Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 96-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study

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Summary

Background Long-acting cabotegravir and rilpivirine administered monthly or every 2 months might address the challenges associated with daily oral antiretroviral therapy. The ATLAS-2M week 48 results showed non-inferiority of long-acting cabotegravir and rilpivirine administered every 8 weeks compared with that of every 4 weeks. In this study, we report the efficacy, safety, and tolerability results from the week 96 analysis.

Methods ATLAS-2M is a randomised, multicentre, open-label, phase 3b, non-inferiority trial conducted in 13 countries, evaluating the safety and efficacy of maintenance treatment with intramuscular injections of long-acting cabotegravir and rilpivirine, administered every 8 weeks versus every 4 weeks, to people living with HIV-1. Virologically suppressed adults with HIV-1, either already receiving intramuscular long-acting cabotegravir and rilpivirine every 4 weeks (ie, ATLAS study rollover participants) or oral standard of care, were randomly assigned (1:1), in an unblinded fashion, to receive either intramuscular long-acting cabotegravir (600 mg) and rilpivirine (900 mg) every 8 weeks (ie, the every 8-week dosing group) or intramuscular long-acting cabotegravir (400 mg) and rilpivirine (600 mg) every 4 weeks (ie, the every 4-week dosing group). Randomisation was generated using the GlaxoSmithKline-validated randomisation software RANDALL NG (version 1.3.3). The primary endpoint at week 48 was the proportion of participants with plasma HIV-1 RNA measurements of 50 copies per mL or more (ie, the US Food and Drug Administration [FDA] Snapshot algorithm), which has been published previously. Here, we present the week 96 results: the proportion of participants with plasma HIV-1 RNA measurements of less than 50 copies per mL (FDA Snapshot algorithm), with a non-inferiority margin of –10%; the proportion of participants with plasma HIV-1 RNA measurements of 50 copies per mL or more (FDA Snapshot algorithm), with a non-inferiority margin of 4%; the proportion of participants with protocol-defined confirmed virological failure (ie, two consecutive plasma HIV-1 RNA measurements ≥200 copies per mL); safety; pharmacokinetics; and tolerability. This study is registered with ClinicalTrials.gov, number NCT03299049, and is currently ongoing.

Findings Between Oct 27, 2017, and May 31, 2018, a total of 1149 participants were screened; of whom, 1049 (91%) were randomly assigned and 1045 (91%) initiated treatment (522 in the every 8-week dosing group and 523 in the every 4-week dosing group). The median age was 42 years (IQR 34–50). 280 (27%) of 1045 participants were assigned female at birth and 764 (73%) were white. At week 96 (FDA Snapshot algorithm), 11 (2%) of 522 participants in the every 8-week dosing group and six (1%) of 523 in the every 4-week dosing group had an HIV-1 RNA measurement of 50 copies per mL or more, with an adjusted treatment difference of 1·0 (95% CI –0·6 to 2·5), meeting the prespecified non-inferiority threshold of 4%; 475 (91%) of 522 participants in the every 8-week dosing group and 472 (90%) of 523 in the every 4-week dosing group maintained an HIV-1 RNA measurement of less than 50 copies per mL, with an adjusted treatment difference of 0·8 (95% CI –2·8 to 4·3), which met the prespecified non-inferiority threshold of –10%. One participant in the every 8-week dosing group met the confirmed virological failure criterion since the week 48 analysis at week 88, resulting in a total of nine participants in the every 8-week dosing group and two in the every 4-week dosing group having confirmed virological failure. No new safety signals were identified, and no treatment-related deaths occurred. Injection site reactions were the most common adverse event, occurring in 412 (79%) of 522 participants in the every 8-week dosing group and 400 (76%) of 523 in the every 4-week dosing group. Most injection site reactions were grade 1 or 2 (7453 [99%] of 7557 in both groups), with a median duration of 3 days (IQR 2–5).

Interpretation Long-acting cabotegravir and rilpivirine dosed every 8 weeks had non-inferior efficacy compared with that of every 4 weeks through the 96-week analysis, with both regimens maintaining high levels of virological suppression. These results show the durable safety, efficacy, and acceptability of dosing long-acting cabotegravir and rilpivirine monthly and every 2 months as maintenance therapy for people living with HIV-1.

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Introduction

Since the approval of the first antiretroviral therapy (ART) more than 30 years ago, ART has transformed HIV from a progressive fatal disease to a chronic, yet manageable, condition.[1,2] Over time, ART has substantially lowered the rate of mortality and morbidity in people living with HIV.[3–5] Current guidelines recommend that initial ART regimens should consist of at least two fully active drugs, usually comprising an integrase strand transfer inhibitor with one or two nucleoside reverse transcriptase inhibitors.[6–9]

Current standard of care for people living with HIV entails an oral regimen of these drugs in daily tablet formulations,[6,10] which requires sustained and continuous daily adherence to maintain virological suppression.[11] Poor adherence to ART has been shown to be associated with an increased likelihood of drug resistance and disease progression, increased incidence of hospitalisation, and reduced quality of life.[11–13] In addition, the substantial number or size of pills associated with daily oral therapy might lead to treatment fatigue, a decreased desire or motivation to maintain vigilance in adhering to a treatment regimen.[14] Furthermore, the stigma that surrounds people living with HIV, and the fear of inadvertent disclosure because of daily pill taking, increases the risk of depression and anxiety, decreases a person's overall quality of life, and negatively affects their adherence to treatment.[15] Therefore, there has been an interest in ART regimens for people living with HIV that require less frequent dosing.[16]

Cabotegravir, an integrase strand transfer inhibitor, and rilpivirine, a non-nucleoside reverse transcriptase inhibitor, are two antiretrovirals for which long-acting intramuscular injection formulations have been developed

Research in context

Evidence before this study

We searched PubMed for clinical trials, reviews, and cohort studies that contained the terms "cabotegravir", "rilpivirine", "antiretroviral therapy", "long-acting treatment", and "injectable treatment." Searches were done on Oct 16, 2020, with no date limit and restricted to papers in English. From the search, it was apparent that interest is increasing in long-acting therapies that offer less frequent dosing intervals versus daily oral antiretroviral therapy (ART). Although standard ART has transformed HIV infection into a manageable, chronic condition, people living with HIV face substantial challenges due to the need for daily oral dosing. Most challenges revolve around the burden of lifelong daily adherence and fear of stigmatisation due to inadvertent disclosure of HIV status, which has been shown to result in increased levels of treatment fatigue, anxiety, and depression. Additionally, adverse effects such as drug–food and drug–drug interactions have been known to further exacerbate these challenges. As a result, long-acting parenteral therapies that bypass the gastrointestinal tract have gained considerable interest over recent years. The only long-acting drug regimen currently indicated for the treatment of HIV-1 infection is the combination of cabotegravir and rilpivirine, which has been approved for use in Canada, the USA, Australia, and Europe for the maintenance of virological suppression based on several clinical studies. The phase 3 ATLAS and FLAIR studies have shown non-inferiority over 48 weeks of long-acting cabotegravir and rilpivirine dosed intramuscularly every 4 weeks compared with daily oral ART. The potential for dosing every 8 weeks was initially shown in the phase 2b LATTE-2 study, which supported further investigation in the phase 3 ATLAS-2M study. The 48-week ATLAS-2M data showed non-inferiority of dosing at every 8 weeks versus every 4 weeks, with a similar safety profile between regimens.

