COMMUNIQUE DE PRESSE
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L'Hôpital Européen, établissement précurseur dans le traitement contre le VIH

Le Dr Patrick PHILIBERT, médecin référent dans le traitement du VIH à l'Hôpital Européen, a piloté sur Marseille une étude internationale qui a fait l'objet d'une publication le 4 mars 2020 dans le prestigieux New England Journal of Medicine, puis dans The Lancet, le 8 avril 2021 (voir article ci-après).

Cette étude rapporte un progrès significatif dans le traitement de patients atteints de VIH. L'infection par le Virus de l'Immunodéficience Humaine (VIH) est responsable d'un déficit immunitaire en rapport avec un virus de la famille des rétrovirus, il provoque une infection chronique de l'organisme. Les patients se voyaient dispenser un traitement lourd, celui-ci a été simplifié mais leur impose encore une prise de médicaments quotidienne.

Cette étude internationale démontre l'efficacité de l'utilisation d'un nouveau traitement injectable à durée d'action longue. Ce nouveau protocole prévoit un traitement injectable en intramusculaire, dispensé toutes les 8 semaines. Augmentant de façon significative la qualité de vie des patients et le maintien de leur autonomie, ce traitement est disponible en France depuis décembre 2021.

Ce traitement est disponible en officine de ville et dans les hôpitaux, les premières injections doivent être réalisées à l'hôpital avec un accompagnement spécialisé, le relai peut être assuré en ville par des infirmières et infirmier en libéral.

Toutes les personnes vivant avec le VIH ne peuvent pas bénéficier de cette forme injectable, seul le médecin spécialisé peut évaluer au cas par cas son indication. Il s'agit d'une prise en charge personnalisée qui est aujourd'hui adaptée à chaque personne.

Une évaluation clinique et biologique tous les six mois, voire tous les ans par le médecin spécialiste est ensuite recommandée, en étroite collaboration avec le médecin traitant et l'infirmière libérale.

Le Dr Patrick Philibert souligne l'implication de l'équipe d'infectiologie de l'Hôpital Européen en matière de recherche clinique et notamment dans le domaine du VIH : *« Depuis plus de 5 ans, l'Hôpital Européen a été le seul établissement de la région à pouvoir proposer à ses patients un traitement injectable intramusculaire à durée d'action longue. Nous avons pu contribuer à mettre en évidence l'efficacité et la bonne tolérance de cette thérapeutique innovante. »*

Le service d'infectiologie de l'Hôpital Européen

Le service d'infectiologie et son pôle Suivi Immunovirologique, intégré au pôle de médecine interne et maladies infectieuses, est composé d'une équipe médicale et paramédicale dédiée à la prise en charge des infections VIH, hépatites, maladies infectieuses et parasitaires. Ses activités sont médicales, sociales et psychologiques dans le domaine de l'infection VIH, des coinfections VIH - virus des hépatites et proposent des consultations d'éducation thérapeutique et de diététique.

L'activité de recherche clinique est depuis toujours un pôle d'excellence de l'Hôpital Européen.
Nous disposons d'une unité transversale pluridisciplinaire avec une équipe motivée, il est garant des bonnes pratiques cliniques et il a acquis la confiance de nos partenaires publics et privés afin de proposer aux patients la plupart des traitements innovants.

Le pronostic de l'infection VIH a été grandement amélioré depuis l'avènement des traitements antirétroviraux hautement efficaces, mais il nécessite une prise en charge régulière multidisciplinaire comme proposée à l'Hôpital Européen.

Les prises en charge s'articulent sur la réalisation d'un bilan médical, paraclinique et biologique permettant l'évaluation des traitements, de leur efficacité et de leur tolérance qui s'intègrent dans un projet global de soins.

Le traitement de l'infection VIH/SIDA et des co-infections constitue l'un des pôles d'excellence de l'Hôpital Européen.

Le saviez-vous ?

Le VIH ou Virus de l'Immunodéficience Humaine est un rétrovirus humain sexuellement transmissible. Il affaiblit le système immunitaire, et en l'absence de traitement, est responsable du sida. Chaque année, en France, environ 5 000 personnes découvrent leur séropositivité. Dans le monde, on dénombre plus 1,7 million de personnes infectées.

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Long-acting cabotegravir plus rilpivirine for treatment in adults with HIV-1 infection: 96-week results of the randomised, open-label, phase 3 FLAIR study

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Summary

Background There is a need for more convenient, less frequent treatment to help address challenges associated with daily oral HIV treatment in people living with HIV, including stigma, pill burden, drug–food interactions, and adherence. The phase 3 ATLAS and FLAIR studies showed non-inferiority of long-acting cabotegravir and rilpivirine dosed every 4 weeks compared with standard oral therapy for the maintenance of virological suppression in adults with HIV-1 over 48 weeks. We present the 96-week findings.

Methods FLAIR is a randomised, phase 3, open-label, multicentre study done in 11 countries investigating whether switching to long-acting cabotegravir and rilpivirine is non-inferior to daily dolutegravir, abacavir, and lamivudine in virologically suppressed adults living with HIV-1. Antiretroviral therapy (ART)-naive participants received induction therapy with daily oral dolutegravir (50 mg), abacavir (600 mg), and lamivudine (300 mg) for 20 weeks. After 16 weeks, participants with less than 50 HIV-1 RNA copies per mL were randomly assigned (1:1) to continue the standard of care regimen (standard care group) or switch to receive daily oral cabotegravir 30 mg and rilpivirine 25 mg for at least 4 weeks followed by long-acting cabotegravir 400 mg and rilpivirine 600 mg, administered as two 2 mL intramuscular injections, every 4 weeks for at least 96 weeks (long-acting group). Randomisation was stratified by baseline (preinduction) HIV-1 RNA (<100 000 or ≥100 000 copies per mL) and sex at birth and used GlaxoSmithKline-verified randomisation software (RandAll NG, version 1.3.3) for treatment assignment. The primary endpoint was the proportion of participants with plasma HIV-1 RNA of 50 copies per mL or more assessed as per the US Food and Drug Administration (FDA) Snapshot algorithm at week 48, which has been reported previously. Here, we report the proportion of participants with 50 or more HIV-1 RNA copies per mL using the FDA Snapshot algorithm at week 96 (intention-to-treat population; non-inferiority margin 6%). The trial is registered with ClinicalTrials.gov, NCT02938520.

Findings Between Oct 27, 2016, and March 24, 2017, 809 participants were screened. 631 (78%) participants entered the induction phase and 566 (70%) were randomly assigned to either the standard care group (283 [50%] participants) or the long-acting group (283 [50%]). Median age was 34 years (IQR 29 to 43), 62 (11%) were 50 years or older, 127 (22%) were women (sex at birth), and 419 (74%) were white. At week 96, nine (3%) participants in each arm had 50 or more HIV-1 RNA copies per mL, with an adjusted difference of 0·0 (95% CI −2·9 to 2·9), consistent with non-inferiority established at week 48. Across both treatment groups, adverse events leading to withdrawal were infrequent (14 [5%] participants in the long-acting group and four [1%] in the standard care group). Injection site reactions were the most common adverse event, reported by 245 (88%) participants in the long-acting group; their frequency decreased over time. Median injection site reaction duration was 3 days (IQR 2 to 4), and 3082 (99%) of 3100 reactions were grade 1 or 2. No deaths occurred during the maintenance phase.

Interpretation The 96-week results reaffirm the 48-week results, showing long-acting cabotegravir and rilpivirine continued to be non-inferior compared with continuing a standard care regimen in adults with HIV-1 for the maintenance of viral suppression. These results support the durability of long-acting cabotegravir and rilpivirine, over an almost 2-year-long period, as a therapeutic option for virally suppressed adults with HIV-1.

