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Review

Long-acting injectable antiretroviral therapy: will it change the future of HIV treatment?

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***Abstract*:** The treatment of human immunodeficiency virus (HIV) has greatly advanced over the past few decades from complex regimens, with high toxicities, multiple daily dosing, and incomplete viral suppression to more simplified, highly effective, daily oral regimens. Although these advancements greatly improved access and tolerability, the need for daily antiretroviral (ARV) administration remained until recently. With long-acting (LA) injectable ARV options emerging, patients may choose how they want to receive treatment. By eliminating the barrier of daily medication adherence, LA injectable ARV formulations have the potential to not only improve health outcomes for the individual, but also the community by reducing HIV transmission. At the time of this writing cabotegravir/rilpivirine (LA-CAB/RPV) is the only LA injectable ARV regimen approved as a complete regimen for the treatment of HIV in adults and adolescents (⩾35 kg and ⩾12 years of age) who are virologically suppressed. However, additional studies of LA-CAB/RPV in expanded populations, and of other LA ARVs, are underway. The goal of this article was to summarize clinical data and review pertinent clinical considerations for the use of LA-CAB/RPV in the management of HIV.

Keywords: antiretroviral therapy, cabotegravir, HIV, injections, intramuscular, rilpivirine

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Introduction

The treatment of human immunodeficiency virus (HIV) has greatly advanced over the past few decades from complex regimens, with high toxicities, multiple daily dosing, and incomplete viral suppression to more simplified, highly effective, daily oral regimens. Although these advancements have improved access and tolerability for HIV treatment and established therapies for HIV prevention, there remains the need for the daily administration of these medications, which is not ideal for many individuals. Concerns with treatment fatigue, difficulty swallowing, and inability to sustain daily medication adherence has left many individuals hopeful for alternative formulations for antiretroviral (ARV) agents.

The current standard of care for HIV treatment includes at least two agents from two different classes of oral ARV agents administered daily. Despite these regimens being simplified in terms of pill burden with fixed dose combinations and single tablet regimens, social determinants and individual factors continue to prevent many people living with HIV (PLWH) from consistently taking these medications on a daily basis. Several studies have demonstrated ARV adherence rates ranging from 27% to 80% across various populations of PLWH.[1] High adherence rates to antiretroviral therapy (ART) are required for viral suppression and the prevention of HIV transmission. One meta-analysis identified the most frequently reported individual barriers to ART adherence to include forgetting to take the medication, being away from home, and change to daily routine.[2] Long-acting (LA) ARV formulations have the possibility of eliminating these barriers, improving not only adherence and health outcomes for the individual but also reducing HIV infections in the community.

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With LA injectable ART options emerging, additional treatment options may change the way patients choose to receive treatment. At the time of this writing cabotegravir/rilpivirine (LA-CAB/RPV) is the only LA injectable ARV regimen approved in adults and adolescents (⩾35 kg) as a complete regimen for the treatment of HIV. The goal of this article was to summarize clinical data (Table 1) and review pertinent clinical considerations for the use of LA-CAB/RPV in the management of HIV.

Clinical trial data

LATTE trial

LATTE was a phase 2b, randomized, multicenter, partly masked, dose-ranging trial that compared oral CAB 10, 30, or 60 mg once a day, or oral efavirenz (EFV) 600 mg once a day with dual nucleoside reverse transcriptase inhibitors (NRTIs) in treatment-naïve patients.[3] Eligible patients were >18 years of age, ARV naive, had CD4 count ⩾200 cells/mm^3, had HIV-RNA levels of ⩾1000 copies/mL at baseline, and had no major drug resistance–associated mutations. Patients were randomly assigned 1:1:1:1 to receive oral CAB 10, 30, or 60 mg daily, or EFV 600 mg daily in combination with investigator-selected background NRTIs for 24 weeks. At week 24, patients whose HIV-RNA level was <50 copies/mL were transitioned to the maintenance phase of the study, where background NRTIs were discontinued in the oral CAB groups and replaced with RPV 25 mg once daily for an additional 72 weeks. Patients in the EFV group remained on dual NRTI background therapy. Treatment assignments were stratified by baseline HIV-RNA levels and NRTI background therapy. Patients and investigators were masked to doses of oral CAB, but not to the assignment of CAB *versus* EFV. Patients with confirmed virologic failure (CVF), which was indicated by two consecutive HIV-RNA levels of 200 copies/mL or greater, discontinued their assigned treatment.

The primary endpoint measure was the percentage of patients with an HIV-RNA level of <50 copies/mL at week 48, determined with the use of the FDA snapshot algorithm.[3] The primary efficacy analysis included all patients who received at least one dose of study medication. The criteria for efficacy was a difference of more than 8% between the CAB dose groups. A total 244 patients were randomly allocated to treatment groups, and 243 patients received at least one dose of study drug and were included in the analysis.

After 48 weeks, 82% of patients in the oral CAB groups and 71% of patients in the EFV group had HIV-RNA levels <50 copies/mL.[3] After 96 weeks, which included 72 weeks of maintenance therapy, 76% of patients in the oral CAB groups and 63% of patients in the EFV group had HIV-RNA levels <50 copies/mL. Differences in responses were contributed to an excess of adverse events leading to discontinuation in the EFV group and a lower rate of virologic non-responders in CAB groups. In addition, 84% of CAB 60 mg, 75% of CAB 30 mg, and 68% of CAB 10 mg groups had HIV-RNA levels <50 copies/mL at week 48. Differences in response rates were attributed to discontinuations of treatment and virologic non-response. An efficacy analysis at 96 weeks in the intention-to-treat population was performed to evaluate virologic response between the different CAB doses, and patients receiving CAB 60 and 30 mg doses had numerically higher values of patients with HIV-RNA levels <50 copies/mL (93% and 85%, respectively) compared with patients receiving CAB 10 mg (79%). Treatment-related adverse events were more common in the EFV group than the CAB groups (68% *versus* 51%). Adverse events leading to discontinuation were also more common in the EFV group (15%) compared with oral CAB groups (2%, 2%, and 7% in the 10, 30, and 60 mg groups, respectively).

Results of the LATTE study demonstrate that two-drug maintenance therapy with oral CAB and RPV provides similar virologic activity compared with EFV plus dual NRTIs. Based on efficacy and tolerability, oral CAB 30 mg once daily was chosen as the dose for further assessment into future studies of long-acting injectable formulations.