Added value of this study

The week 96 results from ATLAS-2M provide the longest phase 3 data to date of long-acting cabotegravir and rilpivirine dosed every 8 weeks versus that of every 4 weeks for the maintenance of virological suppression in adults with HIV-1. The week 96 data build on the week 48 results by showing the durability and continued safety of long-acting cabotegravir and rilpivirine dosed every 8 weeks and every 4 weeks over an approximate 2-year period. These data, taken together with the previous week 48 results, support the use of long-acting cabotegravir and rilpivirine dosed either every 8 weeks or every 4 weeks in virologically suppressed adults living with HIV-1.

Implications of all the available evidence

These results are a continuation of the first large phase 3 study to evaluate long-acting cabotegravir and rilpivirine dosed every 8 weeks as a maintenance therapy for people living with HIV. The week 96 results show the durability of this dosing regimen for the maintenance of virological suppression after nearly 2 years of therapy. In the week 48 ATLAS-2M analysis, the intramuscular long-acting dosing regimen of every 8 weeks was preferred by most participants over both the dosing of every 4 weeks and the daily oral dosing. The ATLAS-2M week 96 results further support the evidence that long-acting cabotegravir and rilpivirine, dosed either monthly or every 2 months, is an effective therapeutic alternative to daily oral ART. Long-acting cabotegravir and rilpivirine might alleviate challenges faced by those who find daily pill taking burdensome because of treatment fatigue or fear of inadvertent disclosure of HIV status, which might be beneficial for those who struggle with adherence.

and approved for maintenance of virological suppression. Long-acting cabotegravir and rilpivirine, dosed monthly and every 2 months, is approved in Europe and Australia, with a monthly dosing schedule also approved in the USA and Canada. Daily oral cabotegravir and rilpivirine has also been developed to allow an oral lead-in phase before injections and to manage planned missed doses of the long-acting regimen.[17–19] The ongoing phase 3 ATLAS[20] (NCT02951052) and FLAIR[21] (NCT02938520) studies, which evaluated long-acting cabotegravir and rilpivirine dosed every 4 weeks as maintenance therapy, showed non-inferiority of the long-acting regimen compared with continuing daily oral ART over 48 weeks and 96 weeks of treatment, with a similarly low number of participants with confirmed virological failure (two consecutive plasma HIV-1 RNA measurements ≥200 copies per mL) between both groups. The safety profiles were comparable between the long-acting regimen group and the daily oral ART group, except for drug-related adverse events—namely, injection site reactions. Injection site reactions were common, although nearly all were mild or moderate in severity and were short in duration.[20–24]

The ATLAS-2M[23] study provided evidence for the regulatory approval of every 2 months dosing, as it showed that every 8 weeks dosing of long-acting cabotegravir and rilpivirine is non-inferior to every 4 weeks dosing over 48 weeks, with a similar safety and tolerability profile. Further, most participants preferred the less frequent every 8 weeks dosing over both every 4 weeks and oral ART.[23] In this study, we report the long-term 96-week results of the phase 3b ATLAS-2M study, comparing the efficacy and safety of long-acting cabotegravir and rilpivirine dosed every 8 weeks with every 4 weeks for the maintenance of virological suppression in people living with HIV.

Methods

Study design and participants

ATLAS-2M is a randomised, multicentre, open-label, phase 3b, non-inferiority trial conducted in 13 countries (Argentina, Australia, Canada, France, Germany, Italy, Mexico, Russia, South Africa, South Korea, Spain, Sweden, and the USA), evaluating the safety and efficacy of maintenance treatment with intramuscular injections of long-acting cabotegravir and rilpivirine, administered every 8 weeks versus every 4 weeks, to people living with HIV-1. The full eligibility and exclusion criteria as well as study design have been presented previously.[23] Briefly, eligible participants were aged 18 years or older and must have received an uninterrupted first or second oral standard-of-care regimen for 6 months or longer. Additionally, participants must have had no previous virological failure and had at least two 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, must have completed the 52-week comparative phase, with an ATLAS-2M screening plasma HIV-1 RNA measurement of less than 50 copies per mL. As such, eligible participants could enter ATLAS-2M either from the clinic on the standard-of-care regimen or as ATLAS study rollover participants from either the standard-of-care group or the long-acting cabotegravir and rilpivirine group dosed every 4 weeks.

The full study protocol is available online.[25] ATLAS-2M was conducted in accordance with the Declaration of Helsinki. We obtained written informed consent from all participants. The study protocol, any amendments, the informed consent, and other information that required pre-approval were reviewed and approved by a national, regional, or investigational centre ethics committee or institutional review board.

Randomisation and masking

Full details of randomisation have been presented previously.[23] Briefly, participants were randomly assigned (1:1), in an unblinded fashion, to receive either long-acting cabotegravir and rilpivirine every 8 weeks (ie, the every 8-week dosing group) or long-acting cabotegravir and rilpivirine every 4 weeks (ie, the every 4-week dosing group), using the GlaxoSmithKline-validated randomisation software RANDALL NG (version 1.3.3). The randomisation schedule comprised of a series of blocks, with equal treatment allocation within each block. These sequences were shared across centres via central randomisation. Randomisation was stratified by previous exposure of cabotegravir and rilpivirine (0 weeks, 1–24 weeks, and >24 weeks) to account for those individuals entering from the ATLAS study.

Procedures

Participants who were naive to cabotegravir and rilpivirine received an oral lead-in of 4 weeks or more with daily oral cabotegravir (30 mg) plus rilpivirine (25 mg) after being randomly assigned to either the every 8-week dosing group or every 4-week dosing group. Participants from the ATLAS study transitioned to ATLAS-2M at the completion of the ATLAS maintenance phase or throughout the extension phase as their site received study approval for ATLAS-2M; consequently, participants from ATLAS entered ATLAS-2M with a range of exposure durations to cabotegravir and rilpivirine.[20] Participants who previously received long-acting cabotegravir and rilpivirine every 4 weeks in ATLAS transitioned to either intramuscular long-acting cabotegravir (600 mg) and rilpivirine (900 mg) every 8 weeks or remained on intramuscular long-acting cabotegravir (400 mg) and rilpivirine (600 mg) every 4 weeks. Participants who completed the 100-week maintenance phase had the choice to continue long-acting cabotegravir and rilpivirine with either dosing schedule in the extension phase. Any participant who received at least one dose of long-acting cabotegravir and rilpivirine

and withdrew for any reason entered a 52-week long-term follow-up period in which they started an alternative, investigator-selected ART regimen.

