Initiation of long-acting cabotegravir plus rilpivirine as direct-to-injection or with an oral lead-in in adults with HIV-1 infection: week 124 results of the open-label phase 3 FLAIR study

Chloe Orkin, Enrique Bernal Morell, Darrell H S Tan, Harold Katner, Hans-Jürgen Stellbrink, Elena Belonosova, Rebecca DeMoor, Sandy Griffith, Shanker Thiagarajah, Rodica Van Solingen-Ristea, Susan L Ford, Herta Crauwels, Parul Patel, Amy Cutrell, Kimberly Y Smith, Kati Vandermeulen, Eileen Birmingham, Marty St Clair, William R Spreen, Ronald D'Amico

Summary

Background Previous work established non-inferiority of switching participants who were virologically suppressed from daily oral standard of care to monthly long-acting intramuscular injections of cabotegravir plus rilpivirine over 96 weeks following a cabotegravir plus rilpivirine oral lead-in. Here, we report an evaluation of switching participants from standard of care oral regimens to long-acting cabotegravir plus rilpivirine via direct-to-injection or oral lead-in pathways.

Methods This study reports the week 124 results of the FLAIR study, an ongoing phase 3, randomised, open-label, multicentre (11 countries) trial. Antiretroviral therapy (ART)-naive participants who were virologically suppressed (HIV-1 RNA <50 copies per mL) during the 20-week induction phase with standard of care were randomly assigned (1:1) to continue the standard of care oral regimen or switch to long-acting cabotegravir plus rilpivirine (283 per group) in the 100-week maintenance phase. Randomisation was stratified by sex at birth and baseline (pre-induction) HIV-1 RNA (<100 000 or ≥100 000 copies per mL). Participants randomly assigned to long-acting therapy at baseline received a cabotegravir (30 mg) plus rilpivirine (25 mg) once daily oral lead-in for at least 4 weeks before first injection and could choose to continue long-acting cabotegravir (400 mg) plus rilpivirine (600 mg) every 4 weeks from week 100 or withdraw. At week 100, participants in the oral comparator ART group, in discussion with the investigator, could elect to switch to long-acting therapy (extension switch population), either direct-to-injection or with a 4 week oral lead-in (oral lead-in group), or withdraw. Week 124 endpoints included plasma HIV-1 RNA 50 or more copies per mL and less than 50 copies per mL (US Food and Drug Administration [FDA] Snapshot), confirmed virological failure (two consecutive HIV-1 RNA ≥200 copies per mL), and safety and tolerability. The study is registered at ClinicalTrials.gov, NCT02938520.

Findings Screening occurred between Oct 27, 2016, and March 24, 2017. At week 100, 232 (92%) of 253 participants transitioned to long-acting cabotegravir plus rilpivirine in the extension phase (111 [48%] in the direct-to-injection group and 121 [52%] in the oral lead-in group; extension switch population). 243 (86%) of the 283 who were randomly assigned to the long-acting therapy group continued the long-acting regimen into the extension phase. One (<1%) participant in each extension switch group had 50 or more HIV-1 RNA copies per mL; 110 (99%) participants in the direct-to-injection group and 113 (93%) participants in the oral lead-in group remained suppressed (HIV-1 RNA <50 copies per mL) at the week 124 Snapshot. The lower suppression rates in the oral lead-in group were driven by non-virological reasons. For participants in the randomly assigned long-acting group, 227 (80%) of 283 participants remained suppressed; at the week 124 Snapshot, 14 (5%) participants had HIV-1 RNA 50 or more copies per mL, including five additional participants since the week 96 analysis. The remaining 42 (15%) participants in the randomly assigned long-acting group had no virological data. Adverse events leading to withdrawal were infrequent, occurring in three (1%) participants in the extension switch population (one in the direct-to-injection group and two in the oral lead-in group) after 24 weeks of cabotegravir plus rilpivirine therapy, and 15 (5%) participants in the randomly assigned long-acting group up to 124 weeks of therapy. No deaths occurred in the extension phase. Overall, cabotegravir plus rilpivirine adverse event type, severity, and frequency were similar across all groups. Injection site reactions were the most common adverse event, occurring after 914 (21%) of 4442 injections in the extension switch population and 3732 (21%) of 17 392 injections in the randomly assigned long-acting group. Injection site reactions were mostly classified as mild-to-moderate in severity and decreased in incidence over time. Four (2%) of 232 participants in the extension switch population and seven (2%) of 283 in the randomly assigned long-acting group withdrew due to injection-related reasons.

Interpretation After 24 weeks of follow-up, switching to long-acting treatment with or without an oral lead-in phase had similar safety, tolerability, and efficacy, supporting future evaluation of the simpler direct-to-injection approach. The week 124 results for participants randomly assigned originally to the long-acting therapy show long-acting cabotegravir plus rilpivirine remains a durable maintenance therapy with a favourable safety profile.

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Department of Infection and Immunity, Royal London Hospital, London, UK (Prof C Orkin MBBCh); **Sección de Enfermedades Infecciosas, Hospital General Universitario Reina Sofía, Murcia, Spain** (E Bernal Morell MD); **Division of Infectious Diseases, Department of Medicine, St Michael's Hospital, Toronto, ON, Canada** (D H S Tan MD); **Mercer University Medical School, Macon, GA, USA** (Prof H Katner MD); **ICH Study Center, Hamburg, Germany** (Prof H-J Stellbrink MD); **Orel Regional Center for AIDS, Orel, Russia** (E Belonosova MD); **Infectious Diseases Research & Development Biostatistics, GlaxoSmithKline, Collegeville, PA, USA** (R DeMoor MS); **Research and Development** (S Grittith PharmD, P Patel PharmD, K Y Smith MD, W R Spreen PharmD, R D'Amico DO), **Translation Medical Research** (M St Clair BS), **and Research and Statistics** (A Cutrell MS), **ViiV Healthcare, Research Triangle Park, NC, USA; Safety and Medical Governance Pharma Safety, GlaxoSmithKline, London, UK** (S Thiagarajah MBChB); **Janssen Research & Development, Beerse, Belgium** (R Van Solingen-Ristea MD, H Crauwels PhD, K Vandermeulen MS); **Clinical Pharmacology, GlaxoSmithKline, Research Triangle Park, NC, USA** (S L Ford PharmD); **Janssen Research & Development,**

Raritan, NJ, USA
(E Birmingham MD)

Correspondence to:
Prof Chloe Orkin, Department of Infection and Immunity, Royal London Hospital, London E1 1BB, UK
c.m.orkin@qmul.ac.uk

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Introduction

Contemporary antiretroviral therapy (ART) has revolutionised HIV treatment, with sustained virological suppression an achievable target for nearly all people with HIV with access to ART. Guideline-recommended regimens generally consist of one or two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with an integrase strand transfer inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a boosted protease inhibitor.[1,2]

Current regimens require strict adherence to daily oral therapy for sustained virological suppression. Poor adherence, which results in insufficient drug concentrations, is associated with virological failure, emergent resistance, and worse outcomes.[3–5] Because modern regimens are highly effective, the emphasis of HIV care has shifted from solely efficacy to quality of life improvements through treatment simplification, better tolerability, and patient satisfaction, which can positively influence adherence. These drivers have led to the development of two-drug oral regimens, with the aim of reducing cumulative drug exposure compared with standard three-drug therapy.[6,7]

