

Long-Term Efficacy, Safety, and Durability of Cabotegravir and Rilpivirine as 2-Drug Oral Maintenance Therapy After 6 Years of Study

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Background. In the LATTE study, daily oral cabotegravir + rilpivirine demonstrated higher rates of efficacy than efavirenz + 2 nucleoside reverse-transcriptase inhibitors (NRTIs) through Week 96 in antiretroviral therapy (ART)-naive adults with human immunodeficiency virus (HIV)-1. We present the results from 6 years of continued treatment with oral cabotegravir + rilpivirine.

Methods. LATTE was a phase IIb, randomized, multicenter, partially blinded, dose-ranging study in ART-naive adults with HIV-1. After a 24-week induction phase with cabotegravir + 2 NRTIs, participants with HIV-1 ribonucleic acid (RNA) <50 copies/mL were randomized to receive cabotegravir (10, 30, or 60 mg) + rilpivirine (25 mg) in the maintenance phase through Week 96 and switched to cabotegravir 30 mg + rilpivirine 25 mg in the open-label phase through Week 312.

Results. Of 160 participants who entered the maintenance phase, 111 completed the study at Week 312. At Week 312, 105 (66%) participants maintained HIV-1 RNA <50 copies/mL, 15 (9%) had HIV-1 RNA ≥50 copies/mL, and 40 (25%) had no virologic data. Eight participants met protocol-defined virologic failure criteria through Week 312, 2 of whom met protocol-defined virologic failure criteria after Week 144. Six participants developed treatment-emergent resistance to 1 or both agents during the study, 3 of whom developed integrase inhibitor resistance substitutions. Two participants (1%) reported drug-related serious adverse events. Few adverse events led to withdrawal during the open-label phase (n = 5, 3%).

Conclusions. Oral cabotegravir + rilpivirine demonstrated efficacy in the majority of participants and an acceptable safety profile through 6 years of treatment, demonstrating its durability as maintenance therapy for HIV-1.

Keywords. 2-drug regimen; antiretroviral; HIV; integrase strand transfer inhibitor; nonnucleoside reverse-transcriptase inhibitor.

Daily oral combination antiretroviral therapy (ART) regimens are highly effective at maintaining human immunodeficiency virus (HIV)-1 suppression, extending the life expectancy of people with HIV-1 infection to that of the general population [1–3]. However, the need for lifelong daily oral therapy can pose significant challenges [4]. Individuals taking daily oral medications may develop pill fatigue, feelings of anxiety over their daily dosing schedule, and fear of stigmatization from the disclosure of their HIV status [5]. These difficulties may contribute to medication nonadherence, potentially leading to treatment failure and reduced quality of life [4, 5]. Alternatives to daily

oral dosing, such as long-acting (LA) injectable regimens, may be desirable for people with HIV-1 infection who experience such challenges, although adherence data for LA injectable regimens in real-world settings are needed [5].

Cabotegravir, an integrase strand transfer inhibitor (INSTI), has been developed as both a once-daily oral medication and an LA injectable ART agent with a long half-life and unique physicochemical properties that permit infrequent dosing [6, 7]. Cabotegravir LA in combination with an LA formulation of rilpivirine, a nonnucleoside reverse-transcriptase inhibitor (NNRTI), compose the first LA injectable ART regimen for HIV-1 treatment [6, 8]. Cabotegravir + rilpivirine LA dosed intramuscularly every 4 weeks was noninferior to daily oral ART in maintaining virologic suppression at Week 48 in the ATLAS phase III study and at Weeks 48 and 96 in the FLAIR phase III study [9–11]. In the ATLAS-2M phase IIb study, cabotegravir + rilpivirine LA dosed every 8 weeks was noninferior to dosing every 4 weeks at Weeks 48 and 96 [12, 13].

In clinical practice, once-daily oral cabotegravir + rilpivirine is administered as an oral lead-in regimen for approximately 4 weeks to assess the tolerability of the regimen in each patient before beginning monthly LA injections [14–16]. Oral therapy

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with cabotegravir + rilpivirine tablets can also be used in clinical practice as a bridge between LA injections should there be an unavoidable dosing delay. Patients may receive once-daily oral cabotegravir + rilpivirine to cover the period between monthly LA injections for up to 2 consecutive missed injection visits or to cover 1 missed injection visit with dosing every 2 months.