Viral genotype and phenotype were analysed from plasma samples using PhenoSense GT (Monogram Biosciences, South San Francisco, CA, USA), PhenoSense Integrase (Monogram Biosciences, South San Francisco, CA, USA), or GenoSeq Integrase assays (Monogram Biosciences, South San Francisco, CA, USA) at suspected virological failure (first visit at which HIV-1 RNA measurement was ≥200 copies per mL). Baseline archived HIV-1 resistance was retrospectively assessed in individuals with confirmed virological failure with next-generation sequencing using the GenoSure Archive assay (Monogram Biosciences, South San Francisco, CA, USA) of peripheral blood mononuclear cells. The threshold for detecting archived mutations in the GenoSure Archive assay was 10% or more.

Outcomes

The primary endpoint was the proportion of participants with a plasma HIV-1 RNA measurement of 50 copies per mL or more at week 48 in the intention-to-treat exposed population, which has been published previously,[23] as per the US Food and Drug Administration (FDA) Snapshot algorithm.[26]

The secondary endpoints assessed at week 96 were the proportion of participants with a plasma HIV-1 RNA measurement of less than 50 copies per mL using the FDA Snapshot algorithm (ie, the intention-to-treat exposed population), the proportion of participants with a plasma HIV-1 RNA measurement of 50 copies per mL or more (FDA Snapshot algorithm), and the proportion of participants with protocol-defined confirmed virological failure (ie, two consecutive plasma HIV-1 RNA measurements ≥200 copies per mL). Absolute values and changes from baseline in viral load and CD4-positive cell count, including by subgroup, were also assessed alongside the incidence and severity of adverse events and laboratory abnormalities, the proportion of participants who discontinued treatment due to adverse events, any changes from baseline in laboratory parameters over time, plasma pharmacokinetic parameters for long-acting cabotegravir and long-acting rilpivirine, demographic parameters, and incidence of treatment-emergent genotypic and phenotypic resistance to cabotegravir or rilpivirine, or both, in participants with confirmed virological failure.

Statistical analysis

The study was designed to determine whether administering long-acting cabotegravir and rilpivirine every 8 weeks was non-inferior to administering long-acting cabotegravir and rilpivirine every 4 weeks at week 48. The efficacy analysis at week 96 was a repeat evaluation of the week 48 primary and secondary efficacy analyses, whereby the proportions of participants with a plasma HIV-1 RNA measurement of 50 copies per mL or more and less than 50 copies per mL were summarised using the FDA Snapshot algorithm. No adjustment was made for multiplicity, as the week 96 analyses are secondary endpoints. The statistical analysis of the efficacy measures and rationale has been presented previously.[23] Briefly, the efficacy analysis included all participants who had received at least one dose of long-acting cabotegravir and rilpivirine during the study (ie, the intention-to-treat exposed population). Additionally, efficacy was analysed in the per-protocol population, including all participants in the intention-to-treat exposed population except for major protocol violators. The primary comparison was made at a one-sided 2·5% level of significance, and non-inferiority of the every 8-week dosing group relative to the every 4-week dosing group was demonstrated if the upper boundary of the two-sided 95% CI for the difference in proportion of participants with a plasma HIV-1 RNA measurement of 50 copies per mL or more in the intention-to-treat exposed Snapshot analysis was below 4%. For the secondary efficacy analysis, non-inferiority of the every 8-week dosing group to the every 4-week dosing group was demonstrated if the lower boundary of the 95% CI for the difference in proportion of participants with a plasma HIV-1 RNA measurement of less than 50 copies per mL in the intention-to-treat exposed Snapshot analysis was above –10%.

We did all statistical analysis using SAS (version 9.4). This study is registered with ClinicalTrials.gov, number NCT03299049, and is currently ongoing.

Role of the funding source

The funders of the study participated in study design, data collection, data analysis, data interpretation, writing of the report, and in the decision to submit for publication.

Results

Between Oct 27, 2017, and May 31, 2018, a total of 1149 participants were screened; of whom, 1049 (91%) were randomly assigned and 1045 (91%) initiated treatment (522 in the every 8-week dosing group and 523 in the every 4-week dosing group—ie, the intention-to-treat exposed population; figure). The proportion of participants completing the 100-week maintenance phase of treatment (477 [91%] of 522 in the every 8-week dosing group and 473 [90%] of 523 in the every 4-week dosing group) and entering the extension phase (473 [91%] in the every 8-week dosing group and 470 [90%] in the every 4-week dosing group) were similar in both groups. Overall, 95 (9%) of 1045 participants in the intention-to-treat exposed population withdrew from the maintenance phase (45 in the every 8-week dosing group and 50 in the every 4-week dosing group), representing a further 17 participants withdrawing since the 48-week analysis (nine in the every 8-week dosing group and eight in the every 4-week dosing group). The

most common reasons for withdrawal for participants in the every 8-week dosing group were adverse events (18 [3%] of 522, including one participant who withdrew after completing the maintenance phase), lack of efficacy (ten [2%]), and withdrawal by participant (eight [2%]). For participants in the every 4-week dosing group, the most common reason for withdrawal was withdrawal by participant (22 [4%] of 523), followed by adverse events (19 [4%]), and lack of efficacy (three [<1%]). No discontinuations were due to COVID-19 infection.

Baseline characteristics of the intention-to-treat exposed population are shown in the appendix (p 1). Participants had a median age of 42·0 years (IQR 34–50) and 280 (27%) of 1045 were assigned female at birth. 764 (73%) of 1045 participants were white and 798 (76%) had baseline CD4-positive counts of 500 cells per mm^3 or more. The median body-mass index (BMI) at baseline was 25·8 kg/m^2 (IQR 23·1–29·0). Overall, 391 (37%) of 1045 participants entered the study having previously received long-acting cabotegravir and rilpivirine in the ATLAS study for either 1–24 weeks (137 [35%] of 391) or more than 24 weeks (254 [65%]), while the remaining 654 (63%) participants were cabotegravir and rilpivirine naive.