People with HIV have expressed increasing interest in long-acting ART to afford greater convenience with daily routines and travel,[8–11] which together with a reduced dosing frequency might support improved treatment adherence.[12,13] Furthermore, long-acting therapy might alleviate the psychological burden of daily oral therapy, including fear of inadvertent disclosure of HIV status and possible stigmatisation.[14,15] Additionally, some people with HIV have reported that daily ART restricts their

Research in context

Evidence before this study

We searched PubMed for publications on antiretroviral therapy (ART), long-acting HIV therapies, and treatment adherence using the search terms "antiretroviral therapy", "cabotegravir", "rilpivirine", "HIV injectable therapy", "long-acting treatment", and "HIV treatment adherence" from the inception of the database until April 12, 2021. Since 2012, there has been increasing interest in long-acting HIV therapies, with several studies evaluating their use in people with HIV. The need for long-acting ART focuses on improving adherence to regimens, with the acknowledgment that, despite the high efficacy of daily oral ART regimens, current treatment regimens have intrinsic challenges associated with the need for daily pill taking that might negatively affect long-term adherence. These challenges include pill burden, drug–drug or drug–food interactions that occur in the gastrointestinal tract, worries related to fear of stigma resulting from inadvertent disclosure, and the daily reminder of their HIV status. In addition, for some, daily oral pill taking is physically problematic (eg, due to swallowing problems or cognitive impairment). Long-acting injectable ARTs have the potential to address these challenges. The two-drug regimen of cabotegravir and rilpivirine is the only approved long-acting antiretroviral regimen indicated for the maintenance of HIV-1 suppression, administered monthly or every 2 months. Approval was made primarily on the basis of the phase 3 ATLAS (NCT02951052) and FLAIR (NCT02938520) studies and the phase 3b ATLAS-2M (NCT03299049) study. The phase 3 programme evaluating long-acting cabotegravir plus rilpivirine employed an oral lead-in with daily cabotegravir (30 mg) plus rilpivirine (25 mg) to assess individual tolerability before starting the long-acting intramuscular therapy.

Added value of this study

Because oral therapy can be burdensome for some people, and as a result of not observing significant safety concerns with cabotegravir plus rilpivirine that would be mitigated by oral lead-in, across clinical studies of more than 1000 participants, we investigated long-acting intramuscular cabotegravir plus rilpivirine as a direct-to-injection regimen, without an oral lead-in, for the first time during the extension phase (ie, as of week 100) of the FLAIR study. Such a strategy would remove the need for an initial introduction of oral cabotegravir plus rilpivirine followed by a switch to long-acting formulations of cabotegravir plus rilpivirine. The results showed that initiating long-acting cabotegravir plus rilpivirine direct-to-injection has a similar safety and pharmacokinetic profile to initiation following an oral lead-in, with no diminution of efficacy. These data, taken with the previous clinical results, support the use of long-acting cabotegravir plus rilpivirine every 4 weeks in virologically suppressed adults living with HIV-1, with this analysis supporting direct initiation of a long-acting cabotegravir plus rilpivirine regimen.

Implications of all the available evidence

Current oral ART requires continuous high levels of adherence and daily good decision making, which can be difficult to sustain long term. Initiation of cabotegravir plus rilpivirine direct-to-injection is a practical treatment simplification strategy that has similar initial tolerability, safety, efficacy, and pharmacokinetics to commencing the regimen with an oral lead-in. The longer-term data suggest that long-acting cabotegravir plus rilpivirine is a durable therapeutic alternative to daily oral therapy and might help overcome some of the challenges associated with life-long daily oral therapy.

daily life.[16] This patient-first approach to HIV treatment aims to improve quality of life and health outcomes for people with HIV.[17]

The only currently approved long-acting ART regimen is an NRTI-sparing two-drug combination comprising the INSTI cabotegravir and the NNRTI rilpivirine.[18–20] Long-acting cabotegravir plus rilpivirine is an intramuscular injectable regimen administered monthly or every 2 months indicated for the maintenance of virological suppression in adults with HIV-1 and is recommended in treatment guidelines.[2,21] In two large phase 3 studies, ATLAS (NCT02951052)[18] and FLAIR (NCT02938520),[19] long-acting cabotegravir plus rilpivirine dosed every 4 weeks had non-inferiority for the maintenance of virological suppression compared with continuing daily comparator ART over 48 weeks, both individually and in a pooled analysis.[22] The safety profiles of long-acting cabotegravir plus rilpivirine and oral comparator ART, excluding injection site reactions, were similar. Injection site reactions were mostly mild, short-lived, and decreased in incidence over time. In the large phase 3b ATLAS-2M study (NCT03299049),[20] long-acting cabotegravir plus rilpivirine dosed every 8 weeks had non-inferior efficacy compared with dosing of the same drugs every 4 weeks, with a similar safety profile.[20] In all three studies, cabotegravir plus rilpivirine was taken once a day as an oral lead-in to assess individual tolerability for 4 weeks or more before initiating the long-acting regimen, and was also used to manage interruptions in scheduled long-acting dosing.[18–20] No significant safety concerns with cabotegravir plus rilpivirine that would be mitigated by an oral lead-in were identified across the phase 2 and 3 programme,[18–20,23] providing the rationale to investigate long-acting cabotegravir plus rilpivirine administered directly without an oral lead-in (direct-to-injection), which would simplify the regimen.

We report efficacy and safety findings from the extension phase of the FLAIR study for participants who switched to long-acting therapy either with or without an oral lead-in, after having previously been randomly assigned to receive oral standard of care for 100 weeks. In addition, longer-term week 124 data for those randomly assigned originally to receive long-acting therapy are also presented.

Methods

Study design and participants

FLAIR is a phase 3, randomised, open-label, multicentre study evaluating the efficacy, safety, and tolerability of long-acting cabotegravir plus rilpivirine compared with continuing the daily oral combination of dolutegravir, abacavir, and lamivudine. For participants who were HLA-B*5701 positive, dolutegravir was taken with a non-abacavir NRTI backbone chosen by the investigator. The study was done in 108 centres in 11 countries (Canada [six centres], 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]). Eligibility criteria and full details of the study design through the maintenance phase (week 100) have been reported previously.[19]

