reaction, with the most frequently reported injection-site reactions being pain, swelling, tenderness, or a nodule (Table 2). Three participants had at least 1 grade 3 injection-site reaction (pain). Two participants discontinued treatment owing to an injection-site reaction (grade 1 and grade 2).

PREGNANCY

Four pregnancies were reported during the trial, with two pregnancies occurring in each step. Both of the participants who became pregnant in step 2 were in the cabotegravir–rilpivirine group, one of whom had virologic failure and resistance-associated mutations (Participant A, Fig. 3). All four pregnancies resulted in live births, and no congenital abnormalities were reported.

DISCUSSION

The LATITUDE trial showed the superiority of monthly injections of long-acting cabotegravir–

rilpivirine over standard care with oral ART in reducing the risk of regimen failure in persons with HIV who face barriers to treatment adherence. The results appeared to be similar within subgroups in a vulnerable population that is frequently excluded from clinical trials. Although observational data showing benefits of this approach have recently accrued, this trial provides randomized clinical trial data that indicate efficacy of long-acting injectable ART as a strategy to reduce the risk of regimen failure in persons with HIV for whom oral ART has not proved effective.

This trial was launched when HIV treatment guidelines limited the use of long-acting injectable ART to persons with HIV with sustained viral suppression who were receiving oral ART. Thus, to foster viral suppression in a population that was viremic at the time of enrollment, the trial provided comprehensive adherence support and financial incentives that were contingent on the reduction of viral load during step 1. The adherence support provided to the individual participants in this trial reflected routine clinical practice, and the implementation of financial incentives that are tied to virologic benchmarks in a viremic population has precedence.[19,20] However, the usefulness of alternative strategies to best initiate a long-acting injectable regimen in persons with viremia will benefit from further systematic research. To date, "direct-to-inject" approaches show promise in clinical studies,[7-9] and our trial showed no virologic failure or treatment discontinuation in 23 of the 24 participants who started cabotegravir–rilpivirine without viral suppression. An ongoing trial is further evaluating the use of cabotegravir–rilpivirine administered every other month as compared with standard care with oral ART in persons with HIV who have a detectable viral load (ClinicalTrials.gov number, NCT06694805).

Among the five participants in the cabotegravir–rilpivirine group who had virologic failure, the main risk factors for failure were a higher BMI and lower concentrations of cabotegravir and rilpivirine early in treatment, which have been identified as risk factors in other studies.[17,18] In addition, needle lengths of less than 2 in. were used for administration in these participants. This inverse relationship between BMI and trough concentrations is known,[21] and thus longer needle lengths (2 in.) are typically recommended to ensure adequate drug exposure. Although comparative thresholds to historical pharmacokinetic data were used in our analysis,[18,22] a threshold that is clearly associated with virologic breakthrough has not been identified. Of note, none of the participants with virologic failure had missed injections, and three participants had short delays (≤5 days) in the administration of cabotegravir–rilpivirine at a maximum of two time points.

This trial is strengthened by the broad trial population of persons in whom viral suppression had not been achieved owing to coexisting mental health conditions, substance and alcohol use, and unstable housing, among other factors. These characteristics are representative of the population of persons with HIV who are not receiving care in the United States[23] (see Table S5.5 in the Supplementary Appendix), and are reflected by the finding that regimen failure occurred in almost 40% of the participants assigned to receive standard care during this trial. This observation shows the potential public health contributions of long-acting injectable regimens to ending the HIV epidemic. Protocol modifications were made to address slow accrual and a lower-than-expected transition from step 1 to step 2 and to overcome barriers imposed by the coronavirus disease 2019 public health emergency. Although these factors could have led to heterogeneity in the trial population, the results from the subgroup and stratified analyses by protocol version indicated no substantial variability. Similarly, although the use of conditional economic incentives could arouse concerns about the generalizability of this strategy, the financial support was time-limited and was not included in step 2, which allowed for a direct comparison between cabotegravir–rilpivirine and standard care with oral ART.

The results of this trial showed that long-acting cabotegravir–rilpivirine was superior to standard care in reducing the risk of regimen failure among persons with HIV who faced barriers to adherence. This strategy provides a key intervention for preventing both disease progression and HIV transmission. Wide implementation of this treatment strategy in the people who need it most will require a multidisciplinary approach to maximize its benefit and reach.

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