Efficacy, safety, and tolerability of switching to long-acting cabotegravir plus rilpivirine versus continuing fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide in virologically suppressed adults with HIV, 12-month results (SOLAR): a randomised, open-label, phase 3b, non-inferiority trial

Moti N Ramgopal, Antonella Castagna, Charles Cazanave, Vicens Diaz-Brito, Robin Dretler, Shinichi Oka, Olayemi Osiyemi, Sharon Walmsley, James Sims, Giovanni Di Perri, Kenneth Sutton, Denise Sutherland-Phillips, Alessandro Berni, Christine L Latham, Feifan Zhang, Ronald D'Amico, Miguel Pascual Bernáldez, Rodica Van Solingen-Ristea, Veerle Van Eygen, Parul Patel, Vasiliki Chounta, William R Spreen, Harmony P Garges, Kimberly Smith, Jean van Wyk

Summary

Background Cabotegravir plus rilpivirine is the only approved complete long-acting regimen for the maintenance of HIV-1 virological suppression dosed every 2 months. The SOLAR study aimed to compare long-acting cabotegravir plus rilpivirine every 2 months with continued once-daily bictegravir, emtricitabine, and tenofovir alafenamide for the maintenance of HIV-1 virological suppression in adults living with HIV.

Methods SOLAR is a randomised, open-label, multicentre, phase 3b, non-inferiority study. The study was done in 118 centres across 14 countries. Participants with HIV-1 RNA less than 50 copies per mL were randomly assigned (2:1), stratified by sex at birth and BMI, to either long-acting cabotegravir (600 mg) plus rilpivirine (900 mg) dosed intramuscularly every 2 months or to continue daily oral bictegravir (50 mg), emtricitabine (200 mg), and tenofovir alafenamide (25 mg). Participants randomly assigned to long-acting therapy had a choice to receive cabotegravir (30 mg) plus rilpivirine (25 mg) once daily as an optional oral lead-in for approximately 1 month. The primary efficacy endpoint was the proportion of participants with virological non-response (HIV-1 RNA ≥50 copies per mL; the US Food and Drug Administration snapshot algorithm, 4% non-inferiority margin; modified intention-to-treat exposed population) at month 11 (long-acting start with injections group) and month 12 (long-acting with oral lead-in group and bictegravir, emtricitabine, and tenofovir alafenamide group). The study is registered with ClinicalTrials.gov, NCT04542070, and is ongoing.

Findings 837 participants were screened between Nov 9, 2020, and May 31, 2021, and 687 were randomly assigned to switch treatment or continue existing treatment. Of 670 participants (modified intention-to-treat exposed population), 447 (67%) switched to long-acting therapy (274 [61%] of 447 start with injections; 173 [39%] of 447 with oral lead-in) and 223 (33%) continued bictegravir, emtricitabine, and tenofovir alafenamide. Baseline characteristics were similar; median age was 37 years (range 18–74), 118 (18%) of 670 were female sex at birth, 207 (31%) of 670 were non-White, and median BMI was 25·9 kg/m² (IQR 23·3–29·5). At month 11–12, long-acting cabotegravir plus rilpivirine showed non-inferior efficacy versus bictegravir, emtricitabine, and tenofovir alafenamide (HIV-1 RNA ≥50 copies per mL, five [1%] of 447 *vs* one [<1%] of 223), with an adjusted treatment difference of 0·7 (95% CI −0·7 to 2·0). Excluding injection site reactions, adverse events and serious adverse events were similar between groups. No treatment-related deaths occurred. More long-acting group participants had adverse events leading to withdrawal (25 [6%] of 454 *vs* two [1%] of 227). Injection site reactions were reported by 316 (70%) of 454 long-acting participants; most (98%) were grade 1 or 2.

Interpretation These data support the use of long-acting cabotegravir plus rilpivirine dosed every 2 months as a complete antiretroviral regimen that has similar efficacy to a commonly used integrase strand transfer inhibitor-based first-line regimen, while addressing unmet psychosocial issues associated with daily oral treatment.

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Midway Immunology and Research Center, Fort Pierce, FL, USA (M N Ramgopal MD); **Vita-Salute San Raffaele University Scientific Institute, Milan, Italy** (Prof A Castagna MD); **Department of Infectious Diseases, Pellegrin Hospital, University Hospital of Bordeaux, Bordeaux, France** (C Cazanave MD); **Department of Infectious Diseases, Parc Sanitari Sant Joan de Deu, Sant Boi de Llobregat, Spain** (V Diaz-Brito MD); **Infectious Disease Specialists of Atlanta, Decatur, GA, USA** (R Dretler MD); **AIDS Clinical Center, National Center for Global Health and Medicine, Tokyo, Japan** (S Oka MD); **Triple O Research Institute PA, West Palm Beach, FL, USA** (O Osiyemi MD); **University Health Network, Toronto, ON, Canada** (S Walmsley MD); **St Hope Foundation, Houston, TX, USA** (J Sims MD); **Department of Medical Sciences, Unit of Infectious Diseases, University of Turin, Turin, Italy** (G Di Perri MD); **ViiV Healthcare, Durham, NC, USA** (K Sutton MSc, D Sutherland-Phillips MD, C L Latham MS, R D'Amico DO MSc, P Patel PharmD,

W R Spreen PharmD, H P Garges MD, K Smith MD); **GSK, Brentford, UK** (A Berni MSc); **GSK, Collegeville, PA, USA** (F Zhang PhD); **ViiV Healthcare, Madrid, Spain** (M Pascual Bernáldez PharmB); **Janssen Research & Development, Beerse, Belgium** (R Van Solingen-Ristea MD, V Van Eygen MSc); **ViiV Healthcare, Brentford, UK** (V Chounta MSc, J van Wyk MB ChB)

Correspondence to: Dr Jean van Wyk, ViiV Healthcare, Brentford, UK
jean.x.andre-van-wyk@viivhealthcare.com

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 Oct 19, 2022. From the search, it was apparent that publications covering long-acting therapies that offer less frequent dosing intervals versus daily oral antiretroviral therapy (ART) are increasing. Although standard ART has transformed HIV infection into a manageable, chronic condition, people living with HIV face substantial challenges, partly 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 is associated with increased rates of treatment fatigue, anxiety, and depression. Long-acting cabotegravir plus rilpivirine dosed monthly or every 2 months has been authorised by regulatory agencies and is recommended by treatment guidelines for the maintenance of HIV-1 virological suppression. Approval was based primarily on the key phase 3 ATLAS (NCT02951052) and FLAIR (NCT02938520) studies and the phase 3b ATLAS-2M (NCT03299049) study. There was a paucity of literature found that directly compares the efficacy, safety, and tolerability of long-acting cabotegravir plus rilpivirine dosed every 2 months versus continuing contemporary daily fixed-dose single-pill regimens in people living with HIV-1.

Added value of this study

This is, we believe, the first large phase 3b study to directly compare switching to long-acting cabotegravir plus rilpivirine dosed every 2 months with continuing daily oral bictegravir, emtricitabine, and tenofovir alafenamide in people living with HIV-1. The month 12 results show that the efficacy of switching from daily oral bictegravir, emtricitabine, and tenofovir alafenamide to long-acting cabotegravir plus rilpivirine dosed every 2 months was non-inferior to continuing bictegravir, emtricitabine, and tenofovir alafenamide among virologically suppressed people living with HIV-1, with respect to the primary and secondary endpoints of plasma HIV-1 RNA per the US Food and Drug Administration snapshot algorithm. Overall safety and tolerability of long-acting cabotegravir plus rilpivirine and oral bictegravir, emtricitabine, and tenofovir alafenamide were consistent with previous clinical experience. The majority of participants reported a preference for long-acting cabotegravir plus rilpivirine dosed every 2 months over daily oral bictegravir, emtricitabine, and tenofovir alafenamide.