LATTE-2 trial

LATTE-2 was a phase 2b, randomized, multicenter, open-label, dose-ranging trial that compared LA-CAB/RPV dosed every 8 weeks (Q8W) or every 4 weeks (Q4W) in treatment-naïve patients.[4] Eligible patients were ⩾18 years of age, ARV naive, had CD4 count ⩾200 cells/mm^3, had HIV-RNA levels of ⩾1000 copies/mL at baseline,

Table 1. Phase 2 and 3 clinical trials of CAB/RPV for the treatment of HIV-1.

Study	Treatment	Design	Population	Treatment outcomes			Drug-related AE[a] (incidence ⩾10%)	
				Week 48	Week 96	Long-term	Non-ISR	ISR
LATTE	Induction: Oral CAB 10, 30, or 60 mg, or EFV 600 mg daily with two NRTIs for 24 weeks. Maintenance: Oral CAB 10, 30, or 60 mg with RPV 25 mg daily or EFV 600 mg daily with two NRTIs for 76 weeks	Phase 2b, randomized, multicenter, partly masked, dose-ranging trial	Treatment-naïve patients (⩾18 years) with CD4 ⩾ 200 cells/mm^3, HIV-RNA ⩾1000 copies/mL	HIV-RNA <50 copies/mL in 82% of CAB groups *versus* 71% in EFV group	HIV-RNA <50 copies/mL in 76% of CAB groups *versus* 63% in EFV group	–	Nausea (17%) Headache (15%) Diarrhea (10%)	–
LATTE-2	Induction: Oral CAB + ABC/3TC for 20 weeks, RPV was added to regimen for weeks 16–20 in those randomized to injectable therapy. Maintenance: Q8W: LA-CAB/RPV IM injection every 8 weeks. Q4W: LA-CAB/RPV IM injection every 4 weeks. Oral therapy: CAB + ABC/3TC	Phase 2b, randomized, multicenter, open-label, dose-ranging trial	Treatment-naïve patients (⩾18 years) with CD4 ⩾200 cells/mm^3, HIV-RNA ⩾1000 copies/mL, and no DRMs	36-week data: HIV-RNA <50 copies/mL in 95% of Q8W group, 94% of Q4W group, and 91% of oral therapy group	HIV-RNA <50 copies/mL in 94% of Q8W group, 87% of Q4W group, and 84% of oral therapy group	256-week data: HIV-RNA <50 copies/mL in 81% of randomized Q8W/Q4W groups and 93% of switch from oral to Q8W/Q4W groups	96-week data: Nausea (10% Q4W)	96-week data: Pain (95% Q8W and 97% Q4W) Nodule (25% Q8W and 30% Q4W) Swelling (25% Q8W and 30% Q4W) Pruritus (21% Q8W and 29% Q4W) Induration (24% Q8W and 22% Q4W) Warmth (19% Q8W and 18% Q4W) Swelling (17% Q8W and 12% Q4W) Erythema (10% Q8W and 17% Q4W)
FLAIR	Induction: Oral DTG/ABC/3TC for 16 weeks. Maintenance: Injectable group: Oral CAB 30 mg + oral RPV 25 mg daily for 4 weeks followed by LA-CAB/RPV IM injection every 4 weeks. Oral group: DTG/ABC/3TC	Phase 3, randomized, multicenter, open-label, non-inferiority trial	Treatment-naïve patients (⩾18 years) with HIV-RNA ⩾1000 copies/mL, and no DRMs	HIV-RNA ⩾50 copies/mL in 2.1% of Q4W group and 2.5% of oral therapy group	HIV-RNA ⩾50 copies/mL in 3% of Q4W group and 3% of oral therapy group	124-week data: HIV-RNA <50 copies/mL in 80% of randomized Q4W group, 99% in the direct to injection switch group, and 93% of the oral lead-in to injection switch group	Headache (14%) Diarrhea (10%)	Pain (80%)
ATLAS	Injectable group: Oral CAB 30 mg + oral RPV 25 mg daily for 4 weeks followed by LA-CAB/RPV IM injection every 4 weeks. Oral group: INSTI, NNRTI or PI + 2 NRTIs	Phase 3b, randomized, multicenter, open-label, non-inferiority trial	Treatment-experienced patients (⩾18 years) with HIV-RNA <50 copies/mL, and no DRMs	HIV-RNA <50 copies/mL in 92.5% of Q4W group and 95.5% of oral therapy group	HIV-RNA <50 copies/mL in 100% of Q4W group and 97% of switch Q4W group	-		Pain (60%)
ATLAS-2M	Q8W: LA-CAB/RPV IM injection every 8 weeks. Q4W: LA-CAB/RPV IM injection every 4 weeks. If patients were not transitioned from ATLAS study then they received oral CAB 30 mg + oral RPV 25 mg daily for 4 weeks prior to injectable therapy	Phase 3b, randomized, multicenter, open-label, non-inferiority trial	Treatment-experienced patients (⩾18 years) with HIV-RNA <50 copies/mL, and no DRMs	HIV-RNA ⩾50 copies/mL in 2% of Q8W group and 1% of Q4W group	HIV-RNA ⩾50 copies/mL in 2% of Q8W group and 1% of Q4W group	154-week data: HIV-RNA ⩾50 copies/mL in 3% of Q8W group and 1% of Q4W group		Pain (72% Q8W and 70% Q4W) Nodule (10% Q8W and 17% Q4W)

3TC, lamivudine; AE, adverse event; ABC, abacavir; CAB, cabotegravir; DRMs, drug resistance mutations; DTG, dolutegravir; EFV, oral efavirenz; HIV RNA, ribonucleic acid; IM, intramuscular; INSTI, integrase strand transfer inhibitor; ISR, injection site reactions; kg, kilogram; LA, long-acting; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.
[a]Adverse effects reported in 48-week data.

and had no major drug resistance–associated mutations. All patients were assigned to take 30 mg oral CAB and 600 mg/300 mg abacavir/lamivudine (ABC/3TC) as a daily oral regimen for the initial 20 weeks, with 25 mg oral RPV once daily added for the last 4 weeks. At week 24, patients whose HIV-RNA level was <50 copies/mL were randomly assigned 2:2:1 to receive IM injections Q8W (LA-CAB 600 mg and LA-RPV 900 mg), IM injections Q4W (LA-CAB 400 mg and LA-RPV 600 mg), or continue oral CAB and ABC/3TC in the 96 week maintenance period. At week 96, patients randomized to long-acting injectable therapy continued on therapy into the extension period, and patients on oral therapy could switch to the long-acting injectable group of their choice. Patients with CVF, which was indicated by two consecutive HIV-RNA levels of 200 copies/mL or greater, discontinued their assigned treatment.

