Safety of combined long-acting injectable cabotegravir and long-acting injectable rilpivirine in virologically suppressed adolescents with HIV (IMPAACT 2017/MOCHA): a phase 1/2, multicentre, open-label, non-comparative, dose-finding study

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Summary

Background Long-acting cabotegravir and long-acting rilpivirine constitute a completely intramuscular antiretroviral therapy (ART) regimen for adults with HIV. We aimed to assess the safety, antiviral activity, and pharmacokinetics of oral cabotegravir and rilpivirine followed by a combination of long-acting cabotegravir and long-acting rilpivirine in virologically suppressed adolescents with HIV.

Methods The IMPAACT 2017/MOCHA study is a phase 1/2, multicentre, open-label, non-comparative, dose-finding trial being conducted at 18 sites across Botswana, South Africa, Thailand, Uganda, and the USA. In cohort 2 of this study, adolescents (aged 12–18 years; weight ≥35 kg) with HIV and no serious comorbidities who were receiving stable combination ART with confirmed virological suppression and had either previously enrolled in the first cohort or had not previously participated in the study were eligible for inclusion. Participants stopped their background combination ART and received oral cabotegravir 30 mg once daily and oral rilpivirine 25 mg once daily orally for 4–6 weeks, followed by long-acting injectable cabotegravir 600 mg (3 mL) and long-acting injectable rilpivirine 900 mg (3 mL) intramuscularly at weeks 4 and 8, and every 8 weeks thereafter. The primary outcome was safety, including all adverse events, at week 24. Primary safety outcome measures were summarised as frequencies, percentages, and exact Clopper-Pearson 95% CIs in the evaluable analysis population, which included participants who were treated exclusively with the regimen and either completed all scheduled treatments or experienced severe adverse events, permanently discontinued the treatment, or died, whichever occurred first; and in the all-treated analysis population, which included all participants who received at least one dose of any study product. This study is registered with ClinicalTrials.gov (NCT3497676) and is ongoing.

Findings Between July 26, 2021, and Aug 27, 2022, 44 (80·0%) of 55 adolescents who participated in cohort 1 and 100 (87·0%) of 115 screened study-naive adolescents were enrolled in cohort 2. 74 (51·4%) participants were female and 70 (48·6%) were male. Overall, 15 (10·8% [95% CI 6·2–17·2]) of all 139 participants in the evaluable analysis population had at least one adverse event of grade 3 or above by week 24. Among 142 participants who received at least one injection, 43 (30%) experienced at least one injection site reaction (ISR). All 106 ISRs were either grade 1 (98 [92·5%]) or grade 2 (eight [7·5%]), and 97 (91·5%) resolved within 7 days. No participant experienced a drug-related serious adverse event or prematurely discontinued treatment due to a drug-related adverse event.

Interpretation Long-acting injectable cabotegravir and long-acting injectable rilpivirine, administered to adolescents at recommended adult dosages every 8 weeks, showed no unanticipated safety concerns in the 24 weeks following administration.

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Introduction

Current combination antiretroviral therapy (ART) for people living with HIV includes many potent, well tolerated dosing options, such as simplified daily (one pill) regimens. Nevertheless, despite the relatively low pill burden and improved side-effect profile of these regimens, treatment adherence remains a challenge for many individuals, including adolescents.[1,2] Currently, over 1·1 million adolescents are receiving oral antiretrovirals worldwide;[3] however, their treatment

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Research in context

Evidence before this study

Long-acting injectable antiretroviral therapies (ARTs) have the potential to address many of the challenges faced with daily oral therapy in people living with HIV, particularly for adolescents. Cabotegravir, a potent integrase strand transfer inhibitor, and rilpivirine, a potent non-nucleoside reverse transcriptase inhibitor, are highly effective ARTs in virologically suppressed individuals with HIV. At the time of IMPAACT 2017/MOCHA study conceptualisation in early 2017, there were no data on long-acting cabotegravir or long-acting rilpivirine for the treatment of adolescents with HIV. In 2023, data from cohort 1 of the IMPAACT 2017/MOCHA study showed that the use of the approved adult dosing of long-acting cabotegravir or long-acting rilpivirine (every 4 or 8 weeks) in virologically suppressed adolescents (aged 12–18 years; weight ≥35 kg) with HIV (HIV-1 RNA <50 copies per mL) on stable background combination ART had similar pharmacokinetics for cabotegravir and rilpivirine to those in adults and were within the targeted range. Long-acting cabotegravir and long-acting rilpivirine also showed an acceptable safety profile and good tolerance in this study population. We searched PubMed on Nov 4, 2024, for any study published to date, using the terms "long acting cabotegravir, long acting rilpivirine, treatment and adolescents". We excluded studies that enrolled adults only, used long-acting cabotegravir for pre-exposure prophylaxis (not treatment), and studies that focused on the potential benefits or impact of long-acting ARTs, including surveys, opinion pieces, and discrete choice experiments. This search found three relevant published studies only: data from cohort 1 of the IMPAACT 2017/MOCHA trial, acceptability data from this study, and one real-world application of off-label use of long-acting rilpivirine and long-acting cabotegravir in 19 adolescents with detectable HIV-1 viral loads.

Added value of this study

In this analysis of week-24 data from cohort 2 of the IMPAACT 2017/MOCHA trial, long-acting cabotegravir and long-acting rilpivirine showed a favourable safety profile in virologically suppressed adolescents who switched to this completely injectable regimen until week 24 of the study period. These findings also support the use of this regimen in adolescents at recommended adult dosages.

