Safety and pharmacokinetics of oral and long-acting injectable cabotegravir or 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 Combined intramuscular long-acting cabotegravir and long-acting rilpivirine constitute the first long-acting combination antiretroviral therapy (ART) regimen approved for adults with HIV. The goal of the IMPAACT 2017 study (MOCHA [More Options for Children and Adolescents]) was to assess the safety and pharmacokinetics of these drugs in adolescents.

Methods In this phase 1/2, multicentre, open-label, non-comparative, dose-finding study, virologically suppressed adolescents (aged 12–17 years; weight ≥35 kg; BMI ≤31·5 kg/m²) with HIV-1 on daily oral ART were enrolled at 15 centres in four countries (Botswana, South Africa, Thailand, and the USA). After 4–6 weeks of oral cabotegravir (cohort 1C) or rilpivirine (cohort 1R), participants received intramuscular long-acting cabotegravir or long-acting rilpivirine every 4 weeks or 8 weeks per the adult dosing regimens, while continuing pre-study ART. The primary outcomes were assessments of safety measures, including all adverse events, until week 4 for oral cabotegravir and until week 16 for long-acting cabotegravir and long-acting rilpivirine, and pharmacokinetic measures, including the area under the plasma concentration versus time curve during the dosing interval (AUC_{0-tau}) and drug concentrations, at week 2 for oral dosing of cabotegravir and at week 16 for intramuscular dosing of cabotegravir and rilpivirine. Enrolment into cohort 1C or cohort 1R was based on the participant's pre-study ART, meaning that masking was not done. For pharmacokinetic analyses, blood samples were drawn at weeks 2–4 after oral dosing and weeks 4–16 after intramuscular dosing. Safety outcome measures were summarised using frequencies, percentages, and exact 95% CIs; pharmacokinetic parameters were summarised using descriptive statistics. This trial is registered at ClinicalTrials.gov, NCT03497676, and is closed to enrolment.

Findings Between March 19, 2019, and Nov 25, 2021, 55 participants were enrolled: 30 in cohort 1C and 25 in cohort 1R. At week 16, 28 (97%, 95% CI 82–100) of the 29 dose-evaluable participants in cohort 1C and 21 (91%; 72–99) of the 23 dose-evaluable participants in cohort 1R had reported at least one adverse event, with the most common being injection-site pain (nine [31%] in cohort 1C; nine [39%] in cohort 1R; none were severe). One (4%, 95% CI 0–22) participant in cohort 1R had an adverse event of grade 3 or higher, leading to treatment discontinuation, which was defined as acute rilpivirine-related allergic reaction (self-limiting generalised urticaria) after the first oral dose. No deaths or life-threatening events occurred. In cohort 1C, the week 2 median cabotegravir AUC_{0-tau} was 148·5 (range 37·2–433·1) μg·h/mL. The week 16 median concentrations for the every-4-weeks and every-8-weeks dosing was 3·11 μg/mL (range 1·22–6·19) and 1·15 μg/mL (<0·025–5·29) for cabotegravir and 52·9 ng/mL (31·9–148·0) and 39·1 ng/mL (27·2–81·3) for rilpivirine, respectively. These concentrations were similar to those in adults.

Interpretation Study data support using long-acting cabotegravir or long-acting rilpivirine, given every 4 weeks or 8 weeks, per the adult dosing regimens, in virologically suppressed adolescents aged 12 years and older and weighing at least 35 kg.

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See Online for appendix

Research in context

Evidence before this study

Cabotegravir is a potent integrase strand transfer inhibitor with attributes allowing formulation and delivery as a long-acting parenteral product. Rilpivirine, also formulated as a long-acting product, is a diarylpyrimidine derivative and a potent non-nucleoside reverse-transcriptase inhibitor with in vitro activity against wild-type HIV-1 and select non-nucleoside reverse-transcriptase inhibitor-resistant mutants. In clinical trials for adults, long-acting cabotegravir and long-acting rilpivirine exhibited an acceptable safety profile and were well tolerated and efficacious as a dual-injectable combination antiretroviral therapy (ART) in treatment-naive (ie, step down, maintenance therapy after oral three-drug ART-induction therapy) and treatment-experienced (ie, virologically suppressed on stable ART regimen) people with HIV. Before writing the study proposal, we searched PubMed on Jan 1, 2017, with no date restrictions, using the search terms "long-acting cabotegravir", "long-acting rilpivirine", "adolescents", and "HIV" and found no studies. IMPAACT 2017 is the first study to administer long-acting cabotegravir and long-acting rilpivirine to adolescents with HIV and to assess the safety, pharmacokinetics, acceptability, and tolerability of this two-drug injectable regimen.

Added value of this study

Study findings showed that approved adult dosing of long-acting cabotegravir or long-acting rilpivirine (every 4 weeks or every 8 weeks) in adolescents had similar exposure to that in adults, with no unanticipated safety concerns. Preliminary findings informed the US Food and Drug Administration's decision to approve combined long-acting cabotegravir and rilpivirine for adolescents aged 12 years and older and weighing at least 35 kg who are virologically suppressed (HIV-1 RNA <50 copies per mL) on stable ART, with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine. This approval marks the first long-acting HIV treatment available for a paediatric population.

Implications of all the available evidence

Study safety and pharmacokinetics results will be used as part of the submission package to seek regulatory approval for treating adolescents with this all-injectable ART regimen in other countries. The IMPAACT 2017 results have also informed the design and planned dosing of this combined long-acting cabotegravir and rilpivirine regimen in IMPAACT 2036, a study examining the safety, pharmacokinetics, and acceptability of this regimen in children aged 2–11 years. Real-world experience using this all-injectable ART regimen is described in adults and is awaited in adolescents. The feasibility and risk–benefit of this regimen in adolescents and adults struggling with adherence to daily oral ART needs to be evaluated.

Introduction

Combination antiretroviral therapy (ART) for HIV includes many potent, well tolerated dosing options, including daily one-pill regimens. Successful HIV treatment requires long-term, sustained adherence to daily ART, which can be especially challenging for adolescents.[1,2] Long-acting injectable antiretrovirals have changed the framework of HIV treatment and prevention.[3,4] Combined long-acting cabotegravir and rilpivirine given through intramuscular injections monthly (every 4 weeks) or every 2 months (every 8 weeks) is the first all-injectable ART regimen for virally suppressed people with HIV-1.[5–9]

The International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) 2017 study (also referred to as MOCHA [More Options for Children and Adolescents]) included two cohorts of virologically suppressed adolescents with HIV-1. In cohort 1, the safety and pharmacokinetics of cabotegravir and rilpivirine were evaluated separately, after administration of oral cabotegravir followed by long-acting cabotegravir (cohort 1C) or oral rilpivirine followed by long-acting rilpivirine (cohort 1R) added to and based on the participant's ongoing pre-study ART regimen. The cohort 1 study design enabled confirmation of adult-matched exposure and pharmacokinetics and gathering of initial safety information about adult dosing of cabotegravir or long-acting cabotegravir and rilpivirine in adolescents, without changing the participants' ongoing ART. Here, we report the results from the final cohort 1 analysis. IMPAACT 2017 cohort 2, which evaluates the safety, pharmacokinetics, antiviral activity, and acceptability and tolerability of combined long-acting cabotegravir and rilpivirine in adolescents, will be reported separately. All cohort 1 participants were offered the opportunity to join cohort 2, eligibility permitting. Evaluating the dosing and safety of this regimen in children (aged 2–11 years) is planned in the IMPAACT 2036 study (NCT03497676).