The primary endpoint measures were the percentage of patients with an HIV-RNA level of <50 copies/mL at week 32, determined with the use of the FDA snapshot algorithm.[4] The primary analysis included patients in the intention-to-treat, maintenance population who received at least one dose of long-acting therapy. The criteria for non-inferiority was a difference of more than 10% between the LA-CAB/RPV group and oral group. A total 309 patients were randomly allocated to treatment groups, and 286 patients completed the 20-week induction period and were included in the analysis.

After 32 weeks, 95% of patients in Q8W group (95% confidence interval, –4.8 to 12.2 *versus* oral treatment), 94% of patients in the Q4W group (95% confidence interval, –5.8 to 11.5 *versus* oral treatment), and 91% of patients in the oral group had HIV-RNA levels <50 copies/mL.[4] These results met the criteria for non-inferiority. After 96 weeks, 94% of patients in Q8W group, 87% of patients in the Q4W group, and 84% of patients in the oral group had HIV-RNA levels <50 copies/mL. About 97% of the patients in the Q4W group and 96% of patients in the Q8W group reported injection site reactions (mild or moderate severity for 99% of cases and median symptom duration of 3 days). At week 96, >99% of patients who had been assigned to the LA injectable groups were satisfied with the regimen.

In the extension period through week 256, the oral ART group was offered to switch to either the Q4W group or the Q8W group at week 96.[5] After 256 weeks, 81% of patients in the randomized Q8W/Q4W groups and 93% of patients in the group switch from oral to Q8W/Q4W groups had HIV RNA levels <50 copies/mL. Twenty-five patients had adverse effects leading to withdrawal and 20 of these patients were in the Q4W groups.

Results of the LATTE-2 study show therapy with LA-CAB/RPV every 4 weeks or every 8 weeks was non-inferior to three-drug oral therapy at maintaining HIV suppression and was well-tolerated with high satisfaction.

FLAIR trial

FLAIR was a Phase 3, randomized, multicenter, open-label, non-inferiority trial that compared monthly LA-CAB/RPV *versus* oral daily dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) in treatment-naïve patients. Eligible patients were ⩾18 years of age, ARV naive, and had HIV-RNA levels of ⩾1000 copies/mL at baseline.[6] Patients were excluded if they had any history of integrase strand transfer inhibitor (INSTI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) exposure, had history of resistance to INSTI or NNRTI (except K103N), or chronic hepatitis B. All patients were assigned to take 50 mg DTG, 600 mg ABC, and 300 mg 3TC as a daily oral regimen for the initial 16 weeks. At week 16, patients whose HIV-RNA level was <50 copies/mL were randomized in a 1:1 ratio into the two treatment groups. Treatment assignments were stratified by baseline HIV-RNA level (<100,000 and ⩾100,000 copies/mL) and sex at birth. One group continued the DTG/ABC/3TC daily oral regimen for the next 100 weeks. The other group switched to CAB/RPV with the initial 4-week oral lead-in (30 mg CAB and 25 mg RPV daily). This was followed by the one-time initiation injections (600 mg CAB injection and 900 mg RPV injection). Patients then received maintenance injections every 4 weeks, which was the 400 mg CAB injection and 600 mg RPV injection for a total of 100 weeks. Patients with CVF, which was indicated by two consecutive HIV-RNA levels of 200 copies/mL or greater, discontinued their assigned treatment.

The primary endpoint measure was the percentage of patients with an HIV-RNA level of ⩾50 copies/mL at week 48, determined with the use of the FDA snapshot algorithm.[6] The primary efficacy analysis included all patients who received at least one dose of the assigned trial drugs during the maintenance phase. For the primary endpoint, a non-inferiority margin of six percentage points was set based on clinical considerations of the two regimens. A total 629 patients initiated oral induction therapy, with 63 of those patients withdrawing before randomization because of lack of efficacy. The remaining 566 patients were randomly assigned to their maintenance phase treatment.

After 48 weeks, 2.1% of patients on the LA monthly injectable regimen and 2.5% of patients on the daily oral regimen had HIV-RNA levels ⩾50 copies/mL (95% confidence interval, –2.8 to 2.1).[6] These results met the criteria for non-inferiority. After 96 weeks, 3% of patients on the LA monthly injectable regimen and 3% of patients on the daily oral regimen had HIV-RNA levels ⩾50 copies/mL (95% confidence interval, –2.9 to 2.9).[7] These results met the criteria for non-inferiority. Of note, 3 of 54 patients in the LA therapy group who had the L74I integrase polymorphism at baseline had CVF. About 86% of the patients who received LA injectable therapy reported injection site reactions (mild or moderate severity for 99% of cases and decreased throughout the study). At week 48, 98% of patients who had been assigned to the LA injectable group were satisfied with the regimen and preferred it over the oral daily regimen.

In the extension period through week 124, the oral ART group was offered to switch to the Q4W group at week 100.[8] In the group of patients who switched, 48% were switched directly from DTG/ABC/3TC to injection and 52% were given the oral lead-in. After 124 weeks, 80% of patients in the randomized group, 99% in the direct to injection switch group, and 93% of the oral lead-in switch group had HIV RNA levels <50 copies/mL. Eighteen patients had adverse effects leading to withdrawal.

Results of the FLAIR study show therapy with LA-CAB/RPV was non-inferior to oral therapy with DTG/ABC/3TC at maintaining HIV suppression and was well-tolerated with high satisfaction.