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Introduction

Considerable progress has been made in the treatment of HIV-1 infection since the approval of the first antiretroviral drug, zidovudine, in 1987.[1] Efficacy of modern oral combination antiretroviral therapy (ART) exceeds 90% and approaches 95% in modern clinical

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Research in context

Evidence before this study

We searched PubMed for publications using the search terms "antiretroviral therapy", "cabotegravir", "rilpivirine", "HIV injectable therapy", and "long-acting treatment" for articles published from the inception of the database to July 7, 2020. Considerable progress has been made over the past four decades in the efficacy and tolerability of antiretroviral therapy (ART). This progress means that attaining undetectable viral loads and preventing progression to AIDS is an achievable target for most people living with HIV. Advances in treatment have also yielded ART with greater convenience, with most therapies offering once-daily, fixed-dose combinations administered as single-tablet regimens. Despite this, several challenges associated with the need for daily ART remain, including poor adherence, drug–drug interactions, and fear of stigmatisation. Publications reveal that long-acting therapy would be a welcome alternative to daily oral therapy for some people living with HIV, as has been proven in other medical areas. Of note, the search yielded two phase 3 studies, ATLAS and FLAIR, which showed the long-acting regimen of cabotegravir and rilpivirine given every 4 weeks was non-inferior to daily oral ART regimens on the key primary and secondary efficacy endpoints (proportion of participants with 50 or more HIV-1 RNA copies per mL plasma and proportion of those with less than 50 HIV-1 RNA copies per mL at week 48 per US Food and Drug Administration [FDA] Snapshot algorithm). ATLAS and FLAIR also showed consistent and similar safety profiles, and that a high proportion of participants strongly preferred the long-acting therapy over daily oral therapy.

Added value of this study

This analysis of the FLAIR study is the first to investigate long-acting cabotegravir and rilpivirine over approximately 2 years in a phase 3 study and builds on the 48-week results by providing additional data regarding the durability and continued safety of the regimen. This study showed that, consistent with the 48-week results, long-acting cabotegravir and rilpivirine was non-inferior to continuing current antiretroviral therapy (ART) with respect to the primary and secondary endpoints of plasma HIV-1 RNA at week 96 per FDA Snapshot algorithm. Of note, no participants in the long-acting group experienced confirmed virological failure (two consecutive viral loads ≥200 copies per mL) between the week 48 and week 96 analyses; however, one participant in the standard care group did meet the confirmed virological failure criterion. Over 96 weeks, injection site reactions remained mostly low grade (grade 1 or 2) and reporting continued to decrease beyond the 48-week timepoint, supporting the continued acceptance of the intramuscular injections. Participants also continued to show more treatment satisfaction for the long-acting regimen compared with the current antiretroviral regimen. Taken together, the 96-week findings provide important evidence to support the long-term use of long-acting cabotegravir and rilpivirine in virologically suppressed people living with HIV-1.

Implications of all the available evidence

Many drugs in the HIV therapy pipeline are being developed as long-acting injections or implantable formulations. Long-acting therapy has the potential to alleviate the daily pill taking requirement of contemporary ART and provide a discreet treatment alternative for those who might feel stigma, anxiety, or fear of inadvertent disclosure of HIV status with daily oral dosing. This might alleviate the adherence challenges faced by people living with HIV. Long-acting injectable therapy also bypasses the gastrointestinal tract, eliminating many first pass drug–food and drug–drug interactions. Therefore, long-acting cabotegravir and rilpivirine provides a therapeutic alternative to daily oral therapy, which might be preferable to oral therapy for some people living with HIV-1.

trials.[2–4] Treatment cessation due to adverse events, participant decision, and virological failure is now an infrequent occurence.[5]

Guidelines generally recommend that initial ART regimens comprise an integrase strand transfer inhibitor (INSTI) in combination with one or two nucleoside reverse transcriptase inhibitors (NRTIs).[6,7] Most of these recommended regimens are available as convenient daily single-tablet coformulations.[6] Despite these advances, ART still relies on sustained and continuous adherence to daily oral therapy for viral suppression.[8,9] Poor adherence to ART is associated with drug resistance, disease progression, and increased mortality.[10–12] Furthermore, the lifelong daily dosing requirement might be perceived as a burden by people living with HIV.[13] Surveys of people with HIV have indicated an interest in long-acting ART treatments with reduced dosing frequencies.[14,15] This has increased the emphasis on developing treatments that not only have high efficacy and long-term tolerability, but also have more convenient, less frequent dosing intervals, which could reduce the psychological effect of living with HIV and improve regimen adherence. Therefore, the HIV drug development pipeline contains several drugs that deliver long-acting therapy via non-oral formulations.[16] Non-oral formulations would also eliminate many drug–drug and drug–food interactions that could occur in the gastrointestinal tract with standard daily ART.

Cabotegravir, an INSTI, and rilpivirine, an approved oral non-NRTI, are two drugs formulated for long-acting injectable therapy.[17–19] In conjunction with the long-acting therapy, an oral cabotegravir formulation was also developed in combination with oral rilpivirine to assess the safety profile and side-effects before commencing injectable dosing and for management of planned interruptions of long-acting dosing.[20,21] Following the successful phase 2b LATTE-2 study,[22] the long-acting

cabotegravir and rilpivirine intramuscular regimen dosed every 4 weeks was investigated in two phase 3 studies (FLAIR[20] and ATLAS[21]).

The FLAIR[20] and ATLAS[21] studies are similarly designed randomised controlled trials investigating whether long-acting cabotegravir and rilpivirine as maintenance therapy is non-inferior to continuing current antiretroviral regimen in virally suppressed adults with HIV-1.[20,21] The FLAIR[20] and ATLAS[21] studies each showed that long-acting cabotegravir and rilpivirine dosed every 4 weeks was non-inferior (6% margin) to current antiretroviral regimen with regard to the proportion of participants with virological failure (HIV-1 RNA ≥50 copies per mL) at week 48 (primary endpoint) as per the US Food and Drug Administration (FDA) Snapshot algorithm. A pooled analysis showed non-inferiority to a more stringent 4% margin.[23] The key secondary non-inferiority endpoint of virological success at week 48 was also met, with 94% of participants in FLAIR[20] and 93% of participants in ATLAS[21] with less than 50 HIV-1 RNA copies per mL at the week 48 Snapshot analysis. Both studies showed that the long-acting regimen was generally well tolerated, with participants preferring and having improved satisfaction with the long-acting intramuscular therapy after 48 weeks of treatment. Following the results of these successful large phase 3 studies, monthly long-acting cabotegravir and rilpivirine was approved in Canada, Europe, and the USA. On the basis of these and other clinical studies, along with supporting pharmacokinetic modelling data,[22] the long-acting cabotegravir and rilpivirine regimen is being investigated at a reduced dosing frequency (every 8 weeks) in the ATLAS-2M study,[24] for which the 48-week results showed non-inferior efficacy compared with every 4 weeks dosing.[24]

Here, we report the 96-week findings of the FLAIR study, with the objective of comparing the virological efficacy and safety of long-acting cabotegravir and rilpivirine versus continuing standard oral therapy for the maintenance of viral suppression in adults living with HIV-1.

Methods

Study design and participants

FLAIR is a randomised, multicentre, parallel-group, open-label, phase 3 study evaluating the efficacy, safety, and tolerability of long-acting intramuscular cabotegravir and rilpivirine for maintenance of viral suppression following a switch from a dolutegravir-based daily oral regimen in adults with HIV-1 (appendix p 1). The study was done at 108 centres in 11 countries (Canada [six], France [eight], Germany [11], Italy [five], Japan [three], the Netherlands [four], Russia [13], South Africa [eight], Spain [18], the UK [seven], and the USA [25]). The full inclusion and exclusion criteria, study design,[20] and protocol were published previously.