Methods

Study design

IMPAACT 2017 was a phase 1/2, multicentre, open-label, non-comparative, dose-finding study. The primary objective was to evaluate the safety and pharmacokinetics of oral cabotegravir, long-acting cabotegravir, and long-acting rilpivirine in virologically suppressed adolescents (aged 12–17 years) with HIV-1. The study was approved by applicable Institutional Review Boards at each participating site. Starting Nov 13, 2020, submissions were made to the central Institutional Review Board, Advarra, which served as the single Institutional Review

Board for the US-based sites. The current version of the study protocol can be found on the IMPAACT Network website (https://www.impaactnetwork.org/studies/impaact2017).

The study design included two cohorts, and each cohort included two steps: cohort 1, step 1 included oral cabotegravir or rilpivirine and step 2 included intramuscular long-acting cabotegravir or intramuscular long-acting rilpivirine (figure 1). In cohort 2, step 3 included oral cabotegravir and rilpivirine, and step 4 included intramuscular long-acting cabotegravir and rilpivirine. Cohort 1, the results from which are described in this manuscript, enrolled participants at eight US centres and seven international centres including two in Botswana, three in South Africa, and two in Thailand.

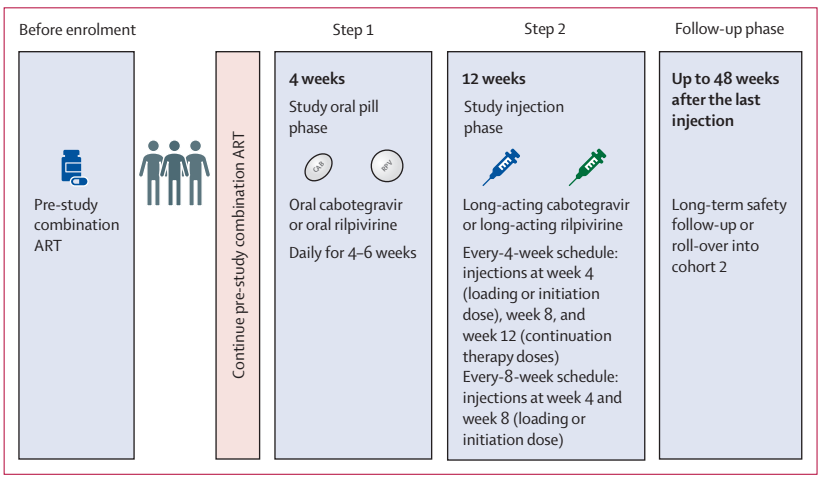

Figure 1: **Cohort 1 overview**
Assignment to cabotegravir versus rilpivirine was based on pre-study combination ART, which continued during steps 1 and 2. ART=antiretroviral therapy.

Participants

To be eligible for inclusion, adolescents had to be 12–17 years of age, weigh 35 kg or more, have a BMI of 31·5 kg/m² or less, and have confirmed HIV-1 disease with an HIV-1 viral load of less than 50 RNA copies per mL on stable combination ART (consisting of two or more drugs from two or more classes of antiretroviral agents). All participants and their parent or legal guardian provided their written assent and consent, as applicable. Exclusion criteria included two consecutive documented HIV-1 RNA values of greater than or equal to the lower limit of quantification of the assay, known or suspected resistance to rilpivirine or integrase strand transfer inhibitors, and active tuberculosis, hepatitis B, or hepatitis C infection.

All participants continued their pre-study ART throughout cohort 1 and during step 1, adolescents received either oral cabotegravir (cohort 1C) or oral rilpivirine (cohort 1R) for 4–6 weeks (figure 1). Sex data were collected based on self-report; options provided were male, female, and other.

Procedures

Assignment to cohort 1C or cohort 1R was based on the participant's pre-study ART and not random assignment. Participants on a non-nucleoside reverse transcriptase inhibitor-based or protease inhibitor-based pre-study ART were assigned to cohort 1C. Participants on an unboosted integrase strand transfer inhibitor-based pre-study ART were assigned to cohort 1R. This assignment prevented more than one non-nucleoside reverse transcriptase inhibitor or integrase strand transfer inhibitor in the participants' combination ART therapy when adding the study drug. The assignment also prevented participants with a pre-study ART that included a boosted protease inhibitor from getting rilpivirine, given the known drug–drug interactions.

During step 2, long-acting cabotegravir (cohort 1C) or long-acting rilpivirine (cohort 1R) intramuscular injections were to be administered in the gluteus medius by using a 1·5-inch 23-gauge needle; however, if the participant's BMI exceeded 30 kg/m², a 2-inch needle could be used.

Study drug dosing was initially planned as follows (under protocol version 2.0). Cohort 1C: 30 mg cabotegravir once daily orally for 4–6 weeks to assess individual participant tolerability during oral lead-in (step 1), followed by three intramuscular injections of long-acting cabotegravir every 4 weeks (step 2). The three injections included one 600 mg dose at week 4, followed by 400 mg doses at week 8 and week 12. Cohort 1R: 25 mg rilpivirine once daily orally for 4–6 weeks (with length based on scheduling and logistics; step 1), followed by three intramuscular injections of long-acting rilpivirine every 4 weeks (step 2). The three injections included one 900 mg dose, followed by two 600 mg doses. Based on interim safety and ad-hoc pharmacokinetics-modelling analyses, step 2 dosing was changed for newly enrolling cohort 1C and cohort 1R participants from every 4 weeks to every 8 weeks (protocol version 3.0 and onwards). Every-8-weeks dosing included one injection of long-acting cabotegravir (600 mg) or one injection of long-acting rilpivirine (900 mg) at week 4 and a repeat injection of the same dose and drug at week 8. Note that the first injection with every-4-weeks dosing and the first two injections 1 month apart for every-8-weeks dosing constitute the loading or initiation dose. Subsequent injections that were at every 4 weeks or 8 weeks, based on the dosing schedule, constituted continuation therapy. Although no doses were administered at week 16, pharmacokinetic samples obtained then represent trough concentrations 4 weeks after the last dose in the every-4-weeks regimen and 8 weeks after the last dose in the every-8-weeks regimen. The week 16 trough concentration (C_{16WK}) sample, obtained 8 weeks after the second injection of the loading or initiation dose in the every-8-weeks regimen, was considered sufficient for pharmacokinetic assessments. Therefore, a continuation

therapy dose was not given. Cabotegravir and rilpivirine were quantified via liquid chromatographic–tandem mass spectrometry; assays were validated per the US Food and Drug Administration (FDA) bioanalytical recommendations, and their lower limits of quantification were 0·025 µg/mL cabotegravir and 1 ng/mL rilpivirine. Pharmacokinetic samples were collected in amber vials and protected from light throughout handling, given the light sensitivity of rilpivirine.[10,11]