Implications of all the available evidence

These results provide important data on the safety and pharmacokinetics of long-acting cabotegravir and long-acting rilpivirine, which could be used to model recommended doses for younger children (aged <12 years) with HIV and those experiencing challenges with treatment adherence.

outcomes remain suboptimal, with adolescents experiencing disproportionately poorer treatment outcomes.[4] A 2023 meta-analysis reported ART adherence rates of 65% among 53 000 adolescents in sub-Saharan Africa, with viral load suppression rates of 55% and unsuppressed viral load rates of 41%.[5] The recent success of long-acting injectable ARTs has reshaped the paradigm of HIV treatment and prevention.[6] Long-acting cabotegravir plus long-acting rilpivirine given through intramuscular injections every 4 weeks or 8 weeks is now available as the first all-injectable combination ART regimen for virally suppressed adults living with HIV.[7–12]

The IMPAACT 2017 study (also referred to as MOCHA) is an ongoing trial aiming to evaluate the safety and pharmacokinetics of oral cabotegravir, long-acting cabotegravir, and long-acting rilpivirine in virologically suppressed adolescents with HIV (NCT03497676). The findings from cohort 1 of this study, which assessed the safety and pharmacokinetics of taking either long-acting cabotegravir or long-acting rilpivirine while participants continued their background combination ART, have been published separately.[13] Herein, we report the findings of cohort 2, in which participants stopped their background combination ART and received both long-acting cabotegravir and long-acting rilpivirine in combination. We aimed to assess the safety, antiviral activity, and pharmacokinetics of oral cabotegravir and oral rilpivirine followed by a combination of long-acting cabotegravir and long-acting rilpivirine in virologically suppressed adolescents living with HIV.

Methods

Study design

The IMPAACT 2017/MOCHA study is a phase 1/2, multicentre, open-label, non-comparative, dose-finding trial being conducted at 18 sites across Botswana, South Africa, Thailand, Uganda, and the USA. The study includes two cohorts, each comprising an oral phase (4–6 weeks) and an injection phase (12 weeks in cohort 1 and 96 weeks in cohort 2; figure 1). The main objective of cohort 1 was to establish the appropriate dosage of long-acting injectable cabotegravir and long-acting injectable rilpivirine in virologically suppressed adolescents (aged 12–18 years; weight ≥35 kg) and to assess the pharmacokinetics across different age and weight bands. In cohort 1, participants retained their background combination ART and received either daily oral cabotegravir or rilpivirine (for 4–6 weeks) followed by intramuscular long-acting cabotegravir or long-acting rilpivirine, either every 4 weeks or every 8 weeks. In cohort 2, participants stopped their background combination ART and received both oral cabotegravir 30 mg once daily and oral rilpivirine 25 mg once daily for 4 weeks, with an additional 2 weeks permitted to facilitate scheduling of visits (ie, totalling 4–6 weeks). Participants then switched to a 600 mg (3 mL) intramuscular injection of long-acting cabotegravir and a 900 mg (3 mL) intramuscular injection