Eligible participants, who were 18 years old or older and ART naive at study entry, entered an induction phase with dolutegravir (50 mg), abacavir (600 mg), and lamivudine (300 mg) for 20 weeks (study week –20 to day 1; appendix p 1). Individuals who had less than 50 HIV-1 RNA copies per mL at week –4 were randomly assigned on day 1 to receive long-acting cabotegravir plus rilpivirine every 4 weeks intramuscularly into the gluteal muscle or to continue daily oral dolutegravir, abacavir, and lamivudine (or dolutegravir plus two alternative NRTIs) during the maintenance phase for 100 weeks. Participants randomly assigned to receive long-acting therapy received an initial oral lead-in of once-daily cabotegravir (30 mg) plus rilpivirine (25 mg) for at least 4 weeks (study day 1 to week 4) to assess tolerability before receiving their first injection. The first long-acting dose (loading dose) comprised cabotegravir (600 mg) plus rilpivirine (900 mg) administered by a health-care professional as two separate 3 mL injections into the gluteal muscle at week 4. At week 8 and every 4 weeks thereafter, participants were administered cabotegravir (400 mg) plus rilpivirine (600 mg) as separate 2 mL injections. Participants randomly assigned to receive oral comparator ART who completed the maintenance phase and had viral suppression at week 96 had the option to switch to long-acting cabotegravir plus rilpivirine in the extension phase (extension switch population) or be withdrawn from the study. In the original protocol, an oral lead-in before long-acting therapy was mandatory; however, the study protocol was amended for the extension switch population to add the option to transition directly to an injection of long-acting cabotegravir plus rilpivirine (direct-to-injection group) or with an oral lead-in, as used in participants randomly assigned to receive long-acting therapy at the start of the maintenance phase (oral lead-in group). The decision to use an oral lead-in was made by the participant after discussion with, and having attained the agreement of, the investigator. In the direct-to-injection group, the last dose of randomly assigned oral comparator ART and first loading injection of long-acting therapy was at week 100. In the oral lead-in group, oral cabotegravir plus rilpivirine began at week 100 and continued once daily for 4 weeks or more, with the last oral dose coinciding with the loading long-acting injection at week 104. Participants randomly assigned originally to the long-acting group who completed the maintenance phase had the option to continue their therapy in the extension phase or withdraw. Any participant who was administered one or more doses of intramuscular cabotegravir or intramuscular rilpivirine and withdrew for any reason entered long-term follow-up for 52 weeks.

See Online for appendix

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

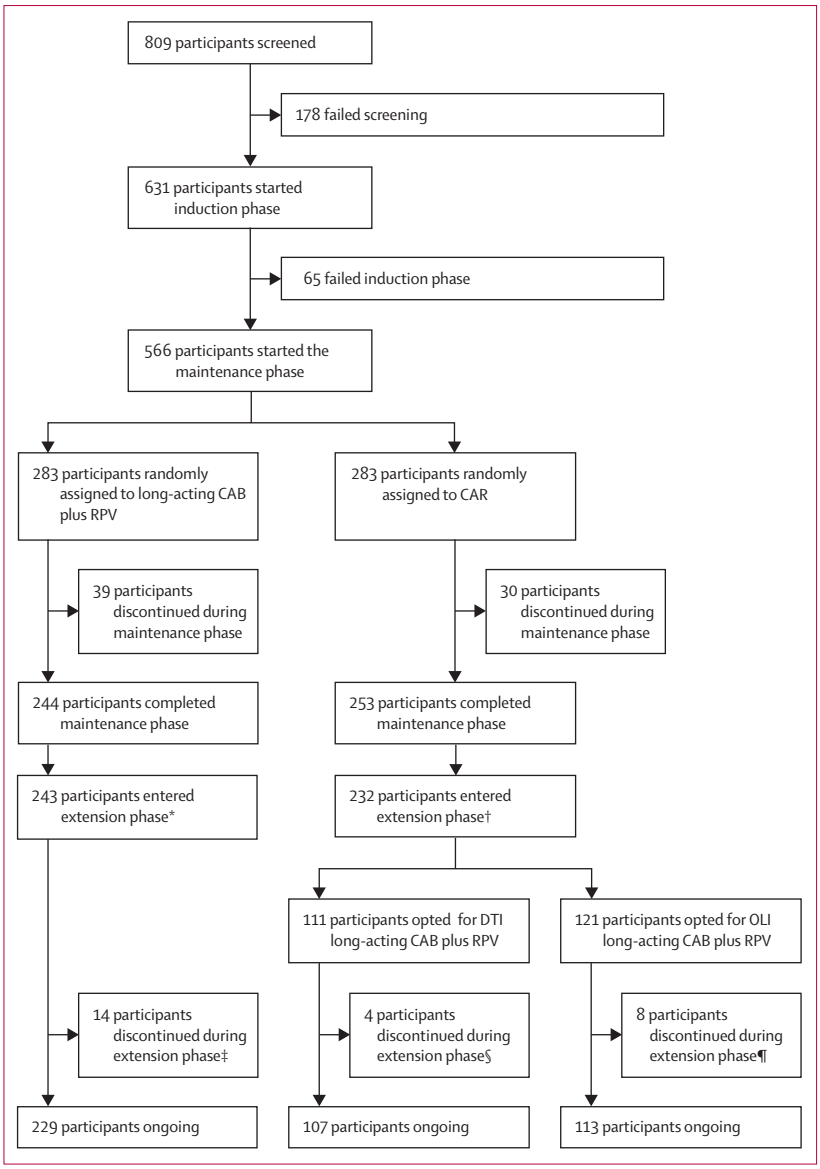

Figure 1: **Trial profile**
CAB=cabotegravir. CAR=current antiretroviral therapy. DTI=direct-to-injection. OLI=oral lead-in. RPV=rilpivirine. *One participant completed the maintenance phase and went into long-term follow-up. †21 participants completed the maintenance phase and did not enter the extension phase. ‡Reasons for discontinuation: nine participants decided to discontinue (frequency of injections [n=1]; frequency of visits [n=3]; intolerability of injections [n=1]; relocation [n=3]; and other reasons [n=14]); two due to a lack of efficacy (insufficient viral load response [n=1]; confirmed virological failure [n=1]); two due to physician decision (pregnancy); and one had an adverse event (paracetamol overdose); participants could report more than one reason for withdrawal. §Reasons for discontinuation: two participants decided to discontinue (intolerability of injections [n=1]; other reasons [n=2]); one had an adverse event (Hodgkin lymphoma); and one had a lack of efficacy (confirmed virological failure); participants could report more than one reason for withdrawal. ¶Reasons for discontinuation: four participants decided to discontinue (burden of procedures [n=1]; burden of travel [n=1]; intolerability of injection [n=2]; relocation [n=1]; and other reasons [n=2]); two had adverse events (injection site pain [n=1]; weight increase [n=1]); one had a protocol deviation (a prohibited medication [dexamethasone]); and one due to physician decision (pregnancy); participants could report more than one reason for withdrawal.

FLAIR was done in accordance with the Declaration of Helsinki.[24] All participants provided written informed consent. The study protocol, amendments, 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. Central random assignment with interactive response technology was used for randomisation and treatment assignment (block randomisation). Randomisation was stratified by sex at birth and baseline (pre-induction) HIV-1 RNA (<100 000 or ≥100 000 copies per mL). Full details of randomisation to maintenance therapy have been presented previously.[19,25] The extension phase was done as an open-label, non-randomised study (ie, participants switching to long-acting therapy elected either direct-to-injection or oral lead-in in consultation with the investigator). The procedures carried out to assess the endpoints are as presented previously.[19,25]

Outcomes

Efficacy endpoints assessed at week 124 included the proportion of participants with virological non-response (HIV-1 RNA ≥50 copies per mL) and virological suppression (HIV-1 RNA <50 copies per mL) as per the US Food and Drug Administration Snapshot algorithm (week 124 Snapshot). Other efficacy endpoints at week 124 were the proportion of participants with confirmed virological failure (two consecutive plasma HIV-1 RNA measurements ≥200 copies per mL after previous suppression to <200 copies per mL) and absolute values and change from baseline in CD4 cell counts over time. The incidence of treatment-emergent genotypic and phenotypic resistance to cabotegravir and rilpivirine was also assessed. Safety endpoints were the incidence and severity of adverse events, including injection site reactions, and laboratory abnormalities over time, the proportion of participants who discontinued treatment due to adverse events over time, and absolute values and change in laboratory parameters over time. In the extension switch population, plasma cabotegravir and rilpivirine concentrations were assessed in the direct-to-injection group at week 100 and week 104 and in the oral lead-in group at week 104. All endpoints were protocol defined.