ATLAS study

The ATLAS study was a phase 3, randomized, multicenter, parallel group, open-label, non-inferiority trial that compared switching to monthly LA-CAB/RPV injections *versus* staying on a three-drug ARV regimen in treatment-experienced patients.[9] Patients enrolled were ⩾18 years of age, taking two NRTIs plus an INSTI, NNRTI, or protease inhibitor (PI), on a stable ARV regimen for ⩾6 months prior, and had HIV-RNA levels of <50 copies/mL for ⩾6 months prior. Although the primary study population was treatment-experienced patients, exclusion criteria included anyone with a history of virologic failure, INSTI or NNRTI (except K103N) resistance, or chronic hepatitis B. Also, patients taking DTG/ABC/3TC were excluded to maximize generalizability, as this prior regimen was evaluated in the FLAIR trial. Patients were randomly assigned in a 1:1 ratio to either continue their three-drug oral ART for 52 weeks or to switch to the oral CAB and RPV lead-in for the first 4 weeks, followed by initiation and continuation IM CAB and RPV injections every 4 weeks for the remaining 48 weeks.

The primary endpoint was the percentage of patients with an HIV-RNA level of ⩾50 copies/mL at week 48, determined with the use of the FDA snapshot algorithm.[9] The primary efficacy analysis included all patients who received at least one dose of their assigned treatment. For the primary endpoint, a non-inferiority margin of six percentage points was set based on the potential clinical advantages of LA therapy. A total 618 patients were randomly allocated to treatment groups, and 616 patients received at least one dose of study drug and were included in the analysis.

The primary endpoint of HIV-RNA ⩾50 copies/mL occurred in 1.6% of patients in the LA injectable group compared with 1.0% in the oral therapy group (95% confidence interval, –1.2 to 2.5).[9] These results met the criteria for non-inferiority for the primary endpoint. About 83% of patients reported injection site pain, which was mild to moderate in most cases and only 1% withdrew from the study due to injection site pain. The frequency of injection site reactions declined progressively, reaching 11% at week 48. About 86% of patients who received the LA therapy preferred the regimen over previous oral therapy.

In the extension period through week 96, study patients were offered to switch to ATLAS-2M, or enter the extension phase to continue Q4W injections or switch from oral ART to Q4W injections at week 56.[10] A majority of patients (88%) chose to transition to ATLAS-2M. Therefore, only 52 patients were included in the 96-week analysis. After 96 weeks, 100% of patients in the randomized Q4W group and 97% of patients in the group switch from oral to Q4W group had HIV RNA levels <50 copies/mL.

The ATLAS study showed that monthly LA injections of CAB/RPV were non-inferior to standard triple oral therapy for HIV treatment and provided a high rate of treatment satisfaction despite injection-related side effects.

ATLAS-2M study

The ATLAS-2M study was a phase 3b, randomized, multicenter, open-label, non-inferiority trial that compared LA-CAB/RPV injections Q8W *versus* Q4W in treatment-experienced patients.[11] Patients enrolled were ⩾18 years of age, taking an oral, standard-of-care, ARV regimen for ⩾6 months prior, and had HIV-RNA levels of <50 copies/mL. Patients were also enrolled directly from the ATLAS study from the LA-CAB/RPV Q4W or oral standard-of-care groups. Although the primary study population was treatment-experienced patients, exclusion criteria included anyone with a history of virologic failure, INSTI or NNRTI resistance (except K103N), or chronic hepatitis B. Patients were randomly assigned in a 1:1 ratio to LA-CAB/RPV Q8W or Q4W. Patients with no previous exposure to CAB or RPV received the 4-week oral lead-in (30 mg CAB and 25 mg RPV daily) prior to staring injectable therapy.

The primary endpoint was the percentage of patients with an HIV-RNA level of ⩾50 copies/mL at week 48, determined with the use of the FDA snapshot algorithm.[11] The primary efficacy analysis included all patients who received at least one dose of their assigned treatment. For the primary endpoint, a non-inferiority margin of four percentage points was set. A total 1049 patients were randomly allocated to treatment groups, and 1045 patients received at least one dose of study drug and were included in the analysis.

The primary endpoint of HIV-RNA ⩾50 copies/mL occurred in 2% of patients in the Q8W compared with 1% in the Q4W group (95% confidence interval, –10.6 to 2.2).[11] These results met the criteria for non-inferiority for the primary endpoint. After 96 weeks, 2% of patients in the Q8W compared with 1% in the Q4W group had HIV-RNA levels ⩾50 copies/mL (95% confidence interval, –0.6 to 2.5).[12] These results met the criteria for non-inferiority. About 76% of patients in the Q8W group and 75% of patients in the Q4W group reported injection site pain, which was mild to moderate in most cases and only 1% withdrew from the study due to injection site pain. In the 154-week data, the Q8W group remained non-inferior to the Q4W group with HIV-RNA levels ⩾50 copies/mL in 3% and 1% of patients, respectively.[13]

The ATLAS-2M study showed that monthly LA-CAB/RPV Q4W and Q8W had similar efficacy and safety. Although both regimens provided high treatment satisfaction, patients preferred Q8W dosing over the Q4W dosing and previous oral ART regimens.[14]

CARISEL study

Early results from the CARISEL study were presented at the 24th International AIDS Conference in 2022. The CARISEL study was a phase 3b, multicenter, open-label, hybrid type 3 implementation-effectiveness trial evaluating participants switching from daily oral therapy to LA-CAB/RPV dosed every 2 months (Q2M).[15] Patients enrolled were ⩾18 years of age, receiving ART for ⩾6 months, no prior history of CVF, and had HIV-RNA levels of <50 copies/mL. Exclusion criteria were not presented. The primary endpoint was the percentage of patients with an HIV-RNA level of ⩾50 copies/mL and <50 copies/mL at month 12, determined with the use of the FDA snapshot algorithm. Patients were assigned to receive oral CAB and RPV lead-in for the first 4 weeks, followed by initiation and continuation of IM CAB and RPV injections every 2 months. A total 430 patients, across 18 European clinics, were included in the analysis. At month 12, 87% (95% confidence interval, 83.2 to 89.8) of patients maintained HIV-RNA <50 copies/mL, and 0.7% (95% confidence interval, 0.1 to 2) of patients had an HIV-RNA level of ⩾50 copies/mL. About

12.6% of patients had no virologic data at month 12 during the FDA snapshot algorithm. Injection site reactions were reported in 86% of patients, with 6% of patients discontinuing treatment for injection-related reasons. The number of patients reporting injection site reactions decreased with each visit through month 14.