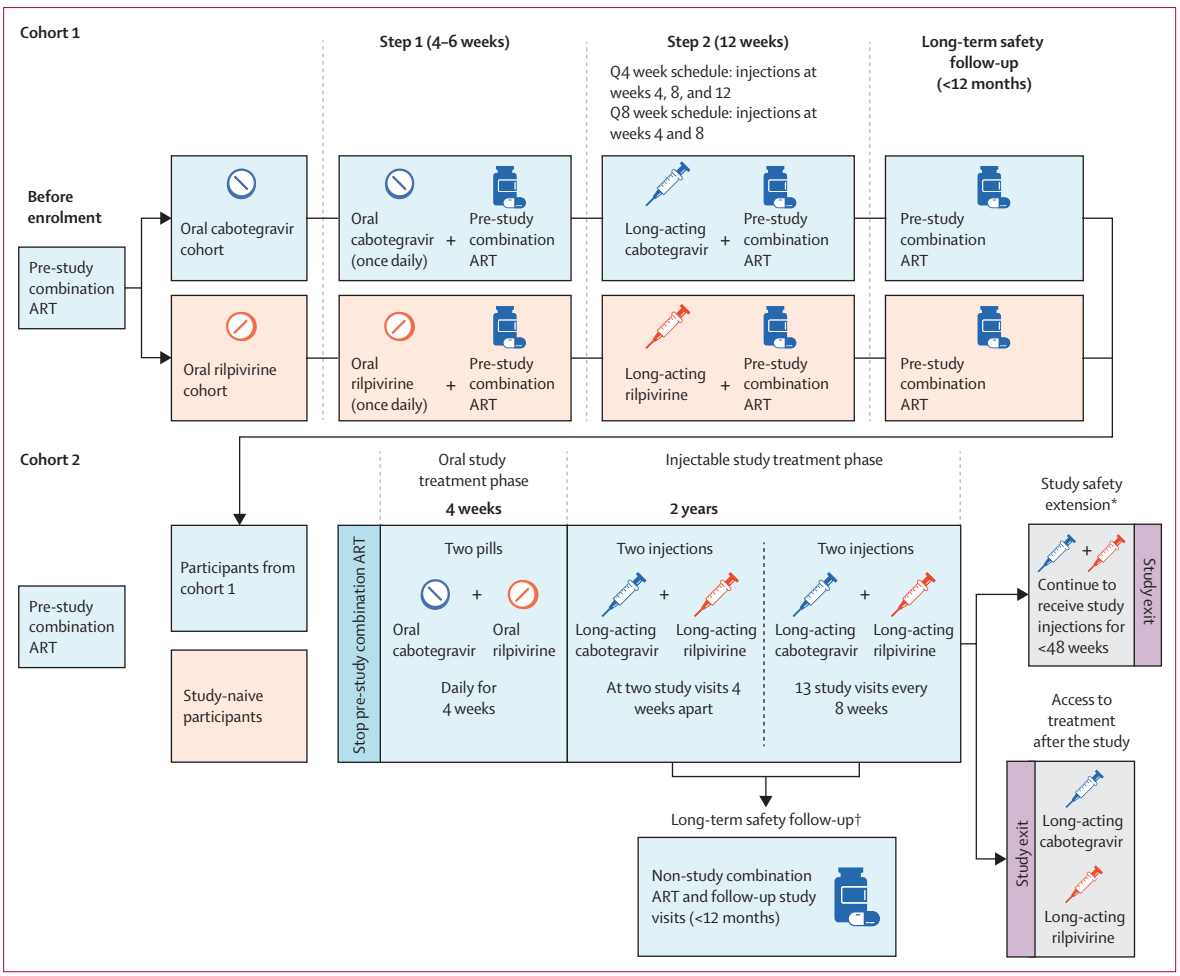

Figure 1: **Study design**
ART=antiretroviral therapy. Q=quarter. *For participants without access to study products outside of study. †For participants who discontinued long-acting study products.

of long-acting rilpivirine, administered at week 4 and week 8, and then every 8 weeks thereafter. All participants in cohort 2 received an oral lead-in.

The study was approved by applicable institutional review boards. The study protocol is available online.[14] This study is registered with ClinicalTrials.gov (NCT3497676) and is ongoing.

Participants

Adolescents who had previously enrolled into the first cohort of the IMPAACT 2017/MOCHA study and those who had not previously participated in the study (ie, study-naive participants) at participating sites were eligible for inclusion in cohort 2. Adolescents (aged 12–18 years) were eligible for enrolment if they weighed at least 35 kg, were receiving stable combination ART (consisting of two or more drugs from two or more classes of ART agents), showed virological suppression (viral load <50 HIV-1 RNA copies per mL at enrolment and <18 months before), had no serious comorbidities, and were not pregnant. Female participants also had to be willing and able to adhere to reliable contraceptive methods. Adolescents with documented viraemia, poor adherence to their oral ART, significant comorbidities (eg, congestive cardiac failure, hepatitis B or C, and hepatic failure), buttock implants, or a history of resistance to either rilpivirine or integrase strand transfer inhibitors were excluded.

Full participant inclusion and exclusion criteria for each cohort and for each stage of the study are provided in the appendix (pp 2–8). Written assent and consent were obtained from participants and their parent or legal guardian in English or their local language (languages varied by site).

See Online for appendix

Procedures

Contraceptive counselling was provided to all participants at each study visit and all female participants took rapid pregnancy tests to exclude the possibility of pregnancy before any study product was administered. As per protocol, long-acting cabotegravir was ideally administered in the contralateral gluteus medius muscle

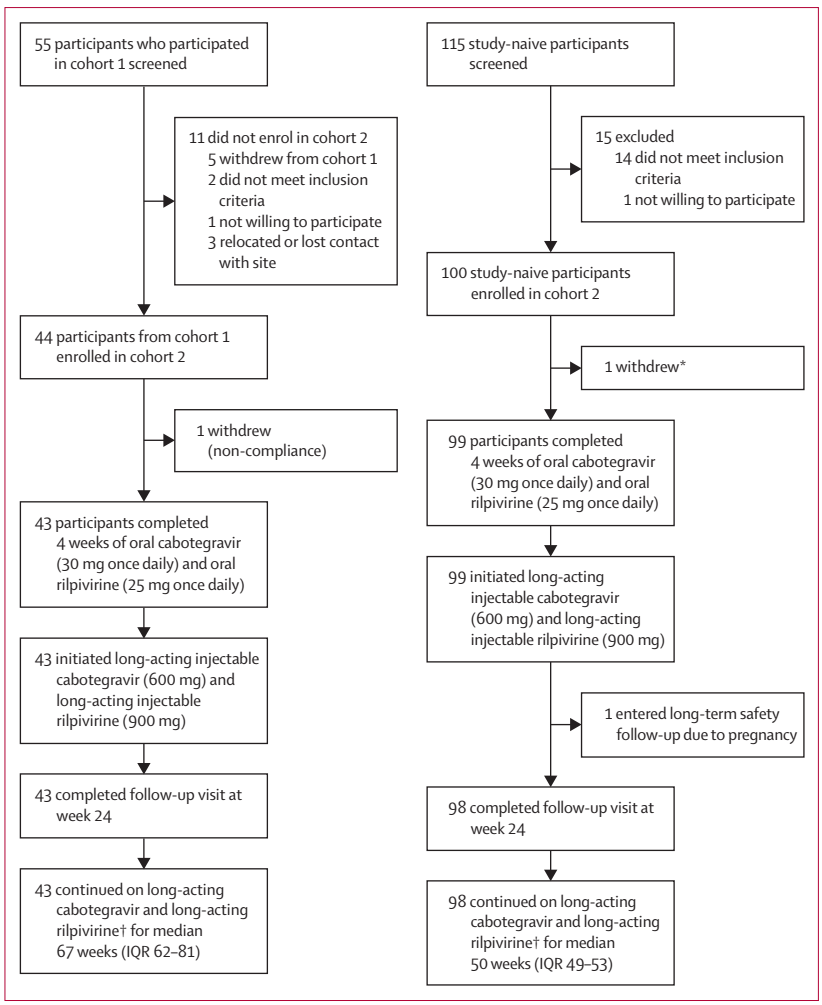

***Figure 2*: Study profile**
*It was found after study entry that this participant was not on stable combination antiretroviral therapy before study entry. †As of June 7, 2023, when the data were extracted.

to where long-acting rilpivirine had been administered; however, injections could both be administered on the same side as long as injection sites were at least 2 cm apart. Study staff were required to document where on the gluteus medius muscle each injection had been administered for assessing adverse reactions to injections. Injection site reactions (ISRs) were defined as an adverse event that resulted in pain disproportionate to what would be expected when a person receives an intramuscular injection (eg, tenderness, erythema, redness, induration or swelling, or pruritis), following administration of an injection.