The LATTE phase IIb study was designed to select a daily oral dose of cabotegravir and evaluate the initial efficacy of cabotegravir + rilpivirine as maintenance therapy in virologically suppressed adults with HIV-1 infection [17]. Participants were randomized to receive either oral cabotegravir (10, 30, or 60 mg) or oral efavirenz (600 mg) in combination with 2 nucleoside reverse-transcriptase inhibitors (NRTIs) through Week 24. In participants receiving cabotegravir who had HIV-1 ribonucleic acid (RNA) <50 copies/mL, background NRTIs were replaced with oral rilpivirine 25 mg through Week 96. In the intention-to-treat-exposed population, a greater proportion of participants maintained virologic suppression with oral cabotegravir + rilpivirine versus oral efavirenz + 2 NRTIs at the Week 48 primary endpoint (82% vs 71%) and in a subsequent analysis at Week 96 (76% vs 63%), demonstrating the durability of cabotegravir + rilpivirine as maintenance therapy [17]. After Week 96, all participants randomized to cabotegravir were switched to receive 30 mg of cabotegravir, which was selected for further evaluation based on the study results, in combination with 25 mg of rilpivirine in the open-label phase. In this study, we report the long-term, end-of-study efficacy, safety, and tolerability results of oral cabotegravir + rilpivirine over a 6-year period in the LATTE study.

METHODS

Study Design and Participants

LATTE was a phase IIb, randomized, multicenter, partially blinded, dose-ranging study in ART-naive adults with HIV-1 infection conducted in Canada and the United States (ClinicalTrials.gov identifier, NCT01641809; <https://clinicaltrials.gov/ct2/show/NCT01641809>). Eligible participants were aged ≥ 18 years with HIV-1 RNA ≥ 1000 copies/mL, CD4⁺ cell count ≥ 200 cells/mm³, ≤ 10 days of previous ART, and no major drug resistance-associated mutations. Exclusion criteria have been previously described [17].

Participants were randomized to receive once-daily doses of either cabotegravir (10, 30, or 60 mg) or efavirenz, both in combination with investigator-selected background NRTIs (abacavir/lamivudine or tenofovir disoproxil fumarate/emtricitabine) (Figure 1A). After Week 24, participants in the cabotegravir groups with HIV-1 RNA <50 copies/mL were transitioned to the maintenance phase through Week 96, during which background NRTIs were replaced with 25 mg of rilpivirine. Participants in the cabotegravir group who successfully completed the maintenance phase could enter the open-label phase, during which

they received daily oral cabotegravir 30 mg + rilpivirine 25 mg until study completion at Week 312.

Patient Consent Statement

The study was approved by investigational center ethics committees or institutional review boards and conducted in accordance with the principles of the 2008 Declaration of Helsinki. All participants provided written informed consent.

Study Assessments

The primary endpoint was the proportion of participants achieving plasma HIV-1 RNA <50 copies/mL at Week 48 using the US Food and Drug Administration Snapshot algorithm. Secondary endpoints for the Week 312 analysis included the proportion of participants with plasma HIV-1 RNA <50 copies/mL over time, change from baseline in CD4⁺ cell count, incidence of disease progression (eg, HIV-associated conditions), and incidence of treatment-emergent genotypic and phenotypic resistance to cabotegravir and rilpivirine in participants who met protocol-defined virologic failure (PDVF) criteria.

Protocol-defined virologic failure was defined as either virologic nonresponse or virologic rebound. Virologic nonresponse was defined as 2 consecutive plasma HIV-1 RNA measurements ≥ 200 copies/mL 2 to ≤ 4 weeks apart without prior suppression to <200 copies/mL. Virologic rebound was defined as plasma HIV-1 RNA ≥ 200 copies/mL after prior suppression to <200 copies/mL or 2 consecutive plasma HIV-1 RNA measurements that demonstrated an increase of >0.5 log₁₀ copies/mL from the nadir value on study. Protocol-defined virologic failure was confirmed with a repeat plasma HIV-1 RNA measurement 2 to 4 weeks after suspected PDVF. Participants with confirmed PDVF were withdrawn from the study. Samples collected at baseline and at suspected PDVF were sent for resistance testing.

