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Acceptability and tolerability of longacting injectable cabotegravir or rilpivirine in the first cohort of virologically suppressed adolescents living with HIV IMPAACT 2017MOCHA a second analysis of a phase 12 multicentre openlabel noncomparative dos

E Lowenthal; j Chapman; R Ohrenschall; k calabrese; Faeezah Patel ...

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Acceptability and tolerability of long-acting injectable cabotegravir or rilpivirine in the first cohort of virologically suppressed adolescents living with HIV (IMPAACT 2017/MOCHA): a secondary analysis of a phase 1/2, multicentre, open-label, non-comparative dose-finding study

Elizabeth D Lowenthal, Jennifer Chapman, Rachel Ohrenschall, Katherine Calabrese, Kristin Baltrusaitis, Barbara Heckman, Dwight E Yin, Allison L Agwu, Conn Harrington, Rodica M Van Solingen-Ristea, Cynthia C McCoig, Adeola Adeyeye, Jared Kneebone, Vasiliki Chounta, Christiana Smith-Anderson, Andres Camacho-Gonzalez, Jessica D'Angelo, Allison Bearden, Herta Crauwels, Jenny Huang, Sarah Buisson, Ryan Milligan, Shawn Ward, Carolyn Bolton-Moore, Aditya H Gaur*, IMPAACT 2017 Collaborators†, for the IMPAACT 2017 Team*

Lancet HIV 2024; 11: e222–32

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*Joint senior authors

†Study group and protocol team members are listed in the appendix (pp 8–9)

The Children's Hospital of Philadelphia, Division of General Pediatrics and Global Health Center, Philadelphia, PA, USA (E D Lowenthal MD MSCE, J Chapman MPH); **University of Pennsylvania Perelman School of Medicine, Departments of Pediatrics and Biostatistics, Epidemiology and Informatics, Philadelphia, PA, USA** (E D Lowenthal); **University of Pennsylvania School of Nursing, Philadelphia, PA, USA** (R Ohrenschall BSN); **FHI 360 IMPAACT Operations Center, Durham, NC, USA** (K Calabrese MPH, S Buisson MSW MPH); **Center for Biostatistics in AIDS Research, Harvard T.H. Chan School of Public Health, Boston, MA, USA** (K Baltrusaitis PhD); **Frontier Science Foundation, Amherst, NY, USA** (B Heckman BS, J Kneebone PhD, R Milligan MB, S Ward MS); **National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS, National Institutes of Health (NIH), Rockville, MD, USA** (D E Yin MD PhD, A Adeyeye MD MPA); **Johns Hopkins University School of Medicine, Baltimore, MD, USA** (A L Agwu MD ScM); **ViiV Healthcare, Research Triangle Park, NC, USA** (C Harrington BA, V Chounta MPharm MSc, J Huang PhD); **Janssen Research and Development, Beerse, Belgium** (R M Van Solingen-Ristea MD,

Summary

Background Long-acting injectable cabotegravir and rilpivirine have demonstrated safety, acceptability, and efficacy in adults living with HIV-1. The IMPAACT 2017 study (MOCHA study) was the first to use these injectable formulations in adolescents (aged 12–17 years) living with HIV-1. Herein, we report acceptability and tolerability outcomes in cohort 1 of the study.

Methods In this a secondary analysis of a phase 1/2, multicentre, open-label, non-comparative dose-finding study, with continuation of pre-study oral combination antiretroviral treatment (ART), 55 adolescents living with HIV-1 were enrolled to receive sequential doses of either long-acting cabotegravir or rilpivirine and 52 received at least two injections. Participants had a body weight greater than 35 kg and BMI less than 31·5 kg/m² and had been on stable ART for at least 90 consecutive days with an HIV-1 viral load of less than 50 copies per mL at a participating IMPAACT study site. Participants had to be willing to continue their pre-study ART during cohort 1. The primary objectives of the study were to confirm doses for oral and injectable cabotegravir and for injectable rilpivirine in adolescents living with HIV. This analysis of participant-reported outcomes included a face scale assessment of pain at each injection and a Pediatric Quality of Life Inventory (PedsQL) at baseline and week 16 for participants in the USA, South Africa, Botswana, and Thailand. A subset of 11 adolescents and 11 parents or caregivers in the USA underwent in-depth interviews after receipt of one or two injections. This trial is registered at ClinicalTrials.gov, NCT03497676.