Outcomes

Safety and pharmacokinetic evaluations were done during cohort 1 assessments until 16 weeks and during long-term safety and washout pharmacokinetics follow-up (LSFU; for up to 48 weeks, given the long tail of cabotegravir and rilpivirine pharmacokinetics after intramuscular administration). Electrocardiograms were conducted at screening, week 9 (for participants with every-8-weeks dosing only), week 13 (for participants with every-4-weeks dosing only), and week 16. The primary outcomes were assessments of safety measures, including all adverse events and those grade 3 and greater, until week 4 for oral cabotegravir and until week 16 for long-acting cabotegravir and rilpivirine and pharmacokinetics measures, including area under the plasma concentration versus time curve (AUC) during the dosing interval (AUC_{0-tau}) and drug concentrations, at week 2 for oral dosing of cabotegravir and at week 16 for intramuscular dosing of cabotegravir and rilpivirine. The secondary outcome of monitoring viral load suppression until week 16 is reported in this paper and evaluation of tolerability and acceptability of long-acting cabotegravir and rilpivirine is reported in the Article by Elizabeth Lowenthal and colleagues.[12] Primary and secondary outcome measures are detailed in sections 9·2 and 10·3 of the IMPAACT 2017 protocol.

An injection-site reaction was defined as an adverse event that resulted in pain out of proportion to what would be expected when a person gets an intramuscular injection, tenderness, erythema, redness, induration or swelling, or pruritis, regardless of when it occurs after administration of an injection. The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events was used throughout the study.[13]

Antiviral activity, acceptability, and tolerability were also assessed as secondary objectives. All participants completed questionnaires, and a subset of US participants completed in-depth qualitative interviews. Additionally, parents and caregivers of a subset of US participants were enrolled to complete qualitative interviews, the assessments of which are described by Lowenthal and colleagues.[12]

Statistical analysis

The sample size was determined using Monte Carlo simulations based on existing pharmacokinetics models in adults with extrapolation to the study population characteristics. These simulations estimated the variability for selected primary and secondary parameters and CIs across the possible weight, age, and sex at birth distributions. Up to 55 participants were intended to be enrolled into cohort 1 to for approximately 15–20 evaluable individuals in cohort 1C and 15 evaluable individuals in cohort 1R. The evaluable population in each cohort 1 group was to include at least four female adolescents, at least four male adolescents, at least five adolescents weighing 35–49 kg at study entry, and at least five adolescents weighing at least 50 kg at study entry. Additional details are provided in section 9.4 of the IMPAACT 2017 protocol. The dose-evaluable analysis set included participants treated exclusively with the dose being evaluated for a given cohort and having either completed all scheduled treatments until the relevant visit (either week 4 or week 16), or having experienced any of the following events: death attributable to the study products, study product-related grade 3 or greater adverse events (excluding injection-site reaction), or permanent discontinuation of treatment due to study product-related adverse event (regardless of grade). This analysis set excludes all participants who discontinued the study drug for other reasons or were lost to follow-up. The all-treated analysis set included all participants who received any amount of the study drug. Safety outcome measures were summarised using percentages and exact (Clopper–Pearson) 95% CIs and are presented by group (cohort 1C and cohort 1R) in the dose-evaluable and all-treated analysis sets. Injection-site reactions are presented for the all-treated analysis set. Frequencies and percentages were included for all relevant categorical summaries.

For all HIV-1 RNA summaries, if plasma HIV-1 RNA viral load results were less than the lower limit of quantification, the value of the test was assigned as one unit less than the lower limit of quantification. HIV-1 RNA summaries are provided for the all-treated analysis set. All analyses were carried out using SAS software version 9.4.

Non-compartmental pharmacokinetics parameters of each cohort 1C participant were analysed using plasma cabotegravir concentration–time data after oral administration of cabotegravir. Step 1 pharmacokinetics samples were collected at pre-dose, 1 h, 2 h, 3 h, 4 h, 8 h, and 24 h after dosing at week 2. Oral rilpivirine therapy in adolescents had previous FDA and European Medicines Agency approval. Therefore, assessing oral rilpivirine's pharmacokinetics profile was not a study objective, and week 2 pharmacokinetics sampling was sparse compared with sampling for cabotegravir.

Pharmacokinetics parameters included AUC_{0-tau}, maximum concentration (C_{max}), time to C_{max} (T_{max}), trough concentration, and apparent clearance (CL/F). C_{max} and T_{max} were taken directly from the observed concentration–time data. AUC_{0-tau} was assessed using the linear up and log down trapezoidal method. After an interim pharmacokinetics analysis, the duration of pharmacokinetics sample collection was reduced to 8 h after dose, and

C_0 was used to estimate $C_{24\ h}$ in AUC calculations. The oral cabotegravir target median AUC_{0-tau} was 46–277 μg·h/mL based on adult values. The pharmacokinetics sampling scheme for every 4-week dosing was as follows: week 4 pre-first-dose and 2 h post-dose sampling; week 5 day 3–7 post-first-dose sampling; week 6 day 10–14 post-first-dose sampling; week 8 pre-second-dose sampling; week 12 pre-third-dose and 2 h post-third-dose sampling; week 13 day 3–7 post-third-dose sampling; week 14 day 10–14 post-third-dose sampling; and week 16 day 28 post-third-dose sampling. For every 8-week dosing was as follows: week 4 pre-first-dose and 2 h post-first-dose sampling; week 5 day 3–7 post-first-dose; week 8 pre-second-dose; week 9 day 3–7 post-second-dose; week 12 day 28 post-second-dose; and week 16 day 56 post-second-dose.