Since the week 48 analysis cutoff, 6123 (97%) of 6281 injections were received within the 15-day dosing window, with a total treatment compliance over the maintenance phase of 98% (5776 of 5908 in the every 8-week dosing group and 11218 of 11438 in the every 4-week dosing group). All missed injection visits were bridged with either cabotegravir (30 mg) and rilpivirine (25 mg) oral therapy (six in the every 8-week dosing group and 25 in the every 4-week dosing group) or other oral ART (three in the every 8-week dosing group and two in the every 4-week dosing group). No participant who had met the confirmed virological failure criterion at the week 48 analysis, nor any participant who met confirmed virological failure or suspected virological failure between the week 48 and week 96 analyses, had injection visits of more than 7 days later than the scheduled visit date.

ATLAS-2M showed non-inferior antiviral activity for long-acting cabotegravir and rilpivirine dosed every 8 weeks compared with that dosed every 4 weeks after 96 weeks of therapy (table 1). At week 96 (FDA Snapshot algorithm), 11 (2%) of 522 participants in the every 8-week dosing group and six (1%) of 523 in the every 4-week dosing group had an HIV-1 RNA measurement of 50 copies per mL or more, with an adjusted treatment difference in proportions of 1·0% (95% CI –0·6 to 2·5), meeting the prespecified non-inferiority threshold of 4%. For the key secondary endpoint at week 96, 475 (91%) of 522 participants in the every 8-week dosing group and 472 (90%) of 523 in the every 4-week dosing group had an HIV-1 RNA measurement of less than 50 copies per mL. The adjusted treatment difference in proportions was 0·8% (95% CI –2·8 to 4·3), which met the prespecified non-inferiority threshold of –10%. Tests for homogeneity were not significant by randomisation strata for either the HIV-1 RNA measurement of 50 copies per mL or more (p=0·197) or less than 50 copies per mL (p=0·642) endpoints (table 1). Results for the per-protocol population were consistent with those of the intention-to-treat exposed population, with ten (2%) of 516 participants in the every 8-week dosing group and six (1%) of 514 in the every 4-week dosing group having an HIV-1 RNA measurement of 50 copies per mL or more, whereas

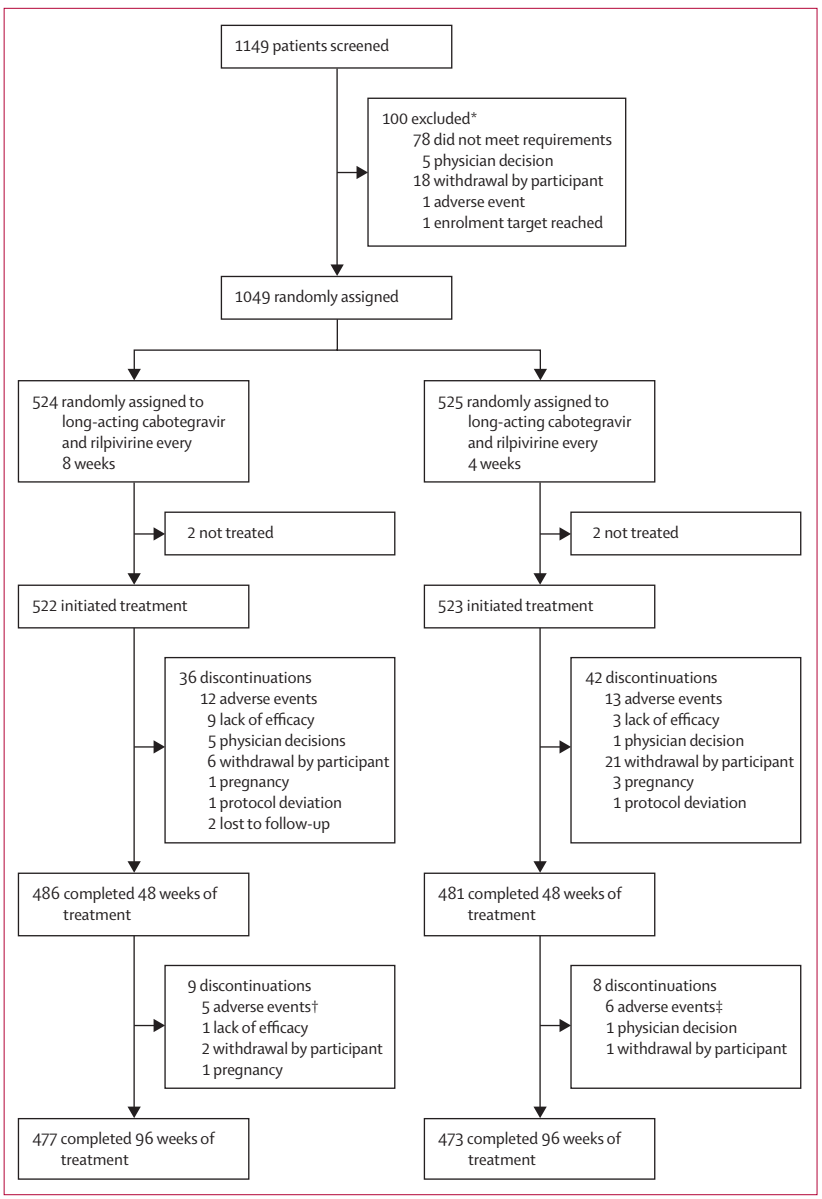

Figure: **Participant disposition**
*Individuals could meet more than one criterion, so the total exceeds 100. †Adverse events leading to discontinuation in the every 8-week dosing group since week 48 were injection site pain, malaise, headache, hyperhidrosis, breast cancer, testicular neoplasm, and osteonecrosis (participants could report more than one adverse event). ‡Adverse events leading to discontinuation in the every 4-week dosing group since week 48 were disturbance in attention, sleep disorder, completed suicide, nausea, myalgia, drug hypersensitivity, myocardial infarction, and vertigo (participants could report more than one adverse event).

