Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 48-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study

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Summary

Background Phase 3 clinical studies showed non-inferiority of long-acting intramuscular cabotegravir and rilpivirine dosed every 4 weeks to oral antiretroviral therapy. Important phase 2 results of every 8 weeks dosing, and supportive modelling, underpin further evaluation of every 8 weeks dosing in this trial, which has the potential to offer greater convenience. Our objective was to compare the week 48 antiviral efficacy of cabotegravir plus rilpivirine long-acting dosed every 8 weeks with that of every 4 weeks dosing.

Methods ATLAS-2M is an ongoing, randomised, multicentre (13 countries; Australia, Argentina, Canada, France, Germany, Italy, Mexico, Russia, South Africa, South Korea, Spain, Sweden, and the USA), open-label, phase 3b, non-inferiority study of cabotegravir plus rilpivirine long-acting maintenance therapy administered intramuscularly every 8 weeks (cabotegravir 600 mg plus rilpivirine 900 mg) or every 4 weeks (cabotegravir 400 mg plus rilpivirine 600 mg) to treatment-experienced adults living with HIV-1. Eligible newly recruited individuals must have received an uninterrupted first or second oral standard-of-care regimen for at least 6 months without virological failure and be aged 18 years or older. Eligible participants from the ATLAS trial, from both the oral standard-of-care and long-acting groups, must have completed the 52-week comparative phase with an ATLAS-2M screening plasma HIV-1 RNA less than 50 copies per mL. Participants were randomly assigned 1:1 to receive cabotegravir plus rilpivirine long-acting every 8 weeks or every 4 weeks. The randomisation schedule was generated by means of the GlaxoSmithKline validated randomisation software RANDALL NG. The primary endpoint at week 48 was HIV-1 RNA ≥50 copies per mL (Snapshot, intention-to-treat exposed), with a non-inferiority margin of 4%. The trial is registered at ClinicalTrials.gov, NCT03299049 and is ongoing.

Findings Screening occurred between Oct 27, 2017, and May 31, 2018. Of 1149 individuals screened, 1045 participants were randomised to the every 8 weeks (n=522) or every 4 weeks (n=523) groups; 37% (n=391) transitioned from every 4 weeks cabotegravir plus rilpivirine long-acting in ATLAS. Median participant age was 42 years (IQR 34–50); 27% (n=280) female at birth; 73% (n=763) white race. Cabotegravir plus rilpivirine long-acting every 8 weeks was non-inferior to dosing every 4 weeks (HIV-1 RNA ≥50 copies per mL; 2% *vs* 1%) with an adjusted treatment difference of 0·8 (95% CI −0·6–2·2). There were eight (2%, every 8 weeks group) and two (<1%, every 4 weeks group) confirmed virological failures (two sequential measures ≥200 copies per mL). For the every 8 weeks group, five (63%) of eight had archived non-nucleoside reverse transcriptase inhibitor resistance-associated mutations to rilpivirine at baseline. The safety profile was similar between dosing groups, with 844 (81%) of 1045 participants having adverse events (excluding injection site reactions); no treatment-related deaths occurred.

Interpretation The efficacy and safety profiles of dosing every 8 weeks and dosing every 4 weeks were similar. These results support the use of cabotegravir plus rilpivirine long-acting administered every 2 months as a therapeutic option for people living with HIV-1.

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Introduction

Advances over the past 25 years in the potency, tolerability, and dosing convenience of combination antiretroviral therapy (ART) have facilitated incremental improvements in HIV treatment effectiveness.[1] Notwithstanding these advancements, ART remains a lifelong challenge that necessitates high medication adherence to maintain viral suppression and prevent the emergence of drug

Research in context

Evidence before this study

We searched PubMed for manuscripts reporting data from clinical trials and cohort studies as well as review articles using the search terms "antiretroviral therapy", "cabotegravir", "rilpivirine", "injectable treatment", AND "long-acting treatment". Searches were carried out on Feb 14, 2020, with no date limit. On the basis of this search, although contemporary antiretroviral therapy (ART) has transformed HIV-1 infection into a chronic treatable condition, the need for daily suppressive oral therapy by itself poses substantial challenges. These challenges can be grouped in two areas: the individual challenges of lifelong daily medication adherence and the fear of stigmatisation as a result of inadvertent disclosure of HIV status, and treatment-specific challenges, including adverse effects and drug–food interactions. As a result, there is considerable interest in long-acting therapies that eliminate the need for daily dosing, thereby attenuating the psychological burden of daily ART. Data from long-acting injectable ART regimens containing cabotegravir and rilpivirine were submitted to health authorities on the basis of several published clinical studies, most notably the phase 3 ATLAS and FLAIR studies showing cabotegravir plus rilpivirine long-acting injectable formulations, dosed intramuscularly every 4 weeks, are non-inferior to daily oral ART regimens and preferred by a majority of study participants over oral therapy. Importantly, data from the phase 2b LATTE-2 study supported the evaluation of cabotegravir plus rilpivirine long-acting at longer, potentially more convenient, every 8 weeks dosing regimen.

Added value of this study

This study (ATLAS-2M) provides evidence that cabotegravir plus rilpivirine long-acting dosed every 8 weeks is non-inferior to dosing every 4 weeks for maintenance of viral suppression over a period of 48 weeks on both the primary endpoint (proportion of participants with plasma HIV-1 RNA ≥50 copies per mL) and key secondary endpoint (proportion of participants with plasma HIV-1 RNA <50 copies per mL). Patient-reported outcomes from ATLAS-2M also show a clear preference for dosing every 8 weeks over either dosing every 4 weeks or oral cabotegravir plus rilpivirine dosing. The safety profile from ATLAS-2M was consistent with that reported in ATLAS and FLAIR. Injection site reactions were common (reported after 23% of all injections); however, these decreased in frequency over the study period, were mild to moderate in intensity (98% grade 1 or 2), short in duration, and rarely caused treatment discontinuation.

Implications of all the available evidence

This study is, we believe, the first large phase 3 study to evaluate an HIV-1 treatment that consists of an injectable long-acting ART regimen with dosing every 8 weeks. The 48-week results show that the efficacy of dosing every 8 weeks is non-inferior to dosing every 4 weeks, with similar tolerability profiles in people living with HIV-1 with viral suppression. Moreover, the every 8 weeks regimen was preferred by study participants compared with dosing every 4 weeks and daily oral dosing. On the basis of the ATLAS-2M results, cabotegravir plus rilpivirine long-acting should be studied in other populations, for example adults and adolescents with adherence challenges with oral ART, as these populations might benefit from long-acting therapy. In addition, 96-week outcomes from the ATLAS-2M study will provide important data to understand long-term durability of intramuscular cabotegravir plus rilpivirine long-acting therapy.

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resistance, treatment failure, and clinical disease progression.