Implications of all the available evidence

Oral ART requires high rates of continuous adherence and daily resolve, both of which might be challenging for some people living with HIV. This study showed that switching to long-acting cabotegravir plus rilpivirine dosed every 2 months from daily oral bictegravir, emtricitabine, and tenofovir alafenamide was efficacious, well tolerated, improved treatment satisfaction, and was preferred by most participants. There were two participants with on-time injections who had confirmed virological failure in the long-acting cabotegravir plus rilpivirine group, both with on-treatment resistance-associated mutations, versus none in the bictegravir, emtricitabine, and tenofovir alafenamide group.Previous phase 3b data (ATLAS-2M) showed similar efficacy, safety, and tolerability when comparing monthly and every 2 months dosing of long-acting cabotegravir plus rilpivirine, with a strong patient preference for every 2 months dosing. Before the SOLAR study, only indirect evidence was available comparing every 2 months dosing with various daily oral comparator therapies from phase 3 studies. The available evidence supports long-acting cabotegravir plus rilpivirine every 2 months as a potential alternative treatment to daily oral therapies for the maintenance of virological suppression.

Introduction

The development of antiretroviral therapy (ART) regimens has significantly reduced the morbidity and mortality associated with HIV infection, transforming HIV from a fatal condition to a manageable chronic disease.[1,2] Early ART regimens required lifelong administration of multiple oral ARTs, containing at least two active drugs from two or more classes.[2] As a means of reducing pill burden, standard of care ART regimens include once-daily, fixed-dose regimens with two or three drugs in combination. Biktarvy is an example of a three-drug regimen, comprised of a fixed-dose combination of bictegravir, emtricitabine, and tenofovir alafenamide, and is recommended by treatment guidelines as one of the choices for initial therapy for people with HIV-1 infection.[2–4]

Although effective and generally well tolerated, high rates of adherence to lifelong daily oral ART regimens are essential to achieve and maintain virological suppression, as well as prevent a negative outcome and mitigate against the development of potential drug resistance that might emerge in patients with suboptimal adherence.[3] Looking beyond clinical parameters, daily oral ART regimens might pose inherent challenges for some people living with HIV, including stigma and fear of disclosure due to the necessity of keeping tablets at home, anxiety related to staying adherent, and the daily reminder of HIV status.[5,6] These challenges might negatively affect overall health, quality of life, adherence, and treatment satisfaction. It has been proposed that the Joint UN Programme on HIV/AIDS 90-90-90 goals for HIV include a fourth 90 to ensure that 90% of people with viral load suppression have good health-related quality of life.[7] The advent of a novel, complete long-acting injectable regimen has the potential to address the burdens of daily oral treatments and their associated psychosocial stressors.

Cabotegravir, an integrase strand transfer inhibitor (INSTI), plus rilpivirine, a non-nucleoside reverse transcriptase inhibitor (NNRTI), dosed monthly or every 2 months is the first complete long-acting regimen approved and recommended by treatment guidelines for the maintenance of HIV-1 virological suppression.[2–4,8–11] Long-acting therapies might address some of the challenges associated with daily oral ART for people living with HIV, and have been acknowledged by treatment guidelines for their potential to improve quality of life for individuals with pill fatigue, adherence difficulties, concerns about disclosure of HIV status, or the stigma associated with daily oral medication.[2,3,6] These sentiments are supported by data collected in the phase 3/3b clinical trial programme of long-acting cabotegravir plus rilpivirine, showing that most participants preferred long-acting therapy over their previous daily oral therapy.[8,12,13] The main reasons for choosing long-acting treatment included convenience and discretion.[12]

Here, we report the efficacy, safety, and patient-reported outcomes of switching to long-acting cabotegravir plus rilpivirine dosed every 2 months from bictegravir, emtricitabine, and tenofovir alafenamide administered orally once daily, compared with continuing bictegravir, emtricitabine, and tenofovir alafenamide, for 12 months from the SOLAR (Switch Onto Long Acting Regimen) study. Although both regimens have been shown in clinical trials to be potent and to have acceptable safety profiles,[8,10,11,13–17] this is, we believe, the first study to directly compare bictegravir, emtricitabine, and tenofovir alafenamide with long-acting cabotegravir plus rilpivirine every 2 months in people living with HIV.

Methods

Study design and participants

SOLAR is a randomised, multicentre, active-controlled, open-label, phase 3b, non-inferiority study evaluating the efficacy and safety of switching to long-acting cabotegravir plus rilpivirine versus continuing bictegravir, emtricitabine, and tenofovir alafenamide. The study was done in 118 clinical centres across 14 countries: Australia, Austria, Belgium, Canada, France, Germany, Ireland, Italy, Japan, the Netherlands, Spain, Switzerland, the UK, and the USA. Eligible participants were at least 18 years of age and currently receiving an uninterrupted regimen of bictegravir, emtricitabine, and tenofovir alafenamide with an undetectable HIV-1 viral load (<50 copies per mL) for at least 6 months before screening. Bictegravir, emtricitabine, and tenofovir alafenamide must have been the participant's first or second regimen. If it was the second regimen, the participant's first regimen must have been an INSTI-based regimen. Any history of non-INSTI regimens was not permitted. Known or suspected presence of resistance mutations, as defined by the International Antiviral Society–USA resistance guidelines, to bictegravir, emtricitabine, and tenofovir alafenamide, rilpivirine, or cabotegravir was exclusionary. SOLAR had a protocol-defined target of approximately 20% female enrolment (sex at birth). Participants who were female sex at birth and of reproductive potential agreed to use a highly effective method of contraception. The complete eligibility criteria are provided in the appendix (pp 9–13).

See Online for appendix

SOLAR is designed with both a maintenance phase (up to month 12) and an extension phase (post-month 12); the extension phase is intended to provide continued access to long-acting cabotegravir plus rilpivirine until local regulatory approval and commercial product availability. In the maintenance phase, participants were randomly assigned (2:1) at day 1 to switch to long-acting cabotegravir (600 mg) plus rilpivirine (900 mg) injections every 2 months or continue oral daily bictegravir (50 mg), emtricitabine (200 mg), and tenofovir alafenamide (25 mg; figure 1). For those randomly assigned to long-acting therapy, participants had a choice to either receive cabotegravir (30 mg) plus rilpivirine (25 mg) once daily as an oral lead-in (OLI) or to transition directly to long-acting cabotegravir plus rilpivirine injections (start with injections [SWI]) in accordance with treatment initiation choices offered in the product label. The decision whether to use an OLI or SWI was made by the participant in consultation with the investigator. Participants who elected for an OLI received oral cabotegravir plus rilpivirine once daily for 1 month. The administration of their first long-acting cabotegravir plus rilpivirine injections occurred at the month 1 clinic visit after their final oral dose, following safety assessments. The second long-acting injections were given at the month 2 visit, with subsequent injections administered every 2 months thereafter. Participants who chose to SWI received long-acting cabotegravir plus rilpivirine injections on day 1, with the second injections administered at month 1 and subsequent injections administered every 2 months thereafter. Irrespective of whether participants received an OLI, all participants receiving long-acting therapy who completed the maintenance phase had seven doses of long-acting cabotegravir plus rilpivirine by the time of the primary analysis endpoint. In the extension phase, eligible participants (HIV-1 RNA <50 copies per mL at month 11 [SWI] to 12 [OLI]) were given an option to continue their randomised long-acting cabotegravir plus rilpivirine regimen dosed every 2 months or, for those originally randomly assigned to the bictegravir, emtricitabine, and tenofovir alafenamide group, to start long-acting cabotegravir plus rilpivirine every 2 months (SWI or with an OLI), with clinical visits every 2 months. Any participant who had confirmed virological failure (CVF, two consecutive measurements of HIV-1 RNA ≥200 copies per mL) at any point in the study was discontinued, and any participant who received at least one dose of long-acting cabotegravir or rilpivirine but