In brief, eligible participants were aged 18 years or older and ART naive (≤10 days of previous therapy with any antiretroviral agent following diagnosis). FLAIR was done in accordance with the Declaration of Helsinki[25] and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. All participants provided written informed consent. The study protocol, any amendments, the informed consent, and other information that required preapproval were reviewed and approved by a national, regional, or investigational centre ethics committee or institutional review board.

Randomisation and masking

Participants were randomly assigned (1:1) to continue with their current antiretroviral regimen (standard care group) or receive oral cabotegravir and rilpivirine followed by long-acting cabotegravir and rilpivirine (long-acting group). The randomisation schedule comprised a series of blocks (size 4) that were shared across centres via central randomisation, with equal treatment allocation within each block. Randomisation and treatment assignment were facilitated by the interactive response technology through the central Randomisation and Medication Ordering System Next Generation (RAMOS NG, GlaxoSmithKline, Collegeville, PA, USA) system. Following eligibility criteria being met, study site personnel registered participants by means of RAMOS NG for assignment of a unique identifier. A unique treatment number was assigned to each participant, which was used to designate randomisation and treatment assignment. Randomisation was stratified by participants' induction baseline (week –20) HIV-1 RNA (<100 000 copies per mL or ≥100 000 copies per mL) and sex at birth. This was an open-label study; as such all participants, trial staff, and researchers involved in the trial were unmasked.

Procedures

The study involved an induction phase, maintenance phase, and extension phase. In the induction phase, participants received a fixed-dose, single-tablet combination of daily oral dolutegravir (50 mg), abacavir (600 mg), and lamivudine (300 mg; the current antiretroviral regimen) for 20 weeks (week –20 to day 1) to suppress HIV-1 RNA to less than 50 copies per mL. For participants who were HLA-B*5701 positive or for tolerability management related to this current antiretroviral regimen, a non-abacavir NRTI backbone was chosen by the investigator. Participants were randomly assigned to continue the current antiretroviral regimen (standard care group) or to receive long-acting cabotegravir and rilpivirine (long-acting group) in the maintenance phase. Participants in the long-acting group received cabotegravir 30 mg and rilpivirine 25 mg oral lead-in therapy for at least 4 weeks to assess safety and side-effects before initiating long-acting therapy. Long-acting cabotegravir 400 mg and rilpivirine 600 mg were administered as two 2 mL intramuscular injections every 4 weeks for at least 96 weeks. At the start of the

See Online for appendix

For the **protocol** see https://clinicaltrials.gov/ct2/show/NCT02938520

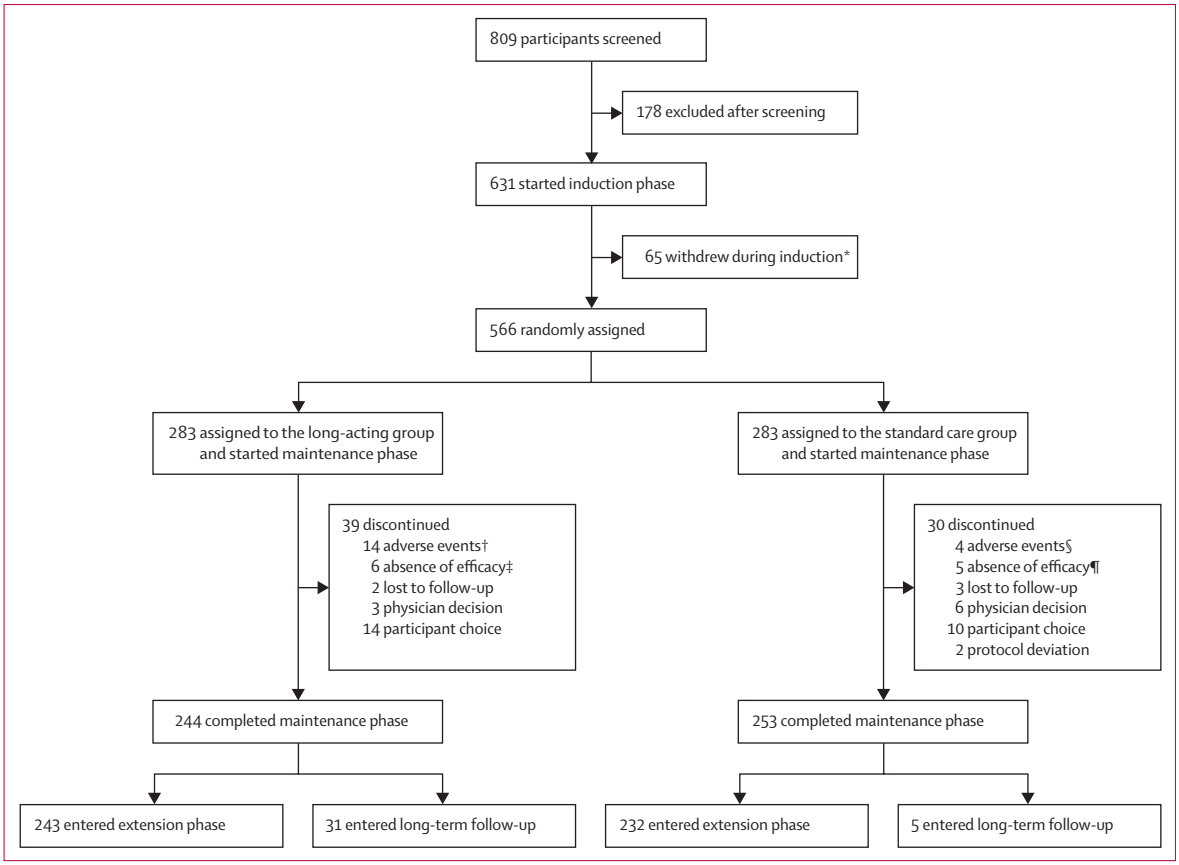

Figure 1: **Trial profile**
Participants who completed the maintenance phase had the option to continue into the extension phase. Participants who received at least one dose of long-acting drugs and discontinued for whatever reason during the maintenance phase entered the long-term follow-up phase for 52 weeks (reasons were not collected for those who did not enter long-term follow-up). *Two participants were withdrawn before receiving study drug. †Three with hepatitis A, three with injection site pain, two with acute hepatitis B, two with depression, one with acute hepatitis C, one with hepatitis C, one with secondary syphilis, one with discomfort, one with diarrhoea, one with vomiting, one with aminotransferase increased, one with adenocarcinoma of colon, participants could discontinue because of more than one adverse event. ‡Includes four due to confirmed virological failure and two with insufficient viral load response. §One with fatigue, one with suicide attempt, one with nausea, one with amnesia, one with disturbance in attention, one with dizziness, one with dysarthria, one with renal failure, participants could discontinue because of more than one adverse event. ¶Includes four due to confirmed virological failure and one with insufficient viral load response.

extension phase at week 100, participants in the standard care group had the option to switch to the long-acting group or complete the study; participants in the long-acting group could continue to receive intramuscular cabotegravir and rilpivirine or withdrew. Any participant who had confirmed virological failure (two consecutive plasma HIV-1 RNA concentrations ≥200 copies per mL) at any point in the study was discontinued. Any participant who received at least one dose of long-acting cabotegravir or rilpivirine but discontinued for any reason entered long-term follow-up for 52 weeks. Planned analyses were done after participants had completed their visits at weeks 48 and 96, with an additional analysis planned for week 124 for participants in the extension phase.