Guideline-recommended first-line ART regimens are largely based on the integrase strand transfer inhibitor (INSTI) class of antiretrovirals with either one or two nucleoside reverse transcriptase inhibitors (NRTIs).[2,3] Sustaining durable viral suppression remains a challenge of HIV care, in part because all available oral ART regimens have an intrinsic requirement for high levels of adherence over time, which can be affected by forgetfulness, busy lifestyle, changes to daily routine, depression, alcohol or substance misuse, and fear of disease disclosure.[4] In addition, so-called treatment fatigue results in decreasing vigilance towards maintaining adherence to chronic treatment regimens.[5] The emotional effect of living with HIV is negatively influenced by the daily dosing requirement of ART.[6] Consequently, improved ART regimens with less frequent dosing strategies remain highly desired by people living with HIV.[7]

Intense research has focused on the development of long-acting antiretroviral formulations to reduce dosing frequency.[8,9] Administration as a directly observed therapy combined with an extended dosing interval has the potential to improve long-term adherence. Cabotegravir and rilpivirine are two antiretrovirals for which long-acting, intramuscular formulations have been developed.[8,9] Cabotegravir is an INSTI in phase 3 development for HIV-1 treatment (in combination with long-acting rilpivirine) and also as a single agent for HIV-1 prevention, with both oral and long-acting intramuscular formulations.[8–10] Rilpivirine, an oral non-nucleoside reverse transcriptase inhibitor (NNRTI) approved for use as part of combination ART, is being studied as a long-acting intramuscular agent.[8,9,11] The ongoing phase 3 ATLAS (NCT02951052) and FLAIR (NCT02938520) studies evaluated the two-drug ART long-acting regimen of cabotegravir and rilpivirine (cabotegravir plus rilpivirine long-acting) dosed every 4 weeks as maintenance therapy, and showed non-inferiority of the long-acting regimen compared with continuing daily oral ART over 48 weeks (ATLAS and FLAIR) and through to 96 weeks in the FLAIR study.[8,9,12]

Longer-term clinical data from the LATTE-2 study (NCT02120352), which was the first study of cabotegravir

plus rilpivirine long-acting dosed every 4 weeks and every 8 weeks, support continued investigation of this combination regimen dosed every 8 weeks.[13] Here, we report results of a phase 3b study (ATLAS-2M) with the objective of comparing virological efficacy and safety of cabotegravir plus rilpivirine long-acting treatment dosed every 8 weeks with every 4 weeks dosing for the maintenance of viral suppression in people living with HIV-1.

Methods

Study design and participants

ATLAS-2M is a randomised, multicentre, parallel-group, open-label, phase 3b, non-inferiority study, done in 13 countries (Australia, Argentina, Canada, France, Germany, Italy, Mexico, Russia, South Africa, South Korea, Spain, Sweden, and the USA) assessing the efficacy and safety of maintenance treatment with intramuscular cabotegravir plus rilpivirine long-acting administered every 8 weeks versus every 4 weeks to adult people living with HIV-1 with viral suppression (plasma HIV-1 RNA <50 copies per mL). All participants provided written informed consent. The full study protocol is available online.[14]

Eligible participants entered the study from two groups. The first group consisted of newly recruited participants receiving an oral standard-of-care ART regimen. The second group was enrolled directly from the ATLAS study, from both the cabotegravir plus rilpivirine long-acting every 4 weeks and standard-of-care groups (figure 1A).

To be eligible, newly recruited individuals must have received an uninterrupted first or second oral standard-of-care regimen for at least 6 months, without previous virological failure (≥400 copies per mL), and not have a known INSTI or NNRTI resistance-associated mutation, except for K103N.[15] In addition to a screening plasma HIV-1 RNA <50 copies per mL and no previous virological failure, participants in this group were required to have at least two additional plasma HIV-1 RNA measurements of less than 50 copies per mL in the previous year. Eligible participants from the ATLAS trial, from both the oral standard-of-care and long-acting groups, were required to have completed the 52-week comparative phase with an ATLAS-2M screening plasma HIV-1 RNA less than 50 copies per mL. ATLAS-2M was designed to enrol at least 25% females (sex at birth). Inclusion and exclusion criteria for ATLAS-2M are provided in appendix (pp 1–5). Any participant who withdrew from long-acting intramuscular dosing entered a 52-week long-term follow-up period and started an alternative, investigator-selected antiretroviral regimen. ATLAS-2M was done in accordance with the Declaration of Helsinki.[16]

See Online for appendix

Randomisation and masking

Participants were randomly assigned 1:1 to receive cabotegravir plus rilpivirine long-acting maintenance dosing of either every 8 weeks (cabotegravir 600 mg plus rilpivirine 900 mg) or every 4 weeks (cabotegravir 400 mg plus rilpivirine 600 mg), with both agents given separately as single 3 mL (every 8 weeks) or 2 mL (every 4 weeks) injections into the gluteal muscle in an unmasked fashion (figure 1A). Randomisation was stratified by three categories of previous cabotegravir plus rilpivirine (oral plus intramuscular) exposure—0, 1–24, and greater than 24 weeks—to account for those individuals entering from the ATLAS study. Participants with no previous exposure to cabotegravir plus rilpivirine initially received 4 weeks of once-daily oral lead-in (OLI) treatment with cabotegravir 30 mg plus rilpivirine 25 mg to assess individual tolerability before long-acting administration, followed by initial loading injections (cabotegravir 600 mg plus rilpivirine 900 mg) before maintenance every 8 weeks or every 4 weeks injections.

The randomisation schedule was generated by means of the GlaxoSmithKline validated randomisation software RANDALL NG. The randomisation schedule comprised a series of blocks, with equal treatment allocation within each block, which were shared across centres via central randomisation. Randomisation and study treatment assignment were facilitated by the interactive response technology through the central Randomisation and Medication Ordering System Next Generation (RAMOS NG, BioClinica, Princeton, NJ, USA) system. Following fulfilment of study entry criteria, study site personnel registered participants by means of RAMOS NG for assignment of a unique identifier (designating the participant's randomisation code and treatment sequence assignment). A unique treatment number was assigned to each participant.

Procedures

Phenotypic and genotypic resistance (Sanger sequencing) testing for HIV-1 reverse transcriptase, protease, and integrase (Monogram Biosciences, South San Francisco, CA, USA) was done at suspected virological failure (SVF; visit before confirmed virological failure [CVF]). Archived HIV-1 resistance retrospectively found to be present at study baseline was assessed in individuals with CVF by genotypic testing (next-generation sequencing) of stored baseline peripheral blood mononuclear cells (PBMCs).

Change from baseline in total treatment satisfaction score was measured by means of the HIV Treatment Satisfaction Questionnaire (status version; HIVTSQs) at weeks 24 and 48 (or withdrawal). Results were stratified by previous cabotegravir plus rilpivirine exposure (preplanned analysis). Preference for cabotegravir plus rilpivirine every 8 weeks dosing versus previous daily oral dosing, and cabotegravir plus rilpivirine every 8 weeks dosing versus previous every 4 weeks or oral dosing, was assessed with a preference questionnaire at week 48; this consisted of three questions evaluating preference along with reasons for said preference.