Safety, efficacy, and pharmacokinetics evaluations were performed at weeks 2, 4, 5, 8, 16, and 24 (appendix pp 9–16). Acceptability and tolerability, including perceptions of injection and questionnaires on study medication satisfaction, have been published previously[15] for cohort 1 and will be reported separately for cohort 2.

Cabotegravir and rilpivirine concentrations were quantified with liquid chromatography–tandem mass spectrometry by use of assays validated as per bioanalytical recommendations by the US Food and Drug Administration (FDA). Lower limits of quantification were 0·025 μg/mL for cabotegravir and 1·0 ng/mL for rilpivirine.[16–20] Blood samples for the pharmacokinetics analysis were protected from light before the analysis was performed.

At week 2, samples for the pharmacokinetics analysis were drawn before the oral dose was administered and 3 h after the dose was administered. At week 4, samples were collected before the intramuscular dose was administered and 2 h after the dose was administered. At week 5, a single sample was drawn 3–7 days after the intramuscular dose was administered. At weeks 8, 16, and 24, a single sample was obtained before the intramuscular dose was administered.

Outcomes

The primary outcome for cohort 2 was the assessment of safety measures until week 24. The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events was used for grading adverse events throughout the study.[21] The following primary safety outcome measures were considered: any adverse event assessed as grade 3 or above, any adverse event assessed as grade 3 or above that was related to any study product, any serious adverse event meeting International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use criteria assessed as related to any study product, permanent discontinuation of any study product due to any adverse event that was related to any study product, and death due to any adverse event that was related to any study product.

Secondary endpoints were the efficacy of the ART regimen, as measured by antiviral activity (HIV-1 viral load measurements), and the evaluation of pharmacokinetics at week 24 (appendix pp 9–16). All primary and secondary outcome measures until week 24 are presented in this Article; further secondary outcome measures on the safety, efficacy, and pharmacokinetics of the regimen until week 48 will be reported separately.

Statistical analysis

We aimed to recruit approximately 70 study-naive participants who received the final recommended doses of cabotegravir and rilpivirine until week 24. This sample size was driven primarily by the precision of exact Clopper-Pearson 95% CIs for the proportion of binomial safety events, industry standards, and sample sizes used in previous registrational pharmacokinetics studies.

The evaluable analysis population included participants who were treated exclusively with the dose that was confirmed in cohort 1 (every 8 weeks) and either completed all scheduled treatments until week 24 or experienced any of the following events: death attributable to study

products, adverse events related to the study products that were considered to be grade 3 or above (excluding ISRs), or permanent discontinuation of treatment due to any adverse event related to the study products (regardless of grade). Study-naive participants were treated as the primary subgroup of the evaluable analysis population. The all-treated analysis population included all participants who had received at least one dose of any study product, including participants who had enrolled in both cohort 1 and 2.

Continuous variables were summarised as the number of observations (n), mean (SD), or median (IQR). Categorical variables were summarised as the frequency of events (n [%]) in each category. All safety data were considered from first participant exposure to study treatment to week 24 (primary) and from first exposure until June 7, 2023, the date that data were extracted (supplemental).

Primary safety outcome measures were summarised as percentages and exact Clopper-Pearson 95% CIs in the evaluable analysis population (primary estimand) and in the all-treated analysis population (supplementary for primary). For the primary analysis, events that could affect the existence or interpretation of safety outcome measures (ie, intercurrent events) were handled in the following ways. First, discontinuation of cabotegravir, rilpivirine, or both due to toxicity was handled with a so-called while-on-treatment strategy (ie, the observation time of the participant was censored at the time of treatment discontinuation). Second, any death related to cabotegravir, rilpivirine, or both was handled with a composite strategy (ie, these events were incorporated into the definition of the outcome variable). Third, discontinuation of cabotegravir, rilpivirine, or both due to reasons other than toxicity or death unrelated to the drugs was handled with a principal stratum approach (ie, participants were excluded from the evaluable analysis set). Fourth, all other intercurrent events were handled with a treatment policy strategy (ie, the intercurrent event was ignored).

ISRs are presented for the evaluable analysis population and for the all-treated analysis population. As per the FDA snapshot algorithm, the secondary outcome of virological success was measured with an HIV-1 RNA viral load measurement cutoff value of less than 50 copies per mL and less than 200 copies per mL in the evaluable analysis population (secondary estimand) and less than 50 copies per mL and less than 200 copies per mL in the all-treated analysis population at week 24. After oral and intramuscular administration of cabotegravir or rilpivirine, cabotegravir and rilpivirine concentrations and accumulation ratios with the long-acting formulations were summarised for the pharmacokinetics analysis as descriptive statistics. All statistical analyses were performed with SAS (version 9.4).