Adverse events were graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. Treatment satisfaction was measured by the change from maintenance baseline in HIV Treatment Satisfaction Questionnaire status version, acceptability of injection site reactions (ISRs) was assessed as part of the Perception of Injection questionnaire, and general treatment acceptance was measured by the Chronic Treatment Acceptance questionnaire. Integrase was genotyped retrospectively from plasma samples collected at baseline and at the time of suspected virological failure.

Outcomes

The primary endpoint was the proportion of participants with plasma HIV-1 RNA of 50 copies per mL or more assessed with the FDA Snapshot algorithm at week 48, which has been reported previously.[20] The key secondary efficacy endpoints assessed at week 96 were the proportion of participants with 50 or more HIV-1 RNA copies per mL and the proportion with less than 50 HIV-1 RNA copies per mL (using the FDA Snapshot algorithm). Other protocol-defined endpoints assessed at week 96 included virological outcome across

randomisation strata, absolute values and changes from baseline in CD4 lymphocyte count over time, incidence of confirmed virological failure (two consecutive HIV-1 RNA ≥200 copies per mL), treatment-emergent genotypic resistance, the incidence and severity of adverse events and absolute values and changes in laboratory abnormalities over time, change from baseline in fasting lipids over time, the number of discontinuations for adverse events, cabotegravir and rilpivirine plasma concentrations collected at specific timepoints between week 48 and week 96, and participant adherence to dosing schedule. Participant-reported outcomes assessed at week 96 included satisfaction, acceptance of pain and ISRs, tolerability of injections, health-related quality of life, health status, and general treatment acceptance. Virological outcome by participant characteristic was exploratory. Additionally, following the findings of the Leu74Ile integrase polymorphism in the three participants with confirmed virological failure in the 48-week analysis, a post-hoc analysis was done to understand the effect of this substitution on virological outcome at the week 96 Snapshot.

Statistical analysis

The study was designed to determine whether long-acting cabotegravir and rilpivirine was non-inferior at week 48 compared with continuing current antiretroviral regimen. The efficacy analysis at week 96 was a repeat evaluation of the week 48 primary and secondary efficacy analysis, in which the proportion of participants with 50 or more HIV-1 RNA copies per mL and those with less than 50 HIV-1 RNA copies per mL were summarised at week 96 using the FDA Snapshot algorithm. No adjustment was made for multiplicity because the week 96 analyses are secondary.

The statistical analysis for the efficacy measures and rationale have been presented previously.[20] The efficacy analysis included all participants who received at least one dose of study drug during the maintenance phase (intention-to-treat population). For the primary efficacy analysis, non-inferiority of the long-acting regimen to the standard care regimen was concluded if the upper bound of a two-sided 95% CI for the difference in the proportion of participants with 50 or more HIV-1 RNA copies per mL between the two treatment groups was less than 6%. For the proportion of participants with less than 50 HIV-1 RNA copies per mL, a non-inferiority margin of –10% was used with a one-sided significance level of 2·5%. The efficacy analysis endpoints were repeated for the per-protocol population, which excluded all participants with major protocol violations (eg, study treatment not administered per protocol, biological sample deviations, particpants not meeting the inclusion criteria, and protocol-prohibited medication administered. The trial is registered with ClinicalTrials.gov, NCT02938520.

Role of the funding source

This study was funded by ViiV Healthcare and Janssen Research and Development. The funders participated in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Results

Screening took place between Oct 27, 2016, and March 24, 2017. In total, 809 participants were screened, 631 (78%) of whom entered the induction phase. 566 (90%) of the 629 participants who then initiated study drug (intention-to-treat population) entered the maintenance phase and were randomly assigned to the long-acting group (283 [50%] participants) or the standard care group (283 [50%] participants; figure 1). Of those in the intention-to-treat population, 244 (86%) participants in the long-acting group and 253 (89%) participants in the standard care group completed the maintenance phase (100 weeks). 39 (14%) participants did not complete the study in the long-acting group, the most common reasons for which were adverse events (14 [36%] participants) and withdrawal by participant (14 [36%] participants). 30 (11%) participants did not complete the study in the standard care group, the most common reason for which was withdrawal by the participant (ten [33%]). 243 (86%; one participant completed the maintenance phase but did not enter the extension phase) participants in the long-acting group and

	Long-acting group (n=283)	Standard care group (n=283)	Total (n=566)
Median age (IQR), years	34 (29–42)	34 (29–43)	34 (29–43)
Age ≥50 years	33 (12%)	29 (10%)	62 (11%)
Sex*			
Female	63 (22%)	64 (23%)	127 (22%)
Male	220 (78%)	219 (77%)	439 (78%)
Transgender† (male to female)	2 (<1%)	0	2 (<1%)
Race			
White	216 (76%)	203 (72%)	419 (74%)
Black or African American	47 (17%)	56 (20%)	103 (18%)
Other	20 (7%)	24 (8%)	44 (8%)
Median body-mass index (IQR), kg/m²	24 (22–27)	24 (22–27)	24 (22–27)
HIV-1 RNA, copies per mL			
<100 000	227 (80%)	227 (80%)	454 (80%)
≥100 000	56 (20%)	56 (20%)	112 (20%)
Median baseline CD4 lymphocyte count (IQR), cells per µL	437 (314–609)	452 (321–604)	444 (320–604)
<200 cells per µL	16 (6%)	23 (8%)	39 (7%)
Median day 1 CD4 lymphocyte count (IQR), cells per µL	624 (473–839)	625 (472–799)	625 (473–818)
HIV-1 and HCV co-infection	19 (7%)	9 (3%)	28 (5%)

All data are n (%) unless otherwise stated. Baseline is induction baseline (week –20) unless stated otherwise. HCV=hepatitis C virus. *Sex at birth. †Self-reported gender.

Table 1: **Baseline characteristics**

232 (82%; 21 participants completed the maintenance phase but did not enter the extension phase) in the standard care group entered the extension phase.

Baseline characteristics were similar between the two groups.[20] Participants in the intention-to-treat population had a median age of 34 years (IQR 29–43), 62 participants (11%) were 50 years or older, 127 (22%) were women (sex at birth), and 419 (74%) were white (table 1).[20] In both groups, 14 (5%) participants received an alternate NRTI other than abacavir at the end of the induction phase (appendix p 7).

In the long-acting group, 278 (98%) participants received at least one injection in the maintenance phase, and had 6005 expected injection visits after the first injection visit at week 4. 5842 (97%) of 6005 injection visits occurred within 7 days of the expected dosing visit, with 2556 (43%) of the 6005 injection visits occurring on the planned visit day. Of the 152 (3%) injection visits more than 7 days before or after the dosing visit, 14 (9%) occurred more than 14 days after the planned visit day; no injections occurred more than 14 days before the planned visit (appendix p 2). 11 (<1%) injection visits were missed across ten participants; ten (91%) of the missed visits were covered by oral bridging with cabotegravir and rilpivirine. Virological suppression was maintained in all participants who had missed visits.

At week 96 (FDA Snapshot algorithm), nine (3%) participants in each group had 50 or more HIV-1 RNA copies per mL, with an adjusted difference of 0·0 (95% CI –2·9 to 2·9) supporting the 48-week non-inferiority findings of the primary endpoint (table 2). Similarly, 245 (87%) participants in the long-acting group and 253 (89%) participants in the standard care group had less than 50 HIV-1 RNA copies per mL, with an adjusted difference at week 96 of –2·8 (–8·2 to 2·5), similar to the 48 week results.[20] Both efficacy endpoints were similar in the per-protocol population (table 2). There was no statistically significant treatment difference by sex at birth for participants with 50 or more HIV-1 RNA copies per mL (p=0·63) and those with less than 50 HIV-1 RNA copies per mL (p=0·49). There was also no significant difference between viral load at induction baseline (week –20) in those with 50 or more HIV-1 RNA copies per mL (p=0·65) and those with less than 50 HIV-1 RNA copies per mL (p=0·31). Treatment differences were also generally consistent across other baseline subgroups (appendix pp 3–4). Median CD4 lymphocyte count increased from maintenance phase baseline to week 96 by 57 (IQR –43 to 181) cells per µL in the long-acting group (246 [87%] participants) and 109·5 (18 to 228) cells per µL in the standard care group (254 [90%] of 283 participants).