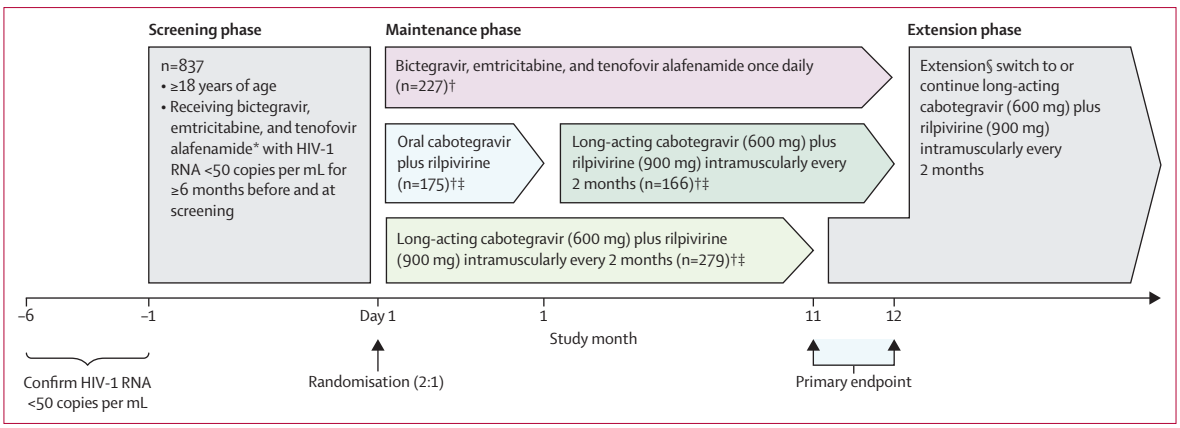

Figure 1: **Trial design**

*A single previous integrase inhibitor regimen is allowed if bictegravir, emtricitabine, and tenofovir alafenamide is a second-line regimen 6 months before screening. Any previous change in regimen, defined as a change of a single drug or multiple drugs simultaneously, must have been done for tolerability and safety, access to medications, or convenience and simplification reasons, and must not have been done because of treatment failure (HIV-1 RNA ≥400 copies per mL). †n values are based on the safety population. ‡Participants randomly assigned to the long-acting group were offered an optional oral lead-in; the decision was made by the participants following informed consent discussions with the investigator. §The extension phase will continue study treatment until long-acting cabotegravir and long-acting rilpivirine are either locally approved and commercially available, the participant no longer derives clinical benefit, the participant meets a protocol-defined reason for discontinuation, or until development of either long-acting cabotegravir or long-acting rilpivirine is terminated. Visits will continue to occur every 2 months.

discontinued for any reason entered long-term follow-up (suppressive ART for ≥52 weeks). A protocol amendment was instituted to permit participants who became pregnant to continue on long-acting cabotegravir plus rilpivirine (but not on bictegravir, emtricitabine, and tenofovir alafenamide, as the label at the time of protocol creation did not contain language supportive of continuing bictegravir, emtricitabine, and tenofovir alafenamide during pregnancy) and remain on study if permitted by the local regulatory authority and institutional review board.

SOLAR was done in accordance with the Declaration of Helsinki.[18] All participants provided written informed consent. The study protocol, amendments, 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

A randomisation sequence generated by GSK-verified randomisation software (RandAll NG, GlaxoSmithKline, Durham, NC, USA, version 1.3.3) was used for treatment assignments, with stratification by sex at birth and BMI (<30 kg/m² *vs* ≥30 kg/m²). Randomisation and study treatment assignment were facilitated by the interactive response technology through the central Randomisation and Medication Ordering System Next Generation system. Central randomisation, done with blocks shared across sites, concealed the treatment schedule to prevent selection bias, with a 2:1 randomisation ratio to either long-acting cabotegravir plus rilpivirine or bictegravir, emtricitabine, and tenofovir alafenamide within each block.

Procedures

Viral genotypes and phenotypes were analysed from plasma samples by means of PhenoSense GT, PhenoSense Integrase, and GenoSeq Integrase assays (Monogram Biosciences, South San Francisco, CA, USA) at suspected virological failure (SVF; first of two consecutive measurements of HIV-1 RNA ≥200 copies per mL, confirmed by initiating a repeat of the HIV-1 RNA assessment within 2–4 weeks). Baseline archived HIV-1 resistance was retrospectively assessed in individuals with CVF with next-generation sequencing by means of the GenoSure Archive assay (Monogram Biosciences) on peripheral blood mononuclear cells. Adverse events were graded according to the Division of AIDS Table for Grading the Severity of Adult and Paediatric Adverse Events (version 2.1). Participant fear of disclosure of their HIV status, adherence anxiety, and daily reminder of HIV status was evaluated at baseline by means of the Patient Emotional Well-being and Adherence Considerations questionnaire (composite version). Treatment satisfaction was measured by the change from Maintenance baseline in HIV Treatment Satisfaction Questionnaire status version (HIVTSQs). Preference for long-acting cabotegravir plus rilpivirine versus bictegravir, emtricitabine, and tenofovir alafenamide was assessed with a preference questionnaire at months 11–12; this consisted of three questions evaluating preference along with attributes supporting said preference.

Outcomes

The primary efficacy endpoint was the proportion of participants with virological non-response (HIV-1 RNA ≥50 copies per mL) at month 11 (long-acting SWI group) and month 12 (long-acting with OLI group and bictegravir,

emtricitabine, and tenofovir alafenamide group) as per the US Food and Drug Administration (FDA) snapshot algorithm. Additional secondary efficacy endpoints were the proportion of participants with virological suppression (HIV-1 RNA <50 copies per mL) per the FDA snapshot algorithm, and the proportion of participants with CVF, as well as absolute values and change from baseline in CD4 cell counts over time at month 11 (long-acting SWI) or month 12 (long-acting OLI and bictegravir, emtricitabine, and tenofovir alafenamide). The incidence of on-treatment genotypic and phenotypic resistance was assessed at month 11 (long-acting SWI) or month 12 (long-acting OLI and bictegravir, emtricitabine, and tenofovir alafenamide) in participants with CVF. Safety endpoints included the incidence and severity of adverse events and laboratory abnormalities over time, the proportion of participants who discontinue treatment due to adverse events over time, and changes in laboratory parameters over time. The OLI period was not excluded from any analyses of efficacy or safety. For participants on long-acting cabotegravir plus rilpivirine who developed CVF, cabotegravir and rilpivirine plasma trough concentrations were analysed at the time of SVF. Patient-reported outcomes included change in treatment satisfaction (HIVTSQs) at month 11 (long-acting SWI) or month 12 (long-acting OLI and bictegravir, emtricitabine, and tenofovir alafenamide), and participant treatment preference evaluated by means of a preference questionnaire at month 11 (long-acting SWI) or month 12 (long-acting OLI and bictegravir, emtricitabine, and tenofovir alafenamide), or withdrawal. Participants' emotional wellbeing and adherence considerations were evaluated at baseline. Weight and metabolic changes, evaluated in a systematic and standardised manner, will be presented in a separate publication.