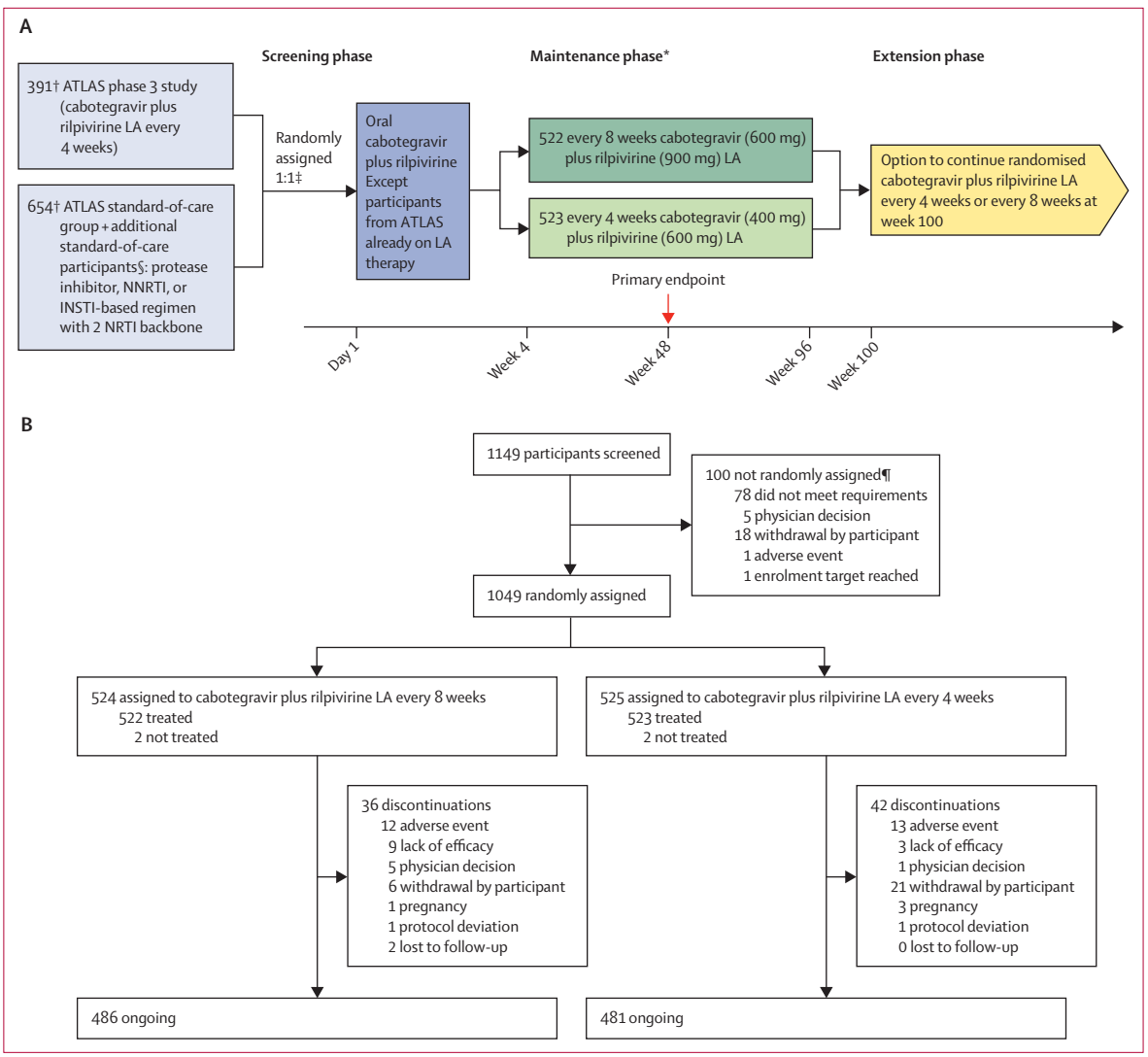


Figure 1: **Study design and participant disposition**
(A) Study design. (B) Study disposition through to week 48. INSTI=integrase strand transfer inhibitor. LA=long-acting. NNRTI=non-nucleoside reverse transcriptase inhibitor. NRTI=nucleoside reverse transcriptase inhibitor. *ATLAS participants on every 4 weeks group—transition to ATLAS-2M day 1 onwards: cabotegravir LA (400 mg) plus rilpivirine LA (600 mg) intramuscularly every 4 weeks or cabotegravir LA (600 mg) plus rilpivirine LA (900 mg) intramuscularly every 8 weeks. New ATLAS-2M participants naive to LA at day 1—all participants initiate 4-week oral lead-in followed by LA injections: every 4 weeks group—loading dose of cabotegravir LA (600 mg) plus rilpivirine LA (900 mg) intramuscularly at week 4, then cabotegravir LA (400 mg) plus rilpivirine LA (600 mg) intramuscularly every 4 weeks; every 8 weeks group—initial dose of cabotegravir LA (600 mg) plus rilpivirine LA (900 mg) at week 4 and week 8, then continue same intramuscular dose every 8 weeks. Participants who withdraw from the intramuscular regimen must go into 52-week long-term follow-up if randomised regimen is not yet locally approved and commercially available. Doses were scheduled on the basis of a fixed treatment date, and that target date of the month or every other month was carried forward. For participants transitioning from standard of care in either group and those transitioning from every 4 weeks to every 8 weeks, there was a −7-day dosing window for the second and third intramuscular injections and a ±7-day window thereafter. For those continuing every 4 week dosing from ATLAS, there was a ±7-day window for injections. †Intention-to-treat exposed population. ‡1149 participants were screened, and 1049 participants were randomly assigned. However, four participants did not receive study drug and were therefore not part of the intention-to-treat exposed population. §Standard-of-care participants not transitioning from the ATLAS study were to be on uninterrupted current regimen (either the initial or second combined ART regimen) for at least 6 months before screening. Documented evidence was required of at least two plasma HIV-1 RNA measurements <50 copies per mL in the 12 months before screening: one within the 6–12-month window, and one within 6 months before screening. Participants were excluded if they had a history of virological failure; evidence of viral resistance based on the presence of any resistance-associated major INSTI or NNRTI mutation (except K103N) from previous genotype assay results; or current or previous history of etravirine use. ¶Participants may have more than one reason for failure.

Blood samples for pharmacokinetic assessment of cabotegravir and rilpivirine plasma concentrations were drawn before the first intramuscular injection (day 1 in those with previous cabotegravir plus rilpivirine exposure or week 4 at the end of OLI for those without previous exposure) and predose in both the every 8 weeks and every 4 weeks dosing groups at weeks 8, 16, 24, 32, 40, and 48, or at withdrawal.

Outcomes

The primary objective was to compare the week 48 antiviral efficacy of cabotegravir plus rilpivirine long-acting dosed every 8 weeks with that of every 4 weeks dosing. The primary efficacy endpoint was the proportion of participants with plasma HIV-1 RNA ≥50 copies per mL at week 48 in the intention-to-treat exposed (ITT-E) population, per the US Food and Drug Administration's Snapshot algorithm.[17]

The key secondary efficacy endpoint was the proportion of participants with plasma HIV-1 RNA less than 50 copies per mL at week 48 (ITT-E; Snapshot algorithm). Other secondary efficacy endpoints included the proportion of participants with CVF (two consecutive plasma HIV-1 RNA measurements ≥200 copies per mL) through to the week 48 analysis; incidence of treatment-emergent genotypic and phenotypic resistance in participants having CVF; and absolute values and changes from baseline in plasma HIV-1 RNA and $CD4^+$ cell counts over time. A preplanned exploratory analysis of the primary and key secondary efficacy endpoints by subgroup included age, sex at birth, body-mass index category, and duration of previous cabotegravir plus rilpivirine long-acting exposure.

Secondary endpoints included plasma pharmacokinetic parameters for cabotegravir long-acting and rilpivirine long-acting (when evaluable, C_{trough}, concentrations post dose [approximately C_{max}], and area under the curve [AUC]), preference for cabotegravir long-acting plus rilpivirine long-acting every 8 weeks and cabotegravir long-acting plus rilpivirine long-acting every 4 weeks compared with oral antiretroviral therapy and preference for cabotegravir long-acting plus rilpivirine long-acting every 8 weeks compared with cabotegravir long-acting plus rilpivirine long-acting every 4 weeks and change from baseline (day 1) in total treatment satisfaction score, and the safety parameters: incidence and severity of adverse events, laboratory abnormalities, changes in laboratory parameters over time, and discontinuations due to adverse events through to week 48 (nominal cutoff point—contains data collected for participants with dosing beyond week 48). Adverse events and laboratory abnormalities were graded per the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (version 2.1).[18] In addition to the preplanned analysis of PBMC DNA for those with CVF, a post-hoc PBMC DNA analysis of stored whole blood at baseline was done.