After intramuscular administration of long-acting cabotegravir or rilpivirine, pharmacokinetic parameters were summarised using descriptive statistics. C_{16WK} was the primary measure of interest. The target median cabotegravir C_{16WK} for this study was 0·71–6·7 μg/mL. The estimated C_{16WK} 5th percentile of greater than 0·45 μg/mL was calculated from the geometric mean, assuming a log-normal distribution; the 5th percentile was greater than the observed 5th percentile trough after the first injection in ATLAS/FLAIR.[14] The target median rilpivirine C_{16WK} for this study was 25–100 ng/mL and the estimated C_{16WK} 5th percentile target was greater than 17·3 ng/mL: the observed 5th percentile trough after first injection in ATLAS/FLAIR.[15] At each visit, the 5th and 95th percentile concentrations were estimated via bootstrapping for graphical representation.[16] In the

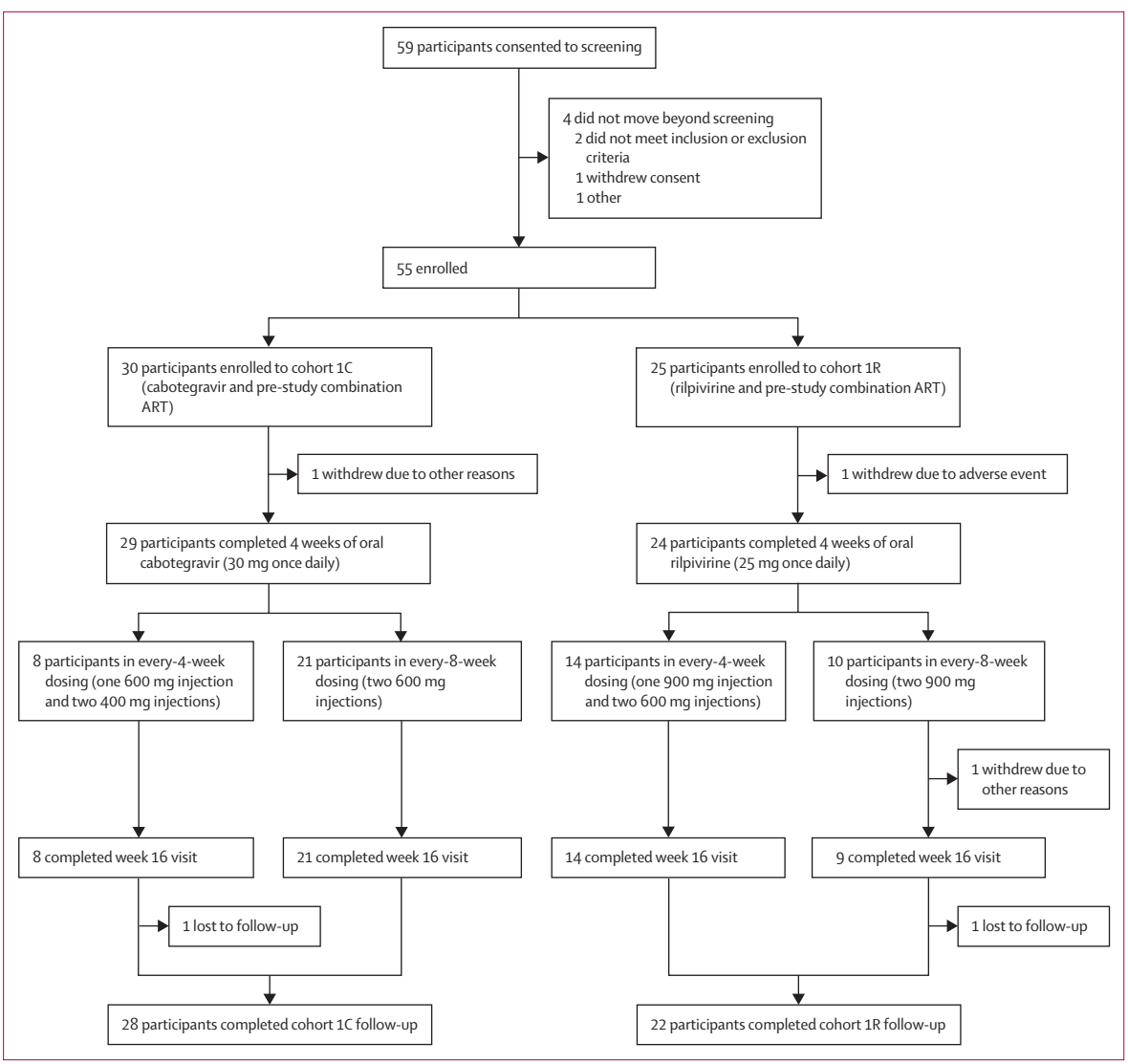

Figure 2: **Cohort 1 trial profile**
Enrolment into cohort 1C or cohort 1R was based on the participant's ongoing pre-study ART regimen. ART=antiretroviral therapy.

	Cohort 1C (cabotegravir; n=30)	Cohort 1R (rilpivirine; n=25)	Total (n=55)
Age (years)	15 (14–16)	16 (15–17)	15 (14–17)
Sex at birth			
Male	16 (53%)	13 (52%)	29 (53%)
Female	14 (47%)	12 (48%)	26 (47%)
Race			
Asian	9 (30%)	0	9 (16%)
Black or African American	21 (70%)	21 (84%)	42 (76%)
White	0	4 (16%)	4 (7%)
Ethnicity			
Not Hispanic or Latino	30 (100%)	22 (88%)	52 (95%)
Hispanic or Latino	0	3 (12%)	3 (6%)
Country			
Botswana	0	5 (20%)	5 (9%)
Thailand	8 (27%)	0	8 (15%)
USA	8 (27%)	17 (68%)	25 (46%)
South Africa	14 (47%)	3 (12%)	17 (31%)
BMI (kg/m²)	19·6 (18·1–21·5)	20·7 (18·0–24·7)	19·9 (18·0–24·1)
Baseline weight			
35–49 kg	17 (57%)	10 (40%)	27 (49%)
≥50 kg	13 (43%)	15 (60%)	28 (51%)
Baseline CD4 count (cells per mm³)*	701 (586–924)	788 (610–1041)	725 (586–985)
HIV mode of transmission			
Horizontal	0	4 (16%)	4 (7%)
Vertical	29 (97%)	20 (80%)	49 (89%)
Unknown	1 (3%)	1 (4%)	2 (4%)
Pre-study regimen continued at trial start			
One INSTI and two NRTIs	0	25 (100%)	25 (46%)
One NNRTI and two NRTIs	13 (43%)	0	13 (24%)
Two NRTIs	1 (3%)	0	1 (2%)
One PI and two NRTIs	16 (53%)	0	16 (29%)
Pre-study regimen duration (months)	36 (21–49)	15 (12–24)	24 (14–40)

Data are median (IQR) or n (%). INSTI=integrase strand transfer inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor. NRTI=nucleoside reverse transcriptase inhibitor. PI=protease inhibitor. *For cohort 1R, n=24; for total, n=54.

Table 1: **Baseline demographics and disease characteristics (all-treated analysis set)**

bootstrapping, 1000 replications were used, and a non-parametric 95% CI was derived.

The accumulation from dose 1 trough to C_{16WK} was assessed for cabotegravir and rilpivirine. The observed cabotegravir and rilpivirine concentration profiles were also compared with predicted concentrations based on simulations of adult population pharmacokinetics models, with adjustment for weight differences using a standard allometric approach.[14,15]

An independent IMPAACT Study Monitoring Committee monitored participant safety through routine and as-needed reviews of study data. IMPAACT 2017 is registered with ClinicalTrials.gov, NCT03497676.