Statistical analysis

Primary and secondary analyses were based on the modified intention-to-treat exposed (mITT-E) population as crucial findings were identified that related to significant and persistent non-compliance to protocol entry requirements at one study site. After consultation with a masked external statistician, the intention-to-treat exposed (ITT-E) population was modified to exclude all 11 participants from this one study site before the month 12 analysis. The primary analysis at month 11 (long-acting SWI) or month 12 (long-acting OLI and bictegravir, emtricitabine, and tenofovir alafenamide) was made at a one-sided 2·5% level of significance, with the differences between the randomised treatment group and associated 95% CIs calculated by means of a stratified Cochran–Mantel–Haenszel analysis adjusted for sex at birth and BMI (<30 or ≥30 kg/m²). Non-inferiority of long-acting cabotegravir plus rilpivirine every 2 months versus bictegravir, emtricitabine, and tenofovir alafenamide was shown in the primary efficacy analysis if the upper boundary of the two-sided 95% CI of the Cochran–Mantel–Haenszel-adjusted difference in the proportion of participants with plasma HIV-1 RNA of at least 50 copies per mL in the mITT-E FDA snapshot analysis at month 11 (long-acting SWI) or month 12 (long-acting OLI and bictegravir, emtricitabine, and tenofovir alafenamide) was less than 4%. A sensitivity analysis of the efficacy endpoints was done by the same method described above on the ITT-E population. For the key secondary efficacy analysis, the proportion of participants with plasma HIV-1 RNA of less than 50 copies per mL by means of the snapshot algorithm at month 11 (long-acting SWI) or month 12 (long-acting OLI and bictegravir, emtricitabine, and tenofovir alafenamide) was judged against a prespecified non-inferiority margin of –12%. A sample size of 654 participants randomly assigned in a 2:1 ratio provided approximately 85% power to show non-inferiority of long-acting cabotegravir plus rilpivirine every 2 months to bictegravir, emtricitabine, and tenofovir alafenamide for the proportions of participants with HIV-1 RNA of at least 50 copies per mL at month 12 at a 4% margin, by means of a 2·5% one-sided significance level and assuming population-level proportions of 2% in the long-acting cabotegravir plus rilpivirine every 2 month group and 1% in the bictegravir, emtricitabine, and tenofovir alafenamide group, as suggested by historical data.[10,19,20] Although the protocol allowed switch participants the option to transition either directly to injections or to commence with an initial OLI, no formal statistical comparison between these groups was done. Changes in treatment satisfaction (HIVTSQs) were evaluated by means of a mixed model for repeated measures with visit as the repeated factor, including the following variables: treatment, visit, treatment × visit, maintenance baseline score, sex at birth, baseline BMI (<30 kg/m² or ≥30 kg/m²), age (<50 years or ≥50 years), and race (White or non-White). Given the well-established safety and efficacy data obtained from several large phase 2b/3/3b studies, coupled with the well-characterised safety profile of the bictegravir, emtricitabine, and tenofovir alafenamide regimen used in the comparator group, no independent data monitoring committee was required. However, accumulating data from the study were regularly reviewed in aggregate by the cabotegravir safety review team, and an interim analysis was part of the statistical plan of SOLAR, which was done when all participants completed the month 6 visit. These actions provided comprehensive data monitoring. Statistical analyses were done with R (version 4.1.2) and SAS (r) Proprietary Software (version 9.4). The study is registered with ClinicalTrials.gov, NCT04542070.

Role of the funding source

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

Results

Screening occurred between Nov 9, 2020, and May 31, 2021 and, of 837 participants assessed for eligibility, 687 participants were enrolled and randomly assigned (2:1; figure 2). Six participants did not receive study treatment at day 1 (withdrawal by participant [n=4], physician decision [n=1], and protocol deviation [n=1]). Of the remaining 681 participants, 454 (67%) of 681 switched to long-acting cabotegravir plus rilpivirine every 2 months and 227 (33%) of 681 continued bictegravir, emtricitabine, and tenofovir alafenamide (ITT-E population). For the long-acting every 2 months group, 279 (61%) of 454 elected to SWI. Among the 175 (39%) of 454 participants initiating long-acting therapy with an OLI, nine participants discontinued treatment before receiving injections (two participant decision; one physician decision; six drug-related adverse events). As mentioned previously, 11 participants (seven in the long-acting cabotegravir plus rilpivirine group; four in the bictegravir, emtricitabine, and tenofovir alafenamide group) were excluded from the ITT-E population (n=681) because of critical findings related to significant and persistent non-compliance to protocol entry requirements at one study site (full details provided in the appendix p 14). The most common reasons for study withdrawal were adverse events (12 [3%] of 447) and withdrawal by participant (12 [3%] of 447) in the long-acting group, and withdrawal by participant (nine [4%] of 223) in the bictegravir, emtricitabine, and tenofovir alafenamide group. Two pregnancies were confirmed for participants receiving long-acting cabotegravir plus rilpivirine during the maintenance phase, both of whom had elective terminations and remained on study.

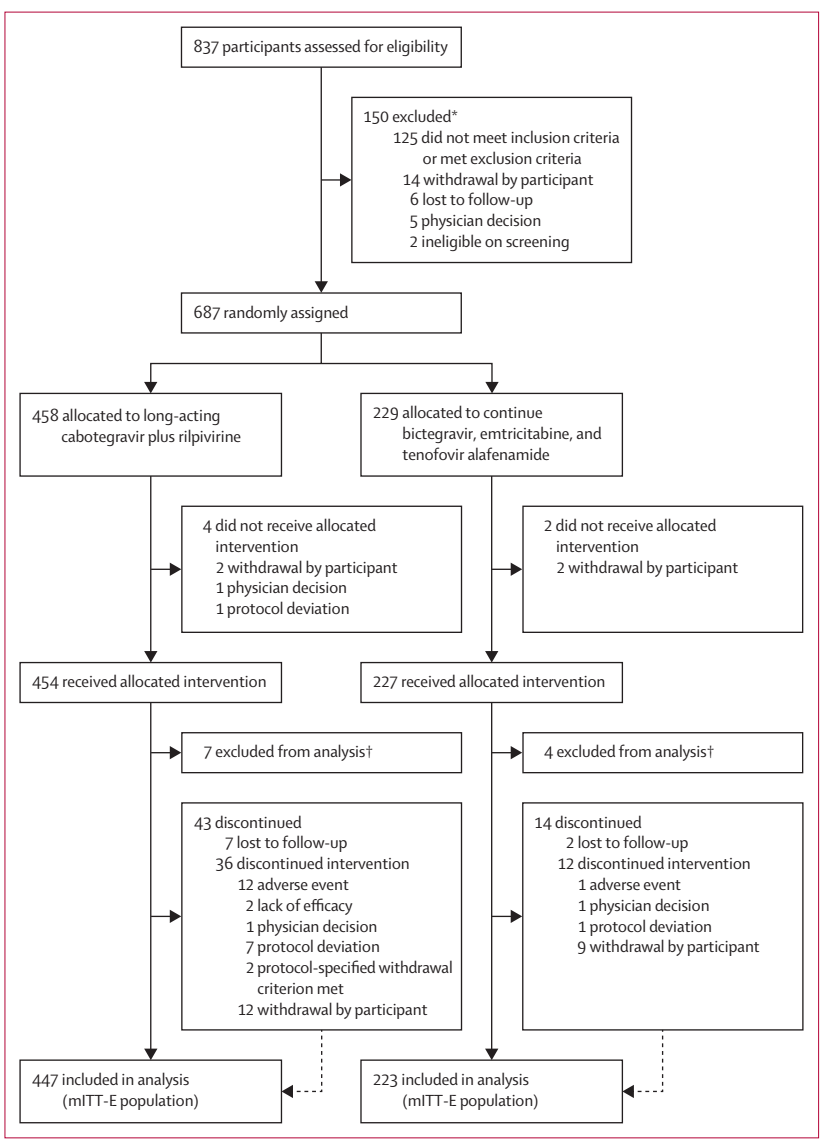

Figure 2: **Trial profile**

*Participants could have more than one reason for exclusion. †Excluded owing to crucial findings relating to non-compliance to protocol entry requirements at one study site (enrolled participants did not meet the entry criterion number 5—participants must be on an uninterrupted current regimen of bictegravir, emtricitabine, and tenofovir alafenamide for at least 6 months before screening with an undetectable HIV-1 viral load for at least 6 months before screening. Bictegravir, emtricitabine, and tenofovir alafenamide must be the participant's first or second regimen. If bictegravir, emtricitabine, and tenofovir alafenamide is the second regimen, the first regimen must be an integrase inhibitor regimen). mITT-E=modified intention-to-treat exposed.