Statistical analysis

The primary analysis was based on the ITT-E population and the primary comparison was made at a one-sided 2·5% level of significance. The differences between the randomised treatment groups and associated 95% CIs for the primary and key secondary efficacy endpoints at week 48 were calculated by means of a stratified Cochran-Mantel-Haenszel analysis adjusted for previous exposure to cabotegravir plus rilpivirine long-acting (0, 1–24, or >24 weeks). Non-inferiority of dosing every 8 weeks to dosing every 4 weeks was shown in the primary efficacy analysis if the upper boundary of the 2-sided 95% CI of the Cochran-Mantel-Haenszel-adjusted difference in proportion of participants with plasma HIV-1 RNA ≥50 copies per mL in the ITT-E Snapshot analysis at week 48 was below 4%.

In the secondary efficacy analysis, non-inferiority of dosing every 8 weeks to dosing every 4 weeks was shown if the lower boundary of the 95% CI about the Cochran-Mantel-Haenszel-adjusted difference in proportion of participants with plasma HIV-1 RNA <50 copies per mL in the ITT-E Snapshot analysis at week 48 was above –10%. A sensitivity analysis of the primary and key secondary efficacy endpoints was done by means of the same analytical procedure on the basis of the per-protocol subset of the ITT-E population without any major protocol violations.

Homogeneity of the treatment differences between study groups was examined across subgroups of participants on the basis of previous exposure to cabotegravir plus rilpivirine (0, 1–24, >24 weeks) by means of weighted least squares χ-squared statistics and a one-sided 10% level of significance. The 95% CIs for the treatment differences of the primary and key efficacy endpoints by demographic and baseline characteristic subgroups were calculated by means of an unconditional exact method based on the two inverted one-sided tests.

For the primary efficacy endpoint, a sample size of 510 participants per group provided at least 85% power to show non-inferiority of dosing every 8 weeks for the proportion of participants with plasma HIV-1 RNA ≥50 copies per mL at week 48 at a 4% margin, by means of a 2·5% one-sided significance level and assuming population-level proportions of 3% in the every 8 weeks group and 2% in the every 4 weeks group, as suggested by earlier data from the phase 2b LATTE-2 study.[13] Assuming the observed proportion of participants with plasma HIV-1 RNA at least 50 copies per mL in the every 4 weeks group was 2%, the largest observed treatment difference to achieve non-inferiority at a 4% margin with this sample size is 1·92%.

For the key secondary efficacy endpoint, a sample size of 510 participants per group provided at least 90% power to show non-inferiority of dosing every 8 weeks for the proportion of participants with plasma HIV-1 RNA less than 50 copies per mL at week 48 at a –10% margin, by means of a 2·5% one-sided significance level and a population-level every 8 weeks versus every 4 weeks treatment difference of up to approximately 3%. Assuming a 92% population-level proportion with plasma HIV-1 RNA less than 50 copies per mL in both treatment groups at week 48, based on data from LATTE-2, there was at least 99% power to show non-inferiority. An independent data monitoring committee provided external medical and statistical review of efficacy and safety data. ATLAS-2M is registered with ClinicalTrials.gov, NCT03299049.

Role of the funding source

The funders participated in the data collection, data analysis, data interpretation, writing of the report, and in the decision to submit for publication. All authors vouch for the accuracy and completeness of the data, data analyses, and interpretation and fidelity to the protocol, and approved the final manuscript for submission.

Results

A total of 1149 individuals were screened between Oct 27, 2017, and May 31, 2018; 1049 were randomly assigned. Two individuals in each group were not treated (withdrawal by participant, n=3; physician decision, n=1) resulting in an overall ITT-E population of 1045 (every 8 weeks, n=522; every 4 weeks, n=523). Baseline characteristics of the ITT-E population are shown in table 1. Participants were mostly white (763 [73%] of 1045), with a median age of 42 years (IQR 34–50), 280 [27%] of 1045 were female at birth, and the median CD4⁺ count was 661 cells per µL (IQR 508–849). Overall, 391 (37%) of 1045 participants entered ATLAS-2M having previously received cabotegravir plus rilpivirine long-acting every 4 weeks in ATLAS (≥1 long-acting injection), most of whom (254 [65%] of 391) had greater than 24 weeks of previous exposure.

Overall, there were 78 treatment discontinuations (every 8 weeks, 36 [7%] of 522; every 4 weeks, 42 [8%] of 523; figure 1B). Discontinuation rates owing to adverse events were infrequent and without distinguishing patterns of adverse event types between the every 8 weeks (12 [2%] of 524) and every 4 weeks groups (13 [2%] of 525). Participant disposition, with reasons for discontinuation, is shown in figure 1B. A summary of important protocol deviations is provided in the appendix (p 6). Overall, there were 15 (1%) of 1045 exclusions from the per-protocol population, the reasons for which are provided in the appendix (p 7).

In the every 8 weeks dosing group, 3641 (98%) of 3719 injections were administered within the protocol-specified 7 days of the planned visit and in the every 4 weeks dosing group, 7238 (99%) of 7346 injections were administered within the protocol-specified 7 days of the planned visit. In total, eight injection visits were substituted (every 8 weeks, n=1; every 4 weeks, n=7) with pre-emptively administered oral cabotegravir plus rilpivirine bridging therapy to cover the period following the planned long-acting dosing interruption. All participants resumed long-acting dosing, except one (every 8 weeks group) who withdrew owing to a non-serious adverse event (injection site discomfort). No cases of CVF or virological blips were observed during the period of oral therapy or following resumption of cabotegravir plus rilpivirine long-acting dosing.

At week 48 (Snapshot algorithm), nine (2%) of 522 participants in the every 8 weeks dosing group and five (1%) of 523 in the every 4 weeks dosing group had plasma HIV-1 RNA ≥50 copies per mL, with an adjusted

	Every 8 weeks group (n=522)	Every 4 weeks group (n=523)
Age, years	42·0 (34–51)	42·0 (34–50)
Sex at birth		
Female	137 (26%)	143 (27%)
Male	385 (74%)	380 (73%)
Participant-reported gender		
Female	142 (27%)	146 (28%)
Male	380 (73%)	377 (72%)
Race		
White	370 (71%)	393 (75%)
Black or African American	101 (19%)	90 (17%)
Other	51 (10%)	40 (8%)
Hispanic or Latino ethnicity	71 (14%)	65 (12%)
Previous antiretroviral therapy*		
Non-nucleoside reverse transcriptase inhibitor	368 (70%)	382 (73%)
Integrase strand transfer inhibitor	334 (64%)	341 (65%)
Protease inhibitor	115 (22%)	111 (21%)
Body-mass index, kg/m²	25·7 (23·0–29·1)	25·9 (23·1–28·9)
Range	17·8–48·3	16·6–77·5
≥30	113 (22%)	98 (19%)
Weight, kg	77·5 (68·7–88·0)	78·0 (69·0–88·7)
Previous exposure to cabotegravir plus rilpivirine long-acting†		
None	327 (63%)	327 (63%)
1–24 weeks	69 (13%)	68 (13%)
>24 weeks	126 (24%)	128 (24%)
CD4⁺ cell count, cells per µL	642 (499–827)	688 (523–878)
CD4⁺ cell category, cells per µL		
<350	35 (7%)	27 (5%)
350 to <500	96 (18%)	89 (17%)
≥500	391 (75%)	407 (78%)
Co-infection		
Hepatitis B virus‡	2 (<1%)	1 (<1%)
Hepatitis C virus	5 (1%)	6 (1%)
Laboratory parameters		
Alanine aminotransferase, IU/L	19·0 (14·0–27·0)	20·0 (14·0–26·0)
Aspartate aminotransferase, IU/L	21·0 (17·0–26·0)	21·0 (17·0–25·0)
Total bilirubin, µmol/L	8·0 (6·0–12·0)	8·0 (6·0–12·0)
Triglycerides, mmol/L	1·18 (0·82–1·66)	1·10 (0·80–1·63)
Total cholesterol, mmol/L	4·75 (4·10–5·60)	4·78 (4·15–5·45)
HDL cholesterol, mmol/L	1·30 (1·15–1·65)	1·35 (1·10–1·65)