Role of the funding source

The Division of AIDS provided regulatory oversight. Clinical sites were monitored by an independent group under a National Institutes of Health (NIH) contract. ViiV Healthcare and Janssen provided study products and funds to the NIH but were not involved in sponsorship or regulatory oversight. Representatives of NIH, ViiV Healthcare, and Janssen participated in the study design, data interpretation, and manuscript writing. The funders of the study had no role in data collection or data analysis.

Results

Between March 19, 2019, and Nov 25, 2021, 59 individuals consented to be screened and 55 were enrolled in the study (figure 2). 30 participants were assigned to cohort 1C and 25 to cohort 1R, from 15 sites across four countries (table 1). Accrual was paused between March 19, 2020, and Feb 2, 2021, due to the COVID-19 pandemic. The last participant completed the cohort 1 study on May 18, 2022.

Pre-study ART regimens of cohort 1C included efavirenz (seven [23%] of 30), rilpivirine (five [17%]), nevirapine (one [3%]), lopinavir–ritonavir (16 [53%]), or dual nucleoside reverse transcriptase inhibitor abacavir–lamivudine (one [3%]). Those of cohort 1R included dolutegravir (18 [72%] of 25) and bictegravir (seven [28%]).

Eight (27%) cohort 1C and 15 (60%) cohort 1R participants were enrolled in protocol version 2.0 (every-4-weeks dosing), and 22 (73%) cohort 1C and ten (40%) cohort 1R participants in version 3.0 (every-8-weeks dosing). Five participants, two in cohort 1C and three in cohort 1R, prematurely discontinued the study (figure 2). One participant discontinued study treatment due to a rilpivirine-related adverse event, two were lost to follow-up during LSFU (one from each cohort), and two discontinued study treatment for other reasons (one from each cohort).

Per the protocol definition, the week 16 dose-evaluable analysis set included 29 (96%) cohort 1C and 23 (92%) cohort 1R participants who were either in the study until week 16 or discontinued due to a grade 3 or higher adverse event. Three participants were deemed not dose-evaluable by the Clinical Management Committee: one cohort 1C participant discontinued treatment before the first injection; one cohort 1R participant received the wrong dose at week 8; and one cohort 1R participant did not receive the drug at week 4.

All participants received at least one dose of any study product (ie, all enrolled participants were included in the all-treated analysis set), and 52 (95%) received at least one injection. The only serious adverse event was alcohol-related haemorrhagic gastritis assessed as not related to the study drug (table 2; appendix pp 1–10).

By week 16, 28 (97%; 95% CI 82–100) of the 29 cohort 1C dose-evaluable participants reported at least one adverse event of any grade (table 2). Nine (31%; 15–51) were reported as having drug-related adverse events of any grade, with the most common being injection-site pain. One (3%, 0–18) participant experienced self-resolving (in 5 days) study drug-related grade 3 insomnia after

	Cohort 1C (cabotegravir)		Cohort 1R (rilpivirine)	
	Week 4 (evaluable)	Week 16 (dose-evaluable)	Week 4 (evaluable)	Week 16 (dose-evaluable)
Evaluable				
Any adverse event	13/30 (43%; 25–63)	28/29 (97%; 82–100)	18/25 (72%; 51–88)	21/23 (91%; 72–99)
Grade 3 or higher adverse event	0/30 (0–12)	7/29 (24%; 10–44)	3/25 (12%; 3–31)	5/23 (22%; 7–44)
Grade 3 or higher drug-related adverse event	0/30 (0–12)	1/29 (3%; 0–18)	1/25 (4%; 0–20)	1/23 (4%; 0–22)
Serious adverse event*	0/30 (0–12)	1/29† (3%; 0–18)	0/25 (0–14)	0/23 (0–15)
Serious drug-related adverse event	0/30 (0–12)	0/29 (0–12)	0/25 (0–14)	0/23 (0–15)
Premature permanent discontinuation of treatment due to drug-related adverse event	0/30 (0–12)	0/29 (0–12)	1/25 (4%; 0–20)	1/23 (4%; 0–22)
Death due to drug-related adverse event	0/30 (0–12)	0/29 (0–12)	0/25 (0–14)	0/23 (0–15)
All treated				
Any adverse event	13/30 (43%; 25–63)	29/30 (97%; 83–100)	18/25 (72%; 51–88)	23/25 (92%; 74–99)
Grade 3 or higher adverse event	0/30 (0–12)	8/30 (27%; 12–46)	3/25 (12%; 3–31)	6/25 (24%; 9–45)
Grade 3 or higher drug-related adverse event	0/30 (0–12)	1/30 (3%; 0–17)	1/25 (4%; 0–20)	1/25 (4%; 0–20)
Serious adverse event*	0/30 (0–12)	1/30† (3%; 0–17)	0/25 (0–14)	0/25 (0–14)
Serious drug-related adverse event	0/30 (0–12)	0/30 (0–12)	0/25 (0–14)	0/25 (0–14)
Premature permanent discontinuation of treatment due to drug-related adverse event	0/30 (0–12)	0/30 (0–12)	1/25 (4%; 0–20)	1/25 (4%; 0–20)
Death due to drug-related adverse event	0/30 (0–12)	0/30 (0–12)	0/25 (0–14)	0/25 (0–14)
Any injection-site reaction‡	NA	9/30 (30%; 15–49)	NA	9/25 (36%; 18–57)
Hypoaesthesia	NA	0/30 (0–12)	NA	1/25 (4%; 0–20)
Nodule	NA	0/30 (0–12)	NA	1/25 (4%; 0–20)
Pain	NA	9/30 (30%; 15–49)	NA	9/25 (36%; 18–57)
Reaction	NA	0/30 (0–12)	NA	1/25 (4%; 0–20)
Swelling	NA	0/30 (0–12)	NA	1/25 (4%; 0–20)

Data are n/N (%; 95% Exact Clopper–Pearson CI), unless otherwise stated. Adverse event grades were as follows: 1=mild, 2=moderate, 3=severe, 4=potentially life-threatening, and 5=death. Drug-relatedness of adverse events was determined by the site. An injection-site reaction was defined as an adverse event that results in pain out of proportion to what would be expected when a person gets an intramuscular injection (eg, tenderness, erythaema, redness, induration or swelling, or pruritis), regardless of when it occurs after administration of an injection. NA=not applicable. *Serious adverse events included only International Conference on Harmonisation-defined serious adverse events and malignancies. †Alcoholic haemorrhagic gastritis deemed not related to study drug. ‡All injection-site reactions were grade 1 or grade 2.

Table 2: **Adverse events by week 4 and week 16 in the evaluable and all-treated analysis sets and injection-site reactions by week 16 in the all-treated analysis set**

receiving the first study injection and continued to receive subsequent injections.

By week 16, 21 (91%, 95% CI 72–99) of 23 dose-evaluable participants in cohort 1R reported at least one adverse event of any grade (table 2). 12 (52%, 31–73) were reported as having drug-related adverse events, with the most common being injection-site pain. One (4%, 0–22) participant permanently discontinued the study treatment due to a drug-related adverse event (grade 3 acute allergic reaction) after the initial oral rilpivirine dose. No electrocardiogram findings met the criteria for repeat readings.