Baseline characteristics were similar between groups; mITT-E participants had a median (range) age of 37 (18–74) years, 19% (128 of 670) were at least 50 years of age, 118 (18%) of 670 were female (sex at birth), 207 (31%) of 670 were non-White, and 145 (22%) of 670 had a BMI of at least 30 kg/m^2 (table 1). The median duration of previous ART was 2·58 years in the long-acting group and 2·47 years in the bictegravir, emtricitabine, and tenofovir alafenamide group. Over 11 months of injections in the long-acting group, 2342 (93%) of 2527 expected injection visits occurred on time within the ±7-day dosing window; 140 (6%) were early (more than 7 days early relative to the projected visit date), with 35 (1%) occurring at least 14 days early, and 43 (2%) were late (more than 7 days late relative to the projected visit date), with seven (0·3%) occurring at least 14 days late. Owing to anticipated delayed injections (outside of the +7-day window), 11 participants in the long-acting group received oral therapy with cabotegravir plus rilpivirine for a median of 22 days. Two participants missed injection visits entirely (two [0·1%] of 2527 injection visits) and were also covered with oral cabotegravir plus rilpivirine; both participants maintained virological suppression. Overall, 404 (90%) of 447 participants in the long-acting cabotegravir plus rilpivirine group and 209 (94%) of 223 participants in the bictegravir, emtricitabine, and tenofovir alafenamide group completed the maintenance phase.

At months 11–12 (snapshot algorithm), five (1%) of 447 participants in the long-acting group and one (<1%) of 223 participants in the bictegravir, emtricitabine, and tenofovir alafenamide group had HIV-1 RNA of at least 50 copies per mL with an adjusted difference of 0·7 (95% CI –0·7 to 2·0), showing non-inferiority for the primary endpoint (mITT-E; 4% non-inferiority margin;

table 2; appendix p 2). Similarly, 403 (90%) of 447 participants in the long-acting group and 207 (93%) of 223 participants in the bictegravir, emtricitabine, and tenofovir alafenamide group had HIV-1 RNA less than 50 copies per mL with an adjusted difference at month 11–12 of –2·7 (–7·0 to 1·7), within the prespecified non-inferiority margin of –12%. Efficacy results for the mITT-E population were consistent with the ITT-E and per-protocol populations (table 2). No association was observed between HIV-1 RNA of at least 50 copies per mL at month 11–12 (snapshot) and delays in study treatment injection. Median change from baseline in CD4 count from day 1 to month 11–12 was 39·0 (IQR –91·0 to 141·0) cells per mm³ for the long-acting group and 20·0 (–72·0 to 121·0) cells per mm³ for the bictegravir, emtricitabine, and tenofovir alafenamide group.

Two (<1%) of 447 participants in the mITT-E population in the long-acting cabotegravir plus rilpivirine group and no participants in the bictegravir, emtricitabine, and tenofovir alafenamide group met the CVF criterion during the maintenance phase. One participant met the CVF criterion at month 6, with a viral load of 1327 copies per mL at SVF followed by a viral load of 1409 copies per mL at the subsequent confirmatory visit. This participant resuppressed on darunavir, cobicistat, emtricitabine, and tenofovir alafenamide during long-term follow-up. The second participant met the CVF criterion at month 11, with a viral load of 6348 copies per mL at SVF followed by a viral load of 419 copies per mL at the subsequent confirmatory visit. They also resuppressed during long-term follow-up on bictegravir, emtricitabine, and tenofovir alafenamide followed by darunavir, cobicistat, emtricitabine, and tenofovir alafenamide. In addition to these two cases described for the mITT-E population, a third participant from the site who was excluded from the main analysis met the CVF criterion at month 3 in the ITT-E population. This participant had a viral load of 3797 copies per mL at SVF followed by a viral load of 928 copies per mL at the subsequent confirmatory visit, resuppressing during long-term follow-up on bictegravir, emtricitabine, and tenofovir alafenamide. The two participants from the mITT-E population had on-treatment rilpivirine or INSTI resistance-associated mutations (RAMs); one participant had cabotegravir-associated RAMs at baseline (appendix p 3), identified from retrospective assessment of peripheral blood mononuclear cells. Retrospective assessment of peripheral blood mononuclear cells was not successful for the third participant from the ITT-E population. The genotype at failure in this participant revealed rilpivirine RAMs, but it is unknown if these were present at baseline. None of the three participants meeting the CVF criterion had late injections outside of the dosing window (+7 days), and their plasma drug concentrations were above respective protein-adjusted 90% inhibitory

	Long-acting cabotegravir plus rilpivirine group (n=447)	Bictegravir, emtricitabine, and tenofovir alafenamide group (n=223)	Total (n=670)
Age, median (range) years	37 (18–74)	37 (18–66)	37 (18–74)
≥50 years	86 (19%)	42 (19%)	128 (19%)
Sex at birth			
Female	77 (17%)	41 (18%)	118 (18%)
Male	370 (83%)	182 (82%)	552 (82%)
Participant-reported gender			
Female	76 (17%)	41 (18%)	117 (17%)
Male	359 (80%)	178 (80%)	537 (80%)
Transgender female	9 (2%)	3 (1%)	12 (2%)
Transgender male	1 (<1%)	0	1 (<1%)
Gender variant or gender non-conforming	1 (<1%)	0	1 (<1%)
Other	1 (<1%)	1 (<1%)	2 (<1%)
Race			
White	307 (69%)	156 (70%)	463 (69%)
Black or African American	95 (21%)	49 (22%)	144 (21%)
Asian	23 (5%)	11 (5%)	34 (5%)
Other race*	22 (5%)	7 (3%)	29 (4%)
Ethnicity			
Hispanic or Latinx	93 (21%)	38 (17%)	131 (20%)
BMI, kg/m²	26·0 (23·2–29·4)	25·4 (23·4–29·6)	25·9 (23·3–29·5)
≥30 kg/m²	93 (21%)	52 (23%)	145 (22%)
Duration of previous antiretroviral therapy before study entry, years†			
<1	44 (10%)	23 (10%)	67 (10%)
1 to <2	122 (27%)	60 (27%)	182 (27%)
2 to <3	83 (19%)	49 (22%)	132 (20%)
3 to <4	52 (12%)	25 (11%)	77 (11%)
≥4	146 (33%)	66 (30%)	212 (32%)
Median duration of previous antiretroviral therapy, years	2·58	2·47	2·55
INSTI regimen before bictegravir, emtricitabine, and tenofovir alafenamide			
Raltegravir	6 (1%)	7 (3%)	13 (2%)
Elvitegravir	110 (25%)	47 (21%)	157 (23%)
Dolutegravir	75 (17%)	50 (22%)	125 (19%)
None	256 (57%)	119 (53%)	375 (56%)
Weight, kg	81·1 (70·1–91·2)	79·0 (69·2–91·7)	80·6 (69·6–91·2)
CD4 count, cells per mm³	649 (477–850)	640 (459–846)	646 (475–847)
CD4 count category, cells per mm³			
<350	54 (12%)	28 (13%)	82 (12%)
350 to <500	74 (17%)	35 (16%)	109 (16%)
≥500	319 (71%)	159 (71%)	478 (71%)
HIV-1 RNA ≥50 copies per mL on day 1‡	7 (2%)	1 (<1%)	8 (1%)

Data are n (%) or median (IQR). INSTI=integrase strand transfer inhibitor. *Other race participants: American Indian or Alaska Native, 14 on long-acting cabotegravir plus rilpivirine and 2 on bictegravir, emtricitabine, and tenofovir alafenamide; Native Hawaiian or other Pacific Islander, 1 on bictegravir, emtricitabine, and tenofovir alafenamide; multiple, 8 on long-acting cabotegravir plus rilpivirine and 4 on bictegravir, emtricitabine, and tenofovir alafenamide. †Including bictegravir, emtricitabine, and tenofovir alafenamide. ‡Range 54–3919 HIV-1 RNA copies per mL.