Data are n (%) or median (IQR). *The median (IQR) duration of previous antiretroviral therapy exposure was 58 months (36–89) in the every 8 weeks and 58 months (37–92) in the every 4 weeks dosing groups. Previous antiretroviral therapy exposure represents overall exposure, not just the previous regimen. †The median (IQR) overall previous cabotegravir plus rilpivirine exposure was 76 days (65–92) for participants with 1–24 weeks of previous exposure in the every 8 weeks dosing group and 68 days (64–91) for participants with 1–24 weeks of previous exposure in the every 4 weeks dosing group (post-hoc analysis). Overall exposure includes oral lead-in. ‡On further testing, these three individuals were not considered to have active hepatitis B co-infection and participated in the study on the basis of clinical determination.

Table 1: **Baseline demographic and disease characteristics**

	Every 8 weeks group (n=522)	Every 4 weeks group (n=523)	Difference in proportion* (95% CI)	Adjusted† difference in proportion (95% CI)
Intention-to-treat exposed analysis				
Plasma HIV-1 RNA <50 copies per mL (key secondary endpoint)‡	492 (94%)	489 (93%)	0·8 (–2·2 to 3·7)	0·8 (–2·1 to 3·7)
Plasma HIV-1 RNA ≥50 copies per mL (primary endpoint)§				
Total	9 (2%)	5 (1%)	0·8 (–0·6 to 2·2)	0·8 (–0·6 to 2·2)
Data in window not below threshold	3 (1%)	2 (<1%)	..	..
Discontinued for lack of efficacy	6 (1%)	2 (<1%)	..	..
Discontinued for other reason while not below threshold	0	1 (<1%)	..	..
Change in background therapy	0	0	..	..
No virological data				
Total	21 (4%)	29 (6%)	..	..
Discontinued study due to adverse event or death	9 (2%)	13 (2%)	..	..
Discontinued study for other reasons	12 (2%)¶	16 (3%)‖	..	..
On study but missing data in window	0	0	..	..
Per-protocol analysis				
Plasma HIV-1 RNA ≥50 copies per mL	7/516 (1%)	5/514 (1%)	0·4 (–0·9 to 1·7)	0·4 (–0·9 to 1·7)
Plasma HIV-1 RNA <50 copies per mL	491/516 (95%)	484/514 (94%)	1·0 (–1·8 to 3·7)	1·0 (–1·7 to 3·7)
Test for homogeneity by stratum for plasma HIV-1 RNA ≥50 copies per mL				
Previous exposure to cabotegravir plus rilpivirine, weeks				
0	5/327 (2%)	5/327 (2%)	0·0 (–2·2 to 2·2)	..
1–24	3/69 (4%)	0/68	4·3 (–1·3 to 12·3)	..
>24	1/126 (1%)	0/128	0·8 (–2·2 to 4·4)	..
p value for test of homogeneity**	..	..	0·35	..
Test for homogeneity by stratum for plasma HIV-1 RNA <50 copies per mL				
Previous exposure to cabotegravir plus rilpivirine, weeks				
0	306/327 (94%)	300/327 (92%)	1·8 (–2·3 to 6·0)	..
1–24	66/69 (96%)	65/68 (96%)	0·1 (–8·3 to 8·6)	..
>24	120/126 (95%)	124/128 (97%)	–1·6 (–7·4 to 3·7)	..
p value for test of homogeneity**	..	..	0·55	..

*Difference: proportion on cabotegravir plus rilpivirine every 8 weeks minus proportion on cabotegravir plus rilpivirine every 4 weeks. †Cochran-Mantel-Haenszel stratified analysis adjusting for previous cabotegravir plus rilpivirine long-acting exposure (0, 1–24, or >24 weeks). ‡Non-inferiority was determined if the lower bound of the 95% CI about the adjusted every 8 weeks–every 4 weeks difference was above –10%. §Non-inferiority was determined if the upper bound of the 95% CI about the adjusted every 8 weeks–every 4 weeks difference was below 4%. ¶Lost to follow-up, two participants; withdrawal by participant, four participants; protocol deviation, one participant; investigator decision, four participants; lack of efficacy, one participant. ‖Protocol-specified withdrawal criteria met (pregnancy), three participants; withdrawal by participant, 12 participants; protocol deviation, one participant. **One-sided p value from weighted least squares χ^2-statistic. A p value <0·10 indicates significant evidence of heterogeneity in the difference in proportions across levels of each analysis stratum.

Table 2: **Primary and key secondary efficacy endpoints at week 48 (Snapshot algorithm)**

treatment difference in proportions of 0·8 (95% CI –0·6–2·2), thus meeting the prespecified non-inferiority criterion of the primary endpoint (table 2; appendix p 15). Similarly, the prespecified non-inferiority criterion of the key secondary efficacy endpoint of plasma HIV-1 RNA <50 copies per mL at week 48 (Snapshot algorithm) was met, with 492 (94%) of 522 participants in the every 8 weeks group and 489 (93%) of 523 in the every 4 weeks group, maintaining viral suppression (adjusted treatment difference in proportions: 0·8 [–2·1–3·7]). The test of evidence against homogeneity of the treatment difference was not significant for previous exposure to cabotegravir plus rilpivirine for either the primary (p=0·35) or secondary efficacy analysis (p=0·55; table 2). The per-protocol sensitivity analyses were consistent with both the primary and key secondary ITT-E analyses (table 2). Treatment differences in the primary and key secondary efficacy endpoints by demographic and baseline characteristic subgroups were generally similar between treatment groups (appendix p 17–18). The median (IQR) change from baseline to week 48 in $CD4^+$ count was 5·0 (–74·0 to 91·0) in the every 8 weeks group and –8·0 (–114·0 to 62·0) in the every 4 weeks group.

There were ten cases of CVF through to 48 weeks: eight in the every 8 weeks group and two in the every 4 weeks group. Viral subtypes observed in CVF participants at SVF were A (n=2), A1 (n=2), B (n=4), C (n=1), and complex (n=1). The majority of CVF cases in the every 8 weeks group (seven [88%] of eight) occurred within the first 24 weeks, whereas the two cases in the every 4 weeks group occurred at weeks 16 and 32. Most participants (seven [70%] of ten) developing CVF had no exposure to cabotegravir plus rilpivirine before enrolling in this study. The remaining three participants with CVF (all every 8 weeks group) received cabotegravir plus rilpivirine (OLI followed by long-acting) for 8, 9, and 13 weeks in the ATLAS study, resulting in a cumulative exposure to cabotegravir plus rilpivirine at the SVF visit of 16, 33, and 61 weeks, respectively.

Genotypic and phenotypic resistance data at baseline and SVF timepoints for the ten participants with CVF are shown in the appendix (pp 8–10). In total, five (63%) of eight participants with CVF in the every 8 weeks dosing group had archived NNRTI resistance-associated mutations to rilpivirine (Y181C plus H221Y; Y188Y/F/H/L; Y188L; E138A; and E138E/A) in baseline PBMC samples, either alone (n=4) or in combination with an archived major INSTI resistance-associated mutation (G140G/R, n=1). Neither of the two every 4 weeks participants with CVF were found to harbour baseline INSTI or NNRTI mutations.