Findings Between March 19, 2019, and Nov 25, 2021, 55 participants were enrolled into cohort 1. Using the six-point face scale, 43 (83%) of participants at week 4 and 38 (73%) at week 8 reported that the injection caused "no hurt" or "hurts little bit", while only a single (2%) participant for each week rated the pain as one of the two highest pain levels. Quality of life was not diminished by the addition of one injectable antiretroviral. In-depth interviews revealed that parents and caregivers in the USA frequently had more hesitancy than adolescents about use of long-acting formulations, but parental acceptance was higher after their children received injections.

Interpretation High acceptability and tolerability of long-acting cabotegravir or rilpivirine injections suggests that these are likely to be favoured treatment options for some adolescents living with HIV.

Funding National Institutes of Health and ViiV Healthcare.

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Introduction

The International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) 2017 phase 1/2 study is titled the More Options for Children and Adolescents (MOCHA) study and is the first study to provide long-acting injectable antiretroviral therapy (ART) for the treatment of HIV-1. Combined long-acting cabotegravir and long-acting rilpivirine is the first long-acting regimen recommended for the maintenance of virological suppression in adults living with HIV-1.[1] The MOCHA study represented the first opportunity to assess the acceptability and tolerability of long-acting ART in children aged 12–17 years. Long-acting ART has been identified as a key area for development to advance treatment of HIV-1 in children,[2] yet have insufficient data on how well these formulations will be accepted and tolerated by young people with HIV and their parents. Increased child or adolescent and parental satisfaction with HIV-1 treatment have been shown to improve adherence and long-term treatment success.[3] This

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Research in context

Evidence before this study

Long-acting injectable cabotegravir and long-acting rilpivirine have been shown to be safe, efficacious, and well-tolerated in adults living with HIV; however, new formulations that are appropriate for adults might not be acceptable to or well tolerated by children and adolescents. We searched PubMed for articles published before writing the study proposal 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. International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) 2017 is the first study to administer long-acting cabotegravir and rilpivirine to adolescents with HIV.

Added value of this study

This study comprehensively evaluated the acceptability and tolerability of long-acting cabotegravir or rilpivirine among the first adolescents who received one of these products as part of the phase 1/2 IMPAACT 2017/More Options for Children and Adolescents (ie, MOCHA) study. The opinions of the parents and caregivers of these adolescents evaluated key areas of concern for long-term implementation success in adolescents.

Implications of all the available evidence

These data suggest that long-acting injectable antiretroviral therapy is a well accepted and well tolerated treatment option for adolescents living with HIV. Taken with the pharmacokinetics and safety data reported separately as a companion manuscript, these data indicate that uptake and continuation of these formulations are likely to be favourable in adolescents.