Table 1: **Demographic and clinical characteristics at baseline (modified intention-to-treat exposed population)**

	Long-acting cabotegravir plus rilpivirine group (n=447)	Bictegravir, emtricitabine, and tenofovir alafenamide group (n=223)	Difference in proportion* (95% CI)	Adjusted difference in proportion† (95% CI)
Modified intention-to-treat exposed analysis				
Plasma HIV-1 RNA ≥50 copies per mL (primary endpoint)‡	5 (1%)	1 (<1%)	0·7 (–0·6 to 2·0)	0·7 (–0·7 to 2·0)
Data in window not below threshold	3 (<1%)	1 (<1%)	..	..
Discontinued for other reason while not below threshold	1 (<1%)	0	..	..
Discontinued for lack of efficacy	1 (<1%)	0	..	..
No virological data	39 (9%)	15 (7%)	..	..
Discontinued study due to adverse events or death	13 (3%)	1 (<1%)	..	..
Discontinued study for other reasons	24 (5%)§	13 (6%)¶	..	..
On study but missing data in window	2 (<1%)	1 (<1%)	..	..
Plasma HIV-1 RNA <50 copies per mL (key secondary endpoint)‖	403 (90%)	207 (93%)	–2·7 (–7·0 to 1·7)	–2·7 (–7·0 to 1·7)
Intention-to-treat exposed analysis				
Plasma HIV-1 RNA ≥50 copies per mL	6/454 (1%)	1/227 (<1%)	0·9 (–0·5 to 2·2)	0·9 (–0·5 to 2·2)
Plasma HIV-1 RNA <50 copies per mL	406/454 (89%)	211/227 (93%)	–3·5 (–7·9 to 0·8)	–3·5 (–7·9 to 0·9)
Per-protocol analysis				
Plasma HIV-1 RNA ≥50 copies per mL	4/433 (1%)	1/218 (<1%)	0·5 (–0·8 to 1·7)	0·5 (–0·8 to 1·7)
Plasma HIV-1 RNA <50 copies per mL	394/433 (91%)	203/218 (93%)	–2·1 (–6·4 to 2·2)	–2·1 (–6·4 to 2·2)

Data are n (%) or n/N (%) unless stated otherwise. *Difference=proportion of participants on long-acting cabotegravir plus rilpivirine–proportion of participants on bictegravir, emtricitabine, and tenofovir alafenamide. †Cochran–Mantel–Haenszel stratified analysis adjusting for sex at birth (male and female) and BMI (<30 kg/m² and ≥30 kg/m²). ‡Non-inferiority was established if the upper bound of the 95% CI about the adjusted long-acting cabotegravir plus rilpivirine–bictegravir, emtricitabine, and tenofovir alafenamide difference was below 4%. §12, withdrawal by participant; 6, lost to follow-up; 5, protocol deviation; 1, investigator decision. ¶9, withdrawal by participant; 2, lost to follow-up; 1, physician decision (pregnancy); 1, protocol deviation. ‖Non-inferiority was established if the lower bound of the 95% CI about the adjusted long-acting cabotegravir plus rilpivirine–bictegravir, emtricitabine, and tenofovir alafenamide difference was above –12%.

Table 2: **Snapshot efficacy outcomes at months 11–12**

concentrations (cabotegravir 0·166 µg/mL; rilpivirine 12 ng/mL) and phase 3 benchmarks (cabotegravir 0·65 µg/mL; rilpivirine 17·3 ng/mL) at SVF timepoints. In addition, one participant had SVF in the long-acting group with a viral load of 425 copies per mL but started darunavir, cobicistat, emtricitabine, and tenofovir alafenamide before the confirmatory visit and was resuppressed.

A safety summary for the long-acting and the bictegravir, emtricitabine, and tenofovir alafenamide groups (table 3) is based on the safety population (any randomly assigned participant who received at least one dose of study treatment, including the 11 participants excluded from the mITT-E population). Adverse events, excluding injection site reactions (ISRs), were common among participants in the long-acting group (349 [77%] of 454) and the bictegravir, emtricitabine, and tenofovir alafenamide group (172 [76%] of 227); most were of maximum grade 1 or 2 severity (long-acting group, 307 [88%] of 349; bictegravir, emtricitabine, and tenofovir alafenamide group, 146 [85%] of 172). Grade 3 and higher events occurred in 55 (12%) of 454 participants in the long-acting group and 26 (11%) of 227 participants in the bictegravir, emtricitabine, and tenofovir alafenamide group. Excluding ISRs, the most common adverse events were COVID-19 infection (coincident with the COVID-19 pandemic), occurring in 74 (16%) of 454 participants in the long-acting group and 39 (17%) of 227 participants in the bictegravir, emtricitabine, and tenofovir alafenamide group, and headaches, which occurred in 49 (11%) of 454 in the long-acting group and 12 (5%) of 227 in the bictegravir, emtricitabine, and tenofovir alafenamide group; no other adverse events occurred in at least 10% of participants in either group (table 3). Drug-related adverse events, excluding ISRs, occurred more frequently in the long-acting group (90 [20%] of 454) versus the bictegravir, emtricitabine, and tenofovir alafenamide group (two [1%] of 227); seven (2%) of 454 participants in the long-acting group had drug-related adverse events of grade 3 and higher compared with no participants in the bictegravir, emtricitabine, and tenofovir alafenamide group. The most commonly reported drug-related adverse events in the long-acting group, excluding ISRs, were pyrexia (13 [3%] of 454), headache (11 [2%] of 454), fatigue (ten [2%] of 454), and diarrhoea (nine [2%] of 454). In the bictegravir, emtricitabine, and tenofovir alafenamide group, the two drug-related adverse events reported were weight gain (one [<1%] of 227) and abnormal hepatic function (one [<1%] of 227). Serious adverse events occurred in 21 (5%) of 454 participants in the long-acting group, and 15 (7%) of 227 in the bictegravir, emtricitabine, and tenofovir alafenamide group; four (1%) of 454 participants in the long-acting group had serious adverse events that were considered

drug-related (one, injection site pain; two, increased alanine aminotransferase; and one, acute myocardial infarction [participant had history of cardiac comorbidities; full case narrative provided in the appendix p 15]). One death was reported during the maintenance phase (brain injury and encephalopathy following a completed suicide by hanging), which occurred in the bictegravir, emtricitabine, and tenofovir alafenamide group; it was not considered related to study treatment.

Through to months 11–12, 25 (6%) of 454 participants in the long-acting group and two (1%) of 227 participants in the bictegravir, emtricitabine, and tenofovir alafenamide group had adverse events leading to withdrawal. Excluding ISRs, nine (2%) of 454 withdrawals in the long-acting group were deemed drug-related by investigators (one, myocardial infarction [reported above]; one, dysaesthesia–limb discomfort–paraesthesia–peripheral swelling; one, dizziness; one, fatigue; one, deafness–ear congestion–fatigue; one, blood pressure fluctuation (participant reported) and depression; one, alanine aminotransferase increase; one, diarrhoea and joint stiffness; one, fatigue–pyrexia). No drug-related adverse events leading to withdrawal were reported in the bictegravir, emtricitabine, and tenofovir alafenamide group.