At the time of SVF in the every 8 weeks group, six participants had rilpivirine resistance-associated mutations (three participants had a rilpivirine resistance-associated mutation that was not present at baseline, per archived DNA analysis), corresponding to a greater than two-times reduced susceptibility to rilpivirine. Five of these six also had INSTI-associated mutations, with between a 1·8-times and 9·1-times reduced susceptibility to cabotegravir. The INSTI genotypic and phenotypic

	Every 8 weeks group (n=522)	Every 4 weeks group (n=523)
Any event	473 (91%)	482 (92%)
Excluding ISRs	403 (77%)	441 (84%)
Discontinuations because of adverse events		
Total	12 (2%)	13 (2%)
Excluding ISRs	8 (2%)	10 (2%)
Discontinuations because of drug-related adverse events		
Total	8 (2%)	11 (2%)
Excluding ISRs	5 (1%)	8 (2%)
Serious adverse events		
Total	27 (5%)	19 (4%)
Excluding ISRs	26 (5%)	19 (4%)
Adverse event maximum grade		
1–2	432 (83%)	433 (83%)
3	38 (7%)	43 (8%)
4	2 (<1%)	6 (1%)
5 (death)	1 (<1%)*	0
Grade 3–4 laboratory abnormalities		
Alanine aminotransferase	2 (<1%)	5 (1%)
Aspartate aminotransferase	3 (1%)	6 (1%)
Total bilirubin	2 (<1%)	2 (<1%)
Triglycerides	4 (1%)	4 (1%)
Total cholesterol	2 (<1%)	3 (1%)
Low-density lipoprotein cholesterol	9 (2%)	4 (1%)
Common non-injection site adverse events (≥5%)		
Nasopharyngitis	71 (14%)	74 (14%)
Upper respiratory tract infection	50 (10%)	71 (14%)
Pyrexia	28 (5%)	44 (8%)
Headache	35 (7%)	36 (7%)
Diarrhoea	33 (6%)	37 (7%)
Back pain	28 (5%)	29 (6%)
Cough	17 (3%)	29 (6%)
Fatigue	13 (2%)	33 (6%)
Gastroenteritis	16 (3%)	28 (5%)
Pharyngitis	16 (3%)	28 (5%)

(Table 3 continues in next column)

(Continued from previous column)

	Every 8 weeks group (n=522)	Every 4 weeks group (n=523)
Participants who received ≥1 injection of study drug	(n=516)	(n=517)
Participants with ISR event	392 (76%)	390 (75%)
Maximum grade or intensity		
Mild or grade 1	364 (71%)	362 (70%)
Moderate or grade 2	140 (27%)	143 (28%)
Severe or grade ≥3†	14 (3%)	21 (4%)
Serious ISR	1 (<1%)	0
Discontinuations owing to injection-related reasons‡	6 (1%)	11 (2%)
Participants with ISRs (≥5% as reported)		
Pain	371 (72%)	363 (70%)
Nodule	54 (10%)	89 (17%)
Induration	41 (8%)	39 (8%)
Discomfort	36 (7%)	41 (8%)
Swelling	32 (6%)	27 (5%)
Pruritus	27 (5%)	25 (5%)

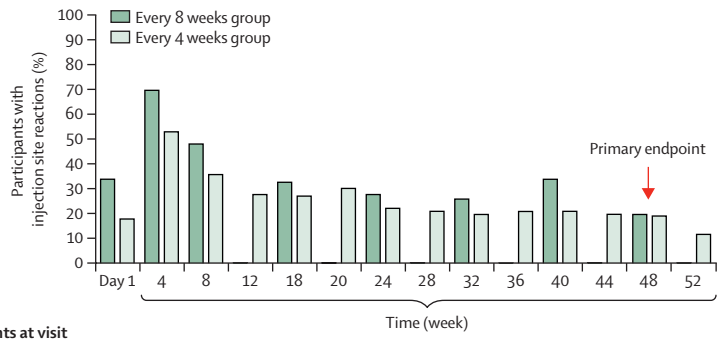
Data are n (%), where n is the number of affected participants. ISR=injection site reaction. *Sepsis; death was not considered to be related to study drug. †There were no potentially life threatening or grade 4 events, or death or grade 5 events. ‡Every 8 weeks, five participants had an ISR leading to withdrawal and one participant withdrew consent from the study owing to injection intolerability; every 4 weeks, five participants had an ISR leading to withdrawal and six participants withdrew consent from the study due to injection intolerability.

Table 3: **Adverse event summary**

data could not be obtained for one participant and the cabotegravir phenotype was unavailable in another. In the every 4 weeks dosing group at the SVF timepoint, both participants with CVF also had either rilpivirine resistance-associated mutations, which conferred a 17-times reduced rilpivirine susceptibility, or an NNRTI polymorphism, which conferred a greater than 100-times reduced rilpivirine susceptibility. These participants also had INSTI resistance-associated mutations conferring a 1·77-times and 4·56-times reduced susceptibility to cabotegravir. Additionally, in the every 8 weeks dosing group, five [63%] of eight participants had an L74I or L74L/I polymorphism at baseline (three of five subtype A or A1 [one of five A, two of five A1], one of five subtype C, and one of five subtype complex). All participants with available INSTI integrase phenotype data maintained phenotypic susceptibility to dolutegravir (Monogram clinical cutoff for dolutegravir=4·0-times change). At the time of SVF, plasma cabotegravir and rilpivirine plasma concentrations for participants with CVF were within the range of cabotegravir and rilpivirine plasma concentrations for the overall study population (appendix pp 8–10). On switching to an alternative regimen, nine (90%) of ten participants with CVF achieved viral resuppression during long-term follow-up.

During the OLI period for participants naive to cabotegravir plus rilpivirine, 209 (32%) of 655 participants had adverse events, of which five (2%) were serious adverse events (none considered related to study drug). Four participants discontinued owing to adverse events, reasons for which, along with common adverse events occurring in at least 1% of participants, are listed in the appendix (p 11).

Overall, cabotegravir plus rilpivirine long-acting was well tolerated in both dosing groups; the majority (865 [91%] of 955) of adverse events were mild (grade 1) or moderate (grade 2) in severity, and 25 (2%) of 1045 participants discontinued treatment owing to an adverse event (table 3). Except for fatigue, abnormal dreams, and hyperhidrosis (all every 4 weeks group), no individual adverse event resulted in discontinuation in more than one participant per treatment group. There



Participants at visit														
Every 8 weeks group	194	321	514	NA	511	NA	502	NA	496	NA	495	NA	493	NA
Every 4 weeks group	196	515	515	513	508	502	503	502	499	492	491	490	488	476

Figure 2: **Incidence of injection site reactions**
Day 1 assessment included only participants with previous cabotegravir plus rilpivirine exposure randomised to continue long-acting injections (every 8 weeks or every 4 weeks). NA=not available.

was a single on-study death from sepsis in a participant from the every 8 weeks dosing group that was considered unrelated to study medication by the site investigator. The sepsis was a late sequela of severe pancreatitis reported as possibly related to study drug by the investigator. One further participant died during screening before receiving study drug (haemorrhage from cerebral aneurysm). Excluding injection site reactions, the most common adverse events were minor infections and general conditions occurring at similar rates in each group (table 3). Only nasopharyngitis (145 [14%] of 1045) and upper respiratory tract infection (121 [12%] of 1045) occurred in at least 10% of participants across both treatment groups. No clinically relevant patterns or differences were observed in clinical laboratory abnormalities, for either chemistry or haematology, between the treatment groups.