Injection-site reactions were reported by nine (30%) of the 30 individuals in cohort 1C and nine (36%) of the 25 individuals in cohort 1R in the all-treated analysis set (table 2). Injection-site reactions were primarily injection-site pain, with injection-site nodule and injection-site swelling reported in one participant each. Median days after injection to onset of injection-site reaction were 1 day (range 0–3) in cohort 1C and 0 days (0–3) in cohort 1R and to resolution of injection-site reaction were 4 days (1–14) in cohort 1C and 3 days (1–8) in cohort 1R. Percentages of participants reporting an injection-site reaction after the first injection (week 4) and second injection (week 8) were 28% (8/29) and 17% (5/29) in cohort 1C and 30% (7/23) and 26% (6/23) in cohort 1R, respectively.

Most (>89% at each study visit) participants remained virologically suppressed (HIV-1 viral load <50 RNA copies per mL) at each study visit until week 16 (appendix p 11). During the LSFU, two participants (one in each cohort) had a viral load of 200 RNA copies per mL or more at week 48, which was attributed to suboptimal oral ART intake. The cohort 1C participant had virological failure (ie, two consecutive HIV-1 viral loads ≥200 RNA copies per mL) and no mutations that affected susceptibility to cabotegravir were identified on resistance testing (appendix p 12). The cohort 1R participant reverted to an HIV-1 viral load of less than 200 RNA copies per mL upon repeat assessment, and no protocol-triggered resistance testing was required.

98% of injections at week 8 and 90% at week 12 fell within the allowed window of 7 days of the target injection date.

Week 2 oral cabotegravir pharmacokinetics profiles were obtained for 29 (97%) of 30 participants (appendix p 16): eight (27%) had 24 h pharmacokinetic plasma sample collections, and 21 (70%) had 8 h collections and an approximation of 24 h concentrations. The median C_{max} was 9·28 µg/mL (range 3·54–21·00), 2·7 h post-dose (appendix pp 13, 16). The median AUC_{0-tau} was 148·5 µg·h/mL (range 37·2–433·0), which was similar between the 8 h and 24 h pharmacokinetic-collection strategies. The median CL/F of oral cabotegravir was 4·23 mL/h per kg (range 1·31–12·83).

For long-acting cabotegravir, two participants had C_{16WK} values that were more than 90% lower than all other cabotegravir concentrations in this study and substantially lower than steady-state troughs in adults in the ATLAS-2M and FLAIR studies (figure 3; appendix p 14).[14] Cabotegravir concentrations in both participants at week 8 were not deemed outliers. The data from both participants were included in the overall summary but excluded from the cabotegravir C_{16WK} 5th percentile calculation. The week 16 median cabotegravir concentration for every-4-weeks dosing was 3·11 µg/mL (range 1·22–6·19) and for every-8-weeks dosing was 1·15 µg/mL (range <0·025–5·29), which exceeded the minimum target for this study (0·71 µg/mL). The overall mean cabotegravir week-16-to-week-8 concentration ratio was 1·45 (SD 0·80). Median cabotegravir C_{16WK} concentrations tended to be higher in female than male participants (2·86 µg/mL *vs* 1·32 µg/mL) and among participants in the lower weight (35–49 kg) versus the higher weight (≥50 kg) category (2·86 µg/mL *vs* 1·19 µg/mL; appendix p16). However, in all subgroups, the median C_{16WK} concentration was within the target range for this study (0·71–6·7 µg/mL; appendix p 16). The estimated C_{16WK} 5th percentile of cohort 1C was 0·496 µg/mL, showing that more than 95% of values exceeded the minimum target (0·450 µg/mL). The threshold of 0·450 µg/mL represents the 5th percentile of the observed cabotegravir trough concentration following the long-acting initiation injection in phase 3 studies FLAIR and ATLAS.

Sparse pharmacokinetics sampling was done for oral rilpivirine at week 2 (appendix pp 13, 17). The week 16 median rilpivirine concentration for every-4-weeks dosing was 52·9 ng/mL (range 31·9–148·0) and for every-8-weeks dosing was 39·1 ng/mL (range 27·2–81·3), exceeding the minimum target (25 ng/mL) for this study, which is more than twice the protein-adjusted 90% inhibitory concentration (PA-IC_{90}; figure 3; appendix p 15).[17] The overall mean rilpivirine week-16-to-week-8 concentration ratio was 1·34 (SD 0·63). Median rilpivirine C_{16WK} tended to be higher in female than male participants (77·4 ng/mL *vs* 42·0 ng/mL) and among participants in the lower weight (35–49 kg) versus the higher weight (≥50 kg) category (56·9 ng/mL *vs* 43·8 ng/mL; appendix p 16). In all subgroups, the median rilpivirine C_{16WK} was within the target range for the overall population for this study (25–100 ng/mL; appendix p 16). The cohort 1R estimated C_{16WK} 5th percentile was 23·5 ng/mL, which exceeded the minimum target (17·3 ng/mL).

Pharmacokinetics for cabotegravir and rilpivirine after discontinuing injections were available in a subset of participants who received at least two injectable doses and went back on pre-study combination ART. All cabotegravir concentrations exceeded the lower quantitative limit (>0·025 µg/mL) at 12 weeks (n=7) and the majority at 36 weeks (n=6) after the last dose. All measured rilpivirine concentrations also exceeded the lower quantitative limit (>1 ng/mL) at 12 weeks (n=12) and 48 weeks (n=7) after the last injection (appendix p 14). Observed concentrations in adolescents were similar to simulated concentrations using adult pharmacokinetic models of cabotegravir and rilpivirine (figure 4).[14,15]

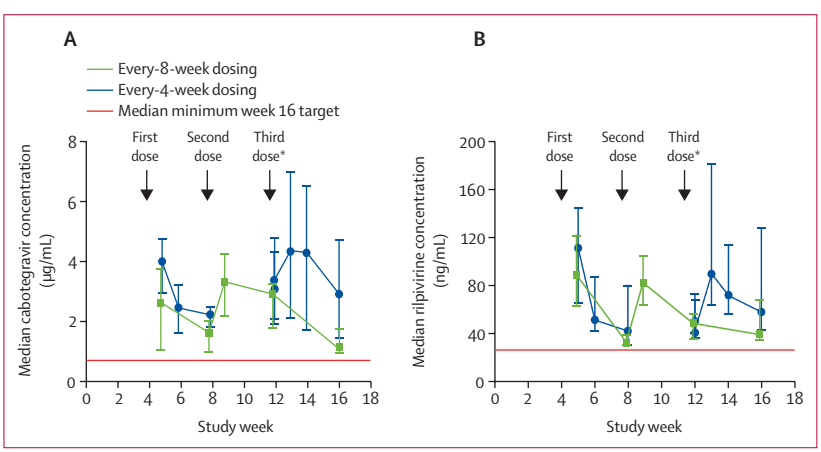

Figure 3: **Median cabotegravir and rilpivirine concentrations after repeated intramuscular administration during step 2**

(A) Cabotegravir. (B) Rilpivirine. Error bars represent the 95% CIs of the medians at each collection point. 95% CIs were generated through bootstrapping with 1000 replications. In the every-4-weeks dosing regimen, study medication was injected at week 4 (loading or initiation dose), week 8, and week 12 (continuation doses); in the every-8-weeks dosing regimen, medication was injected at week 4 and week 8 (loading or initiation dose of two injections, 1 month apart). No interim pharmacokinetic samples were collected between weeks 8 and 12 in the every-4-weeks dosing regimen. Pharmacokinetic profiles after the first and third doses for the every-4-weeks regimen are shown. A continuation therapy dose was deemed unnecessary for pharmacokinetic assessment on the every-8-weeks dosing regimen. *Third doses were for those receiving every-4-week dosing only.