Injection site pain was the most commonly reported ISR, occurring in 283 (62%) of 454 participants. ISR profiles were similar between participants initiating long-acting cabotegravir plus rilpivirine SWI and with an OLI (appendix p 4); 1885 (98%) of 1915 ISRs were grade 1 or 2 in severity with a median duration of 3 days (IQR 2–5). No grade 4 or 5 ISRs were reported. Reported rates of ISRs decreased over time (month 1, 216 [49%] of 439; month 6, 129 [30%] of 424; month 12, 44 [11%] of 409). 11 participants withdrew for injection-related reasons, including ten (2%) of 454 participants who discontinued because of ISR adverse events (seven, injection site pain [one, grade 1; three, grade 2; two, grade 3; one, ungraded]; one, injection site pain or swelling [grade 2]; one, injection site pain [grade 2]–nodule [grade 1]; one, injection site discharge [grade 1]), and an additional participant (one [<1%] of 454) who cited general injection intolerability as their reason for withdrawal.

At baseline, 315 (47%) of 670 participants across the long-acting and bictegravir, emtricitabine, and tenofovir alafenamide groups reported ("always" or "often") having a fear of disclosure, adherence anxiety, or a daily reminder of HIV status (appendix p 5). Treatment satisfaction was greater among participants in the long-acting group compared with those in the bictegravir, emtricitabine, and tenofovir alafenamide group, with larger improvements in satisfaction observed through to month 11–12 (appendix p 8). Mean adjusted HIVTSQs scores improved significantly for long-acting versus bictegravir, emtricitabine, and tenofovir alafenamide participants from baseline (long-acting, 57·88; bictegravir, emtricitabine, and tenofovir alafenamide, 58·38) to months 5–6 (long-acting, +3·86 [95% CI 3·14 to 4·57]; bictegravir, emtricitabine, and tenofovir alafenamide, –0·4 [–1·41 to 0·61]; p<0·001) and months 11–12 (long-acting, +3·36 [2·59 to 4·13]; bictegravir, emtricitabine, and tenofovir alafenamide, –1·59 [–2·71 to –0·47]; p<0·001). Of those participants in the long-acting group who responded to the preference questionnaire at months 11–12 or at time of withdrawal, 382 (90%) of 425 reported a preference for long-acting cabotegravir plus rilpivirine every 2 months, with 22 (5%) of 425 having no preference and the remaining 21 (5%) of 425 reporting a preference for daily oral therapy. The main reasons for preferring long-acting therapy included not having to worry about remembering to take HIV medicine (324 [85%] of 382), convenience (317 [83%] of 382), not having to carry HIV medication

	Long-acting cabotegravir plus rilpivirine group (n=454)	Bictegravir, emtricitabine, and tenofovir alafenamide group (n=227)
Any adverse event	405 (89%)	172 (76%)
Excluding injection site reactions	349 (77%)	..
Any grade ≥3 adverse events	55 (12%)	26 (11%)
Excluding injection site reactions	42 (9%)	..
Any drug-related adverse events	327 (72%)	2 (1%)
Excluding injection site reactions	90 (20%)	..
Any grade ≥3 drug-related adverse events	22 (5%)	0
Excluding injection site reactions	7 (2%)	..
Any adverse event leading to withdrawal	25 (6%)	2 (1%)
Excluding injection site reactions	15 (3%)	..
Drug-related	19 (4%)*	0
Drug-related excluding injection site reactions	9 (2%)	..
Serious adverse events	21 (5%)	15 (7%)
Drug-related	4 (1%)†	0
Adverse events reported in ≥5% of participants in either treatment group, excluding injection site reactions		
COVID-19	74 (16%)	39 (17%)
Headache	49 (11%)	12 (5%)
Pyrexia	32 (7%)	9 (4%)
Diarrhoea	27 (6%)	9 (4%)
Syphilis	27 (6%)	9 (4%)
Nasopharyngitis	26 (6%)	10 (4%)
Fatigue	30 (7%)	6 (3%)
Drug-related adverse events reported in ≥2% of participants in either treatment group, excluding injection site reactions		
Pyrexia	13 (3%)	0
Headache	11 (2%)	0
Fatigue	10 (2%)	0
Diarrhoea	9 (2%)	0

*Oral lead-in period—1, dysaesthesia–limb discomfort–paraesthesia–peripheral swelling; 1, dizziness; 1, fatigue; 1, deafness–ear congestion–fatigue; 1, blood pressure fluctuation (participant reported)–depression; 1, diarrhoea–joint stiffness; injection period—1, myocardial infarction; 1, alanine aminotransferase increase; 1, fatigue–pyrexia; 7, injection site pain; 1, injection site pain or swelling; 1, injection site pain–nodule; 1, injection site discharge. †2, increased alanine aminotransferase; 1, injection site pain; 1, acute myocardial infarction.

Table 3: **Adverse events (maintenance phase; safety population)**

(284 [74%] of 382), not having to think about HIV status every day (233 [61%] of 382), and not having to worry about others seeing or finding HIV pills (227 [59%] of 382; appendix p 6).

Discussion

The month 11–12 results from this phase 3b non-inferiority study show that long-acting cabotegravir plus rilpivirine every 2 months is a highly efficacious therapy with non-inferior efficacy compared with daily oral bictegravir, emtricitabine, and tenofovir alafenamide for the maintenance of virological suppression in adults with HIV-1 infection. These results were consistent whether assessing virological non-response or virological suppression in the mITT-E, ITT-E, or per-protocol populations. Overall, 403 (90%) of 447 participants receiving long-acting cabotegravir plus rilpivirine therapy maintained virological suppression after 11–12 months of long-acting therapy, consistent with the high rates of virological suppression observed in other clinical and real-world studies evaluating this regimen.[8,10,17,21,22] Furthermore, as previously observed in the FLAIR study week 124 analysis,[9] virological outcomes were similar between participants receiving long-acting cabotegravir plus rilpivirine SWI and with an OLI. The high rates of patient preference, adherence, and participant retention with long-acting cabotegravir plus rilpivirine, coupled with the low rate of treatment discontinuation, complement results from other long-acting cabotegravir plus rilpivirine studies, supporting this regimen as an acceptable and feasible option for people living with HIV.[8,10,17]

In this treatment-experienced cohort (median duration of previous ART was 2·55 years), CVF was infrequent, with two participants ([<1%] of 447) receiving long-acting cabotegravir plus rilpivirine meeting the CVF criterion through to month 11–12 in the mITT-E population, and one additional participant receiving long-acting cabotegravir plus rilpivirine meeting CVF in the ITT-E population. Two of the participants had on-treatment rilpivirine or INSTI RAMs, or both (genotypes at failure revealed rilpivirine or INSTI RAMs for all three participants; one participant had cabotegravir-associated RAMs at baseline, identified from retrospective assessment of peripheral blood mononuclear cells). The presence of two or more of three baseline factors (pre-existing rilpivirine RAMs, HIV-1 subtype A6/A1, or BMI ≥30 kg/m², or both) has previously been associated with increased risk of CVF during treatment with long-acting cabotegravir plus rilpivirine in multivariable analyses.[23,24] Neither of the participants with CVF in the mITT-E population had a baseline risk factor. The overall rate of CVF observed in SOLAR is consistent with previous analyses that have shown a CVF rate of 0·4% in participants with no baseline factors.[23] The additional participant in the ITT-E population had a BMI of at least 30 kg/m² (30·5 kg/m²); the presence of pre-existing rilpivirine RAMs at baseline was unknown owing to failure of the genotypic analysis. All participants with CVF had cabotegravir and rilpivirine concentrations at the SVF visit above phase 3 benchmarks of 0·65 µg/mL for cabotegravir and 17·3 ng/mL for rilpivirine. Cabotegravir and rilpivirine trough concentrations in the lowest quartile, alongside pre-existing rilpivirine mutations and A6/A1 virus subtype, were associated with a higher risk of virological failure up to 3 years on long-acting cabotegravir plus rilpivirine in an expanded multivariable analysis; however, incorporating post-baseline pharmacokinetics information into models did not improve their accuracy beyond using only baseline factors (pre-existing rilpivirine RAMs, HIV-1 subtype A6/A1, or BMI ≥30 kg/m²).[23] The use of routine therapeutic drug monitoring with long-acting cabotegravir plus rilpivirine is not recommended because it is impractical in most clinical settings and because there is no established concentration threshold associated with failure.