Statistical analysis

The study was designed to show non-inferiority (6% non-inferiority margin per the Snapshot algorithm) of long-acting cabotegravir plus rilpivirine compared with dolutegravir, abacavir, and lamivudine at week 48 for the primary efficacy endpoint (the proportion of participants with virological non-response [HIV-1 RNA ≥50 copies per mL] at week 48). Full details of the sample size justifications have been described previously.[19] The endpoint analyses at week 124 included all participants who were administered at least one dose of cabotegravir or rilpivirine during the extension phase for the extension switch population or during the maintenance phase for those initially randomly assigned to long-acting therapy (intention-to-treat

exposed population). Extension phase data on participant-elected initiation of cabotegravir plus rilpivirine (direct-to-injection or with an initial oral lead-in) were evaluated descriptively. The study is registered at ClinicalTrials.gov, NCT02938520.

Role of the funding source

This study was funded by ViiV Healthcare and Janssen Research & 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

Between Oct 27, 2016, and March 24, 2017, 809 participants were screened for inclusion in FLAIR, 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 of care group (283 [50%] participants). The analysis cut-off was Feb 21, 2020, at which time the COVID-19 pandemic had not significantly affected the study. 253 participants completed the maintenance phase (week 100), of whom 232 (92%) elected to switch to long-acting therapy and entered the extension phase (extension switch population; figure 1). 111 (48%) participants selected an immediate start to the long-acting therapy (direct-to-injection group) and 121 (52%) participants selected to first have an oral lead-in (oral lead-in group). At the end of the week 124 data collection cut-off, 107 (96%) participants in the direct-to-injection group and 113 (93%) in the oral lead-in group were ongoing in the study. At week 100, 244 participants who were randomly assigned originally to the long-acting group completed the maintenance phase, with 243 (>99%) participants electing to continue long-acting therapy in the extension phase. At week 124, 229 (94%) participants in the randomly assigned long-acting group were ongoing. Of note, withdrawal by participant decision included four (1%) of 283 participants in the long-acting group and three (one [1%] in the direct-to-injection group and two [2%] in the oral lead-in group) in the extension switch population who cited general intolerability of injections.

Participant baseline characteristics were similar between the direct-to-injection and oral lead-in groups (table 1).[19] Overall, the extension switch population had a median age of 37 years (IQR 31–46), 33 (14%) participants were 50 years old or older, most were male (sex at birth; 181 [78%]), white (171 [74%]), with a median body-mass index (BMI) of 25·2 kg/m² (23–28).

There were 1993 expected injection visits in the extension switch population after 24 weeks of therapy; 1937 (97%) occurred within 7 days before or after the intended dosing visit date. One (<1%) participant missed two visits and received oral therapy with cabotegravir plus rilpivirine as a bridge on both occasions. In the randomly assigned long-acting group, 8196 (97%) of 8428 injection visits occurred within 7 days before or after the intended dosing visit date over 124 weeks of long-acting therapy. Up to week 124, injection visits were missed by 11 (4%) of 283 participants (14 [<1%] of 8428 visits) in the randomly assigned long-acting group. One (<1%) of 8428 visits was missed without oral bridging therapy. This participant missed the visit due to meeting liver stopping criteria (acute hepatitis A); upon resolution of the acute hepatitis A, the participant restarted long-acting dosing and remained fully virologically suppressed. No cases of confirmed virological failure or viral blips were observed during the period of oral bridging therapy for missed injections.

In participants in the extension switch population after 24 weeks of cabotegravir plus rilpivirine therapy, one (<1%) participant in each group had 50 or more HIV-1 RNA copies per mL at the week 124 visit. The participant in the direct-to-injection group had met the confirmed virological failure criterion at week 112; the participant in the oral lead-in group was suppressed (HIV-1 RNA <50 copies per mL) throughout the study but experienced a transient blip at week 124 (HIV-1 RNA 57 copies per mL) that went back to less than 50 copies per mL at a subsequent visit. Most participants in the extension switch population maintained virological suppression, with 110 (99%) participants in the direct-to-injection group and 113 (93%) in the oral lead-in group

	DTI group* (n=111)	OLI group* (n=121)	Randomly assigned long-acting group (n=283)
Median age, years	36 (30–45)	38 (31–46)	34 (29–42)
≥50	16 (14%)	17 (14%)	33 (12%)
<35	49 (44%)	43 (36%)	143 (51%)
Sex at birth			
Female	24 (22%)	27 (22%)	63 (22%)
Male	87 (78%)	94 (78%)	220 (78%)
Self-reported gender			
Female	24 (22%)	27 (22%)	65 (23%)
Male	87 (78%)	94 (78%)	218 (77%)
Race			
White	77 (69%)	94 (78%)	216 (76%)
Black or African American	23 (21%)	21 (17%)	47 (17%)
Other	11 (10%)	6 (5%)	20 (7%)
Median body-mass index, kg/m²	26 (23–28)	25 (23–27)	24 (22–27)
Median CD4 cell count, cells per µL	752 (590–988)	718 (595–852)	624 (473–839)

Data are n (%) or median (IQR). DTI=direct-to-injection. OLI=oral lead-in. *Data collected at extension baseline (week 100).

Table 1: **Baseline characteristics**

	DTI group (after 24 weeks of CAB plus RPV; n=111)	OLI group (after 24 weeks of CAB plus RPV; n=121)	Randomly assigned long-acting arm (after 124 weeks of CAB plus RPV; n=283)
HIV-1 RNA <50 copies per mL	110 (99%; 97–100)	113 (93%; 89–98)	227 (80%; 76–85)
HIV-1 RNA ≥50 copies per mL	1 (1%; 0–3)	1 (1%; 0–2)	14 (5%; 2–8)
Data in window not below threshold	0	1 (1%)*	5 (2)
Discontinued due to a lack of efficacy	1 (1%)†	0	8 (3%)
Discontinued for other reason while not below threshold	0	0	1 (<1%)
Change in background therapy	0	0	0
No virological data	0	7 (6%)	42 (15%)
Discontinued due to an adverse event‡	0	2 (2%)§	15 (5%)
Discontinued study for other reason	0	5 (4%)¶	26 (9%)
On study but missing data in window	0	0	1 (<1%)

Data are n (%; 95% CI) or n (%). CAB=cabotegravir. DTI=direct-to-injection. OLI=oral lead-in. RPV=rilpivirine. *Participant had HIV-1 RNA of 57 copies per mL at week 124. †Participant met the confirmed virological failure criterion at week 112. ‡No deaths occurred during the maintenance or extension phases. §Two participants discontinued due to adverse events; one had injection site pain and one had weight gain. ¶Five participants discontinued due to other reasons, which included burden of travel, prohibited medication use, participant relocation, burden of procedures or intolerability of injections, and pregnancy.