See Online for appendix

	Long-acting cabotegravir and rilpivirine every 8 weeks (n=522)	Long-acting cabotegravir and rilpivirine every 4 weeks (n=523)	Adjusted difference* (95% CI)
Intention-to-treat exposed population analysis			
HIV-1 RNA <50 copies per mL†	475 (91%)	472 (90%)	0·8 (−2·8 to 4·3)
HIV-1 RNA ≥50 copies per mL‡	11 (2%)	6 (1%)	1·0 (−0·6 to 2·5)
Data in window not below threshold	2 (<1%)	2 (<1%)	..
Discontinued for lack of efficacy	8 (2%)	3 (1%)	..
Discontinued for other reason while not below threshold	1 (<1%)	1 (<1%)	..
Change in background therapy	0	0	..
No virological data	36 (7%)	45 (9%)	..
Discontinued study because of adverse event or death§	19 (4%)	20 (4%)	..
Discontinued study for other reason¶	16 (3%)	27 (5%)	..
On study but missing data in window‖	3 (1%)	1 (<1%)	..
Test for homogeneity by stratum for HIV-1 RNA ≥50 copies per mL			
Previous exposure to cabotegravir and rilpivirine			
0 weeks	8/327 (2%)	5/327 (2%)	0·9 (−1·4 to 3·4)
1–24 weeks	3/69 (4%)	0/68	4·3 (−1·3 to 12·3)
>24 weeks	0/126	1/128 (1%)	−0·8 (−4·4 to 2·3)
p value test of homogeneity**	..	..	0·197
Test for homogeneity by stratum for HIV-1 RNA <50 copies per mL			
Previous exposure to cabotegravir and rilpivirine			
0 weeks	294/327 (90%)	288/327 (88%)	1·8 (−3·0 to 6·8)
1–24 weeks	63/69 (91%)	64/68 (94%)	−2·8 (−12·9 to 6·8)
>24 weeks	118/126 (94%)	120/128 (94%)	−0·1 (−6·6 to 6·4)
p value test of homogeneity**	..	..	0·642
Confirmed virological failure (intention-to-treat exposed population)			
Between weeks 48 and 96	1 (<1%)	0	..
Total confirmed virological failures through week 96	9 (2%)	2 (<1%)	..

Data are n (%) or n/N (%), unless otherwise specified. *Cochran–Mantel–Haenszel stratified analysis adjusting for previous long-acting cabotegravir and rilpivirine exposure (0 weeks, 1–24 weeks, or >24 weeks). †Non-inferiority was determined if the lower bound of the 95% CI about the adjusted difference was above −10%. ‡Non-inferiority was determined if the upper bound of the 95% CI about the adjusted difference was below 4%. §Two deaths occurred during the maintenance phase (one participant in each dosing group); 37 participants (18 in the every 8-week dosing group and 19 in the every 4-week dosing group) reported one or more adverse events leading to discontinuation. ¶Other reasons included withdrawal by participant (n=7), physician decision (n=5), pregnancy (n=1), lost to follow-up (n=2), lack of efficacy (n=1) in the every 8-week dosing group; and withdrawal by participant (n=21), protocol deviation (n=1), pregnancy (n=3), and physician decision (n=2) in the every 4-week dosing group. ‖Missing data were related to COVID-19. **One-sided p value from weighted least squares χ^2 statistic. A p value of less than 0·10 indicates significant evidence of heterogeneity in the difference in proportions across levels of each analysis stratum.

Table 1: **Primary and key secondary efficacy endpoints at week 96 (US Food and Drug Administration Snapshot algorithm)**

474 (92%) of 516 participants in the every 8-week dosing group and 468 (91%) of 514 in the every 4-week dosing group had an HIV-1 RNA measurement of less than 50 copies per mL. When analysed by demographics and baseline characteristics, no clinically meaningful difference was observed between the two treatment groups for the Snapshot efficacy endpoints at week 96 (appendix pp 4–5).

Since week 48, one additional participant in the every 8-week dosing group met the confirmed virological failure criterion. Through 96 weeks of treatment, 11 participants had confirmed virological failure (nine [2%] of 522 participants in the every 8-week dosing group and two [<1%] of 523 in the every 4-week dosing group). Resistance data on the ten participants with confirmed virological failure before week 48 have been presented previously.[23] Of the 11 participants with confirmed virological failure, six (55%) had two or more of the factors associated with increased risk of confirmed virological failure (pro-viral rilpivirine resistance-associated mutations, HIV-1 subtype A6/A1, and BMI ≥30 kg/m²).[27] Ten (91%) of 11 participants achieved virological re-suppression on oral ART (protease inhibitor-based regimen [n=8] or integrase strand transfer inhibitor-based regimen [n=2]). One (9%) of 11 participants was non-adherent to a protease inhibitor-based ART and was not re-suppressed at month 12 of the long-term follow-up.

The participant in the every 8-weeks dosing group who met the confirmed virological failure criterion after the week 48 analysis did so at week 88 and had two major non-nucleoside reverse transcriptase inhibitor resistance-associated mutations (Lys103Asn and rilpivirine resistance-associated mutation Tyr181Cys) present in baseline pro-viral DNA, which were retained at suspected virological failure. No integrase strand transfer inhibitor resistance-associated mutations were observed in baseline peripheral blood mononuclear cells or suspected virological failure samples, although the integrase polymorphism (Leu74Leu/Ile) was also present at baseline. This participant was male, from the USA, and had a BMI of less than 30 kg/m². The participant had an HIV-1 subtype B infection and had received previous ART with abacavir–lamivudine–zidovudine followed by emtricitabine–tenofovir disoproxil fumarate–efavirenz. At suspected virological failure the participant had a 5·17-fold reduction in phenotypic sensitivity to rilpivirine, based on a rilpivirine biological cutoff of a 2·0-fold change, and phenotypic susceptibility to cabotegravir. Plasma concentrations at suspected virological failure (week 88) were 1·07 µg/mL for cabotegravir and 118 ng/mL for rilpivirine. The participant was later fully re-suppressed after 1 month of long-term follow-up on darunavir–cobicistat–emtricitabine–tenofovir alafenamide.

Long-acting cabotegravir and rilpivirine was well tolerated, with similar adverse event profiles observed between both dosing groups (table 2). Safety events from the oral lead-in period of the maintenance phase were presented in the week 48 analysis.[23] Overall, 987 (94%) of 1045 participants (488 in the every 8-week dosing group and 499 in the every 4-week dosing group) reported at least one adverse event throughout the 96-week study. The most commonly occurring adverse events, excluding injection site reactions, in both dosing groups were nasopharyngitis (90 [17%] of 522 in the every 8-week dosing group and 96 [18%] of 523 in the every 4-week dosing group) and upper respiratory tract infection (72 [14%] in the every 8-week dosing group and 94 [18%] in the every 4-weeks dosing group; table 2). Drug-related adverse events, as reported by the investigator,

were common and comparable across both groups (415 [80%] of 522 in the every 8-weeks dosing group and 413 [79%] of 523 in the every 4-weeks dosing group); most were injection site reactions. Excluding injection site reactions, 122 (23%) of 522 participants in the every 8-week dosing group and 146 (28%) of 523 in the every 4-week dosing group had a drug-related adverse event (table 2).