Plasma HIV-1 RNA was quantified using the Real-Time HIV-1 assay (Abbott Molecular Inc., Des Plaines, IL). CD4⁺ cell count was assessed by flow cytometry. Genotypic and phenotypic resistance analyses were provided by Monogram Biosciences (South San Francisco, CA). Safety was assessed by monitoring adverse events (AEs), clinical laboratory tests, vital signs, and electrocardiographic results.

Efficacy and safety analyses were conducted in the intention-to-treat maintenance-exposed (ITT-ME) and safety maintenance populations, respectively, both of which consisted of all randomized participants who received ≥ 1 dose of cabotegravir + rilpivirine in the maintenance phase.

RESULTS

Study Population

Of 181 participants who initiated cabotegravir treatment, 160 entered the maintenance phase (ITT-ME and safety maintenance populations), 141 entered the open-label phase, and 111

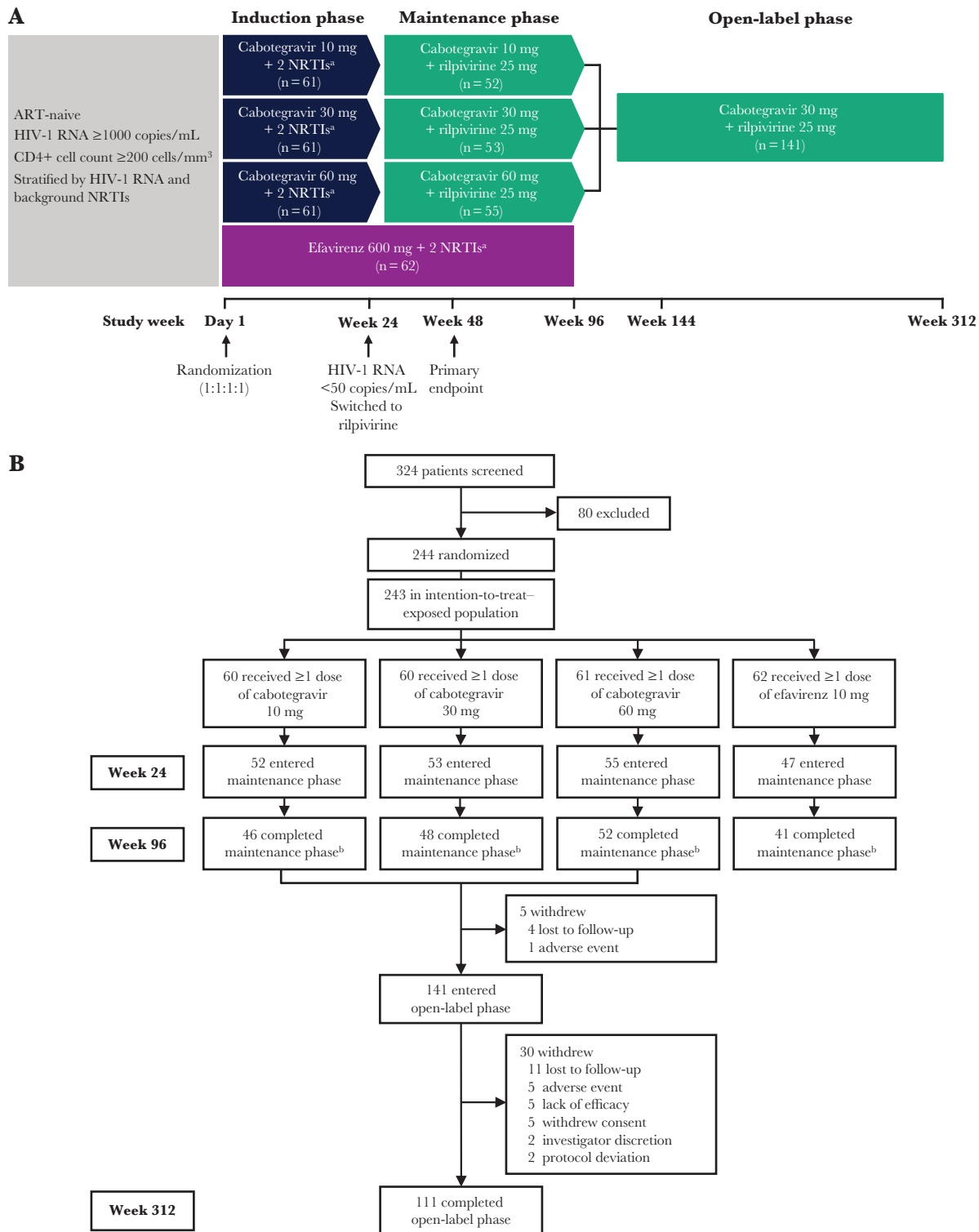


Figure 1. (A) Study design and (B) participant disposition through Week 312. ^aBackground nucleoside reverse-transcriptase inhibitors (NRTIs) were abacavir/lamivudine or tenofovir disoproxil fumarate/emtricitabine. ^bReasons for discontinuation through the maintenance phase have been previously reported [17]. ART, antiretroviral therapy; HIV, human immunodeficiency virus; PDVF, protocol-defined virologic failure; RNA, ribonucleic acid.

completed the study (Figure 1B). The most common reasons for withdrawal during the open-label phase were loss to follow-up (n = 11), AEs (n = 5), lack of efficacy (ie, met PDVF criteria;

n = 5), and withdrawal of consent (n = 5). Baseline characteristics were balanced across the cabotegravir groups (Table 1). Most (96%) participants were men.

Table 1. Baseline Characteristics in the ITT-ME Population

Parameter	Cabotegravir 10 mg (n = 52)	Cabotegravir 30 mg (n = 53)	Cabotegravir 60 mg (n = 55)
Age, median (range), years	32 (19–54)	33 (20–57)	34 (19–56)
Male, n (%)	50 (96)	52 (98)	52 (95)
Race, n (%)			
White	33 (63)	36 (68)	32 (58)
African American/African heritage	19 (37)	14 (26)	16 (29)
Other	0	3 (6)	7 (13)
Baseline HIV-1 RNA			
Median (IQR), log ₁₀ copies/mL	4.29 (4.01–4.72)	4.16 (3.84–4.69)	4.36 (3.95–4.79)
≥100 000, n (%)	6 (12)	6 (11)	10 (18)
Baseline CD4 ⁺ cell count, median (IQR), cells/mm ³	442 (351–541)	406 (324–549)	420 (342–529)