Switching to long-acting cabotegravir plus rilpivirine from bictegravir, emtricitabine, and tenofovir alafenamide was well tolerated, with similar proportions of participants across both groups reporting adverse events (excluding ISRs) and serious adverse events; however, higher rates of drug-related adverse events and discontinuations were recorded for the long-acting group. Most long-acting cabotegravir plus rilpivirine discontinuations were for non-virological reasons, most commonly adverse events or other reasons. Similar findings are common in switch studies and might be attributable to reporting bias (participants and physicians might anticipate and be more likely to investigate adverse events for novel interventions).[25] Furthermore, overall safety and tolerability of both drug regimens were consistent with previous clinical experience.[8,10,11,26,27] Similar to previous findings for the long-acting regimen, 98% of ISRs were grade 1 or 2 (mild to moderate), of short duration, and infrequently led to treatment discontinuation.

Despite entering SOLAR with high treatment satisfaction scores (approximately 58 of a possible maximum of 66), participants switching to long-acting cabotegravir plus rilpivirine from oral daily bictegravir, emtricitabine, and tenofovir alafenamide showed increased treatment satisfaction at month 11–12 compared with participants continuing bictegravir, emtricitabine, and tenofovir alafenamide. Nine of ten participants reported a preference for the long-acting regimen, citing factors associated with the alleviation of daily stresses related to oral regimens, correlating with the fact that 80% of participants reported psychological challenges with their daily therapy at baseline.

The SOLAR study did not permit the enrolment of participants with previous NNRTI or protease inhibitor experience, preventing the generalisation of the results

to treatment-experienced individuals or individuals who have been on multiple regimens. However, several phase 3b/4 long-acting cabotegravir plus rilpivirine studies have previously shown high efficacy, tolerability, and preference for long-acting cabotegravir plus rilpivirine in participants switching from diverse NNRTI-based and protease inhibitor-based regimens.

Also, owing to the fact that participants randomly assigned to receive long-acting cabotegravir plus rilpivirine were given the option of a 1-month OLI, as well as ensuring that all participants receiving long-acting cabotegravir plus rilpivirine received 11 months of injections, participants in two of the study groups (long-acting cabotegravir plus rilpivirine OLI and bictegravir, emtricitabine, and tenofovir alafenamide) have 12 months of follow-up, and participants in the third group (long-acting cabotegravir plus rilpivirine SWI) have 11 months of follow-up included in the analysis. Of note, one participant discontinued in the bictegravir, emtricitabine, and tenofovir alafenamide group during this additional month (lost to follow-up).

In addition, pregnancy and hepatitis B virus co-infection were exclusionary in this study; long-acting cabotegravir plus rilpivirine has not been formally studied in these subgroups, although outcomes for participants who became pregnant across the phase 2/3/3b programme have been reported.[28] It should be noted, however, that if a woman became pregnant during the study, she was given the choice to continue long-acting treatment. Exposures during pregnancy contribute to ongoing surveillance efforts within long-acting cabotegravir plus rilpivirine clinical trials, further elucidating our understanding of safety following exposure during pregnancy. A study assessing safety and pharmacokinetics of long-acting cabotegravir plus rilpivirine during pregnancy is planned.[29]

Since enrolment into the SOLAR study was occurring at the start of the COVID-19 pandemic, we had significant challenges with study recruitment. Consequently, the enrolment of women was slightly lower (18% of the mITT-E population) than the prepandemic target of 20%, partially reflecting the challenges of doing a clinical trial in the midst of a global pandemic. Regardless, targeted inclusion of under-represented populations in clinical trials should be a priority to ensure generalisability of the data.

Finally, the ITT-E population had to be modified for the primary analysis to exclude 11 participants from one study site because of persistent protocol deviations (non-compliance to entry criteria); however, their exclusion did not affect statistical power or affect any interpretations from the study.

Long-acting cabotegravir plus rilpivirine every 2 months was non-inferior versus continuing bictegravir, emtricitabine, and tenofovir alafenamide at months 11–12 among virologically suppressed people living with HIV. Switching to long-acting cabotegravir plus rilpivirine every 2 months from bictegravir, emtricitabine, and tenofovir alafenamide was efficacious, well tolerated, associated with improved treatment satisfaction, and was preferred by 90% of participants. This study adds important health outcomes data to support the Joint United Nations Programme on HIV/AIDS proposed goal of ensuring that 90% of people with viral load suppression have good health-related quality of life.

Contributors

MNR, AC, CC, VD-B, RD, SO, OO, SW, JS, and GDP were study investigators and participated in the conduct of the study, including recruitment and follow-up of participants. KSu, DS-P, AB, CLL, FZ, RD'A, MPB, RVS-R, VVE, PP, VC, WRS, HPG, KSm, and JvW participated in the analysis of the study data and in the conceptualisation and design of the study. KSu and RD'A were responsible for study resources. MNR and KSu accessed and verified the study data. All authors vouch for the accuracy and completeness of the data, data analyses, and interpretation, and fidelity to the protocol. All authors were involved in the drafting and review of the manuscript and approved the final version for submission.

Declaration of interests

MNR reports consulting fees from Merck, Gilead, ViiV Healthcare, and Janssen, and honoraria from AbbVie, Gilead, ViiV Healthcare, and Janssen. RD reports owning stock in Gilead, GSK, BMS, Pfizer, Merck, and Janssen, and financial support for research from Merck, Gilead, ViiV Healthcare, and Janssen. SO reports research grants from ViiV Healthcare and Gilead Sciences, honoraria from ViiV Healthcare, Gilead, and MSD, and participation in advisory boards for ViiV Healthcare. SW reports funding for investigator-initiated clinical trials from Merck, ViiV Healthcare, Gilead, and Janssen, consulting fees from Merck and ViiV Healthcare, honoraria from Merck, ViiV Healthcare, and Gilead, and is the Co-Director of the Canadian HIV Trials Network. GDP reports consulting fees from AbbVie, GS Pharma, Merck, Janssen, ViiV Healthcare, Pfizer, Roche, AstraZeneca, and Atea Pharmaceuticals, honoraria from AbbVie, GS Pharma, Merck, Janssen, ViiV Healthcare, Pfizer, and AstraZeneca, and participation in advisory boards for AbbVie, GS Pharma, Merck, Janssen, ViiV Healthcare, Pfizer, Roche, AstraZeneca, and Atea Pharmaceuticals. KSu, DS-P, CLL, RD'A, MPB, PP, VC, WRS, HPG, KSm, and JvW are employees of ViiV Healthcare and stockholders of GSK. AB and FZ are employees and stockholders of GSK. RVS-R and VVE are employees and stockholders of Janssen. AC, CC, OO, VD-B, and JS declare no competing interests.

Data sharing

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

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