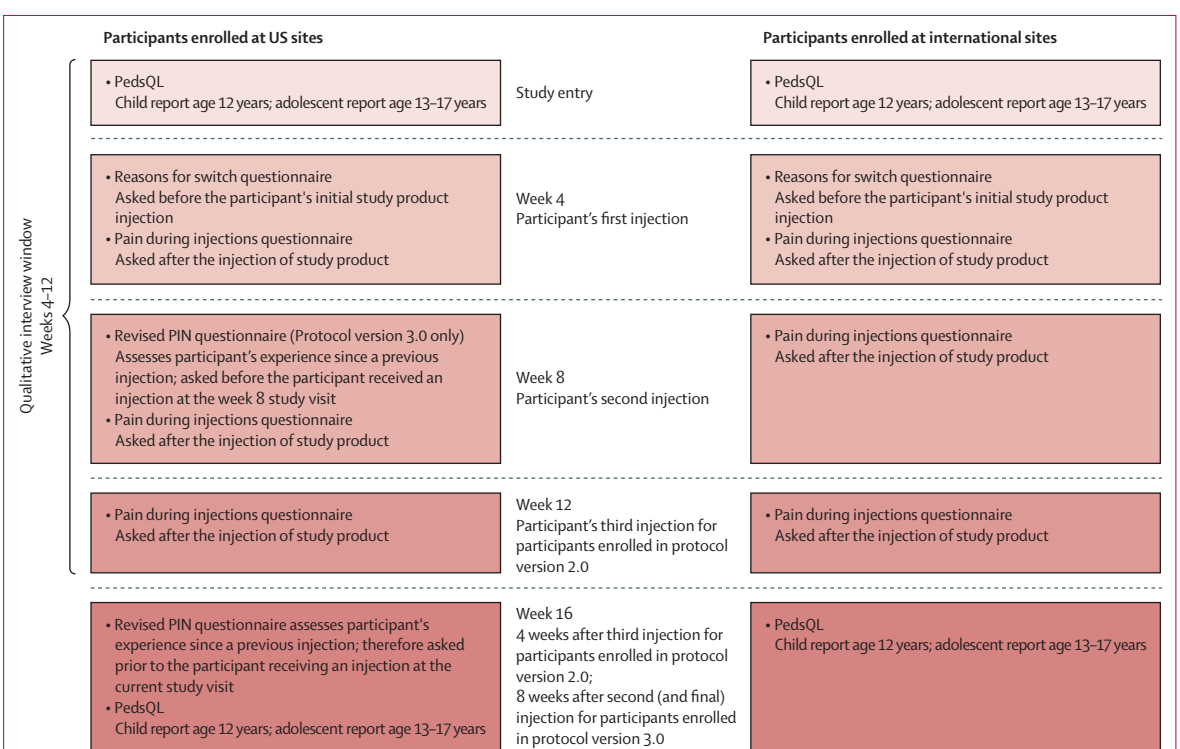

Figure: **Acceptability and tolerability data collection schedule**
The pain during injection questionnaire used a face scale. PIN=perceptions of injections. PedsQL=Pediatric Quality of Life Inventory.

manuscript reports the tolerability and acceptability of long-acting cabotegravir or long-acting rilpivirine among the first adolescents receiving one of these formulations while continuing their daily oral ART, as part of the study done to confirm appropriate dosing for this age group.

In adults with HIV, once-monthly long-acting cabotegravir and long-acting rilpivirine has been found to be highly acceptable in diverse practice sites in the USA, although adverse events were common, with injection site reactions as the most frequently reported adverse event.[4] Transitioning of dosing from monthly to every 2 months has been found to maintain efficacy in adults with the benefit of fewer injections, but higher injection volumes.[5]

Pre-implementation preferences for long-acting injectable ART formulations differ by the population

H Crauwels PhD); **ViiV Healthcare, Madrid, Spain** (C C McCoig MD); **University of Colorado School of Medicine, Aurora, CO, USA** (C Smith-Anderson MD); **Emory University School of Medicine, Atlanta, GA, USA** (A Camacho-Gonzalez MD MSc); **Northwestern University and Lurie Children's Hospital of Chicago, Chicago, IL, USA** (J D'Angelo MSN CPNP); **Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA** (A Bearden MD MPH); **Centre for Infectious Disease Research in Zambia/University of Alabama Birmingham, Lusaka, Zambia** (C Bolton-Moore MSc MBBCh); **St Jude Children's Research Hospital, Memphis, TN, USA** (A H Gaur MD)

Correspondence to:
Dr Elizabeth D Lowenthal, The Children's Hospital of Philadelphia Roberts Center for Pediatric Research, Division of General Pediatrics and Global Health Center, Philadelphia, PA 19146, USA
lowenthale@chop.edu

See **Online** for appendix

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studied, with adolescents showing both a strong interest and a variety of perceived obstacles such as possible challenges with the frequency of clinic visits required for long-acting ART.[6] For treatment of adolescents with chronic diseases, decision making is complex, requiring discussion and collaboration between the adolescents, their parents, and medical providers.[7] We aimed to identify the acceptability and tolerability aspects of long-acting cabotegravir or rilpivirine unique to adolescents and to evaluate their experiences with these treatments in the first group of adolescents to receive them. The MOCHA study has two consecutive cohorts, with cohort 1 establishing the dose, safety, and pharmacokinetics of oral and injectable long-acting cabotegravir and rilpivirine in virologically suppressed adolescents who remain on their pre-study oral ART regimen. This manuscript describes cohort 1 participant-reported outcomes and the experiences of a subset of parents and caregivers. The study is ongoing with cohort 2, in which adolescents are receiving both long-acting cabotegravir and rilpivirine without oral ART.

Effective implementation of evidence-based practices remains a substantial challenge, and participant-reported outcomes can help guide preparation of successful implementation programmes. Determinant frameworks help to elucidate the context in which a practice will be implemented and can aid the sustainable development of processes for implementing new interventions.[8] The work described in this manuscript was guided by the Consolidated Framework for Implementation Research (CFIR)[9] to inform the future implementation of sustainable treatment programmes for adolescents living with HIV-1 who can benefit from receipt of long-acting ART.