Discussion

The IMPAACT 2017 cohort 1 study findings showed that exposure concentrations of long-acting cabotegravir or rilpivirine, given every 4 weeks or 8 weeks per the adult dosing regimens, in virologically suppressed adolescents (aged ≥12 years and weighing ≥35 kg) were similar to those observed in adult clinical trials. No unanticipated safety concerns arose. The study participants were the first adolescents with HIV-1 to receive long-acting cabotegravir or rilpivirine. Interim cohort 1 findings informed FDA approval of the combined long-acting cabotegravir and rilpivirine regimen for virologically suppressed adolescents as of March 29, 2022.[18]

As reported in adult populations, injection-site reactions were very common, self-limiting, and not severe. Despite the injection-site reactions, this regimen

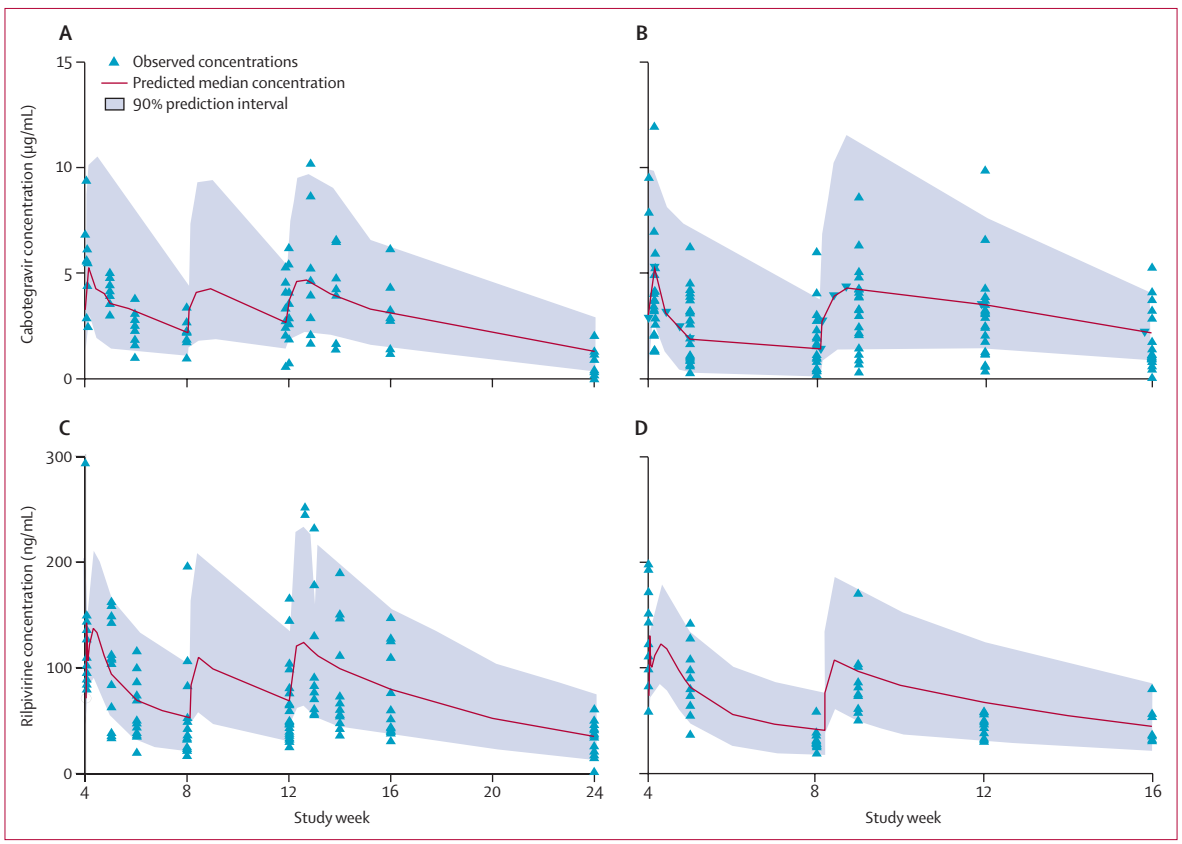

Figure 4: **Observed and predicted cabotegravir and rilpivirine concentrations**
90% prediction intervals (5th and 95th percentiles) were from simulations based on existing population pharmacokinetics models in adult participants.[12,14] (A) Cabotegravir concentrations in cohort 1C participants who received every-4-weeks dosing (ie, long-acting cabotegravir injections at week 4 [loading or initiation dose], week 8, and week 12 [continuation doses]). (B) Cabotegravir concentrations in cohort 1C participants who received every-8-weeks dosing (ie, long-acting cabotegravir injections at week 4 and week 8 [loading or initation dose of two injections, 1 month apart]). (C) Rilpivirine concentrations of cohort 1R participants who received every-4-weeks dosing. (D) Rilpivirine concentrations of cohort 1R participants who received every-8-weeks dosing. A continuation therapy dose was deemed unnecessary for pharmacokinetics assessment on the every-8-weeks dosing regimen.

has been highly accepted among adult study participants.[19] The acceptability and tolerability of long-acting cabotegravir and rilpivirine among IMPAACT 2017 cohort 1 participants and their parents or guardians are described by Lowenthal and colleagues.[12]

Some paediatric centres limit the intramuscular-injection volume to 2 mL in adolescents. However, in this study the 3 mL volume of long-acting cabotegravir and rilpivirine was well tolerated. Before preparing the injections, removing the medications from the refrigerator and waiting at least 15 min to allow the medicines to come to room temperature, along with slow administration, especially for long-acting rilpivirine, can reduce discomfort.[20]

Observed concentrations with long-acting cabotegravir and rilpivirine monthly or every 2 months were aligned with simulations from adult population pharmacokinetics models.[14,15] This finding enables us to allometrically scale the adult clearance of most drugs to adolescents.[21] An FDA review of 92 products found that 95% had equivalent dosing for adult and adolescent patients.[22]

The median C_{16WK} values of both drugs were several folds higher than the PA-IC_{90} and similar to troughs after the initial few injections in adults.[14] The estimated 5th percentiles (95% of C_{16WK} values) also exceeded the PA-IC_{90} for both the every 4-week and 8-week dosing regimens. As expected, the C_{16WK} values were lower for every 8-week dosing than every 4-week dosing due to the longer dose interval and lower overall average daily dose. Median C_{8WK} values also exceeded the minimum targets for cabotegravir and rilpivirine for this study (appendix pp 14–15). There was substantial accumulation between C_{8WK} and C_{16WK} troughs, suggesting that the C_{16WK} concentration had not reached steady state; thus, further accumulation will occur with additional doses, as in adults. The IMPAACT 2017 study team are pursuing long-term pharmacokinetic evaluations to characterise steady-state concentrations and variability and to monitor virological suppression with the combined long-acting cabotegravir and rilpivirine regimen in cohort 2.