Apart from those previously described for the week 48 analysis,[20] no additional participants had confirmed virological failure between week 48 and 96 in the long-acting group. As previously described, four (1%) participants met the criterion in the week 48 analysis (table 2), three of whom selected for on-treatment non-NRTI and INSTI resistance-associated mutations at failure. The Leu74Ile integrase polymorphism was present in these three participants at virological failure, each of whom had HIV-1 subtype A1. The participant with no mutations temporarily discontinued therapy during the oral lead-in period due to a false-positive pregnancy test. On reinitiating therapy, the participant met the confirmed virological failure criterion and was withdrawn before receiving long-acting treatment; this participant had HIV-1 subtype AG. Additional details of the resistance profiles are presented in the 48 week analysis.[20] In the standard care group, in addition to the three (1%) participants with confirmed virological failure at week 48, one (<1%) participant had confirmed virological failure between the week 48 and week 96 analysis. This confirmed virological failure occurred at week 64 and no resistance-associated mutations were detected. In the post-hoc analysis of participants with integrase genotypic results to better understand the role of Leu74Ile and other integrase polymorphisms, pre-existing integrase polymorphisms were found in 96 (37%) of 261 participants in the long-acting group and 90 (34%) of 261 participants in the standard care group; Leu74Ile and glycine to glutamic acid at position 193 (Gly193Glu) polymorphisms accounted for most of those present (appendix p 8). In the long-acting group, 48 (86%) of 56 participants with Leu74Ile and 179 (87%) of 205 participants without Leu74Ile had less than 50 HIV-1 RNA copies per mL at week 96 compared with 44 (88%) of 50 participants with Leu74Ile and 188 (89%) of 211 participants without Leu74Ile in the standard care group. The difference between the two groups (long-acting minus standard of care) was –2·3 (95% CI –16·0 to 11·7) in participants with Leu74Ile and –1·8 (–8·2 to 4·7) in participants without Leu74Ile. For the Snapshot failure endpoint, five (9%) of 56 participants with Leu74Ile and four (2%) of 205 participants without Leu74Ile had 50 or more HIV-1 RNA copies per mL at week 96 in the long-acting group compared with two (4%) of 50 participants with Leu74Ile and seven (3%) of the 211 participants without Leu74Ile in the standard care group. The difference between the two groups (long-acting minus standard of care) was 4·9 (–5·9 to 16·3) for participants with Leu74Ile and –1·4 (–5·1 to 2·1) for those without Leu74Ile.

During the maintenance phase, when excluding ISRs, 264 (93%) of 283 participants in the long-acting group and 242 (86%) of 283 participants in the standard care group had an adverse event (table 3). Of these, 18 events in both groups occurred in participants who had not reported an adverse event before the week 48 nominal cutoff point. The three most common adverse events in both groups, excluding ISRs, were nasopharyngitis, headache, and upper respiratory tract infection (appendix p 9). More participants reported drug-related adverse events (excluding ISRs) in the long-acting group

	Long-acting group (n=283)	Standard care group (n=283)	Difference, percentage points (95% CI)*†	Adjusted difference, percentage points (95% CI)*‡
Snapshot outcomes (intention-to-treat population)				
HIV-1 RNA <50 copies per mL§	245 (87%)	253 (89%)	−2·8 (−8·2 to 2·5)	−2·8 (−8·2 to 2·5)
HIV-1 RNA ≥50 copies per mL§	9 (3%)	9 (3%)	0·0 (−2·9 to 2·9)	0·0 (−2·9 to 2·9)
Data in window not below threshold	3 (1%)	2 (<1%)	..	..
Discontinued for absence of efficacy	6 (2%)	5 (2%)	..	..
Discontinued for other reason while not below threshold	0	2 (<1%)¶	..	..
No virological data in week 96 window	29 (10%)	21 (7%)	..	..
Discontinued due to adverse event‖	12 (4%)	4 (1%)	..	..
Discontinued for other reason	16 (6%)**	17 (6%)††	..	..
On study but missing data in window	1 (<1%)	0	..	..
Snapshot outcomes (per-protocol population)				
HIV-1 RNA <50 copies per mL§	241/278 (87%)	252/281 (90%)	−3·0 (−8·3 to 2·4)	−3·0 (−8·3 to 2·4)
HIV-1 RNA ≥50 copies per mL§	9/278 (3%)	9/281 (3%)	0·0 (−2·9 to 3·0)	0·1 (−2·9 to 2·9)
Confirmed virological failure (intention-to-treat population)				
Confirmed virological failure between week 48 and 96	0	1 (<1%)‡‡	..	..
Total confirmed virological failures at week 96	4 (1%)§§	4 (1%)	..	..
Total treatment-emergent resistance	3 (1%)	0	..	..
Test for homogeneity by stratum for plasma HIV-1 RNA ≥50 copies per mL (intention-to-treat population)				
Sex at birth				
Female	4/63 (6%)	3/64 (5%)	1·7 (−7·9 to 11·4)	..
Male	5/220 (2%)	6/219 (3%)	−0·5 (−3·9 to 2·9)	..
p value for test of homogeneity	..	..	0·625	..
Baseline HIV-1 RNA level				
<100 000 copies per mL	5/227 (2%)	6/227 (3%)	−0·4 (−3·7 to 2·8)	..
≥100 000 copies per mL	4/56 (7%)	3/56 (5%)	1·8 (−8·7 to 12·5)	..
p value for test of homogeneity	..	..	0·645	..
Test for homogeneity by stratum for plasma HIV-1 RNA <50 copies per mL (intention-to-treat population)				
Sex at birth				
Female	52/63 (83%)	57/64 (89%)	−6·5 (−19·6 to 6·4)	..
Male	193/220 (88%)	196/219 (89%)	−1·8 (−8·0 to 4·3)	..
p value for test of homogeneity	..	..	0·492	..
Baseline HIV-1 RNA level				
<100 000 copies per mL	200/227 (88%)	203/227 (89%)	−1·3 (−7·3 to 4·6)	..
≥100 000 copies per mL	45/56 (80%)	50/56 (89%)	−8·9 (−23·0 to 5·1)	..
p value for test of homogeneity	..	..	0·305	..

Data are n (%) or n/N (%), unless otherwise stated. *95% CIs were calculated using an unconditional exact method with two inverted one-sided tests based on the score statistic. †Difference equals proportion in the long-acting group minus proportion in the standard care group. ‡On the basis of the Cochran-Mantel-Haenszel stratified analysis adjusting for the following baseline stratification factors: sex at birth (male or female) and induction baseline (week −20) HIV-1 RNA (<100 000 copies per mL *vs* ≥100 000 copies per mL). §Per US Food and Drug Administration Snapshot algorithm. ¶One relocation, one lost to follow-up. ‖No deaths occurred during the maintenance phase. **In the long-acting group, 16 participants discontinued due to reasons other than adverse events: three relocated, two intended to become pregnant, two because of tolerability of injections, two were lost to follow-up, one needed to initiate prohibited medication, one was incarcerated, one become pregnant, one frequency of visits (study required too many visits), one was unable to travel to the clinic, one changed jobs, one regularly rescheduled visits. ††In the standard care group, 17 participants discontinued due to reasons other than adverse events: four frequency of visits (study required too many visits), three did not comply with study treatment and protocol procedures, two relocated, one decided to stop treatment, one was late to attend visits, one was lost to follow-up, one became pregnant, one was unable to travel to the clinic, one because of substance use, one because of a ViiV Safety and Labelling Committee decision, one unspecified. ‡‡Current antiretroviral therapy confirmed virological failure occurred at week 64 with no resistance mutations. §§One participant had oral cabotegravir and rilpivirine dosing interrupted due to a false-positive pregnancy test; upon re-initiation of oral therapy they had suspected virological failure that was confirmed.