Methods

Study design

This is a secondary analysis of IMPAACT 2017, a phase 1/2, multicentre, open-label, non-comparative dose-finding study with cohort 1 conducted at eight US sites, three South African sites, two Ugandan, two Botswanan sites, and two Thai sites. The study was approved by the applicable institutional review boards at each participating site, with Advarra converting to serve as the single institutional review board for US sites in November 2020. The study protocol can be found on the IMPAACT Network website. Participants in cohort 1 were enrolled under versions 2.0 and 3.0 of the protocol (figure).

For the **protocol** see https://www.impaactnetwork.org/studies/impaact2017

Participants

Participants had confirmed HIV-1 infection, were aged 12–17 years, had a body weight greater than 35 kg and BMI less than 31·5 kg/m², and had been on stable ART for a minimum of 90 days with an HIV-1 viral load of less than 50 copies per mL at a participating IMPAACT study site. Participants on protease inhibitor-based or non-nucleoside reverse transcriptase inhibitor-based ART were assigned to receive long-acting cabotegravir (cohort 1C) and participants on non-boosted integrase inhibitor-based ART were assigned to receive long-acting rilpivirine (cohort 1R), meaning that the trial was not randomised and there was no masking. Since the primary objectives of cohort 1 were to confirm dosing of the investigational products, participants had to be willing to continue their pre-study ART during cohort 1 but were given the option to subsequently participate in cohort 2 where long-acting cabotegravir and long-acting rilpivirine were given as a complete regimen to replace oral treatment. All adolescent participants and their parent or legal guardian provided written assent and consent, as applicable.

For US-based participants, parents or caregivers were also eligible to enrol for in-depth interviews. Eligibility for in-depth interviews for both adolescents and parents or caregivers included being willing to be interviewed in English. Initially, all participants who met in-depth interview inclusion criteria were asked to participate in this component. Later in the enrolment period, the interview team purposively selected in-depth interview participants to improve the balance of adolescent participant sex at birth, age (both older and younger adolescents), and enrolment site in the completed interviews. The eligible parent or caregiver was determined by the enrolled adolescent based on the criterion of who is most involved in supporting their medication taking. Written consent was provided by adult participants.

Sex data were collected by self-report with the options of male, female, or other.

Procedures

For this secondary analysis, enrolled adolescents completed questionnaires related to participant-reported outcomes (figure). Step 1 consisted of oral lead-in dosing of cabotegravir or rilpivirine. Participants who met safety criteria to advance to injectable study product then entered study step 2 and received long-acting cabotegravir or rilpivirine in the gluteus medius by a trained study team member. Participants enrolled to protocol version 2.0 received a total of three individual intramuscular doses of either long-acting cabotegravir or rilpivirine administered 4 weeks apart. The first dose was 3 mL (600 mg cabotegravir or 900 mg rilpivirine) and the second and third doses were 2 mL each (400 mg cabotegravir or 600 mg rilpivirine), which was aligned to the monthly dosing regimen in adults. Participants enrolled to protocol version 3.0 received a first 3 mL intramuscular dose of 600 mg long-acting cabotegravir or 900 mg long-acting rilpivirine and an identical dose 4 weeks later, aligned with the initial doses of the every-2-month dosing regimen previously established for adults. Final follow-up for acceptability endpoints was at week 16.