Injection site reactions, particularly injection site pain, were the most common adverse events. There were 5659 injection site reactions in total, 2507 (44%) of which occurred with every 8 weeks dosing, representing 2507 (30%) of 8470 injections in the every 8 weeks group, and 3152 (56%) occurred with every 4 weeks dosing, representing 3152 (20%) of 15711 injections in the every 4 weeks group (appendix p 12). However, the severity and duration of injection site reactions was similar in both groups, with the majority being grade 1 or 2 (5568 [98%] of 5659 overall), and most (86% [every 8 weeks, 2155 of 2507; every 4 weeks, 2717 of 3152] in both groups) resolving within 7 days (median 3 days). Discontinuation because of injection-related reasons occurred in six (1%) of 522 participants in the every 8 weeks group and 11 (2%) of 523 participants in the every 4 weeks group (table 3). Participants in the every 8 weeks group with previous cabotegravir plus rilpivirine exposure in ATLAS had lower injection site reaction reporting after first injection visit compared with those without previous exposure (65 [34%] of 194 *vs* 225 [70%] of 321), consistent with the reduced ISR rates over time noted in ATLAS. Injection site reaction reporting decreased with time in both groups and, by week 48, the proportion of participants reporting injection site reactions was similar in the two groups (every 8 weeks, 98 [20%] of 493; every 4 weeks, 95 [19%] of 488; figure 2). Overall, 392 [76%] of 516 participants with injections in the every 8 weeks and 390 [75%] of 517 participants with injections in the every 4 weeks groups had at least one injection site reaction event. Participants in both groups had a median of three injection site reaction events each (every 8 weeks IQR, 1–8; every 4 weeks, 1–9).

Both the every 8 weeks and every 4 weeks groups had a median increase in weight of 1·0 kg (every 8 weeks IQR, –1·0 to 3·2; every 4 weeks, –1·0 to 3·0) at week 48 from baseline (median every 8 weeks, 77·5 kg; every 4 weeks, 78·0 kg). Changes in body-mass index from baseline are shown in the appendix (p 13). 18 participants had alanine aminotransferase elevations of at least three times the upper limit of the normal range (appendix p 14). Grade 3 or 4 treatment-emergent alanine aminotransferase abnormalities were observed in two (<1%) participants in the every 8 weeks group and five (1%) in the every 4 weeks group. At baseline and week 48, electrocardiogram data identified no QT prolongation to greater than 500 ms by means of Bazett's method (QTcB) or Fridericia's method (QTcF). At week 48, change from baseline for QTcB interval was greater than 60 ms for four participants in the every 4 weeks group, and change from baseline for QTcF interval was greater than 60 ms for one participant in the every 4 weeks group; none of these changes were clinically relevant.

Week 48 predose geometric mean (95% CI CVb%) plasma cabotegravir concentrations were 1·67 µg/mL (1·58–1·75; 52%) in the every 8 weeks dosing group, and 2·74 µg/mL (2·63–2·85; 41%) in the every 4 weeks dosing group. Week 48 predose geometric mean (CVb%) plasma rilpivirine concentrations were 73·1 ng/mL (69·7–76·6; 48%) in the every 8 weeks group and 97·5 ng/mL (93·3–102; 46%) in the every 4 weeks group. Week 48 concentrations were 64% higher for cabotegravir and 33% higher for rilpivirine following every 4 weeks administration compared with every 8 weeks administration; concentrations were approximately ten times the cabotegravir protein-adjusted concentration required for 90% virus inhibition (PA-IC_{90}) of 0·166 µg/mL in the every 8 weeks groups and 17 times PA-IC_{90} in the every 4 weeks group. Week 48 concentrations were six times the rilpivirine PA-IC_{90} of 12 ng/mL in the every 8 weeks and eight times the rilpivirine PA-IC_{90} in the every 4 weeks group (appendix p 21). These concentrations are similar to those reported following long-acting administration in the FLAIR, ATLAS, and LATTE-2 studies[8,9,13] and following oral cabotegravir (10 mg once daily) and rilpivirine (25 mg once daily) in the LATTE study.[19]

In participants without previous exposure to cabotegravir plus rilpivirine, HIVTSQs total score improved from baseline at weeks 24 and 48 for both the

every 8 weeks and every 4 weeks dosing groups (adjusted mean change [SE] from baseline, week 24, every 8 weeks, 5·07 [0·361]; every 4 weeks, 4·00 [0·359]; week 48, every 8 weeks, 4·86 [0·424]; every 4 weeks, 3·12 [0·422] points). For the adjusted mean change from baseline in total HIVTSQs, every 8 weeks dosing was significantly favoured compared with every 4 weeks dosing (adjusted difference [SE], week 24, 1·1 [0·510], p=0·036; week 48, 1·7 [0·600], p=0·004). In participants with previous exposure to cabotegravir plus rilpivirine, treatment satisfaction was high at baseline (62·22 of 66 [SD 5·41] points for the every 8 weeks group and 61·98 of 66 [SD 6·72] for the every 4 weeks group) and was maintained through to weeks 24 and 48. Of participants randomly assigned to every 8 weeks dosing without previous exposure to cabotegravir plus rilpivirine, 300 [98%] of 306 respondents to the preference survey preferred every 8 weeks dosing over daily oral dosing of cabotegravir plus rilpivirine. Of participants randomly assigned to every 8 weeks dosing with previous exposure to cabotegravir plus rilpivirine, 179 [94%] of 191 respondents preferred every 8 weeks dosing over both daily oral and every 4 weeks dosing (appendix p 22).

Discussion

Cabotegravir plus rilpivirine long-acting is the first complete long-acting HIV treatment regimen, which might facilitate improved adherence and treatment satisfaction by providing an alternative option to daily oral dosing. Cabotegravir plus rilpivirine long-acting dosed every 8 weeks was highly efficacious and non-inferior to dosing every 4 weeks on the basis of both primary (plasma HIV-1 RNA ≥50 copies per mL) and key secondary (plasma HIV-1 RNA <50 copies per mL at week 48) efficacy endpoints. At week 48, 94% (every 8 weeks, n=492; every 4 weeks, n=489) of participants had maintained plasma HIV-1 RNA less than 50 copies per mL in both dosing regimens. Non-inferiority was shown irrespective of previous cabotegravir plus rilpivirine exposure (0, 0–24, or >24 weeks). Importantly, and unseen in recent pivotal clinical studies,[20–23] ATLAS-2M enrolled 280 (27%) of 1045 females (sex at birth), reaching protocol-defined targets for female enrolment, with 18% of the overall population being Black or African American. Furthermore, the study maintained an overall participant retention rate of 967 (at least 93%) of 1045 throughout the 48-week study period.

Overall, a low rate of CVF was observed, occurring in ten (1%) of 1045 participants through to week 48. Nine out of ten participants with CVF achieved viral resuppression on oral ART with protease inhibitor-based or INSTI-based regimens. The remaining participant who failed to achieve viral re-suppression reported poor adherence to a boosted protease inhibitor regimen. It is noteworthy that all nine participants who had CVF (with available INSTI integrase phenotype data) retained phenotypic sensitivity to dolutegravir (see appendix p 8).