Table 2: **Efficacy outcomes at week 96**

(95 [34%] of 283 participants) compared with the standard care group (33 [12%] of 283 participants); only pyrexia (17 [6%]) and headache (15 [5%]) occurred in more than 5% of participants in the long-acting group. Nausea (seven [2%] of 283 participants), fatigue (five [2%]), headache (four [1%]), and decreased creatinine renal clearance (three [1%]) were the only drug-related adverse events in the standard care group that occurred in more than 1% of participants. There were no drug-related hypersensitivity reactions to long-acting therapy.

	Cumulative week 96 data analysis		Cumulative week 48* data analysis		New participants with adverse events between week 48 and week 96 data analysis†	
	Long-acting group (n=283)	Standard care group (n=283)	Long-acting group (n=283)	Standard care group (n=283)	Long-acting group (n=283)	Standard care group (n=283)
Any adverse event	274 (97%)	242 (86%)	267 (94%)	225 (80%)	7 (2%)	17 (6%)
Excluding ISRs	264 (93%)	242 (86%)	246 (87%)	225 (80%)‡	18 (6%)	18 (6%)
Any grade 3–4 adverse event	40 (14%)	16 (6%)	31 (11%)§	11 (4%)	10 (4%)	5 (2%)
Excluding ISRs	29 (10%)	16 (6%)	22 (8%)§	11 (4%)	8 (3%)	5 (2%)
Any drug-related adverse events	246 (87%)	33 (12%)	236 (83%)	28 (10%)	10 (4%)	5 (2%)
Excluding ISRs	95 (34%)	33 (12%)	79 (28%)	28 (10%)‡	16 (6%)¶	6 (2%)‖
Drug-related grade 3–4 adverse events	16 (6%)	0	14 (5%)	0	2 (1%)	0
Any serious adverse event	24 (8%)	22 (8%)	18 (6%)	12 (4%)	6 (2%)	10 (4%)
Drug-related serious adverse events	1 (<1%)	0	1 (<1%)	0	0	0
Adverse events leading to withdrawal	14 (5%)**	4 (1%)††	9 (3%)	4 (1%)	5 (2%)	0
Deaths	0	0	0	0	0	0

All data are n (%). ISR=injection site reaction. *Week 48 is a nominal cutoff point and contains data collected for participants with dosing beyond week 48 (approximately 25% with dosing >64 weeks).[20] †Participants with first reported adverse events of the type specified occurring after the week 48 data analysis reporting date. ‡Includes one participant at week 48 data analysis who was not present at week 96 data analysis. §Includes one participant with grade 4 adverse event at week 48 data analysis but was corrected to grade 2 at week 96 data analysis. ¶Two pyrexia, two fatigue, two dizziness, one headache and nausea, one presyncope, one depressed mood, one pyrexia and chills, one chronic sinusitis and chronic tonsillitis, one back pain and nasopharyngitis, one musculoskeletal pain, one anxiety, one influenza-like illness, and one asthenia and depressed mood. ‖One participant with diarrhoea, abdominal pain, nasopharyngitis, and eye pain; one with insomnia; one with abnormal dreams; one with poor quality sleep; one with nausea; and one with hypercholesterolaemia and a decrease in vitamin D. **Three due to hepatitis A; three due to injection site pain; two due to acute hepatitis B; two due to depression; and one each due to acute hepatitis C, hepatitis C, secondary syphilis, discomfort, diarrhoea, vomiting, aminotransferase increased, and adenocarcinoma of colon; a participant could have more than one reason for withdrawal. ††One each due to fatigue, suicide attempt, nausea, amnesia, disturbance in attention, dizziness, dysarthria, and renal failure; a participant could have more than one reason for withdrawal.

Table 3: **Summary of adverse events**

The incidence of serious adverse events was similar in both groups, occurring in 24 (8%) participants in the long-acting group compared with 22 (8%) participants in the standard care group. Most serious adverse events occurred in participants before the 48-week nominal cutoff (table 3). There were more withdrawals because of adverse events in the long-acting group (14 [5%] participants) compared with the standard care group (four [1%] participants) throughout the maintenance phase. Of these, five (2%) in the long-acting group and three (1%) in the standard care group were drug related. The only adverse events that led to withdrawal in more than one participant, all of whom were in the long-acting group, were hepatitis A (three [1%] participants) and hepatitis B (two [1%] participants), injection site pain (three [1%] participants), and depression (two [1%] participants). Five participants, all in the long-acting group, withdrew between week 48 and 96 because of adverse events (two [1%] due to depression, one [<1%] due to hepatitis A, one [<1%] due to hepatitis C, and one [<1%] due to injection site pain). The two reports of depression and one report of injection site pain were considered related to the study drug. Participant bodyweight increased in both groups from induction baseline to week 96: a median weight gain of 2·0 kg (IQR –0·7 to 6·0) occurred in the long-acting group, an increase of 0·7 kg from week 48; a median weight gain of 2·0 kg (–0·9 to 5·0) occurred in the standard care group, an increase of 0·5 kg from week 48. In the long-acting group, 93 (33%) participants had a more than 5% weight gain and 46 (16%) participants had a more than 10% weight gain compared with 85 (30%) with a more than 5% weight gain and 33 (12%) with a more than 10% weight gain in the standard care group. Body-mass index category shifts representing weight gain between induction baseline and week 96 occurred in 44 (18%) participants in the long-acting group and 45 (18%) participants in the standard care group, with ten (4%) participants in the long-acting group and 19 (7%) participants in the standard care group experiencing shifts indicative of weight loss (appendix p 10).

In total, 278 (98%) of 283 participants received at least one long-acting injection, 245 (88%) of whom experienced an ISR event. However, most were low grade, with only 13 (5%) participants experiencing a grade 3 ISR. There were no grade 4 or grade 5 ISRs. The most frequently occurring ISR was injection site pain, reported by 238 (86%) participants who received at least one injection. The highest incidence of ISRs followed the initial 3 mL injections at week 4, occurring in 199 (72%) participants. There was an overall decrease in the incidence of ISRs over time at the week 96 analysis (figure 2), reducing to 45 (18%) of 245 participants following the week 96 visit. Ten (77%) of 13 participants who had a grade 3 ISR did so on their initiation injections at week 4. Only four grade 3 ISR events were reported after week 8 (these occurred at weeks 52, 64, 88, and 96).