The CARISEL study demonstrated that LA-CAB/RPV dosed Q2M was highly effective and well-tolerated across diverse European clinical settings and patient populations in clinics with limited experience using LA-injectables for treatment of HIV.

MOCHA study

Early results from the MOCHA study were presented at the Conference on Retroviruses and Opportunistic Infections in 2022.[16] The MOCHA study is an ongoing phase I/II, multicenter, noncomparative, open-label study to confirm the dose and evaluate safety, tolerability, acceptability, and pharmacokinetics of LA-CAB and LA-RPV in adolescents ⩾12 to <18 years with HIV. Patients enrolled had HIV-RNA <50 copies/mL on stable ART, which was continued throughout the cohort. Patients were enrolled to receive either CAB 30 mg for 4 weeks, followed by LA-CAB 600 mg/3 mL at week 4, and 400 mg/2 mL at week 8 and 12, or RPV 25 mg for 4 weeks, followed by LA-RPV 900 mg/3 mL at week 4, and 600 mg/2 mL at week 8 and 12. Twenty-three patients were enrolled, and median pharmacokinetic parameters met study targets with Q4W dosing. Thirteen out of 23 patients reported injection site pain, and all injection site reactions were grade 1 or 2, and none led to treatment discontinuation.

The MOCHA study demonstrated similar drug exposure and safety in adolescents of LA-CAB/RPV dosed Q4W compared with adults, which has led to the expanded indication for LA-CAB/RPV in adolescents weighing ⩾35 kg. Additional data are needed to evaluate the pharmacokinetics of LA-CAB/RPV dosed Q8W in adolescents with HIV.

Virologic failure. In FLAIR and ATLAS-2M, virologic failure occurred in the LA-CAB/RPV treatment arms, despite adherence to scheduled injections, which was typically associated with single or dual class resistance.[8,10,13,15] Five out of 283 (2%) of participants had CVF in the week 48 analysis of the FLAIR study, with one additional patient meeting criteria for virologic failure at week 108.[8] One patient failed treatment during the oral lead-in when temporarily discontinuing therapy based on a false-positive pregnancy test. Four of the patients had baseline L74I, three had body mass index (BMI) ⩾30 kg/m^2, and four were classified as HIV-1 subtype A1, but some were later reclassified as HIV-1 subtype A6. Four patients had both NNRTI and INSTI treatment-emergent resistance (K101E and G140R; E138E/A/K/T and Q148R; E138 K and Q148R; V106V/A+V108V/I+E138G+M230L and N155H+R263K). In the 152-week data for ATLAS-2M, a total of 13 patients with CVF [Q8W, n = 11 (2%); Q4W, n = 2 (<1%)] were reported.[13] A majority of failures occurred by week 48 (77%, n = 10/13), and a majority (60%) of patients who had failures at week 48 had ⩾2 baseline risk factors, including RPV resistance associated mutations, HIV-1 subtype A6/A1, or BMI ⩾30 kg/m^2.[13] Of the 10 patients with failures at week 48, five (50%) had baseline NNRTI or INSTI mutations, one (10%) had no mutations, and four (40%) had treatment-emergent resistance (K101E and Q148R; Q148Q/R+N155N/H and E138E/K; N155N/H; E138E/K+Q148R and K101E+M230L). The patient with failure between week 48 and 96 had baseline NNRTI resistance (K103N and Y181C) in addition to the baseline INSTI polymorphism (L74I), was HIV-1 subtype B, and had a BMI <30 kg/m^2.[10] The two patients with failure between week 96 and 152 had no resistance-associated mutations at baseline and had BMI <30 kg/m^2, but one patient had HIV-1 subtype A6 and L74I polymorphism at baseline, and both had treatment-emergent NNRTI and INSTI mutations (E138A+M230M/L and Q148R; E138A+Y181Y/C and Q148R).[13] Six out of 13 CVFs (46%) had no baseline resistance and developed treatment-emergent resistance in ATLAS-2M, with five out of six (83%) developing both NNRTI and INSTI mutations. The CARISEL study had two patients with treatment failure, both with BMI ⩽30 kg/m^2, and with HIV-1 subtype G and B in female and male participants, respectively.[15] The female patient did have an RPV mutation at baseline, E138A, which was also observed at time of treatment failure, and the male patient had no baseline resistance, but E138K and N155N/S were detected at time of failure.

Clinical considerations

Identifying the optimal candidate

Identifying the optimal candidate for LA-CAB/RPV is essential to successful treatment with injectable therapy. In clinical trials, 1.25% of patients treated with LA-CAB/RPV either every 4 weeks or every 8 weeks experienced CVF.[17] Factors associated with virologic failure included ⩾2 RPV resistance–associated mutations, HIV-1 subtype A6/A1 and/or BMI ⩾30 kg/m^2. It is estimated that approximately 10% of ARV-naïve patients with HIV have genotypic baseline factors associated with virologic failure.[18] FLAIR demonstrated virologic failure in 3 of 54 patients who had a baseline L74I integrase polymorphism, which is prevalent in Russia in subtype A6 and to a lesser extent A1, and in West Africa in subtype G and to a lesser extent AG.[6,19,20] ARV-naïve patients should be tested for resistance-associated mutations to RPV and/or CAB prior to initiating treatment with injectable therapy. In patients already virologically suppressed, HIV treatment and genotyping history should be reviewed extensively. LA-CAB/RPV is not indicated in patients with a history of treatment failure, but if clinician and patient feel benefit of treatment outweigh risks, consideration should be made for additional archived genotype testing if patient-specific records are limited. Of note, the Department of Health and Human Services (DHHS) guidelines for treatment of HIV currently do not recommend routine testing for INSTI mutations at baseline, so history of INSTI mutations may be unknown.[21]

Patients with difficulty swallowing, nausea, and/or vomiting may benefit from LA-CAB/RPV. Difficulty swallowing has been associated with an increased risk for acute weight loss in patients with HIV, who may already be in a catabolic state due to progression of HIV.[22] Patients who have difficulty swallowing may struggle with adherence to a daily oral regimen, increasing the risk for virologic failure.[23] Combination ARV therapy often comes in large tablet formulations and data are limited on the pharmacokinetics of crushing therapy, which may also have an unpalatable taste.[24] Few ARV agents have been studied successfully in patients with swallowing difficulties.[25,26] Adolescents and the elderly are more likely to have difficulty swallowing tablets, which can impact patient adherence to ARV regimens.[27] As the HIV population ages, novel formulations of ARV therapy may be necessary to maintain virologic suppression, especially in those who develop neurodegenerative diseases.[28]