Role of the funding source

Clinical sites were monitored by an independent group under a National Institutes of Health (NIH) contract. ViiV Healthcare and Janssen Pharmaceuticals provided study products and funding, but were not involved in sponsorship or regulatory oversight. Representatives of the NIH, ViiV Healthcare, and Janssen Pharmaceuticals participated in study design, data interpretation, and manuscript writing.

	Participants from cohort 1 (n=44)	Study-naive participants (n=100)	Total (n=144)
Age at study enrolment, years	15 (14–17; 12–17)	15 (13–16; 12–17)	15 (14–16; 12–17)
Sex at birth			
Male	25 (57%)	45 (45%)	70 (49%)
Female	19 (43%)	55 (55%)	74 (51%)
Race			
Asian	8 (18%)	28 (28%)	36 (25%)
Black or African American	34 (77%)	72 (72%)	106 (74%)
White	2 (5%)	0	2 (1%)
Ethnicity			
Not Hispanic or Latinx	42 (95%)	99 (99%)	141 (98%)
Hispanic or Latinx	2 (5%)	1 (1%)	3 (2%)
Recruitment country			
Botswana	5 (11%)	20 (20%)	25 (17%)
Thailand	8 (18%)	28 (28%)	36 (25%)
Uganda	0	20 (20%)	20 (14%)
USA	15 (34%)	5 (5%)	20 (14%)
South Africa	16 (36%)	27 (27%)	43 (30%)
Weight, kg	51·0 (45·0–62·6)	46·9 (42·3–54·0)	48·5 (43·5–55·4)
BMI, kg/m^2	20·1 (18·3–22·7)	19·3 (17·3–21·7)	19·5 (17·8–22·0)
CD4 cell count, cells per mm^3	714 (568–882)	752 (606–969)	740 (594–964)
Missing data	0	2 (2%)	2 (1%)
HIV mode of transmission			
Horizontal	3 (7%)	2 (2%)	5 (3%)
Vertical	39 (89%)	93 (93%)	132 (92%)
Unknown	2 (5%)	5 (5%)	7 (5%)
Any previous antiretroviral therapy*			
Integrase strand transfer inhibitor	19 (43%)	65 (65%)	84 (58%)
Non-nucleoside reverse transcriptase inhibitor	23 (52%)	66 (66%)	89 (62%)
Nucleoside reverse transcriptase inhibitor	44 (100%)	100 (100%)	144 (100%)
Nucleoside reverse transcriptase translocation inhibitor	0	1 (1%)	1 (1%)
Protease inhibitor	27 (61%)	43 (43%)	70 (49%)

Data are median (IQR; range), n (%), or median (IQR). Except for age at study enrolment, baseline was defined as the last non-missing record before or on the day of treatment initiation. *Participants might have been counted more than once within each drug class.

Table 1: **Baseline participant characteristics in the all-treated analysis population**

Results

Between July 26, 2021, and Aug 27, 2022, 44 (80·0%) of 55 adolescents who had participated in cohort 1 and 100 (87·0%) of 115 screened study-naive adolescents were enrolled in cohort 2 (figure 2). All participants received at least one dose of any study product. As of June 7, 2023, 116 (80·6%) of all 144 participants had completed the follow-up visit at week 48 and received seven or more

	Participants from cohort 1	Study-naive participants	Total
All-treated analysis population			
Number of participants	44	100	144
Any adverse event	41 (93·2%; 81·3–98·6)	69 (69·0%; 59·0–77·8)	110 (76·4%; 68·6–83·1)
Grade 3 or above*	6 (13·6%; 5·2–27·4)	10 (10·0%; 4·9–17·6)	16 (11·1%; 6·5–17·4)
Grade 3 or above, drug-related†	0 (0·0–8·0)	0 (0·0–3·6)	0 (0·0–2·5)
Serious‡	0 (0·0–8·0)	0 (0·0–3·6)	0 (0·0–2·5)
Serious, drug-related	0 (0·0–8·0)	0 (0·0–3·6)	0 (0·0–2·5)
Premature permanent discontinuation of treatment due to drug-related adverse event	0 (0·0–8·0)	0 (0·0–3·6)	0 (0·0–2·5)
Death due to drug-related adverse event	0 (0·0–8·0)	0 (0·0–3·6)	0 (0·0–2·5)
Evaluable analysis population			
Number of participants	41	98	139
Any adverse event	38 (92·7%; 80·1–98·5)	68 (69·4%; 59·3–78·3)	106 (76·3%; 68·3–83·1)
Grade 3 or above*	5 (12·2%; 4·1–26·2)	10 (10·2%; 5·0–18·0)	15 (10·8%; 6·2–17·2)
Grade 3 or above, drug-related†	0 (0·0–8·6)	0 (0·0–3·7)	0 (0·0–2·6)
Serious‡	0 (0·0–8·6)	0 (0·0–3·7)	0 (0·0–2·6)
Serious, drug-related	0 (0·0–8·6)	0 (0·0–3·7)	0 (0·0–2·6)
Premature permanent discontinuation of treatment due to drug-related adverse event	0 (0·0–8·6)	0 (0·0–3·7)	0 (0·0–2·6)
Death due to drug-related adverse event	0 (0·0–8·6)	0 (0·0–3·7)	0 (0·0–2·6)
Any ISR	9 (22·0%; 10·6–37·6)	34 (34·7%; 25·4–45·0)	43 (30·9%; 23·4–39·3)
Participants who received at least one injection			
Number of participants	43	99	142
Any ISR§	9 (20·9%; 9·8–35·3)	34 (34·3%; 24·8–44·2)	43 (30·3%; 22·5–38·0)
Induration	0 (0·0–8·0)	1 (1·0%; <0·1–5·5)	1 (0·7%; <0·1–3·8)
Nodule	0 (0·0–8·0)	2 (2·0%; 0·2–7·0)	2 (1·4%; 0·2–4·9)
Pain	9 (20·9%; 9·8–35·3)	34 (34·3%; 24·8–44·2)	43 (30·3%; 22·5–38·0)
Pruritus	0 (0·0–8·0)	1 (1·0%; <0·1–5·5)	1 (0·7%; <0·1–3·8)
Swelling	0 (0·0–8·0)	3 (3·0%; 0·6–8·5)	3 (2·1%; 0·4–6·0)