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range; ITT-ME, intention-to-treat maintenance-exposed; RNA, ribonucleic acid.

Efficacy

Of 160 participants in the ITT-ME population, HIV-1 RNA <50 copies/mL was maintained in 137 (86%) participants at Week 96, 122 (76%) at Week 144, and 105 (66%) at Week 312 (Figure 2). Human immunodeficiency virus-1 RNA was ≥50 copies/mL in 13 (8%) participants at Weeks 96 and 144 and in 15 (9%) participants at Week 312. At Week 96, 10 (6%) participants had no virologic data; this increased to 25 (16%) participants at Week 144 and 40 (25%) by Week 312, driven by discontinuations between Weeks 96 and 312 due to AEs or death (n = 6), lack of efficacy (n = 2), and nonvirologic reasons, including loss to follow-up (n = 11) and withdrawn consent (n = 5). Mean ± standard deviation CD4⁺ cell count was 275 ± 193 cells/mm³ (n = 144) at Week 96, 320 ± 223 cells/mm³ (n = 128) at Week 144, and 395 ± 211 cells/mm³ (n = 107) at Week 312.

In addition to 3 participants on cabotegravir + rilpivirine who met PDVF criteria by Week 96 (n = 2 in the 10-mg group and n = 1 in the 30-mg group) [17], 5 participants met PDVF criteria in the open-label phase: 3 originally assigned to the 10-mg cabotegravir group (Weeks 108, 132, and 180) and 1 each originally assigned to the 30-mg (Week 132) and 60-mg (Week 264) groups (Table 2). All 5 participants who met PDVF criteria in the open-label phase had HIV-1 subtype B. Treatment-emergent INSTI and/or NNRTI resistance substitutions developed in 4 participants who met PDVF criteria in the open-label phase. One participant from the 10-mg group developed the INSTI substitution V151V/I at Week 108, with no change in cabotegravir susceptibility. Another participant from the 10-mg group developed INSTI (E138K and Q148R) and NNRTI (K101E) substitutions at Week 132 and an additional INSTI substitution G140A at PDVF (Week 180); this participant had a 116-fold change in sensitivity to cabotegravir and a 21-fold change in sensitivity to rilpivirine at PDVF. Another participant from the 10-mg group developed NNRTI substitutions K101E and M230M/L at Week 132 and demonstrated high-level resistance to all NNRTIs, with a 12-fold change in sensitivity to rilpivirine; integrase genotyping and phenotyping