The most common non-injection site reaction, drug-related adverse event through week 96 was pyrexia (20 [4%] of 522 in the every 8-week dosing group and 25 [5%] of 523 in the every 4-week dosing group); only one (<1%) participant had pyrexia since the week 48 analysis (table 2). Between the week 48 and week 96 analyses, three participants (<1%) had drug-related serious adverse events, none of which were fatal (osteonecrosis [n=1 in the every 8-week dosing group], drug hypersensitivity [a suspected post-injection reaction with same-day resolution; n=1 in the every 4-week dosing group], and myocardial infarction [n=1 in the every 4-week dosing group]). A total of 18 (3%) of 522 participants in the every 8-week dosing group and 19 (4%) of 523 in the every 4-week dosing group had adverse events leading to withdrawal; among these participants, six events in each treatment group occurred after the week 48 analysis. By the week 96 analysis, two deaths occurred, none of which were considered drug related. One of the deaths was due to sepsis in the every 8-week dosing group and one was due to suicide in the every 4-week dosing group, in which the suicide occurred after the 48-week analysis cutoff. Between the week 48 and week 96 analyses, two (<1%) of 523 participants in the every 4-week dosing group reported post-injection reactions consistent with inadvertent (partial intravenous) injection with rilpivirine; one participant had drug hypersensitivity and was withdrawn from the study and the remaining participant had an anaphylactic-like reaction that was non-serious and not related to the study drugs, which did not lead to a discontinuation from the study. No new safety signals were detected throughout the study.

Of the 12 832 injections administered in the every 8-week dosing group, 3400 injection site reactions were

	Cumulative week 96 data analysis		Cumulative week 48 data analysis*		New participants with adverse events between week 48 and week 96 data analyses	
	Long-acting cabotegravir and rilpivirine every 8 weeks (n=522)	Long-acting cabotegravir and rilpivirine every 4 weeks (n=523)	Long-acting cabotegravir and rilpivirine every 8 weeks (n=522)	Long-acting cabotegravir and rilpivirine every 4 weeks (n=523)	Long-acting cabotegravir and rilpivirine every 8 weeks (n=522)	Long-acting cabotegravir and rilpivirine every 4 weeks (n=523)
Any adverse event	488 (93%)	499 (95%)	473 (91%)	482 (92%)	15 (3%)	17 (3%)
Drug-related adverse events†	415 (80%)	413 (79%)	400 (77%)	399 (76%)	15 (3%)	14 (3%)
Excluding injection site reactions	122 (23%)	146 (28%)	109 (21%)	125 (24%)	13 (2%)	21 (4%)
Any grade 2–5 adverse event	325 (62%)	333 (64%)	272 (52%)	287 (55%)	53 (10%)	46 (9%)
Drug related	178 (34%)	187 (36%)	156 (30%)	164 (31%)	22 (4%)	23 (4%)
Leading to withdrawal	18 (3%)‡	19 (4%)	12 (2%)	13 (2%)	6 (1%)	6 (1%)
Drug related	12 (2%)	15 (3%)	8 (2%)	11 (2%)	4 (1%)	4 (1%)
Any serious adverse event	33 (6%)	28 (5%)	27 (5%)	19 (4%)	6 (1%)	9 (2%)
Drug related§	4 (<1%)	3 (1%)	3 (1%)	1 (<1%)	1 (<1%)	2 (<1%)
Fatal serious adverse events	1 (<1%)	1 (<1%)	1 (<1%)¶	0	0	1 (<1%)‖
Drug related	0	0	0	0	0	0
Common non-injection site reaction adverse events (≥5% in either treatment group)						
Nasopharyngitis	90 (17%)	96 (18%)	71 (14%)	74 (14%)	19 (4%)	22 (4%)
Upper respiratory tract infection	72 (14%)	94 (18%)	50 (10%)	71 (14%)	22 (4%)	23 (4%)
Headache	52 (10%)	47 (9%)	35 (7%)	36 (7%)	17 (3%)	11 (2%)
Diarrhoea	44 (8%)	53 (10%)	33 (6%)	37 (7%)	11 (2%)	16 (3%)
Back pain	45 (9%)	48 (9%)	28 (5%)	29 (6%)	17 (3%)	19 (4%)
Pyrexia	38 (7%)	47 (9%)	28 (5%)	44 (8%)	10 (2%)	3 (<1%)
Common non-injection site reaction drug-related adverse events (≥3% in either treatment group)						
Pyrexia	20 (4%)	25 (5%)	19 (4%)	25 (5%)	1 (<1%)	0
Fatigue	11 (2%)	21 (4%)	7 (1%)	19 (4%)	4 (1%)	2 (<1%)

*Week 48 data have been presented previously.[23] †Drug-related adverse events relating to the nervous system occurred in 5% of participants in each group (n=25 in the every 8-week dosing group; n=24 in the every 4-week dosing group). ‡18 participants had adverse events leading to discontinuation during the maintenance phase; however, one (6%) of these participants did not discontinue until after completing the maintenance phase. §Drug-related serious adverse events since the week 48 analysis: osteonecrosis (n=1 in the every 8-week dosing group), drug hypersensitivity (n=1 in the every 4-week dosing group), and myocardial infarction (n=1 in the every 4-week dosing group). ¶Sepsis at week 48. ‖Suicide after week 48.

Table 2: **Summary of adverse events**

	Long-acting cabotegravir and rilpivirine every 8 weeks (n=522)	Long-acting cabotegravir and rilpivirine every 4 weeks (n=523)
Participants with injections	516 (99%)	517 (99%)
Number of injections	12 832	23 855
Number of injection site reaction events	3400	4157
Grade or intensity*		
Grade 1	2745	3446
Grade 2	601	661
Grade 3	54	50
Number of injection site reaction adverse events (≥1% of injections as reported)		
Injection site pain	2662/12 832 (21%)	3295/23 855 (14%)
Injection site nodule	188/12 832 (1%)	297/23 855 (1%)
Injection site discomfort	134/12 832 (1%)	148/23 855 (1%)
Duration (days)		
1–7	2870/3400 (84%)	3547/4157 (85%)
8–14	287/3400 (8%)	318/4157 (8%)
>14	223/3400 (7%)	277/4157 (7%)
Median	3 (2–5)	3 (2–5)
Participants withdrawing for injection-related reasons	7/516 (1%)	11/517 (2%)

Data are n (%), n, n/N (%), or median (IQR). *No grade 4 or 5 injection site reactions were observed.