Table 2: **Efficacy outcomes at week 124**

having less than 50 HIV-1 RNA copies per mL at the week 124 visit (appendix p 2). A lower proportion of participants in the oral lead-in group were suppressed at week 124, primarily due to missing data for non-virological reasons (table 2).

For the randomly assigned long-acting group, after 124 weeks of cabotegravir plus rilpivirine, 227 (80%) of 283 participants maintained suppression, with 14 (5%) participants having 50 or more HIV-1 RNA copies per mL, an increase of five participants since the 96-week analysis.[25] Of the 42 (15%) participants with no virological data at week 124, 41 (14%) discontinued due to adverse events or other reasons (one participant [<1%] was missing data for the study window; table 2). The median CD4 count increased by 103 cells per µL (IQR –49 to 235): from 624 cells per µL (473 to 839) at maintenance baseline (day 1) to 734 cells per µL [547 to 952] at week 124.

One (1%) of the 111 participants in the direct-to-injection group met the confirmed virological failure criterion during the first 24 weeks of cabotegravir plus rilpivirine therapy. The participant had suspected virological failure (first HIV-1 RNA ≥200 copies per mL) at week 112 following three monthly injection doses, with a viral load of 348 copies per mL, followed by a viral load of 1218 copies per mL at the subsequent confirmatory visit. The participant was male (sex at birth), from the USA, had a BMI of 30 kg/m² or more, and had HIV-1 subtype B; no INSTI or NNRTI resistance-associated mutations (RAMs) were detected at induction baseline (week –20). At the time of suspected virological failure, no INSTI RAMs were detected and the participant had full phenotypic susceptibility to cabotegravir and dolutegravir; PhenoSense (Monogram Biosciences, South San Francisco, CA, USA) genotype could not be generated. The participant had plasma cabotegravir and rilpivirine concentrations below the fifth percentiles (cabotegravir 0·349 µg/mL; rilpivirine 16·4 ng/mL) 4 weeks following initiating injections (appendix p 3).

Cumulatively, confirmed virological failure occurred in five (2%) of 283 participants in the randomly assigned long-acting group over 124 weeks of therapy, four of whom were reported in the week 48 analysis (one of whom temporarily discontinued cabotegravir plus rilpivirine during the oral lead-in due to a false-positive pregnancy test and had confirmed virological failure without ever receiving long-acting injections).[19] One additional participant met the confirmed virological failure criterion at week 108 and was male (sex at birth), from Russia, with a BMI less than 30 kg/m². This participant was originally classified as HIV-1 subtype A1, but was reclassified as HIV-1 subtype A6, as were several participants across the FLAIR, ATLAS, and ATLAS-2M studies.[26] The participant had no NNRTI or INSTI RAMs at induction baseline and full phenotypic susceptibility to cabotegravir, rilpivirine, and dolutegravir (the integrase polymorphism Leu74Ile was present at baseline). The participant had a viral load of 887 copies per mL at the suspected virological failure timepoint, followed by 1112 copies per mL at the confirmatory visit. At the time of suspected virological failure, the participant had NNRTI RAMs Val106Val/Ala, Val108Val/Ile, Glu138Gly, and Met230Leu, and INSTI RAMs Asn155His and Arg263Lys; this virus showed reduced susceptibility to rilpivirine (27-times less susceptible) and cabotegravir (nine-times less susceptible). This participant had plasma concentrations of cabotegravir 1·73 µg/mL and rilpivirine 79·5 ng/mL at confirmed virological failure (week 108), which was 10·4-times higher than the in-vitro protein-adjusted 90% inhibitory concentration value for cabotegravir wild-type virus and 6·6-times higher than that for rilpivirine wild-type virus (appendix p 3); lower cabotegravir and rilpivirine concentrations earlier in treatment might have contributed to confirmed virological failure with the development of resistance to both drugs.

Both participants who met confirmed virological failure in the extension phase had virological suppression during long-term follow-up with an alternate ART regimen (the participant in the direct-to-injection group received darunavir, cobicistat, emtricitabine, and tenofovir alafenamide; the participant in the randomly assigned long-acting group received tenofovir disoproxil fumarate and emtricitabine and efavirenz).

A summary of adverse events for the extension switch and long-acting randomly assigned populations is reported in table 3. Adverse events were reported by 102 (92%) participants in the direct-to-injection group and 100 (83%) participants in the oral lead-in group. Injection site pain was the most common adverse event, reported by 84 (76%) participants in the

direct-to-injection group and 73 (61%) participants who received an injection in the oral lead-in group. Excluding injection site reactions, the most common adverse event was nasopharyngitis (20 [18%] in the direct-to-injection group and 13 [11%] in the oral lead-in group), with no other adverse events occurring in 10% or more of participants in either of the extension switch groups (table 3). Serious adverse events occurred in four (4%) participants in the direct-to-injection group and five (4%) participants in the oral lead-in group. The Hodgkin lymphoma reported by one participant in the direct-to-injection group was considered drug-related by the investigator because they could not rule out the possibility of the adverse event being related to study medication; the study sponsor did not consider this serious adverse event to be related to study medication. Withdrawals because of adverse events occurred in one (1%) participant in the direct-to-injection group due to a drug-related serious adverse event (Hodgkin lymphoma) and two (2%) participants in the oral lead-in group due to drug-related adverse events: one had weight gain of 8 kg and the other had injection site pain. No serious adverse events or adverse events leading to withdrawal occurred during the first 4 weeks of transition for either the direct-to-injection or oral lead-in group.

For the randomly assigned long-acting group, nearly all participants reported an adverse event (276 [98%] of 283) over the 124 weeks of follow-up, two of which occurred after the 96 week analysis. Most adverse events (including injection site reactions) continued to be mild-to-moderate in severity, with 49 (17%) of 283 participants reporting a grade 3–4 adverse event up to week 124. No new participants reported grade 4 adverse events since the 96 week analysis; however, one participant reported a grade 4 adverse event of elevated lipase who had previously reported it in the maintenance and induction phases. Serious adverse events occurred in 33 (12%) of 283 participants, one of which was deemed to be drug related (right knee monoarthritis, reported in the 48 week analysis).[19] There was one withdrawal due to an adverse event (paracetamol overdose) following the week 96 analysis.