Potential for weight gain also should be considered when identifying the optimal candidate for LA-CAB/RPV. ARV therapy with INSTIs have been associated with weight gain and increased waist circumference, especially in females, people of Black ethnicity, and patients with elevated HIV-RNA and lower CD4 counts at baseline.[29] In HPTN 077, a clinical trial evaluating LA-CAB for HIV pre-exposure prophylaxis (PrEP) compared with placebo, 146 study participants had paired weights between week 0 and week 41.[30] The median increase in weight was 1.1 kg in the LA-CAB group compared with 1 kg in the placebo group ($p = 0.66$). It is important to note the study participants included in this analysis did not have HIV. In the 48-week analysis of FLAIR, there was a median of 1.3 kg of weight gain in injectable group and 1.5 kg in the oral group.[6] In ATLAS, LA-CAB/RPV was compared with stand-of-care oral therapy, and at 48 weeks, there was a median of 1.8 kg of weight gain in injectable group and 0.3 kg in the oral group.[9] Finally, ATLAS-2M provided 96-week data on the impact of LA-CAB/RPV on weight gain, with a median of 2.1 kg weight gain in the study group who was continued on LA-CAB/RPV for the entirety of the 96 weeks.[12] Additional, long-term data are needed to make any conclusions on the impact of LA-CAB in PLWH.

Clinic hours for injections should be discussed before pursuing treatment with injectable therapy to ensure patients will be able to come in monthly or every two months for their scheduled injections. Potential barriers to adhering to LA-CAB/RPV injections, based on clinical experience and extrapolation of data on oral medication refills, include strict work schedules, parenting/caretaker responsibilities, lack of transportation or distance from administration site, frequent changes in jobs/insurance, immigration/deportation, and/or regular travel out of town.[31] Other populations that may be affected by treatment interruptions could include PLWH who are detained either short-term or long-term in a jail or prison setting, or residing in a skilled nursing facility or

long-term care facility.[32] These patients will require additional coordination by healthcare team to transport patient to and from injection appointments, if possible. In addition, patients should also be aware of how long a visit will take. For instance, once the patient arrives and is checked-in for their appointment, LA-CAB/RPV must be removed from the refrigerator and brought to room temperature, which usually takes around 15 min. The medications must then be visually inspected and drawn up into their respective syringes prior to administration into separate gluteal injection sites.[33]

In the CARISEL study, study staff participants were surveyed to identify their top needs that were met by Q2M LA-CAB/RPV.[34] Staff reported the top need met by LA-CAP/RPV was the elimination of daily oral therapy burden, followed by discretion, convenience, adherence, and stigma-related reasons. In addition, staff reported their patients had positive things to say about taking LA-CAB/RPV instead of oral therapy.

Oral lead-in

Patients may discuss with their healthcare provider whether or not to receive the optional oral lead-in therapy, which includes a 30-day supply of oral CAB 30 mg and oral RPV 25 mg taken daily with a meal of at least 500 calories.[33] The optional oral lead-in helps to identify any side effects to CAB or RPV prior to beginning treatment with the LA formulation, since there is no reversal agent available.

Based on clinical trials, up to 32% of patients experienced at least one side effect with oral lead-in therapy leading to four patients not being able to initiate injectable therapy.[35,36] Side effects related to the oral lead-in therapy were generally mild and did not warrant discontinuation of treatment. The decision to make the oral lead-in optional was supported from data derived from the open-label Phase 3 FLAIR study where 110 patients elected to receive direct-to-injection LA-CAB/RPV compared with 113 who elected to receive an oral lead-in.[8] At week 24, only one participant withdrew due to adverse effects (Hodgkin Lymphoma) compared with two in the oral lead-in group (injection site pain and 8 kg weight gain). Ultimately, the authors concluded that switching to LA-CAB/RPV with or without oral lead-in treatment resulted in similar efficacy, safety, and tolerability.

LA injectable

Patients will receive initiation injections on the last day of their oral lead-in at a dose of 600 mg/3 mL of CAB and 900 mg/3 mL of RPV.[33] Both drugs should be administered IM as two gluteal injections separated on opposite sides or at least 2 cm apart. Although the ventrogluteal site is recommended for IM administration, the dorsogluteal site may be considered as an alternative injection site.

Overweight and obese individuals require additional consideration for appropriate needle length. More than 50% of failed injections in overweight and obese individuals are due to incorrect needle length.[37] For those with BMIs $>30\ kg/m^2$, the use of longer needles for administration (i.e. 2-inch) were associated with higher CAB trough concentrations. The use of longer needles allows for appropriate administration to reach the gluteal muscle.[38]

LA-CAB/RPV is currently approved for every 1-month (Q1M) or Q2M administration (Figure 1).[33] Although the dosage is different, the same injection technique and principles remain the same. Large-volume IM injections of 3 mL or greater have been associated with drug leakage, which could lead to reductions in drug concentrations.[39] Nursing staff should be trained on appropriate administration of LA-CAB/RPV to minimize pain associated with injection and ensure efficacy and safety. The Z-track administration technique, which forces the path of entry of the needle into a zig-zag shape, has been associated with reductions in drug leakage and should be considered for LA-CAB/RPV.