A total of 12 522 injections were administered at week 96, of which 3100 (25%) resulted in an ISR (appendix p 11). Injection site pain was the most common, occurring

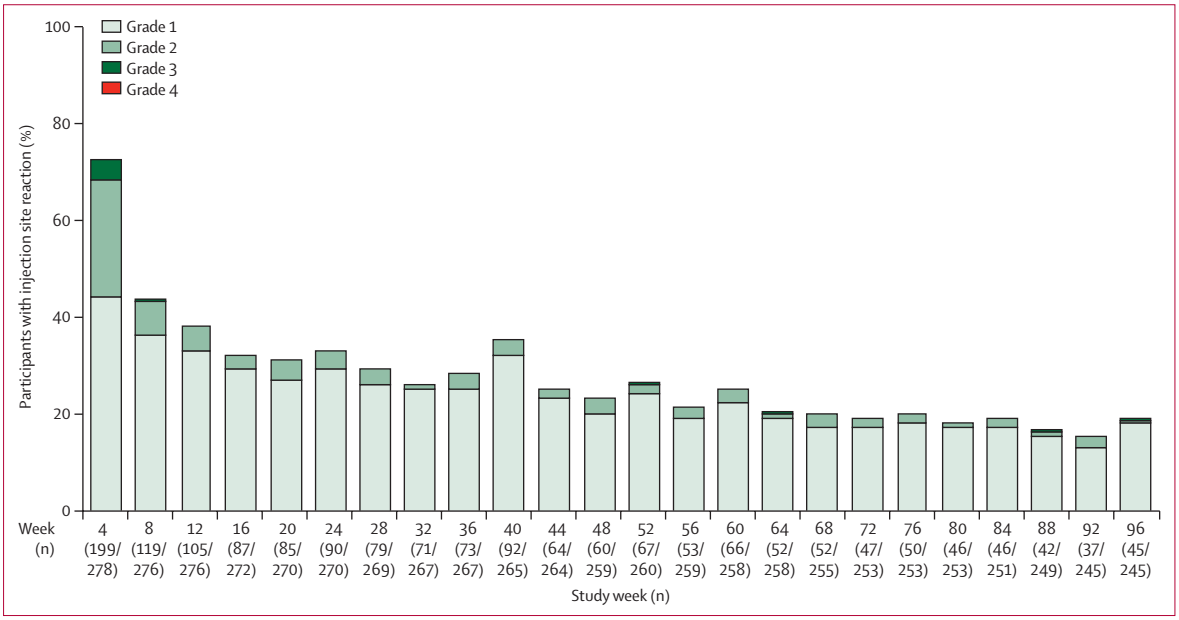

Figure 2: **Injection site reaction incidence over time through week 96**
Incidence is derived relative to the number of participants who received injections at each respective study visit. There were no grade 4 injection site reactions.

after 2613 (21%) of 12 522 injections and accounting for 2613 (84%) of 3100 of all ISRs. Injection site nodule (132 [1%] ISRs) was the only other ISR to occur with 1% or more of injections. No ISRs were reported as serious adverse events. Between weeks 48 and 96, three (1%) participants withdrew due to ISRs, one of whom withdrew after the week 48 analysis. An additional three participants withdrew consent due to intolerability of injections, two of which were included in the week 48 analysis. 2746 (89%) ISRs resolved within 7 days (median duration 3 days [IQR 2–4]).

No clinically relevant differences were observed in 28 clinical laboratory abnormalities relative to maintenance baseline, for either chemistry or haematology, between treatment groups at the week 96 analysis. In the maintenance phase, lipase elevation adverse events were seen in seven (2%) participants in the long-acting group, with four grade 3 or higher events, and four (1%) participants in the standard care group, with two grade 3 or higher events. There was one case of pancreatitis, which occurred in the long-acting group before the week 48 nominal cutoff and was not considered study drug related. Adverse events of creatine blood phosphokinase increases occurred in 11 (4%) participants in the long-acting group and eight (3%) participants in the standard care group; five creatine blood phosphokinase-related grade 3 or 4 events were reported, all in the long-acting group. No elevations in creatine blood phosphokinase were associated with myositis or rhabdomyolysis; these could be explained by participant exertion or exercise. 17 (6%) participants in the long-acting group and six (2%) in the standard care group had aminotransferase elevations at least three times the upper limit of normal. Protocol-defined liver stopping criteria were met by nine (3%) participants in the long-acting group and three (1%) in the standard care group, with two events in the long-acting group and one in the standard care group occurring after the week 48 analysis. Eight of the nine participants with liver stopping criteria in the long-acting group had acute viral hepatitis (three with hepatitis A, three with hepatitis B, and two with hepatitis C); the stopping criteria in the ninth participant was considered to be related to recreational drug use. Of the three participants with liver stopping criteria in the standard care group, one had acute viral hepatitis A, one had acute viral hepatitis E, and one had transaminitis related to acute cholecystitis. None of the hepatitis events were considered to represent drug-induced liver injury.

Plasma cabotegravir and rilpivirine concentrations in the second year of the long-acting regimen remained largely similar to those reported at 48 weeks in the FLAIR,[20] ATLAS,[21] and LATTE-2[22] studies and were similar to those reported following daily oral cabotegravir (10 mg) and rilpivirine (25 mg) in the LATTE study.[26] For the primary analysis at week 48, steady state was confirmed for cabotegravir at week 44, with a small amount of ongoing accumulation for rilpivirine. Steady state was not formally reassessed using data until week 96, but rilpivirine predose concentrations appeared to plateau between week 60 and week 96, with only a small increase in rilpivirine plasma concentration between week 48 and week 96, in line with the long-acting rilpivirine half-life (appendix p 5). This plateauing is evident from the rilpivirine geometric mean concentrations from the final two visits of the maintenance phase (week 96 111·6 ng/mL [95% CI 105·7–117·7]; week 100 109·8 ng/mL [104·2–115·6]).

At week 96, participants in the long-acting group had an improvement in treatment satisfaction from maintenance baseline (study day 1) compared with participants in the standard care group, with an adjusted mean difference of 2·3 (95% CI 1·1 to 3·5; p=0·00029; appendix p 6). There was an improvement (p<0·0001) in the mean from week 5 (2·08 [SD 1·04]) to week 96 (1·71 [0·85]) in the acceptability of ISRs dimension of the Perception of Injection questionnaire. In the long-acting group, 237 (85%) participants considered local reactions and pain as totally acceptable; 227 (82%) considered local reactions and pain as very acceptable following injections at week 96. Mean scores for the general acceptance domain of the Chronic Treatment Acceptance questionnaire were high at baseline in both groups (long-acting group 86·0 [SD 21·27] *vs* standard care group 83·4 [23·68]), and remained high throughout the study duration, with numerical but not statistically significant improvements (p=0·37) in favour of the long-acting group at week 96 (adjusted mean change from baseline in the long-acting group 1·9 [95% CI –1·0 to 4·9]; standard care group 0·0 [–2·8 to 2·9]).

Discussion

The 96-week results of this large phase 3 trial build on the 48-week findings and show that every 4 weeks dosing of the long-acting regimen is a durable therapy for maintaining viral suppression in ART-naive adults with HIV-1 following suppression with 20 weeks of dolutegravir, abacavir, and lamivudine before initiation of the long-acting regimen. Non-inferiority to continuing the dolutegravir-based standard oral regimen was shown across both efficacy endpoints (plasma HIV-1 RNA ≥50 copies per mL and <50 copies per mL at week 96) regardless of sex at birth and viral load at induction baseline.

The number of confirmed virological failures at the week 96 analysis was low (four participants [1%]) in the long-acting group and consistent with other phase 3 switch studies.[3,4] No confirmed virological failures in the long-acting group occurred since the week 48 analysis. The longer term durability of long-acting cabotegravir and rilpivirine shown in this analysis is consistent with data from the LATTE-2 phase 2b study,[27] which showed that the long-acting therapy provided durable viral suppression over 3 years. The post-hoc analysis, done in response to the presence of the Leu74Ile polymorphism in three participants with confirmed virological failure reported in the 48-week analysis,[20] showed that Leu74Ile alone had no effect on the proportion of participants with less than 50 HIV-1 RNA copies per mL at week 96 in the long-acting group (appendix page 4). This is consistent with International Antiviral Society–USA guidelines, which do not consider Leu74Ile an INSTI resistance-associated mutation.[28] The data also suggest that the treatment difference between groups was similar across the Leu74Ile subgroups. The overall effect of Leu74Ile in the context of subtype is not completely understood. Additional research is underway to evaluate the potential for interactions between HIV-1 subtype and the Leu74Ile polymorphism.[29]

The high compliance to the long-acting treatment schedule during the approximately 2 years of therapy, with 97% of injection visits occurring within 7 days of the specified dosing visit, might reflect the inherent flexibility of the regimen. The successful oral bridging of ten planned missed injection visits without any associated virological failures or virological blips is consistent with pharmacokinetic modelling data,[30] and shows that oral bridging is a method to manage missed injections.