A higher frequency of injection site reactions was reported in the direct-to-injection group, with 576 injection site reactions occurring with 2314 total injections compared with 338 occurring with 2128 injections in the oral lead-in group (appendix p 5). After the first injection, 79 (71%) participants in the direct-to-injection group reported an injection site reaction, consistent with what has been reported for the original randomly assigned group: 199 (72%).[25] In the oral lead-in group, 67 (56%) participants reported an injection site reaction after the first injection. The characteristics of injection site reactions were similar between groups in the extension switch population: 908 (>99%) of 914 injection site reactions being grade 1 or 2 in severity, with a median duration of 3 days (IQR 2–4) across both groups. No grade 4 or 5 injection site reactions were reported and no injection site reactions were reported as serious adverse events. Within the extension switch population, one (1%) participant in the oral lead-in group withdrew due to an injection site reaction at week 4 following first injection (two grade 3 adverse events of injection site pain related to each injection at a single visit). An

	DTI group (after 24 weeks of CAB plus RPV; n=111)	OLI group (after 24 weeks of CAB plus RPV; n=121)	Randomly assigned long-acting arm (after 124 weeks of CAB plus RPV; n=283)
Any adverse event	102 (92%)	100 (83%)	276 (98%)
Excluding ISRs	88 (79%)	85 (70%)	271 (96%)
Any grade 3–4 adverse events	5 (5%)	9 (7%)	49 (17%)
Excluding ISRs	4 (4%)	5 (4%)	38 (13%)
Drug-related adverse events	2 (2%)	4 (3%)	17 (6%)
Drug-related adverse events excluding ISRs	1 (1%)*	0	5 (2%)
Drug-related adverse events	86 (77%)	79 (65%)	248 (88%)
Excluding ISRs	22 (20%)	23 (19%)	102 (36%)
Adverse events leading to withdrawal	1 (1%)*	2 (2%)†	15 (5%)
Any serious adverse events	4 (4%)	5 (4%)	33 (12%)
Drug-related serious adverse events	1 (1%)*	0	1 (<1%)‡
Fatal serious adverse events	0	0	0
Common adverse events§			
Nasopharyngitis	20 (18%)	13 (11%)	98 (35%)
Headache	7 (6%)	3 (2%)	55 (19%)
Upper respiratory tract infection	10 (9%)	7 (6%)	53 (19%)
Diarrhoea	2 (2%)	10 (8%)	49 (17%)
Back pain	3 (3%)	3 (2%)	47 (17%)
Influenza	3 (3%)	3 (2%)	42 (15%)
Pyrexia	9 (8%)	4 (3%)	35 (12%)
Gastroenteritis	7 (6%)	3 (2%)	29 (10%)
Syphilis	4 (4%)	6 (5%)	29 (10%)
Dizziness	8 (7%)	4 (3%)	20 (7%)
Common drug-related adverse events¶			
Pyrexia	6 (5%)	2 (2%)	18 (6%)
Fatigue	0	2 (2%)	10 (4%)
Headache	1 (1%)	1 (1%)	15 (5%)
Dizziness	3 (3%)	2 (2%)	6 (2%)

Data are n (%). CAB=cabotegravir. DTI=direct-to-injection. ISR=injection site reaction. OLI=oral lead-in. RPV=rilpivirine. *Grade 4 drug-related serious adverse event (Hodgkin lymphoma) led to withdrawal from the DTI group. †One (1%) discontinued due to injection site pain and one (1%) due to weight gain. ‡One drug-related serious adverse event, right knee monoarthritis, was reported in the week 48 analysis. §Common adverse events that occurred in 5% or more of the extension switch population or 10% or more of the randomly assigned long-acting group, excluding ISRs. ¶Common drug-related adverse events that were reported by 3% or more of the extension switch population or the randomly assigned long-acting group, excluding ISRs.

Table 3: **Summary of adverse events**

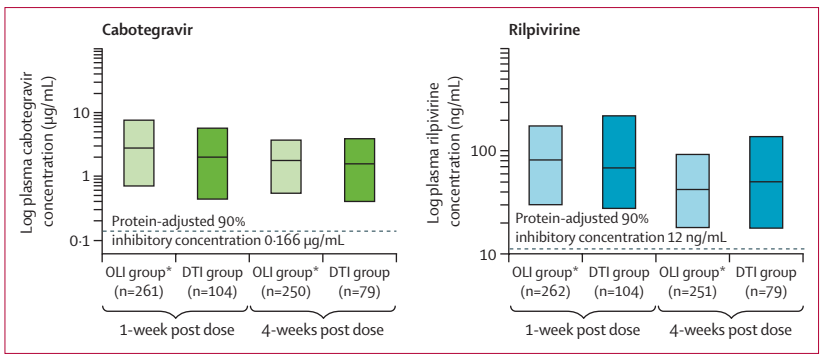

Figure 2: **Initial plasma cabotegravir and rilpivirine concentrations following first injections as DTI and after OLI**

Data are median (5th and 95th percentiles). DTI=direct-to-injection. OLI=oral lead-in. *Historical data: participants who were randomly assigned to receive long-acting cabotegravir plus rilpivirine in the maintenance phase.

additional three (1%) participants (one [1%] in the direct-to-injection group and two [2%] in the oral lead-in group) withdrew citing general intolerability of injections. There was an observable reduction in injection site reactions over time, mainly attributable to a reduction in participants reporting injection site pain (appendix p 4). For the randomly assigned long-acting group, the number of reported injection site reactions was consistent with that observed during the maintenance phase (appendix p 5). No grade 4 or 5 injection site reactions were reported up to week 124. There were no injection site reactions reported as serious adverse events or grade 3 injection site reactions since the week 96 analysis. The number of participants reporting injection site reactions over time remained consistent between week 96 (46 [19%] of 245 participants) and week 124 (42 [18%] of 232 participants in the randomly assigned long-acting group).

There were no drug-related hypersensitivity reactions and no significant creatinine changes from baseline for the extension switch or randomly assigned long-acting groups since the week 96 analysis. There were no clinically significant changes in lipase concentration in the extension switch population (from extension baseline) or the randomly assigned long-acting group; no lipase abnormalities were associated with clinical pancreatitis diagnoses. One (1%) participant in the direct-to-injection group, one (1%) in the oral lead-in group, and two (1%) in the randomly assigned long-acting group (since the week 96 analysis) had alanine aminotransferase concentrations three or more times higher than the upper limit of normal (single episodes each). No participants in the oral lead-in or direct-to-injection groups and only one (<1%) participant in the randomly assigned long-acting group met protocol-defined liver stopping criteria. This participant met liver stopping criteria at week 124 due to secondary syphilis and was treated with penicillin; after completing the treatment course, the participant's alanine aminotransferase and aspartate aminotransferase concentrations normalised. The case was adjudicated by the study sponsor who approved restarting long-acting dosing based on a clear cause and no indications of drug-induced liver injury. There were no cases of drug-induced liver injury in the extension switch population. During the extension phase at week 112, one (<1%) participant in the extension switch population (oral lead-in group) had a grade 1 adverse event: weight gain (progressive weight gain of 8 kg). This adverse event was assessed as study drug related and led to withdrawal. Another participant in the randomly assigned long-acting group had an adverse event of weight gain since the 96-week analysis. This was classified as grade 1 and not related to study drug.

No clinically meaningful differences in cabotegravir and rilpivirine concentrations were observed between the direct-to-injection group and the oral lead-in group (figure 2). At the end of the oral lead-in (week 104), the geometric mean (5th and 95th percentiles) trough plasma cabotegravir concentration was 5·12 µg/mL (2·76, 9·65) and trough rilpivirine concentration was 84·5 ng/mL (37·6, 227·0), consistent with those in the randomly assigned long-acting group at week 4 (after oral lead-in). In the direct-to-injection group 4 weeks after the first long-acting injection, the trough plasma cabotegravir concentration was 1·43 µg/mL (0·40, 3·90) and trough rilpivirine concentration was 48·9 ng/mL (17·7, 138·0).