In adults, BMI, sex, weight, and other clinical factors can affect the absorption rates of long-acting cabotegravir.

Although we observed some indication that sex, weight, and dose regimen might influence cabotegravir and rilpivirine concentrations in adolescents, the small sample size prevented robust statistical evaluation. All subgroups had median C_{16WK} values similar to those in adults. The participants with the lowest weight in cohorts 1C and 1R weighed 35–40 kg, and neither had a C_{16WK} concentration at the high end of the target range for this study.

Concentration–time profiles after intramuscular administration of long-acting cabotegravir or rilpivirine can be affected by factors that are not influential after intravenous or oral administration. The terminal portion of the concentration–time profile for long-acting products represents ongoing absorption (not elimination) from the injection site (known as flip-flop pharmacokinetics). An altered absorption rate can influence steady-state trough concentrations. Therefore, attention to variability and changes in absorption is warranted.

Given that all participants with virological suppression at enrolment continued their pre-study ART while receiving long-acting cabotegravir or rilpivirine in cohort 1, we did not expect any virological failures. For the one participant who met criteria for virological failure 48 weeks after the last long-acting cabotegravir injection, at which point there was no quantifiable cabotegravir, we found no mutations that affected susceptibility to integrase strand transfer inhibitors. In clinical studies of adults receiving combined long-acting cabotegravir and rilpivirine, virological failure remains low.[9,23]

The relatively small sample size of cohort 1, with even smaller every-4-weeks and every-8-weeks dosing subgroups, limited meaningful subgroup analysis and interpretations (eg, sex-based or weight-based trends). Not continuing pharmacokinetic collections through steady state in cohort 1 could also be viewed as a study limitation. That said, given the robust data from studies in adults and related pharmacokinetic modelling, we did not believe that larger enrolment numbers and a longer pharmacokinetic study with no benefit to participants was justified for the primary objective. Additionally, the rapid start of the cohort 2 study and the opportunity for cohort 1 participants to roll over into cohort 2, in addition to new participants in cohort 2, provides larger numbers and pharmacokinetic data timepoints until week 96 for secondary pharmacokinetic analysis. Based on the adult data and pharmacokinetic modelling, we did not deem it necessary to add a direct-to-inject option in cohort 1. Due to cost and logistical considerations, qualitative interviews addressing the applicable secondary objective of the study were limited to participants at US sites only. This decision limited the generalisability of the qualitative in-depth interview data to the USA and similar settings only.

IMPAACT 2017 cohort 1 was a short, visit-intensive pharmacokinetics and safety study that provided no immediate benefit to participants but was crucial for obtaining regulatory approval for this first all long-acting ART regimen in adolescents. FDA and Health Canada approval of the combined long-acting cabotegravir and rilpivirine regimen for virologically suppressed adolescents with HIV-1 also shows that, against a backdrop of robust adult data, pharmacokinetic data from carefully planned multicentre phase 1/2 studies with relatively few participants can, in some circumstances, provide sufficient evidence to support expanding dosing indications for adolescents.

Real-world experience using this all-injectable combination ART regimen is growing and is described in adults.[24,25] Assessing the feasibility and risk–benefit of this regimen in adolescents and adults struggling with adherence to daily oral ART is clinically important.[26] The long-acting combined cabotegravir and rilpivirine regimen advances treatment options for adolescents with HIV-1, particularly for those who find adhering to daily oral therapies challenging.

Contributors

KB, SW, RM, JH, BH, and JLK accessed and verified the data in the study. All authors had final responsibility for the decision to submit for publication. AHG, PS, EDL, BMB, HC, KV, CM, RMVS-R, KC, CBM, EVC, and SLF formulated the overarching research goals and aims. MAM, BH, JLK, CM, KC, JHM, RMVS-R, KV, CBM, AHG, EVC, KB, SW, RM, and PS reviewed, interpreted, and maintained research data. KB, SW, RM, PS, BMB, EVC, MAM, SLF, and JH assisted with analysis plans and analysed and synthesised study data. CM assisted with acquiring the financial support for the project leading to this publication. AHG, ALA, AC-G, SRM, CS-A, and PO implemented the study and collected data. AHG, PS, EDL, BH, HC, CM, RMVS-R, JH, KC, CBM, AA, and EVC developed the protocol. AHG, CBM, AA, ALA, CM, KC, and ET managed and coordinated research activity, planning, and execution. AHG, CM, KC, CMH, and CBM developed and provided study materials and resources. AHG, ALA, AA, JHM, CM, KC, CBM, ET, and PO oversaw and led research activity planning and execution. KB, SW, RM, PS, BMB, EVC, and HC monitored results to verify validity and reproducibility. AHG, CBM, KB, and EVC prepared the visualisation and data presentation of the manuscript. AHG led the initial manuscript writing. All authors contributed to the manuscript development and review.

Declaration of interests

BMB, KB, PS, AHG, MAM, KC, and PO received IMPAACT Network grant funding from the National Institutes of Health (NIH) to support work on this protocol. AHG and PO's institutions have Clinical Trials Agreements (CTAs) with ViiV Healthcare to support the IMPAACT 2017 study. AHG's institution has a CTA with Janssen to support COVID-19 research and AHG is part of the ViiV Healthcare Pediatric Advisory Board. BMB, KB, MAM, SW, and RM's institution receives funding from ViiV Healthcare. MAM is a consultant for Bio-rad and receives royalties from Elsevier; their institution receives funding from Gilead for industry-sponsored research and funding from the NIH for HIV prevention and microbicide-related research. BMB's institution receives grant funding from Janssen for the study. HC, RMVS-R, and KV are employees of Janssen and have stock and stock options with Johnson & Johnson. ALA received grants or contracts from Gilead, Merck, and ViiV; and is content development faculty for the Simply Speaking HIV Prevention Series, an expert witness, an unpaid Advocates for Youth Board Chair, and an unpaid HIVMA Vice Chair. AC-G is a ViiV Healthcare consultant. CM and CMH are employees at ViiV Healthcare. SLF and JH are employees at GSK. SLF and CM own GSK stock or stock options. EVC is a Data Safety and Management Board member for a paediatric antibacterial study with Melinta Pharmaceuticals. 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 could 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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