For those who are starting an every-month dosing schedule, on the last day of the optional oral lead-in, 600 mg (3 mL) of LA-CAB and 900 mg (3 mL) of LA-RPV should be administered IM at two separate sites, then continuation injections should be administered IM on the target treatment date each month at a dose of 400 mg (2 mL) of LA-CAB and 600 mg (2 mL) of LA-RPV. For those who are starting an every 2 month dosing schedule, on the last day of the optional oral lead-in, 600 mg (3 mL) of LA-CAB and 900 mg (3 mL)

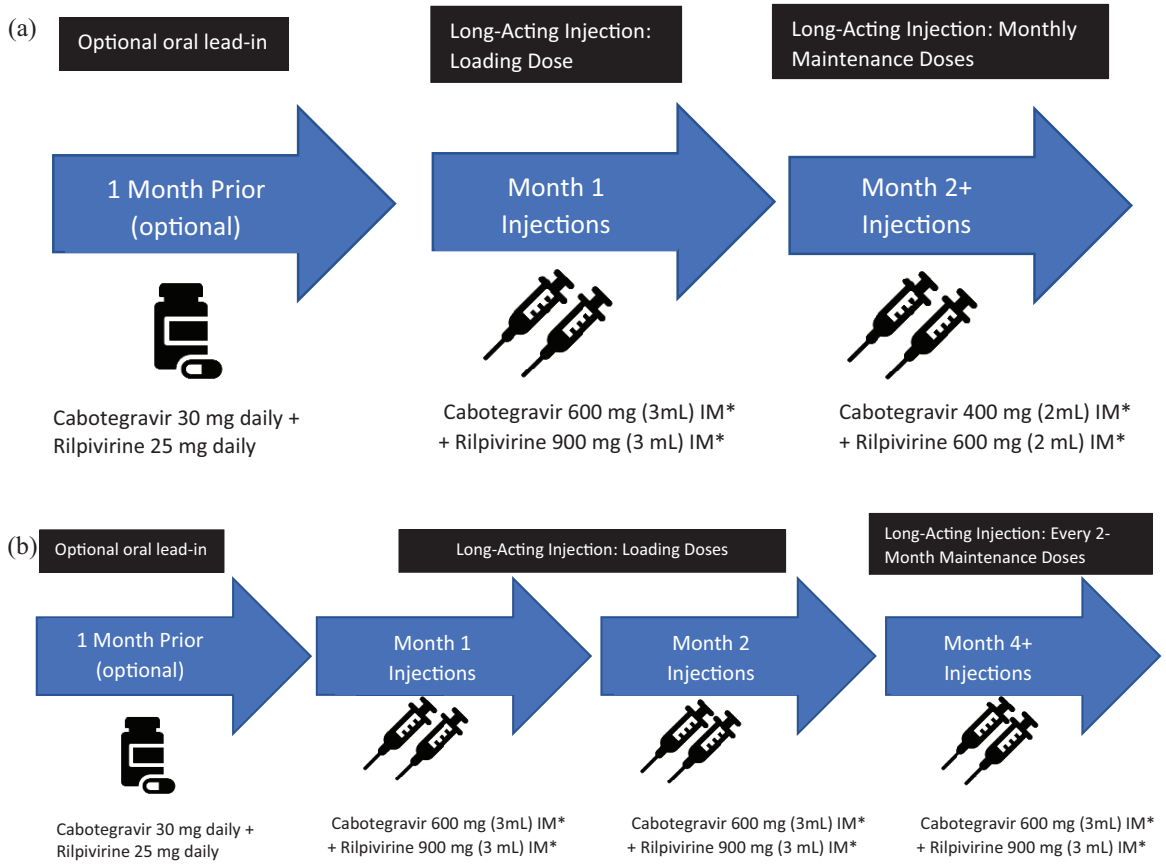

Figure 1. Recommended dosing schedule of cabotegravir/rilpivirine: (a) monthly dosing and (b) every 2-month dosing.
*For gluteal intramuscular injection only.

of LA-RPV should be administered IM at two separate sites for two consecutive months. Then continuation injections should be administered IM on the target treatment date of every other month at a dose of 600 mg (3 mL) of LA-CAB and 900 mg (3 mL) of LA-RPV. For patients already receiving monthly LA-CAB/RPV and interested in transitioning to every 2-month dosing, 600 mg (3 mL) of CAB and 900 mg (3 mL) of RPV should be administered intramuscularly to the patient 1 month after their last monthly injection and every 2 months, thereafter.

The decision to treat with either Q1M or Q2M should be discussed between patient and provider. Although there was no significant difference in efficacy of Q1M *versus* Q2M, risk factors for treatment failure should be reviewed based on a patient-specific basis.[8,10,13,15,19,20] Of note, the pharmacokinetic data in adolescents were based on a Q4W dosing schedule.[16] In the 152-week analysis of ATLAS-2M, 16% of injections in the Q8W arm resulted in injection site pain, *versus* 11% of injections in the Q4W arm.[13] Overall treatment satisfaction increased significantly favored Q8W group over the Q4W group through week 152. Finally, adherence to injection visits should be considered and discussed with patient when deciding between Q1M and Q2M to ensure the treatment schedule is feasible.

Within the United States, there are two options for acquisition of LA-CAB/RPV for IM administration. The first option is through a specialty pharmacy, which allows for patient-specific medication to be sent to the clinic on a monthly basis for administration.[40] The second option is through a buy and bill process, which requires a

clinic to purchase a supply of LA-CAB/RPV directly from a specialty distributor and store medication on the premises until time of administration. The buy and bill process requires the clinic to be responsible for tracking inventory, submitting reimbursement of claims to payers, and collecting medication and/or administration fees directly from patients.

LA injectable – missed dose

A challenge associated with LA-CAB/RPV is the issue of missed appointments for administration. It is recommended that a patient receiving LA-CAB/RPV set and adhere to a target treatment date for each scheduled injection. There is some dosing flexibility which allows LA-CAB/RPV to be administered 7 days before or after the target treatment date.[33] If the patient plans to miss a scheduled injection by more than 7 days after their dose is due, oral therapy with CAB and RPV, or any other fully suppressive oral ART, may be prescribed for up to 2 months. Patients should be instructed to restart oral ART within 7 days of when their next injection is due. During the global SARS-CoV-2 pandemic, data from active clinical trials at the time demonstrated that 93% of patients were able to continue their injection visits as planned. For those unable to adhere to injection visits during the global pandemic, oral ART was permitted where oral CAB and RPV was prioritized for continuation of therapy, but other oral agents were also allowed.[41] Other options to consider would have been to resume the patient on their prior ART just prior to initiating LA-CAB/RPV.

After missed injections, the time since planned injection date should guide dosing regimen, regardless of whether or not patient received oral ART between injections.[33] If it has been less than or equal to 1 month since the planned injection date, then the patient can resume maintenance dosing at previous dose (400 mg of LA-CAB/600 mg of LA-RPV for monthly, 600 mg of LA-CAB/900 mg LA-RPV for bimonthly).