were unavailable for this participant because the sample could not be amplified. The participant from the 60-mg group developed INSTI (G140S and Q148R) and NNRTI (K101K/E and E138E/K) substitutions at Week 264, with a 10-fold change in sensitivity to cabotegravir and a 2-fold change in sensitivity to rilpivirine. The participant from the 30-mg group met PDVF criteria at Week 132, with no change from baseline in integrase or reverse transcriptase genotype, and had INSTI substitution E157Q at both time points.

From the start of the study through Week 312 among all participants who received cabotegravir in LATTE (N = 181), there were 16 reports of HIV-1-associated conditions and/or disease progression, with 1 onset between Weeks 96 and 312 (oropharyngeal candidiasis).

Safety

Adverse events were reported in 152 (95%) of 160 participants in the safety maintenance population from the start of the maintenance phase through Week 312. The most common AEs were upper respiratory tract infection (36%), diarrhea (19%), back pain (13%), fatigue (13%), and bronchitis (13%). Drug-related AEs were reported in 34 (21%) participants; the most common were headache (4%), nausea (3%), depression (3%), and abnormal dreams (3%). Most (71%) drug-related AEs were grade 1 in intensity, grade 3 drug-related AEs were reported in 2 participants (chest discomfort in 1 participant; depression and suicidal ideation in 1 participant), and no grade 4 drug-related AEs were reported. Depression was the only grade 2 to 4 drug-related AE reported in >1 participant (grade 2 in 1 participant and grade 3 in 1 participant). Serious AEs (SAEs) were reported in 32 (20%) participants; the most common were cellulitis, appendicitis, pneumonia, and suicide attempt (n = 3 each). Three drug-related SAEs were reported in 2 participants: suicidal ideation and depression in 1 participant and seizure in the other participant.

Of 160 participants in the safety maintenance population, 8 (5%) withdrew because of AEs by Week 312; 5 participants reported 7 new AEs leading to withdrawal in the open-label phase