Data are n, n (%; exact Clopper-Pearson 95% CI), or n (exact Clopper-Pearson 95% CI). ISR=injection site reaction. *Grade 1: mild; grade 2: moderate; grade 3: severe; grade 4: potentially life-threatening; and grade 5: death. †Drug-relatedness of adverse events was determined by each site. ‡Serious adverse events and malignancies were defined by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. §Defined as an adverse event that resulted in pain disproportionate to what would be expected when a person receives an intramuscular injection (eg, tenderness, erythema, redness, induration or swelling, or pruritis), regardless of when it occurred after administration of an injection. All ISRs were either grade 1 or grade 2.

Table 2: **Adverse events in the all-treated and evaluable analysis populations and among participants who received at least one injection**

injections. The median duration of follow-up was 67 weeks (IQR 62–81) for participants from cohort 1 and 50 weeks (49–53) for study-naive participants. One participant did not meet eligibility criteria and exited the study after 2 weeks. Following entry, this participant reported to have misunderstood the instruction to continue background combination ART during the screening enrolment period and consequently stopped taking combination ART before the first oral dose. This participant was included in the all-treated analysis population but was excluded from the evaluable analysis population. Four additional participants were excluded from the evaluable analysis population: one participant from cohort 1 withdrew from the study due to non-compliance to study visits; two participants from cohort 1 erroneously continued combination ART for 2 weeks during the oral phase; and one study-naive participant became pregnant and discontinued use of the study drug regimen before week 24.

Median age at enrolment was 15 years (range 12–17); 74 (51·4%) participants were female and 70 (48·6%) were male; and most participants were Black or African American (table 1). Median BMI was 19·5 kg/m² (IQR 17·8–22·0), bodyweight was 48·5 kg (43·5–55·4), and baseline CD4 cell count was 739·5 cells per mm³ (594·0–964·0). Most participants had acquired HIV vertically (table 1). Exposure to antiretroviral drugs prior to the first treatment date is shown in table 1.

Among the 98 study-naive participants in the evaluable analysis population, 68 (69·4% [95% CI 59·3–78·3]) reported at least one adverse event of any grade and ten (10·2% [5·0–18·0]) reported at least one grade 3 adverse event by week 24 (table 2). No participant (95% CI 0·0–3·7) in the evaluable analysis population reported a drug-related grade 3 adverse event or serious adverse event, prematurely discontinued treatment due to a drug-related adverse event, or died. No study-naive participant in the evaluable analysis population had an intercurrent event or missed a study visit. Overall, 15 (10·8% [95% CI 6·2–17·2]) of all 139 participants in the evaluable analysis population had at least one adverse event of grade 3 or above by week 24.

In the all-treated analysis population, until the data extraction date, the most commonly reported grade 3 adverse events were raised systolic blood pressure (three participants), elevated creatine phosphokinase (nine participants), and decreased creatinine clearance (three participants; appendix pp 20, 21). One participant had grade 3 injection site pain and grade 3 injection site abscess (related to cabotegravir administration) and another participant had grade 3 injection site abscess (related to rilpivirine administration).

By week 24, 142 participants who had received at least one injection had a total of 106 ISRs (appendix p 22). All ISRs were either grade 1 (98 [92·5%]) or grade 2 (eight [7·5%]), and 97 (91·5%) resolved within 7 days. Overall, the proportion of participants with ISRs peaked at the first injection and generally decreased over time (appendix p 29). No participant withdrew from the study due to an ISR.

As per the FDA snapshot algorithm, virological success defined as HIV-1 RNA of less than 50 copies per mL was reported in 137 (98·6% [95% CI 94·9–99·8]) of 139 participants in the evaluable analysis population and virological failure (HIV-1 RNA ≥50 copies per mL) was reported in two (1·4% [0·2–5·1]) participants at week 24

(appendix pp 23–25). With the HIV-1 RNA cutoff of up to 200 copies per mL as per the algorithm, virological success was reported in all 139 (100% [97·4–100·0]) participants.

In the all-treated analysis population, virological success defined as HIV-1 RNA of less than 50 copies per mL was reported in 139 (97% [95% CI 92·1–98·9]) of 144 participants at week 24. Virological failure was reported in three (2·1% [0·4–6·0]) participants. Virological data were unavailable for two participants who discontinued the study treatments before week 24, with a viral load at treatment discontinuation of less than 50 copies per mL. Overall, with the HIV-1 RNA cutoff of up to 200 copies per mL, virological success was reported in 141 (97·9%) participants at week 24. Virological failure based on this cutoff (two consecutive plasma HIV-1 RNA test results ≥200 copies per mL from two separate specimens) occurred in one study-naive participant. This participant was not included in the evaluable analysis population or considered to have a true virological failure due to pre-existing viraemia at study entry caused by a deviation from enrolment inclusion and exclusion criteria. Five (3·5%) participants (two participants from cohort 1 and three study-naive participants) had at least one viral load measurement of at least 200 copies per mL; however, all five participants showed suppressed viral load on repeat testing.