If a patient misses their monthly dose often, the patient should be reassessed for candidacy of LA-ART.[33] In clinical studies, 98% of patients in the ATLAS study received LA-CAB/RPV within the permitted administration window leaving only a small percentage of trial patients missing their dose.[9] Despite high adherence to injection visits in clinical trials, some patients still experienced treatment failure.[8,10,13,15] If clinician feels it is best for patient to discontinue LA-ART, patient should be counseled on restarting oral ART within 7 days of when their next injection is due.

LA injectable – storage

LA-CAB/RPV requires refrigeration at 2°–8°C (36°–46°F) until ready for administration.[33] This injection should not be frozen or mixed with any other agent. Medication administration should occur once the vials reach room temperature [25°C (77°F)]. The medication vials must be discarded if left at room temperature beyond 6 h or taken out of refrigeration for any extended period of time (i.e. they should not be cycled between room temperature and refrigeration). Once in a syringe, it is best to administer the drugs as soon as possible. The drugs can remain in a syringe for up to 2 h but must not exceed 6 h at room temperature. If CAB or RPV exceed 2 h in a syringe at room temperature, they must be discarded. Again, once drawn up in a syringe, CAB/RPV should not be cycled between refrigeration and room temperature.

Drug interactions

As with many ARVs, certain drug–drug interactions exist with the use of oral CAB + RPV or LA-CAB/RPV which can lead to loss of virologic suppression or increased risk of side effects.[33] Cabotegravir is predominantly metabolized by UGT1A1 and to some extent UGT1A9, whereas RPV is metabolized by CYP3A. Notable contraindications that may lead to loss of virologic suppression while receiving oral or LA-CAB/RPV include certain anticonvulsants (carbamazepine, oxcarbazepine, phenobarbital, and phenytoin), antimycobacterials (rifabutin, rifampin, rifapentine), and more than a single dose of dexamethasone or St. John's Wort. The risk for increased RPV concentrations, and, thus, side effects such as Torsade de Pointes, is a major concern in the presence of macrolide and ketolide antibiotics. Where possible, it is recommended to prioritize azithromycin, which has less effects on increasing RPV concentrations when compared with other antibiotics in that class. Although a

standard dosage adjustment for methadone is not recommended when initiating LA-CAB/RPV, patients receiving methadone as a maintenance medication may require dosage adjustments since methadone drug concentrations can be reduced in the presence of LA-CAB/RPV.

One notable difference with the IM formulation compared with the oral formulation of RPV is the lack of interactions between antacids, H2-blockers, and proton pump inhibitor (PPIs). The oral lead-in still requires separation of antacids and H2-blockers from RPV and is contraindicated with PPIs.[33] Therefore, patients who require PPI therapy should discuss risks *versus* benefits of holding PPI treatment during the oral lead-in period with their healthcare provider prior to pursuing treatment with LA-CAB/RPV.

Finally, concern surrounds CAB/RPV concentrations that can remain in the body due to residual drug circulating for 12 months or longer. Despite a low concentration of circulating CAB/RPV remaining, it is not likely to contribute to significant drug interactions, but more data are needed. While drug interactions may not be a concern, risk of treatment-emergent resistance to CAB and/or RPV is of concern. Patients should be counseled extensively on the importance of restarting oral ART within 7 days of their next injection being due and the risk of INSTI/NNRTI resistance if virologic suppression on oral ART is not maintained for at least 12 months after discontinuation.

Special populations

It should be noted that specific patient populations were not included in clinical trials evaluating LA-CAB/RPV for treatment of HIV. Patients with gluteal implants were excluded from clinical trials based on their potential interaction with ventrogluteal or dorsogluteal IM injections. Studies evaluating alternate sites of administration are currently underway, which may provide the future option of LA-CAB/RPV for patients with gluteal implants.[42] Second, patients with concomitant hepatitis B infections were excluded from clinical trials based on the lack of HBV-active ARVs in LA-CAB/RPV. Therefore, patients should be screened for HBV and vaccinated prior to treatment with LA-CAB/RPV. It is recommended that patients with active HBV remain on HBV-active treatment regimens. Third, patients were excluded if they were pregnant or breastfeeding. When deciding whether or not to initiate patients on LA-CAB/RPV, pregnancy plans should be discussed with women of child-bearing potential. LA-ARVs may remain in plasma for up to 12 months or longer, so risk *versus* benefit of treatment should be discussed.[43] Female patients of child-bearing potential who do not desire to become pregnant while on LA-CAB/RPV should remain on contraception for the entirety of treatment, and at least 12 months after discontinuing treatment. Patients who become pregnant on LA-CAB/RPV and choose to remain on treatment can be enrolled in the ARV registry. Finally, patients were excluded from clinical trials with a history of virologic failure and INSTI or NNRTI resistance (except K103N). The LATITUDE study is actively recruiting patients for a Phase III clinical trial to evaluate LA-CAB/RPV in PLWH who are non-adherent.[44] In addition, CARISEL is the first study providing real-world data on LA-CAB/RPV in PLWH.[34] As additional data emerge, more guidance may be available on treating special populations with LA-CAB/RPV.

Patient education

In addition to side effects and administration, patients should be counseled on the logistics of injectable therapy and treatment expectations. In the acquisition process, patients will need a reliable phone to be contacted regularly by different members of the healthcare team working on acquisition, coordination of optional oral lead-in, patient counseling, and scheduling of injection appointments. Patients should be counseled on the importance of monthly/bimonthly clinic visits for injections and what to do in the setting of planned or unplanned missed doses. Injection-site reactions should also be discussed, including injection site pain, nodules, and swelling.

Conclusion

The era of LA-ART is just beginning and LA-CAB/RPV is a step in the pathway to expansion of treatment options for PLWH. LA-CAB/RPV is only approved for use in adults and adolescents

(⩾35 kg) who are virologically suppressed who meet specific criteria for treatment success. As additional long-acting treatment options emerge, we need more robust ARVs with high genetic barriers to resistance, longer dosing intervals, and potentially implantable options to continue to expand access to novel formulations of ARVs. LA-CAB/RPB has led the way to improve individual choice for treatment options in adults and adolescents with HIV.

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Not applicable.

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Not applicable.

Author contributions
Marisa Brizzi: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing.

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