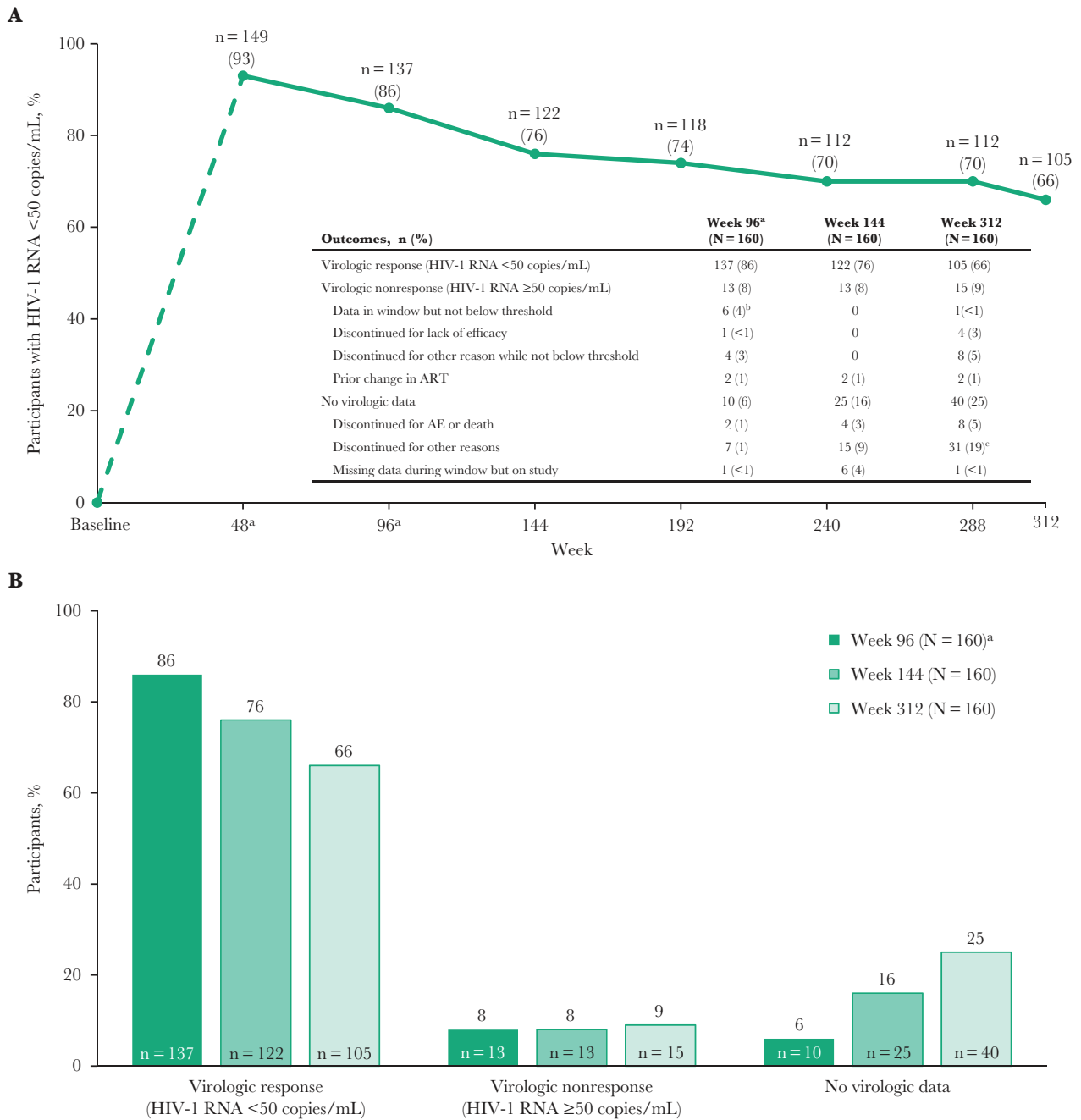


Figure 2. Virologic outcomes in the intention-to-treat maintenance-exposed population (A) over time and (B) at Weeks 96, 144, and 312 by US Food and Drug Administration Snapshot algorithm. ^aData include participants who received any cabotegravir dose (10, 30, or 60 mg). ^bThree of six participants met protocol-defined virologic failure criteria at Weeks 96 and 312 in different categories. ^cReasons for discontinuation in 24 participants who discontinued between Weeks 96 and 312 were loss to follow-up (n = 11), withdrawn consent (n = 5), investigator discretion (n = 2), lack of efficacy (n = 2), protocol deviation (n = 2), and no reason provided (n = 2). AE, adverse event; ART, antiretroviral therapy; HIV, human immunodeficiency virus; RNA, ribonucleic acid.

(Table 3). Of the 7 new AEs leading to withdrawal in the open-label phase, AEs of chest discomfort in 1 participant and depression and suicidal ideation in 1 participant were considered drug related; the remaining 4 new AEs were not considered to be drug related. Two deaths occurred during the open-label phase: 1 due to gastrointestinal bleeding and the other due to cardiac arrest while undergoing elective surgery; neither were considered to be drug related by the investigator.

Through Week 312, the majority (91 of 160; 57%) of participants in the safety maintenance population had treatment-emergent laboratory abnormalities of grade 1 or 2 intensity. Grade 3 or 4 treatment-emergent laboratory abnormalities occurred in 29% of participants during the study through Week 96 and 43% of participants through Week 312; the most common at Week 312 were elevations in creatine kinase (16%) and lipase (10%) (Table 3).