Consistent with the 48-week analysis of both FLAIR[20] and ATLAS,[21] ISRs were the most frequently reported adverse event at the 96 week analysis. Following the previously reported decrease in ISR incidence from 199 (72%) participants at week 4 to 60 (23%) participants at week 48,[20] ISR incidence continued to decrease to 45 (18%) participants at week 96. Similarly, grade 3 ISRs were infrequent after week 48, reported by only 1% of participants. These findings, coupled with the low discontinuation rate due to ISRs (six [2%] of 283 participants), suggest ISRs were acceptable in most participants. Excluding ISRs, adverse events occurred more often in the long-acting group compared with the standard care group. There were also more drug-related adverse events in the long-acting group compared with the current antiretroviral regimen group. The higher incidence of some adverse events (excluding ISRs) in the long-acting group might have been influenced by participants switching to a new therapy versus those continuing with the standard care regimen. This effect in switch studies has been noted previously.[3] The most common adverse events related to long-acting therapy (pyrexia and headache) in this study are consistent with the 48-week findings in the ATLAS trial.[21] There were no study discontinuations attributed to pyrexia. Of note, pyrexia is generally not the objective measurement of fever, but a subjective symptom reported to the investigator. The overall higher rates of withdrawal in the long-acting group are largely attributable to adverse events not related to the study drug (long-acting group, nine [3%] participants *vs* standard care group, one [<1%] participant). In terms of specific adverse events, the higher incidence of hepatitis and ISRs in the long-acting group was the primary reason for the higher number of withdrawals observed. Median weight change at the 96 week analysis was similar between groups and consistent with those reported in previous clinical trials.[31]

Median trough plasma concentrations, including 5th and 95th percentiles, of both cabotegravir and rilpivirine remained well above their respective in vitro protein-adjusted concentrations required for 90% inhibition from week 48 to 96.

Participant-reported outcome data show that participants continued to be highly satisfied with the

long-acting therapy over a period of nearly 2 years, comprising 24 injection visits. The acceptability of ISRs was high following participants' first injection visits and improved significantly over time. High baseline values for treatment satisfaction are a limiting factor for showing clinically meaningful improvements, partly because of ceiling effects of the HIV Treatment Satisfaction Questionnaire. In addition, the improvement in acceptability of ISRs over time, although significant, does not meet the threshold for minimal clinically important difference according to the distribution-based approach. However, these findings are consistent with the low rates of discontinuations and the reduced frequency and severity of ISRs observed over time. Taken together, these findings suggest that participants perceived injections as a beneficial trade-off to obviate the need for daily oral dosing.

Like other medical areas, long-acting cabotegravir and rilpivirine might have benefits for those with adherence challenges due to the reduced dosing frequency. However, in this study, participants were adherent to oral therapy before moving to the long-acting regimen; therefore, this assumption remains speculative. The LATITUDE trial (NCT03635788), which is investigating long-acting cabotegravir and rilpivirine specifically in participants with suboptimal adherence, will provide further information in this regard. Similarly, long-acting cabotegravir and rilpivirine currently require healthcare professionals to directly administer the doses; therefore, the effect of increased clinic visits on patients and services is yet to be fully understood. Research is ongoing to determine the best implementation practices for long-acting cabotegravir and rilpivirine (CUSTOMIZE NCT04001803). An additional limitation is the absence of masking, which might induce bias in both participants and investigator; however, this is inherent with an open-label design. An absence of masking is unlikely to affect the primary efficacy endpoint, which is based on objective viral load measurements. However, the open-label design could have influenced reporting of adverse events by participants and investigators who might be biased by anticipations of adverse events due to a novel intervention.[32] Of note, participants with hepatitis B co-infection were excluded from this study and the long-acting cabotegravir and rilpivirine regimen has not been studied in patients with a hepatitis B co-infection. In addition, this study was not done in a low-income country, which might restrict the generalisability of potential benefits. Finally, although the current analysis builds on the 48-week results by showing that the long-acting regimen is well tolerated over 96 weeks, additional long-term data are important and will be provided by the extension phase.

In summary, long-acting cabotegravir and rilpivirine was non-inferior to continuing standard three-drug oral therapy in adults living with HIV-1 for the maintenance of viral suppression over 96 weeks of therapy. These results support the durability of the long-acting regimen over a 2-year period as a therapeutic option for virally suppressed adults with HIV-1 who might benefit from a less frequent, every 4 weeks, dosing interval.

Contributors

CO, SO, PPh, CB, AB, DG, OD, JGG, EBM, and DHST recruited, enrolled, and followed up participants, and were involved in data acquisition. RD, DD, SG, ST, MSC, RVS-R, HC, SLF, PPa, VC, SV, AC, VVE, KV, DAM, KYS, and WRS analysed the data. RD, DD, SG, ST, MSC, RVS-R, HC, SLF, PPa, VC, SV, AC, VVE, KV, DAM, KYS, and WRS conceptualised and designed the study. DM, RD, SG, WS, and KV were responsible for study resources. RD, DD, and SG verified the study data. All authors were involved in the drafting and review of the manuscript and approved the final version. All authors vouch for the accuracy and completeness of the data, data analyses, and interpretation, and fidelity to the protocol. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

CO reports personal fees for travel to conferences, lectureship fees, contributions to advisory boards and development of slide decks from ViiV Healthcare, Gilead Sciences, MSD, and Janssen and received grants from ViiV Healthcare, Gilead Sciences, MSD, and Janssen. SO reports grants and personal fees from MSD; personal fees from Janssen; grants, personal fees, and non-financial support from Gilead Sciences; personal fees from Trii Pharmaceutical; and grants from ViiV Healthcare, outside of the submitted work. CB reports personal fees as an advisory board member and speaker for Gilead; grants from ViiV Healthcare and Gilead as a speaker; and grants from GlaxoSmithKline, Janssen, and Sangamo as a principle investigator. DG reports personal fees from GlaxoSmithKline, during the conduct of the study. JGG reports grants as an advisory board member for ViiV Healthcare, Gilead Sciences, MSD, Janssen, and Cilag, outside the submitted work. EM reports grants from ViiV Healthcare, during the conduct of the study; and grants, personal fees, and non-financial support from Gilead Sciences, Janssen, and MSD, outside the submitted work. DHST reports grants from Canada Research Chairs Program, during the conduct of the study; grants from Gilead Sciences, ViiV Healthcare, and AbbVie; and has participated as a principle investigator in industry-sponsored clinical trials for GlaxoSmithKline outside the submitted work. DD, SF, and ST are employees and stockholders of GlaxoSmithKline. RD, SG, MSC, DAM, WRS, PPa, VC, AC, and KYS are employees of ViiV Healthcare and stockholders of GlaxoSmithKline. HC, SV, RVS-R, and KV are employees and stockholders of Janssen. VVE is an employee of Janssen and has a patent (method for treating paediatric HIV [Patent Cooperation Treaty international application number 62/870,413 filed on July 3, 2019; Attorney Docket Number TIP1068USPSP1]) pending to Janssen. All other authors 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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