Discussion

This is the first study to investigate direct initiation of long-acting cabotegravir plus rilpivirine injectable therapy without an oral lead-in in a subgroup of stably suppressed participants on oral comparator ART electing for this option. This phase 3 study also shows longer-term durability and safety over 124 weeks. Direct-to-injection long-acting cabotegravir plus rilpivirine administered every 4 weeks is an effective initiation strategy for the maintenance of virological suppression in people with HIV over 24 weeks, with a safety and efficacy profile similar to long-acting cabotegravir plus rilpivirine preceded by an oral lead-in. Furthermore, the longer-term data from participants initially randomly assigned to long-acting therapy add to the previous week 48 and week 96 data[19,25] by showing durability of response, with 80% of participants maintaining less than 50 HIV-1 RNA copies per mL after 124 weeks of cabotegravir plus rilpivirine therapy.

Adherence to the dosing schedule, as shown in the previous analyses,[19,25] remained high during the extension phase of the study, with 97% of injections administered within 7 days before or after the intended dosing visit date. The use of oral cabotegravir plus rilpivirine to manage short-term interruptions in injection therapy was infrequent and not associated with confirmed virological failure or virological blips. This observation is consistent with phase 3 data from ATLAS and ATLAS-2M,[18,20] and supports oral cabotegravir plus

rilpivirine use for the management of planned missed long-acting doses, affording patient flexibility for anticipated missed visits.

The proportion of participants with confirmed virological failure was low across all long-acting groups, with only one (<1%) participant in the extension switch population meeting the confirmed virological failure criterion after 24 weeks of cabotegravir plus rilpivirine therapy. Only one additional participant met confirmed virological failure in the randomly assigned long-acting group since the week 96 analysis, resulting in a total of five (2%) participants up to week 124 of cabotegravir plus rilpivirine therapy. The incidence of confirmed virological failure is similar to those reported in ATLAS and ATLAS-2M[18,20] and other (non-cabotegravir plus rilpivirine) large switch studies over 1–2 years.[6,27] Neither of the two participants who received long-acting cabotegravir plus rilpivirine who met the confirmed virological failure criterion during the extension phase had any INSTI or NNRTI mutations detected at baseline. The additional participant in the randomly assigned long-acting group with confirmed virological failure since the week 96 analysis had the integrase polymorphism Leu74Ile at baseline, consistent with three participants in this group who met the confirmed virological failure criterion during the maintenance phase while on long-acting therapy.[19] A recently published post-hoc multivariable analysis using a pooled population from the FLAIR, ATLAS, and ATLAS-2M studies found that the presence of two or more of the following baseline factors increased confirmed virological failure risk: baseline proviral rilpivirine RAMs, subtype A6 or A1, and a BMI of 30 kg/m² or more.[26] The role of these three factors in confirmed virological failure with long-acting cabotegravir plus rilpivirine has been extensively discussed previously.[26] The two participants who met confirmed virological failure in the extension phase of this study had one of the three factors each: one had a BMI of 30 kg/m² or more and the other had subtype A6. Both participants were resuppressed on alternate regimens.

The safety profile of long-acting cabotegravir plus rilpivirine was similar between the randomly assigned long-acting group and the extension switch population, and it was consistent with previous phase 3 and 3b studies that evaluated switching to cabotegravir plus rilpivirine from a variety of oral comparator ART regimens.[18–20] Initiation of the long-acting regimen with the omission of the oral lead-in period did not give rise to any specific safety concerns, with only three participants withdrawing due to adverse events; none of which occurred during the oral lead-in period. Injection site reactions were the most common adverse events in the extension switch population, and, consistent with previous phase 3 reports, they were mild-to-moderate, of short duration, and decreased over time.[18–20] There were no hypersensitivity reactions related to study treatment in the FLAIR study, which is consistent with the rest of the cabotegravir plus rilpivirine development programme, in which no cases of hypersensitivity reactions have been reported with oral or long-acting cabotegravir plus rilpivirine. No additional new safety signals of clinical concern were identified with long-acting cabotegravir plus rilpivirine in this study. Weight gain has been reported with several INSTIs and tenofovir alafenamide–based regimens.[28,29] We did not do a formal analysis of weight and BMI change due to a scarcity of data sampled during the extension phase. However, the previous FLAIR analysis[25] showed weight gain over 96 weeks was similar to that reported in a pooled analysis of eight randomised controlled clinical trials of treatment-naive people with HIV initiating ART between 2003 and 2015.[28]

There is no clinically meaningful effect of oral lead-in on the cabotegravir and rilpivirine pharmacokinetic profiles after intramuscular injections. Cabotegravir and rilpivirine concentrations at 1 week and 4 weeks after the first injection were similar in participants starting cabotegravir plus rilpivirine therapy with or without oral lead-in.

All previous studies have used an oral lead-in before initiating long-acting injections.[18–20] This study shows direct-to-injection long-acting cabotegravir plus rilpivirine has similar safety, efficacy, and pharmacokinetic profiles to long-acting cabotegravir plus rilpivirine preceded by an oral lead-in. In the 48-week analyses of the FLAIR, ATLAS, and ATLAS-2M studies,[18–20] participants showed high satisfaction and preference for the long-acting regimen over daily oral therapy. The option to initiate direct-to-injection long-acting cabotegravir plus rilpivirine without the oral lead-in might offer a more simple and convenient treatment regimen for people with HIV who wish to avoid the need for daily oral therapy.

All participants in the extension phase had previously tolerated regimens containing dolutegravir, an INSTI with a similar chemical structure to cabotegravir, for 20 weeks in the induction phase. Switching from other non-dolutegravir-based regimens to direct-to-injection long-acting cabotegravir plus rilpivirine has not yet been investigated. The absence of analysis of weight and BMI change in the extension phase is a limitation of this study. Future and ongoing studies, such as the SOLAR study (NCT04542070), will characterise the relationship, if present, between long-acting cabotegravir plus rilpivirine and metabolic perturbations. The extension switch population was not randomly assigned and had a relatively small sample size in each group that precluded adequately powered non-inferiority testing, so all analyses are descriptive in nature. Other clinical trials examining the safety of using an oral lead-in versus a direct-to-injection approach are being done and will provide more information in this regard (eg, the phase 3b SOLAR study, which will use an optional oral lead-in). Additionally, the relatively small proportions of female and non-white participants in the extension

switch population, along with the relatively young median age of participants, restrict generalisability.

In summary, findings from the present study serve as proof of principle for direct-to-injection long-acting cabotegravir plus rilpivirine, supporting the initiation of long-acting cabotegravir plus rilpivirine with or without the oral lead-in. These findings also show that long-acting cabotegravir plus rilpivirine continues to be an effective and durable maintenance therapy for virologically suppressed people with HIV over 124 weeks.

Contributors

CO, EBM, DHST, HK, H-JS, EBe, and RD'A were study investigators and participated in the conduct of the study, including recruitment and follow-up of participants. RD, SG, ST, RVS-R, HC, SLF, PP, AC, KYS, KV, EBi, MSC, WRS, and RD'A analysed the study data and conceptualised and designed the study. SG, KV, WRS, and RD'A were responsible for study resources. RD, SG, and RD'A verified the study data. All authors were involved in the drafting and review of the manuscript and approved the final version. All authors had access to the underlying data.