Table 2. Summary of PDVF and Resistance in the Open-Label Phase

Original Cabotegravir Dose	PDVF Study Visit	HIV-1 RNA at SVF/CVF, Copies/mL	Treatment-Emergent Resistance	
			INSTI	NNRTI
10 mg	Week 108	385/772	V151V/I	—
10 mg	Week 132	836/1727	NA	K101E, M230M/L
10 mg	Week 180	243/1748	E138K, G140A, Q148R ^a	K101E ^a
30 mg	Week 132	908/211	—	—
60 mg	Week 264	656/304	G140S, Q148R	K101K/E, E138E/K

Abbreviations: CVF, confirmed virologic failure; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; NA, not available; NNRTI, nonnucleoside reverse-transcriptase inhibitor; PDVF, protocol-defined virologic failure; RNA, ribonucleic acid; SVF, suspected virologic failure.

^aE138K, Q148R, and K101E emerged at Week 132.

Among all participants who received cabotegravir in the LATTE study (N = 181), median (range) weight at baseline was 78 (50–152) kg. Median (range) weight change from baseline in all 181 participants receiving cabotegravir was +3.0 (–17.7 to +26.7) kg at Week 96 and +6.5 (–14.7 to +32.2) kg at Week 312. Of all 181 participants, 4 (2%) reported AEs of weight increase; only 1 (<1%) of 160 participants in the safety maintenance population reported an AE of weight increase.

DISCUSSION

With the chronicity of HIV-1 therapy, it is important to describe long-term outcomes with novel treatment regimens. This report describes 6 years of efficacy, durability, and safety results

using the 2-drug oral ART regimen of cabotegravir + rilpivirine. Through 6 years of treatment, the majority of participants maintained virologic suppression on oral cabotegravir + rilpivirine, with few meeting PDVF criteria. Long-term treatment with oral cabotegravir + rilpivirine was generally well tolerated, and few AEs led to discontinuation. Although descriptive, the results from this analysis add to other published data and support the overall efficacy and safety of oral cabotegravir + rilpivirine dosing over multiple years of treatment, contributing important information to the development of the LA formulations of each drug.

After 6 years of oral cabotegravir + rilpivirine treatment, 66% of participants maintained virologic suppression by Snapshot algorithm in the ITT-ME population. The cumulative proportion of participants experiencing virologic nonresponse was

Table 3. Summary of AEs in the Safety Maintenance Population

AEs, Number of Participants (%)	Cabotegravir Total (N = 160)	
	Week 96	Week 312
Grade 2–4 drug-related AEs	6 (4)	10 (6)
Serious AEs	15 (9)	32 (20)
Drug related	0	2 (1)
AEs leading to withdrawal	3 (2)	8 (5)
Abnormal electrocardiogram	1 (<1)	1 (<1)
Increased liver function test	0	1 (<1)
Weight loss	0	1 (<1)
Acute hepatitis C virus infection	0	1 (<1)
Burkitt's lymphoma	1 (<1)	1 (<1)
Anxiety disorder	1 (<1)	1 (<1)
Depression	0	1 (<1)
Suicidal ideation	0	1 (<1)
Irritable bowel syndrome	0	1 (<1)
Chest discomfort	0	1 (<1)
Cardiac arrest	0	1 (<1) ^b
Grade 3 or 4 treatment-emergent laboratory abnormalities ^a	46 (29)	69 (43)
Creatine kinase	18 (11)	26 (16)
Lipase	10 (6)	16 (10)
Phosphate	6 (4)	8 (5)
Low-density lipoprotein cholesterol	4 (3)	13 (8)

Abbreviations: AE, adverse event; ITT-ME, intention-to-treat maintenance-exposed.

^aOccurred in ≥5% of participants through Week 312.

^bCardiac arrest was fatal and not related to study drug.

low and did not change significantly between Weeks 96 (8%) and 312 (9%), with only 8 participants meeting PDVF criteria through Week 312 and 2 meeting PDVF criteria after Week 144. Most participants who discontinued the study before Week 312 did so for reasons unrelated to virologic outcome; this was not unexpected given the 6-year duration of the study and was a result of discontinuations due to AEs or other reasons, with loss to follow-up being the most frequent reason for discontinuation.