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	Cohort 1C (LA-cabotegravir)	Cohort 1R (LA-rilpivirine)	Total (n=55)
Total study cohort			
Adolescent ages (years)			
12–13	5/30 (17%)	3/25 (12%)	8/55 (15%)
14–15	14/30 (47%)	7/25 (28%)	21/55 (38%)
16–17	11/30 (37%)	15/25 (60%)	26/55 (47%)
Sex			
Male	16/30 (53%)	13/25 (52%)	29/55 (53%)
Female	14/30 (47%)	12/25 (48%)	26/55 (47%)
Weight			
<50 kg	17/30 (57%)	10/25 (40%)	27/55 (49%)
≥50 kg	13/30 (43%)	15/25 (60%)	28/55 (51%)
Race*			
Asian	9/30 (30%)	0/25	9/55 (16%)
Black	21/30 (70%)	21/25 (84%)	42/55 (76%)
White	0/30	4/25 (16%)	4/55 (7%)
Enrolment country			
Botswana	0/30	5/25 (20%)	5/55 (9%)
Thailand	8/30 (27%)	0/25	8/55 (15%)
South Africa	14/30 (47%)	3/25 (12%)	17/55 (31%)
USA	8/30 (27%)	17/25 (68%)	25/55 (46%)
Protocol version at enrolment			
Version 2.0	8/30 (27%)	15/25 (60%)	23/55 (42%)
Version 3.0	22/30 (73%)	10/25 (40%)	32/55 (58%)
Qualitative interviewees			
Ages			
12–13	2/6 (33%)	1/5 (20%)	3/11 (27%)
14–15	2/6 (33%)	1/5 (20%)	3/11 (27%)
16–17	2/6 (33%)	3/5 (60%)	5/11 (45%)
Sex			
Male	5/6 (83%)	1/5 (20%)	6/11 (55%)
Female	1/6 (17%)	4/5 (80%)	5/11 (45%)
Weight			
<50 kg	3/6 (50%)	1/5 (20%)	4/11 (36%)
≥50 kg	3/6 (50%)	4/5 (80%)	7/11 (64%)
Total number of injections received at the time of interview			
One	2/6 (33%)	0	2/11 (18%)
Two	4/6 (67%)	5/5 (100%)	9/11 (82%)
Enrolment site			
Emory School of Medicine, Atlanta, GA, USA	0/6	3/5 (60%)	3/11 (27%)
Johns Hopkins University, Baltimore, MD, USA	1/6 (17%)	2/5 (40%)	3/11 (27%)
Lurie Children's Hospital, Chicago, IL, USA	1/6 (17%)	0	1/11 (9%)
University of Colorado, Denver, CO, USA	3/6 (50%)	0	3/11 (27%)
University of Southern California, Los Angeles, CA, USA	1/6 (17%)	0	1/11 (9%)
Interviewed parents or caregivers			
Mother†	4/6 (67%)	4/5 (80%)	8/11 (73%)
Father	1/6 (17%)	0/5	1/11 (9%)
Grandmother	1/6 (17%)	1/5 (20%)	2/11 (18%)

Data are n/N (%). Percentages might not sum to 100 due to rounding. All participants in version 2.0 of the protocol were based in the USA since international enrolments were not allowed until version 3.0. Two participants in Cohort 1R enrolled under protocol version 3.0 were based in the USA; all other version 3.0 participants were based outside of the USA. LA=long-acting injectable. *Ethnicity was collected only for US-based participants, three of whom identified as Hispanic and the rest were non-Hispanic. †One mother is counted twice because she is the mother of two enrolled children. The mother was interviewed only once but spoke separately about her experiences with each of her enrolled children.

Table 1: **Participant demographic characteristics for the total cohort completing acceptability and tolerability assessments and qualitative interview participants**

Quantitative assessments were administered by site staff via questionnaires covering reasons for switching from daily oral ART to long-acting study products, participant perceptions of study injections, and quality of life. Training and written standard operating procedures helped ensure uniformity of administration across sites, including strategies for asking sensitive questions, the importance of reading items word-for-word, avoiding educating participants during data collection, and reporting of open-ended responses verbatim. All participant-reported outcome questionnaires were administered to the adolescents at all enrolling sites, except for the perceptions of injection questionnaire. This questionnaire was administered only to adolescents from US sites whose primary language was English or Spanish for proprietary reasons.

A reason for switch questionnaire was created by the study team to document participants' reasons for wanting to try the long-acting study product. Adolescents were asked to select all reasons that applied to them from a list of possible motivations for trying long-acting ART. The final choice option was "other" with a free-text response space to collect reasons that were not identified a priori by the study team. After identifying all applicable reasons, participants specified which reason was the most important to them.

Pain during injections was assessed using the Faces Pain Scale-Revised which includes six visual and text options: "no hurt", "hurts little bit", "hurts little more",