One participant had a positive pregnancy test during the study period (estimated conception at study week 5). This study-naive participant received two injections of long-acting cabotegravir and long-acting rilpivirine before treatment discontinuation and delivered a liveborn female infant at 39 weeks.

Among a total of 142 participants who completed the oral lead-in treatment, 124 (87·3%) showed at least 90% adherence (measured by pill count) to oral cabotegravir and 126 (88·7%) showed at least 90% adherence to oral rilpivirine (appendix p 26). All injections fell within 7 days of the target day at weeks 8, 16, and 24 (appendix p 27).

Among all 139 participants in the all-treated analysis population, the median circulating concentration of cabotegravir before the dose was administered was 2·34 µg/mL (90% CI 1·11–4·15) at week 24 (figure 3A). Comparing this concentration at week 24 with that at week 8, the median accumulation ratio for cabotegravir was 1·27 (90% CI 0·35–4·19). Comparing this concentration at week 24 with the median concentration at week 16, this ratio was 1·00 (0·54–1·88). One participant had a low circulating concentration of cabotegravir before the dose was administered at week 24 (0·03 µg/mL) and week 32 (0·09 µg/mL), but the reason behind this observation was unclear. On subsequent visits, the concentrations for this participant were within the expected range.

Among the 139 participants in the all-treated analysis population, the median concentration of rilpivirine before the dose was administered was 49·5 ng/mL (90% CI 25·9–78·1) at week 24 (figure 3B). Comparing this concentration at week 24 with that at week 8, the median accumulation ratio for rilpivirine was 1·29 (90% CI 0·62–2·75). Comparing this concentration at week 24 with the median concentration at week 16, this ratio was 1·22 (0·69–2·14). No participant showed a substantially lower circulating concentration of rilpivirine than is typically seen in adults. Specific cabotegravir and rilpivirine concentrations from week 2 to week 24 are provided in the appendix (p 28).

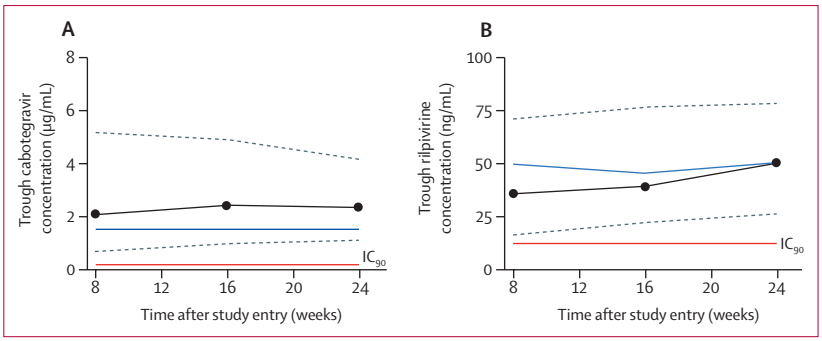

Figure 3: **Median trough concentrations of cabotegravir and rilpivirine in adolescents**
Median values (solid black lines) with 5th–95th percentiles (dashed lines) and 50th percentile from adults in Latte-2 and ATLAS-2M (solid blue lines) of the trough concentrations of cabotegravir (A) and rilpivirine (B) after repeated intramuscular administration from week 8 to week 24 among adolescents in cohort 2 of the MOCHA study.

Discussion

The completely injectable combination ART regimen of long-acting cabotegravir and long-acting rilpivirine has previously shown good safety and efficacy in adults in the FLAIR, ATLAS, and ATLAS-2M studies.[7–12] In the present study, this safety and efficacy has also been replicated in adolescents. As observed in both cohort 1 of the IMPAACT 2017/MOCHA study and adult populations in the FLAIR, ATLAS, and ATLAS-2M studies, ISRs in the present study were common, self-limiting, primarily grade 1, and generally decreased in incidence over time.[13] Despite these ISRs, this regimen was highly accepted among adolescents from cohort 1.[13] Most eligible participants from cohort 1 enrolled in cohort 2, likely reflecting the desire of this population to access this completely injectable regimen. Despite the strict scheduling of study visits, all injections were administered within 7 days of the target date.

Participant eligibility criteria were consistent across both cohorts, other than how participants in cohort 1 were required to have a BMI of at least 31·5 kg/m², and there were no weight or age restrictions for participants recruited from cohort 1. Overall, participants from cohort 1 were slightly older, had higher BMIs, and were predominantly from the USA compared with study-naive participants. The rapid international enrolment (just over 3 months with potential participants on waiting lists) and high adherence to dosing within the target window

showed that this treatment approach is desirable to adolescents across relatively different cultural and geographical regions.

Among participants in cohort 2 at week 24, median circulating concentrations of cabotegravir and rilpivirine before the dose was administered were well above the protein-adjusted inhibition concentration $(IC)_{90}$ values and similar to drug exposures associated with efficacy in studies in adults. The median concentration of cabotegravir before the dose was administered remained approximately the same at weeks 8, 16, and 24; was slightly above median values observed among adults in the LATTE-2 and ATLAS-2M studies; and was within the drug exposure thresholds in which safety has been shown in adults.

The observation of high virological suppression with no confirmed virological failures at week 24 aligns with results from studies in adults and real-world data in adolescents.[22–27] Furthermore, the safety and tolerability profiles were consistent with previous data in adults and data from cohort 1 of the IMPAACT 2017/MOCHA study, and no new safety signals were identified. As additional data become available, it is important to begin planning for the scale-up of long-acting regimens in regions and countries with a high burden of HIV infections. Integration of long-acting regimen commodities into pre-existing Expanded Program for Immunization networks could be considered to ensure the cold chain for distribution of long-acting rilpivirine. Simple treatment aids, such as ice packs and topical anaesthesia, might greatly improve patient comfort and acceptability.