Participants with a known history of treatment failure and primary resistance based on the presence of major INSTI or NNRTI resistance-associated mutations were excluded from the study; however, baseline PBMC DNA analysis of stored whole blood revealed the presence of pre-existing rilpivirine resistance-associated mutations in five (50%) of ten participants (all in the every 8 weeks group), one of whom also had a major INSTI resistance-associated mutation. Although two (40%) of five of these participants have previous NNRTI exposure that might have selected NNRTI-associated mutants, previous transmission of resistance mutations cannot be ruled out for these five participants with viral DNA NNRTI or INSTI RAMs at baseline. A further post hoc PBMC analysis also showed five (50%) of ten CVFs had the L74I INSTI polymorphism at baseline. Previous in vitro work has shown no differential sensitivity to cabotegravir between subtype A1 or B viruses with the L74I polymorphism.[24] However, it is unknown whether HIV subtype A1 with L74I has a greater likelihood of selecting additional INSTI mutations under selection pressure. Further research is ongoing to understand how the interplay of viral and participant factors influence virological response to cabotegravir plus rilpivirine long-acting therapy.

Adverse events were similar between the two dosing schedules and consistent with those reported in previous studies.[8,9] Drug-related serious adverse events were rare, occurring in less than 1% of participants in both groups. The number of participants having injection site reactions was similar across both treatment groups and, consistent with findings reported in the ATLAS and FLAIR studies, were mostly mild, self-resolving pain that was short in duration. The low number of participants who discontinued treatment for injection-related reasons suggests good overall injection tolerability. There was a greater proportion of ISRs relative to number of injections given in the every 8 weeks group compared with the every 4 weeks group. This could be explained by the larger injection volume (3 mL) with every 8 weeks dosing; however, this finding should be balanced against the fact that every 2 month dosing requires half the injection frequency.

Participants adhered well to the planned treatment schedule, with few injections administered outside of the allowable treatment window (±7 days), and the few participants with a planned interruption in injection dosing were covered with oral cabotegravir plus rilpivirine bridging. This is advantageous for future use of cabotegravir plus rilpivirine long-acting in clinical practice, in exceptional circumstances, as it supports temporary use of oral bridging to cover planned interruptions in injection dosing.[25,26]

Week 48 plasma cabotegravir and rilpivirine concentrations were higher in participants in the every 4 weeks group compared with the every 8 weeks group, with the lowest concentrations observed at the first post-injection trough (week 8) for both regimens. Only one participant

with CVF in each group had week 8 cabotegravir and rilpivirine concentrations below the fifth percentiles observed in successfully treated participants (appendix pp 19–20). No clear trend in drug pharmacokinetics was observed in participants with CVF in the every 8 weeks group, suggesting that factors other than or in addition to drug concentrations played a role in virological outcomes. Although diverging from the every 4 weeks group after week 8, cabotegravir and rilpivirine concentrations following every 8 weeks administration remained well above their respective PA-IC_{90} values and were consistent with the every 8 weeks dosing group in the LATTE-2 study (appendix p 21).[13] Further, geometric mean plasma cabotegravir troughs at week 48 were similar to or higher than the mean trough following oral cabotegravir 10 mg (previously shown to be efficacious in the LATTE study), regardless of dosing group, whereas mean plasma rilpivirine troughs were similar to those following oral rilpivirine 25 mg in both dosing groups.[19]

Preference and treatment satisfaction strongly favours cabotegravir plus rilpivirine long-acting over daily oral treatment in this study and is consistent with the findings of the ATLAS and FLAIR studies.[8,9] In addition, ATLAS-2M shows that every 8 weeks dosing was preferred over every 4 weeks dosing in those with experience of both regimens. The high treatment satisfaction reported by participants in both treatment groups is complemented by the low numbers of discontinuations seen through to week 48.

The absence of masked therapy in this study is a limitation; however, it would have been intensive and impractical to incorporate into the study design. In addition, the absence of an oral standard-of-care comparator group prohibits direct comparison of outcomes with oral therapy, which can only be inferred through reference to the ATLAS and FLAIR phase 3 studies (which showed non-inferiority of cabotegravir plus rilpivirine long-acting dosed every 4 weeks *vs* standard of care). When comparing the safety data of the two treatment groups, it should be noted that adverse events in the every 4 weeks group might have been more frequently reported owing to the increased number of clinical assessments, although under-reporting by participants with greater than 48 weeks of previous cabotegravir plus rilpivirine exposure could also have occurred. Furthermore, although cabotegravir plus rilpivirine long-acting could be more beneficial to those with treatment adherence issues, this has yet to be specifically examined in a population with such challenges. Further investigation of cabotegravir plus rilpivirine long-acting in a population with historical suboptimal adherence is ongoing with the LATITUDE study (NCT03635788).[27] In addition, adherence to clinic visits and long-acting therapy among a real-world population has yet to be described.

This study shows that cabotegravir plus rilpivirine long-acting given every 8 weeks is as effective and well-tolerated as every 4 weeks dosing for maintaining HIV-1 viral suppression and is a therapeutic alternative to daily oral treatment in people living with HIV-1. Cabotegravir plus rilpivirine long-acting dosed every 8 weeks is highly preferred by participants and has the potential to improve treatment convenience, adherence, and quality of life for people living with HIV-1 by reducing both frequency of treatment (to only six doses per year) and the daily reminder of disease status that comes with oral therapy.

Contributors

ETO, GRic, GRiz, HJ, CO, FN, FB, MGD, SS, JFA-V, AW, M-AK-J, PB, KJH, and DAM were study investigators or participated in the conduct of the study, including recruitment and follow-up of participants. RVS-R, VvE, HC, SF, CT, PB, YW, KJH, VC, AC, PP, MS, DAM, KYS, SV, and WS participated in the analysis of the study data, and the conceptualisation and design of the studies. All authors were involved in the drafting and review of the manuscript and approved the final version.

Declaration of interests

ETO has received research support to his institution during the conduct of this study, and has served as a consultant for Gilead, Merck, Theratechnologies, and ViiV Healthcare, outside of the submitted work. GRic received grants from Gilead, Merck, TaiMed, and ViiV Healthcare, outside the submitted work. GRiz has received grants and personal fees from Gilead, MSD, and ViiV Healthcare; grants from Janssen, outside of the submitted work. HJ has received research lecture sponsorships or has served as a consultant or speaker on advisory boards for AbbVie, Gilead, GlaxoSmithKline, Janssen-Cilag, MSD Sharp & Dohme, TAD, and ViiV Healthcare. CO reports personal fees (for expert panels) from ViiV Healthcare during the conduct of the study. FN reports personal fees from GlaxoSmithKline during the conduct of the study. MGD reports grants from Janssen, Pharmaceutical Companies of Johnson & Johnson, and ViiV Healthcare, outside the submitted work. SS reports grants from ViiV Healthcare, during the conduct of the study. FB, JFA-V and M-AK-J have nothing to disclose. AW reports grants and personal fees from Gilead, Merck, and ViiV Healthcare, outside the submitted work. RVS-R is an employee of Janssen R&D and reports personal fees from Janssen, Pharmaceutical Companies of Johnson & Johnson. VvE is an employee of Janssen, Pharmaceutical Companies of Johnson & Johnson. HC and SV are employees and stockholders of Janssen, Pharmaceutical Companies of Johnson & Johnson. SF is an employee and stockholder of GlaxoSmithKline, outside the submitted work. CT, MS, AC, PP, VC, PB, KJH, DAM, KYS, and WS are employees of ViiV Healthcare and stockholders of GlaxoSmithKline. YW is an employee and stockholder of GlaxoSmithKline.

Data sharing

Data sharing requests will be considered by the management group on written request to the corresponding author. De-identified participant data or other prespecified data will be available subject to a written proposal and a signed data sharing agreement.

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