Table 3: **Injection site reactions**

observed across 412 (80%) of 516 participants; 2745 (81%) of 3400 were grade 1 and 601 (18%) were grade 2. Of the 23 855 injections administered in the every 4-week dosing group, 4157 injection site reactions were observed across 400 (77%) of 517 participants; 3446 (83%) of 4157 were grade 1 and 661 (16%) were grade 2 (table 3). Out of the total 36 687 injections, injection site pain was the most frequent injection site reaction in both treatment groups, occurring in 5957 (16%) of injections, followed by injection site nodule, which occurred in 485 (1%) of injections. No grade 4 or 5 injection site reactions were observed. The median duration of injection site reactions was 3 days (IQR 2–5) in both groups. Discontinuation due to injection site reactions or tolerability of injections occurred in seven (1%) of 516 participants in the every 8-week dosing group and in 11 (2%) of 517 in the every 4-week dosing group; only one (<1%) participant across both groups withdrew because of an injection site reaction (the participant in the every 8-week dosing group withdrew because of injection site pain). The median number of injection site reaction events per person was four (IQR 1·0–10·0) in the every 8-week dosing group and four (IQR 1·0–10·0) in the every 4-week dosing group. The frequency of injection site reactions decreased over time (115 [23%] of 493 in the every 8-week dosing group and 100 [20%] of 488 in the every 4-week dosing group at week 48; 74 [16%] of 473 in the every 8-week dosing group and 54 [12%] of 468 in the every 4-week dosing group at week 96; appendix pp 6–7).

At week 96, most participants were in the same BMI category as they were at baseline (389 [75%] of 522 in the every 8-week dosing group and 378 [72%] of 523 in the every 4-week dosing group). Median weight change from baseline to week 96 was comparable across both groups (an increase of 1·8 kg in the every 8-week dosing group and an increase of 1·3 kg in the every 4-week dosing group). In the every 8-week dosing group, 34 (15%) of 223 participants who were classified with a normal BMI at baseline became overweight after 96 weeks, two (1%) of 223 participants who were classified with a normal BMI at baseline became obese after 96 weeks, and 21 (12%) of 182 participants who were overweight became obese at week 96. In the every 4-week dosing group, 36 (17%) of 213 participants who were classified with a normal BMI at baseline became overweight after 96 weeks, two (1%) of 213 participants who were classified with a normal BMI at baseline became obese after 96 weeks, and 21 (10%) of 202 participants who were overweight became obese at week 96. Two participants (one in each treatment group) had a normal BMI at baseline that shifted to below normal by week 96 and one participant in the every 4-week dosing group shifted from overweight to below normal. Nine participants (four in the every 8-week dosing group and five in the every 4-week dosing group) had adverse events of weight gain that were considered to be drug related; however, all were grade 1 or 2 and did not lead to withdrawal from the study.

Since the week 48 analysis, no clinically meaningful differences were observed between the two treatment groups for any electrocardiogram parameters, vital signs, or the following clinical analyses: alanine aminotransferase, aspartate aminotransferase, bilirubin, or lipase. No participants met the liver stopping criteria (ie, abnormal ALT and bilirubin concentrations).

At week 96, geometric mean cabotegravir pre-dose concentrations ranged from 1·57 µg/mL to 1·65 µg/mL for the every 8-week dosing group and 2·57 µg/mL to 2·79 µg/mL for the every 4-week dosing group across the three previous cabotegravir and rilpivirine exposure strata and were comparable with the week 48 observations (appendix p 8). Steady state was achieved for cabotegravir within 48 weeks regardless of stratification of previous exposure, and concentrations were similar between week 48 and week 96. Geometric mean rilpivirine pre-dose concentrations at week 96 ranged from 86·4 ng/mL to 101·0 ng/mL for the every 8-week dosing group and 120·0 ng/mL to 137·0 ng/mL for the every 4-week dosing group across the three previous cabotegravir and rilpivirine exposure strata (appendix p 8). In participants with no previous exposure and 1–24 weeks of previous exposure, an increase in pre-dose concentration of rilpivirine was observed from week 48 to week 96 in ATLAS-2M, consistent with ongoing

accumulation in the second year of treatment; this finding is in line with the half-life of long-acting rilpivirine. For participants who had more than 24 weeks of previous exposure before entering ATLAS-2M, rilpivirine steady state was achieved by week 48, with little accumulation from week 48 to week 96. Pharmacokinetic profiles for the ten participants with confirmed virological failure up to week 48 have been presented previously, including median (5th and 95th percentile) cabotegravir and rilpivirine concentrations of those who were suppressed.[23] For the additional participant with confirmed virological failure at week 88, the trough concentration of cabotegravir at suspected virological failure was 1·07 µg/mL and the trough concentration of rilpivirine at suspected virological failure was 118 ng/mL (appendix p 3). For comparison, in the every 8-week dosing group, overall trough cabotegravir geometric mean concentration was 1·59 µg/mL and rilpivirine geometric mean concentration was 91·8 ng/mL.

Discussion

ATLAS-2M is the first phase 3b study to investigate long-acting cabotegravir and rilpivirine dosed every 8 weeks for the maintenance of virological suppression in adults with HIV-1 infection. The 96-week results extend the clinical evidence showing the non-inferiority of long-acting cabotegravir and rilpivirine dosed every 2 months versus that of monthly as an alternative to daily oral ARTs. Long-acting cabotegravir and rilpivirine dosed every 8 weeks was found to be non-inferior to that of every 4 weeks at week 48 (ie, the primary analysis) and week 96, as per the FDA Snapshot algorithm, at maintaining virological suppression in adults with HIV-1 infection. Furthermore, efficacy was maintained regardless of previous cabotegravir and rilpivirine exposure, with no significant differences among strata. Overall, 475 (91%) of 522 participants in the every 8-week dosing group and 472 (90%) of 523 in the every 4-week dosing group maintained virological suppression after approximately 96 weeks of long-acting therapy. This finding supports the durable efficacy of long-acting cabotegravir and rilpivirine over approximately 2 years. Notably, this study actively recruited people assigned female at birth with a goal to enrol a minimum of 25% women, which was successfully met. Additionally, participant retention remained high throughout the 96 weeks, with 91% of participants completing the study in the every 8-week dosing group and 90% in the every 4-week dosing group.

High treatment compliance was observed across both groups, with no injections missed without oral bridging, potentially reflecting the flexibility of the 15-day dosing window that was permitted with this treatment. No cases of confirmed virological failure were observed during the period of oral therapy or following resumption of long-acting cabotegravir and rilpivirine dosing. This finding is promising for real-world applications, as the study visit schedules and corresponding clinical assessments were designed to simulate the anticipated real-world implementation of each dosing regimen.