Declaration of interests

CO reports grants, personal fees, non-financial support, and travel sponsorship during the study from ViiV Healthcare; and grants, personal fees, non-financial support, speaker's bureau, and travel sponsorship from GlaxoSmithKline, Gilead Sciences, Merck Sharp & Dohme, Janssen, and ViiV Healthcare, outside the submitted work. EBM reports grants from ViiV Healthcare, during the study; and grants, personal fees, and non-financial support from Gilead Sciences, Janssen, ViiV Healthcare, and Merck Sharp & Dohme, outside the submitted work. DHST reports grants from the Canada Research Chairs Program, during the study; grants from Gilead Sciences, ViiV Healthcare, and AbbVie; and DHST participated as a site principal investigator in a trial sponsored by GlaxoSmithKline, outside of the submitted work. H-JS reports personal fees from ViiV Healthcare during the study; personal fees from Gilead Sciences, Janssen-Cilag, Theratechnologies, and Merck Sharp & Dohme, outside of the submitted work. RD, ST, and SLF are employees and stockholders of GlaxoSmithKline. SG, PP, AC, KYS, MSC, WRS, and RD'A are employees of ViiV Healthcare and stockholders of GlaxoSmithKline. RVS-R, HC, KV, and EBi are employees and stockholders of 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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References

1 WHO. Update of recommendations on first- and second-line antiretroviral regimens. 2019. https://apps.who.int/iris/bitstream/handle/10665/325892/WHO-CDS-HIV-19.15-eng.pdf?ua=1 (accessed June 18, 2021).

2 US Department of Health and Human Services. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. 2021. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf (accessed April 19, 2021).

3 Bezabhe WM, Chalmers L, Bereznicki LR, Peterson GM. Adherence to antiretroviral therapy and virologic failure: a meta-analysis. *Medicine* 2016; **95:** e3361.

4 Rai S, Mahapatra B, Sircar S, et al. Adherence to antiretroviral therapy and its effect on survival of HIV-infected individuals in Jharkhand, India. *PLoS One* 2013; **8:** e66860.

5 Bangsberg DR, Moss AR, Deeks SG. Paradoxes of adherence and drug resistance to HIV antiretroviral therapy. *J Antimicrob Chemother* 2004; **53:** 696–99.

6 Llibre JM, Hung CC, Brinson C, et al. Efficacy, safety, and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomised, non-inferiority SWORD-1 and SWORD-2 studies. *Lancet* 2018; **391:** 839–49.

7 Cahn P, Madero JS, Arribas JR, et al. Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. *Lancet* 2019; **393:** 143–55.

8 Akinwunmi B, Buchenberger D, Scherzer J, et al. Factors associated with interest in a long-acting HIV regimen: perspectives of people living with HIV and healthcare providers in four European countries. *Sex Transm Infect* 2021; published online Feb 25. https://dx.doi.org/10.1136/sextrans-2020-054648.

9 Dandachi D, Dang BN, Lucari B, Swindells S, Giordano TP. Acceptability and preferences for long-acting antiretroviral formulations among people with HIV infection. *AIDS Care* 2020; **33:** 801–09.

10 Simoni JM, Beima-Sofie K, Wanje G, et al. "Lighten this burden of ours": acceptability and preferences regarding injectable antiretroviral treatment among adults and youth living with HIV in coastal Kenya. *J Int Assoc Provid AIDS Care* 2021; **20:** 23259582211000517.

11 Weld ED, Rana MS, Dallas RH, et al. Interest of youth living with HIV in long-acting antiretrovirals. *J Acquir Immune Defic Syndr* 2019; **80:** 190–97.

12 Nachega JB, Parienti JJ, Uthman OA, et al. Lower pill burden and once-daily antiretroviral treatment regimens for HIV infection: a meta-analysis of randomized controlled trials. *Clin Infect Dis* 2014; **58:** 1297–307.

13 Shubber Z, Mills EJ, Nachega JB, et al. Patient-reported barriers to adherence to antiretroviral therapy: a systematic review and meta-analysis. *PLoS Med* 2016; **13:** e1002183.

14 Tran BX, Phan HT, Latkin CA, et al. Understanding global HIV stigma and discrimination: are contextual factors sufficiently studied? (GAPRESEARCH). *Int J Environ Res Public Health* 2019; **16:** 1899.

15 Zhang C, Li X, Liu Y, et al. Emotional, physical and financial burdens of stigma against people living with HIV/AIDS in China. *AIDS Care* 2016; **28** (suppl 1)**:** 124–31.

16 De Los Rios P, Young B, Marcotullio S, et al. Experiences and emotional challenges of antiretroviral treatment (ART)—findings from the Positive Perspectives Study. *Open Forum Infect Dis* 2019; **6** (suppl 2)**:** S481.

17 Lazarus JV, Safreed-Harmon K, Barton SE, et al. Beyond viral suppression of HIV—the new quality of life frontier. *BMC Med* 2016; **14:** 94.

18 Swindells S, Andrade-Villanueva JF, Richmond GJ, et al. Long-acting cabotegravir and rilpivirine for maintenance of HIV-1 suppression. *N Engl J Med* 2020; **382:** 1112–23.

19 Orkin C, Arasteh K, Górgolas Hernández-Mora M, et al. Long-acting cabotegravir and rilpivirine after oral induction for HIV-1 infection. *N Engl J Med* 2020; **382:** 1124–35.

20 Overton ET, Richmond G, Rizzardini G, et al. Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 48-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study. *Lancet* 2021; **396:** 1994–2005.

21 Saag MS, Gandhi RT, Hoy JF, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2020 recommendations of the International Antiviral Society-USA panel. *JAMA* 2020; **324:** 1651–69.

22 Rizzardini G, Overton ET, Orkin C, et al. Long-acting injectable cabotegravir + rilpivirine for HIV maintenance therapy: week 48 pooled analysis of phase 3 ATLAS and FLAIR trials. *J Acquir Immune Defic Syndr* 2020; **85:** 498–506.

23 Margolis DA, Gonzalez-Garcia J, Stellbrink HJ, et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. *Lancet* 2017; **390:** 1499–510.

24 World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013; **310:** 2191–94.

25 Orkin C, Oka S, Philibert P, et al. 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. *Lancet HIV* 2021; **8:** e185–96.

26 Cutrell AG, Schapiro JM, Perno CF, et al. Predictors of HIV-1 virologic failure to long-acting cabotegravir and rilpivirine: a multivariable analysis across three phase 3 studies. *AIDS* 2021; **35:** 1333–42.

27 Eron JJ, Orkin C, Cunningham D, et al. Week 96 efficacy and safety results of the phase 3, randomized EMERALD trial to evaluate switching from boosted-protease inhibitors plus emtricitabine/tenofovir disoproxil fumarate regimens to the once daily, single-tablet regimen of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) in treatment-experienced, virologically-suppressed adults living with HIV-1. *Antiviral Res* 2019; **170:** 104543.

28 Sax PE, Erlandson KM, Lake JE, et al. Weight gain following initiation of antiretroviral therapy: risk factors in randomized comparative clinical trials. *Clin Infect Dis* 2020; **71:** 1379–89.

29 Venter WDF, Moorhouse M, Sokhela S, et al. Dolutegravir plus two different prodrugs of tenofovir to treat HIV. *N Engl J Med* 2019; **381:** 803–15.