Over the 6-year randomized and open-label study periods, 8 participants who received cabotegravir + rilpivirine met PDVF criteria, with most developing treatment-emergent resistance to INSTIs and/or NNRTIs. Of the 6 participants with treatment-emergent substitutions, none were randomized to the 30-mg cabotegravir dose (5 received cabotegravir 10 mg and 1 received cabotegravir 60 mg) in the maintenance phase. Three participants developed treatment-emergent resistance to both drug classes [17]. These 3 participants developed the INSTI resistance-associated substitution Q148R, with 2 of them also developing additional resistance substitutions of E138K (INSTI) plus K101E (NNRTI) and G140S (INSTI) plus K101K/E and E138E/K, respectively. One additional participant who met PDVF criteria developed the integrase substitution V151V/I, which is not associated with resistance to cabotegravir or other INSTIs [18]. Two participants developed NNRTI resistance alone, with substitutions of K101K/E plus E138E/A and K101E plus M230M/L, respectively [17].

Differences in INSTI resistance patterns were observed between the LATTE study of oral cabotegravir + rilpivirine and the phase III studies of cabotegravir + rilpivirine LA [9, 10, 12]. Although Q148R was reported in 6 participants from the FLAIR and ATLAS-2M studies, only 1 had HIV-1 subtype B virus [10, 12]. Additional integrase substitutions not observed in participants from the LATTE study were reported in FLAIR, ATLAS, and ATLAS-2M, including N155H (n = 6), G140R (n = 1), and T97A (n = 1) [9, 10, 12].

Oral cabotegravir + rilpivirine was generally well tolerated through 6 years of treatment, with no new safety trends observed in participants continuing into the maintenance phase. Few participants reported drug-related SAEs (n = 2) or discontinuations due to AEs (n = 4) after Week 96 [17]. Median weight in all participants receiving cabotegravir increased from 3.0 kg at Week 96 to 6.5 kg at Week 312 relative to baseline; these results are consistent with average per-year weight gain in adults (0.5–1.0 kg) [19]. Overall, these results support the safety of oral cabotegravir + rilpivirine and further support the safety of 2-drug regimens consisting of second-generation INSTIs, such as dolutegravir, and rilpivirine [20].

Efficacy and safety results from the LATTE study support the use of oral cabotegravir + rilpivirine as an oral lead-in and a bridge between planned missed injection dosing visits in clinical practice [14–16]. Oral therapy with cabotegravir + rilpivirine as a bridge between injection dosing visits maintained virologic

suppression in 100% (17/17) of participants who missed injection visits in the phase II/III LA clinical program [21]. In addition, among cabotegravir + rilpivirine clinical trials active during the COVID-19 pandemic, oral cabotegravir + rilpivirine was provided to 94 clinical trial participants who missed LA injection visits because of the pandemic, while another 27 participants with missed injection visits were able to bridge using an investigator-prescribed antiretroviral regimen. None of these 121 trial participants experienced suspected or confirmed virologic failure during an oral bridging period [22]. Therefore, oral therapy with cabotegravir + rilpivirine provides a flexible strategy to maintain continuous ART in patients who miss LA injection visits.

Although generation of long-term data are of significant interest, this study has several notable limitations. It was a phase IIb noncomparative study with small sample size and lacked a control group after Week 96. Participants were mostly male and white, and individuals with baseline CD4⁺ cell count <200 cells/mm³ were excluded, potentially limiting the generalizability of these findings.

CONCLUSIONS

The initial evaluation of oral cabotegravir + rilpivirine in the LATTE study facilitated the LA clinical development program that evaluated different dosing, adherence, and pharmacokinetic considerations. Cabotegravir + rilpivirine LA has been investigated in several trials, including the LATTE-2, ATLAS, FLAIR, ATLAS-2M, and POLAR studies, as an alternative to daily oral therapy and has been approved on the basis of results from ATLAS and FLAIR [7]. Results from this analysis, after 6 years on study, demonstrate the overall efficacy and safety of oral cabotegravir + rilpivirine as well as provide support for its use as a flexible treatment strategy to cover missed injection visits in people with HIV-1 receiving the LA regimen.

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Potential conflicts of interest. K. C. S., M. S. C., and W. R. S. are employees of ViiV Healthcare and may hold stock in GlaxoSmithKline. A. M. has received personal fees from ViiV Healthcare, Gilead, Janssen Pharmaceutica, Merck, and Shionogi. E. D. has received grants and personal fees from Gilead and Janssen and grants from Abbott Laboratories,

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