Overall, the rate of confirmed virological failure was generally low across both groups, with only one participant meeting the confirmed virological failure criterion since the week 48 analysis in the every 8-week dosing group. Most participants with confirmed virological failure in the every 8-week dosing group had pre-existing resistance-associated mutations to rilpivirine at baseline, compared with none in the every 4-week dosing group. The small number of participants with confirmed virological failure in this study limited our ability to form robust conclusions and identify predictors of virological failure. A multivariable analysis, using pooled data from the phase 3 and phase 3b ATLAS, FLAIR, and ATLAS-2M studies, suggests that an increased risk of confirmed virological failure when two or more of the following baseline factors are present: pro-viral rilpivirine resistance-associated mutations, HIV-1 subtype A6/A1, or a BMI of 30 kg/m² or more. Factors such as cabotegravir week 8 trough concentration, baseline integrase Lys74Ile (excluding mixtures with Lys74Met) polymorphism, baseline integrase strand transfer inhibitor mutations, baseline non-nucleoside reverse transcriptase inhibitor resistance-associated mutations (excluding rilpivirine resistance-associated mutations), being assigned female at birth, and dosing regimen were also analysed and were found to not significantly increase the likelihood of virological failure. Furthermore, the presence of any one factor alone was not associated with confirmed virological failure. This finding is important, as six participants who had confirmed virological failure in ATLAS-2M had two or more of the baseline factors associated with increased risk of confirmed virological failure.[27]

The safety profiles of both dosing schedules were generally similar, with comparable proportions of participants reporting serious adverse events, adverse events, and adverse events leading to withdrawal. These results are consistent with previous studies of long-acting cabotegravir and rilpivirine.[20,21] The median weight change found in this study is consistent with a median weight gain of 2·0 kg for long-acting cabotegravir and rilpivirine every 4 weeks observed in the previous phase 3 FLAIR study over 96 weeks,[22] and was similar to those reported in previous clinical trials for other ARTs.[28] The number of injection site reactions reported across both treatment groups was similar and consistent with previous reports in the ATLAS,[20] FLAIR,[21] and ATLAS-2M[23] analyses. Injections were generally well tolerated, with injection site reactions being self-resolving, and the majority being mild with a short duration that rarely led to withdrawal. Injection site reaction incidence continued to decrease over time from week 48 to week 96 in both treatment groups, consistent with the findings of the FLAIR 96-week analysis.[22] The frequency of injection site reactions reported in the every 4-week dosing group decreased with each visit and were

overall comparable with the every 8-week dosing group; however, this difference was not considered to be of clinical significance as the higher incidence of injection site reactions per visit with the every 8-week dosing was offset by the less frequent dosing.

The cabotegravir and rilpivirine plasma concentration data were consistent with those observed in the phase 2b LATTE-2 study.[29] High suppression was maintained for both regimens with no inverse relationship between cabotegravir or rilpivirine pharmacokinetics and virological non-response. Multiple factors, including plasma concentrations and viral phenotype, might be associated with the occurrence of virological failure.[27]

Finally, the COVID-19 pandemic had a negligible effect on the efficacy analysis. In the maintenance phase, 13 participants requested oral bridging because of COVID-19-related reasons; however, no participant withdrew because of COVID-19-related adverse events. As such, COVID-19 had no implications on the conclusions of this study.

The findings from our study are limited by the absence of blinding, which could have influenced an increased frequency of adverse event reporting by participants anticipating such effects due to being administered a novel therapy; however, incorporating blinding into the study design would not have been practical, requiring sham placebo injections in the every 8-week dosing group, nor was it warranted because of the objective nature of the primary and key secondary endpoints. A further limitation was the absence of an oral standard of care comparator group preventing direct comparison of treatments being made, although a post-hoc indirect analysis showed comparability of the every 8-week dosing with standard of care.[30] When comparing the two treatment groups, different numbers of safety assessments were made between the every 8-week dosing group and the every 4-week dosing group because of the dose frequency, which might have increased the number of adverse events reported in the every 4-week dosing group. Additionally, pregnant participants or participants with hepatitis B virus co-infection were not included in this study; long-acting cabotegravir and rilpivirine has not been studied in these subgroups. Furthermore, limited conclusions can be made about improved adherence versus alternative oral ART; however, the LATITUDE (NCT03635788) study is an ongoing trial investigating long-acting cabotegravir and rilpivirine in people living with HIV infection with historical suboptimal adherence and might therefore provide more insight into this specific population.

In summary, this study shows that long-acting cabotegravir and rilpivirine, given monthly or every 2 months, is an effective and well tolerated treatment for maintaining HIV-1 virological suppression over approximately 2 years and is a potential therapeutic alternative to oral standard-of-care therapies in the treatment of people living with HIV infection.

Contributors

HJ, ETO, GRic, GRiz, JFA-V, PDB, KJH, RM, AOH, AT, EB, FA, CME, and DAM were study investigators or participated in the conduct of the study, including recruitment and follow-up of participants. PDB, YW, KJH, SLF, HC, DAM, CLT, KYS, RVS-R, SV, VvE, and WRS participated in the analysis of the study data and the conceptualisation and design of the study. YW, KJH, and WRS verified the data. All authors were involved in the drafting and review of the manuscript and approved the final version.

Declaration of interests

HJ reports non-financial support from GlaxoSmithKline during the conduct of the study; and personal fees and non-financial support from AbbVie, Gilead Sciences, GlaxoSmithKline, Janssen-Cilag, Merck Sharp & Dohme, TAD Pharma, and ViiV Healthcare, outside the submitted work. ETO reports funding from ViiV Healthcare to do research at his institution, during the conduct of the study; consultant fees from Theratechnologies, outside of the submitted work; consultant fees and research support from ViiV Healthcare and Gilead Sciences; and research support from Merck Sharp & Dohme, outside of the submitted work. GRic reports grants from Gilead Sciences, ViiV Healthcare, GlaxoSmithKline, Johnson & Johnson, Taimed, Merck Sharp & Dohme, and Insmed, outside of the submitted work. GRiz has received personal fees from ViiV Healthcare, Angelini, and Janssen; personal fees and non-financial support from Gilead Sciences and AbbVie; and personal fees and fees for participation on a Data Safety Monitoring Board and Advisory Board from Merck Sharp & Dohme, outside of the submitted work. AOH reports non-financial support from PPD, during the conduct of the study; and grants from ViiV Healthcare, and Gilead Sciences, outside of the submitted work. AT reports funding of study costs from ViiV Healthcare and Janssen, during the conduct of the study; and personal fees from GlaxoSmithKline, ViiV Healthcare, and Gilead Sciences, outside of the submitted work. YW, CME, and SLF are employees and stockholders of GlaxoSmithKline. VvE is an employee of Janssen and has a pending patent. HC, RVS-R, and SV are employees and stockholders of Janssen. DAM was an employee of ViiV Healthcare and is a shareholder of GlaxoSmithKline, and has a pending patent. PDB, KJH, CLT, KYS, and WRS are employees of ViiV Healthcare and stockholders of GlaxoSmithKline. JFA-V, RM, EB, and FA declare no competing interests.

Data sharing

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

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