This study has several limitations. By design, the IMPAACT 2017/MOCHA study only included participants with documented good adherence to daily oral combined ART and confirmed viral suppression. Data from adults (from both studies and real-world experience) have shown that the regimen has good suppression rates and high acceptability among individuals who could not otherwise reach or maintain viral suppression due to challenges adhering to oral ART.[19,20,28,29] Clinical trials in adolescents who are unable to reach or maintain viral suppression due to these adherence challenges are still ongoing; however, early data from real-world, off-label use seem promising with reports of viral load suppression in previously unsuppressed adolescent populations.[22,24,26] Reassuringly, the findings of the IMPAACT 2017/MOCHA study support these reports, with good reported uptake and acceptability, good adherence, commonly reported but mostly mild ISRs, and good rates of viral suppression. Transient viraemia has been reported in the real-world setting,[25–27] but the implications of this finding remain unclear at present.

Although the participant eligibility criteria of cohort 2 did not include any criteria related to BMI, median BMI was 19·5 kg/m² (IQR 17·8–22·0). Of note, it is feasible that circulating drug concentrations could differ between populations with a low BMI and those with a high BMI.[30]

The relatively low rate of pregnancy observed in cohort 2 was expected given that we report results up to 24 weeks after study entry and that all study participants underwent contraceptive counselling at each study visit. Given that the present study was designed before pregnancy data were available the protocol mandated that participants stopped receiving study products and entered long-term safety follow-up if pregnancy occurred. As such, pregnancy-related data for the participant who became pregnant were scant, with the reporting of anecdotal information only (eg, the delivery of a liveborn female singleton at 39 weeks).

Given the observed safety and efficacy of this regimen in adolescents, its acceptance and feasibility are currently being assessed in younger children (age 2–12 years) in the IMPAACT 2036 study (NCT05660980). In conclusion, the intramuscular administration of long-acting cabotegravir and long-acting rilpivirine every 8 weeks in adolescents showed no unanticipated safety concerns, substantiated the use of drug dosing that is currently recommended in adults, and maintained viral suppression up to 24 weeks after administration.

Contributors

CBM, AHG, EVC, KB, CM, RMVS-R, EDL, BMB, HC, BH, JH, and CK conceptualised the study. AHG, ALA, AV, LA, GM, VK, and PO conducted the study. CBM, AHG, EVC, KB, CM, RMVS-R, and EDL designed the study methodology. MAM, BH, and CK collected the data. CM, KB, SW, and SB curated the data. CM acquired the funding. EVC, KB, SW, CM, RM, BMB, JH, HC, and SYAC conducted the formal analysis. KB, SW, RM, and SZ validated the data. AHG, CM, CBM, ET, SYAC, ALA, SB, and SZ contributed to project administration and management. AHG, CM, and CBM contributed to resources. AHG, CBM, CM, ET, JHM, ALA, PO, DEY, SB, and SZ supervised the study. KB, SW, AHG, BMB, and EVC created the figures. RMVS-R, AHG, CBM, ET, JHM, JH, HC, VVE, SYAC, DEY, and GR interpreted the data. CBM wrote the original draft. AHG, EVC, KB, SW, MAM, RMVS-R, ET, JHM, EDL, RM, BMB, HC, VVE, SYAC, ALA, LA, DEY, AV, SB, GR, GM, and VK reviewed and edited the manuscript. KB, SW, RM, and SZ have directly accessed and verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

KB, BMB, SB, BMB, AHG, CK, and MAM received IMPAACT Network grant funding from the National Institutes of Health (NIH) to support work on this protocol. KB, RM, and SW's institution receives funding from ViiV Healthcare. AHG's institution has a clinical trial agreement with the IMPAACT Network, ViiV Healthcare, and Janssen to provide support for this and other protocols. AHG received payment from ViiV Healthcare to serve on ViiV-sponsored advisory board meetings and as a panelist on an adolescent treatment and prevention webinar. CBM's institution received salary support from the IMPAACT Network for this protocol. DEY is an employee of the NIH. CM and GR are employees of ViiV Healthcare. SYAC, GR, and JH are employees of GSK. ALA and MAM's institutions received funding from Gilead, ViiV, and Merck. SW and RM's institution received funding from ViiV. KB's institution received funding from Gilead. MAM is a consultant for Bio-Rad and receives royalties from Elsevier. ALA is an expert witness and the chair of the HIV Medicine Association, a board member for The Well Project, and the board chair for Advocates for Youth. VVE is an employee of Janssen Pharmaceutical, which holds a US patent application or patent cooperation treaty for rilpivirine (international application number 62/870,413). CM and GR are shareholders of GSK. SYAC is an employee and shareholder of Certara and a consultant for GSK. HC, VVE, and RMVS-R are shareholders of Johnson & Johnson. HC, RMVS-R, and VVE are employees of Janssen. GR is a shareholder in AstraZeneca.

DEY was formerly an unpaid advisor to the non-profit organisations Cover the Globe and Maipelo Trust. All other authors declare no competing interests.

Data sharing

The data cannot be made publicly available due to the ethical restrictions in the study's informed consent documents and those in the IMPAACT Network's approved human subjects protection plan; public availability may compromise participant confidentiality. However, data are available to all interested researchers upon request to the IMPAACT Statistical and Data Management Center's Data Access Committee (sdac.data@fstrf.org), with the agreement of the IMPAACT Network.

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