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	Cohort 1C (LA-cabotegravir; n=29)	Cohort 1R (LA-rilpivirine; n=24)	Total (n=53)
Reasons for wanting to try long-acting injectable medicine*			
I am interested in research of new treatments.	19 (66%)	21 (88%)	40 (76%)
My doctor or someone else in my clinic asked me to do the study.	5 (17%)	11 (46%)	16 (30%)
My parent or someone else in my family asked me to do the study.	2 (7%)	8 (33%)	10 (19%)
I do not like the way my current medicine makes me feel.	6 (21%)	2 (8%)	8 (15%)
I am worried that my current medicine might cause me problems in the future.	3 (10%)	2 (8%)	5 (9%)
I find it difficult to take my current medication on a regular basis.	7 (24%)	9 (38%)	16 (30%)
I hope that someday I can take medicine that does not make me have to take pills every day.	23 (79%)	21 (88%)	44 (83%)
Some other reason.	4 (14%)	1 (4%)	5 (9%)
Primary reason for wanting to try long-acting injectable medicine			
I am interested in research of new treatments.	9 (31%)	8 (33%)	17 (32%)
My doctor or someone else in my clinic asked me to do the study.	0	0	0
My parent or someone else in my family asked me to do the study.	1 (3%)	0	1 (2%)
I do not like the way my current medicine makes me feel.	1 (3%)	0	1 (2%)
I am worried that my current medicine might cause me problems in the future.	0	1 (4%)	1 (2%)
I find it difficult to take my current medication on a regular basis.	2 (7%)	2 (8%)	4 (8%)
I hope that someday I can take medicine that does not make me have to take pills every day.	16 (55%)	13 (54%)	29 (55%)
Some other reason.	0	0	0
How easy or difficult is it for you to take your pills every day as recommended by your doctor?			
Very easy	11 (38%)	9 (38%)	20 (38%)
Easy	6 (21%)	6 (25%)	12 (23%)
Neither easy nor difficult	11 (38%)	5 (21%)	16 (30%)
Difficult	1 (3%)	4 (17%)	5 (9%)
Very difficult	0	0	0

Data are n (%). Questions and answers are verbatim quotations from the questionnaire. Two US-based participants, one in Cohort 1C and one in Cohort 1R, prematurely discontinued treatment and did not complete questionnaires at the Week 4b visit. LA=long-acting injectable. *Participants were asked to check all reasons that apply for this question; since participants could pick more than one reason, the total of percent endorsing each option is >100%.

Table 2: **Responses to reasons for switch questionnaire**

"hurts even more", "hurts whole lot", and "hurts worst".[10] Pain, other sensations, and changes in function related to receipt of study injections were assessed using the Perceptions of Injection (PIN) questionnaire, an adapted version of the Vaccinees' Perception of Injection Questionnaire. The PIN questionnaire evaluates acceptability and tolerability of injections and injection site reactions, scoring items across four dimensions with a 5-point Likert scale ranging from "totally acceptable" (1) to "not at all acceptable" (5).[11]

A commonly used 23-item Pediatric Quality of Life Inventory, the PedsQL, was used to measure physical, emotional, and social dimensions of health and school functioning.[12]

US participants were eligible to complete a single in-depth interview any time after the first injectable dose and before the week 12 visit. Interviews were conducted by members of the protocol team who were not at an enrolment site and were not known to any study participants. For the interviews, interviewees were in private locations in the clinic or in their own homes, depending on their preference. Example interview guides are available in the appendix (pp 9–18). Interviews were audio recorded through a secure audio conference administered through the Children's Hospital of Philadelphia Information Services and PGi services ReadyConference Plus conferencing system. Recordings were securely transmitted to ADA Transcription (Mount Holly, NJ, USA), which provided professional transcription of the audio files. The interviewer reviewed each transcript for accuracy and completeness before coding.

Outcomes

For the PedsQL, a total score and summary scores for physical, emotional, and social dimensions of health and for school functioning were calculated (by KB, RM, and SW) using published guidelines.[12] All other questionnaire responses were reported based on the number of responses for each item, since no validated summation methods exist. Qualitative outcomes were themes arising from the in-depth interviews, guided by the CFIR Framework. The evaluation of tolerability and acceptability of long-acting cabotegravir and rilpivirine is reported here and the monitoring viral load suppression until week 16 is reported in the Article by Aditya Gaur and colleagues.[13]

Statistical analysis

For cohort 1 of the study, there was a target enrolment of up to 55 participants to achieve at least 15 dose-evaluable adolescents on each long-acting formulation, which was based on Monte Carlo simulations using existing pharmacokinetics models with extrapolation to study population characteristics (eg, age and expected weight distributions). A maximum sample size of 30 interviews was pre-determined with the goal of continuing interviews until thematic saturation was achieved.

Qualitative analysis began during data collection so that an iterative process could be used through which questions and probes were refined to enhance understanding. Topics arising from open-ended inquiries in early interviews were incorporated into prompts for subsequent interviews. Thematic saturation was evaluated during analysis of the transcripts by multiple investigators, based on agreement that new information ceased to arise from new interviews. Analysis used a thematic approach whereby the protocol interview team and coding assistants searched for patterns in the data

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and conceptualised ideas that explained their presence.[14] Analysis began with reading and rereading transcripts until content became intimately familiar.[15] The initial code book was designed using the CFIR framework (appendix p 1) and emergent themes were incorporated into the code book as they arose in the transcripts. Code definitions, including inclusion and exclusion criteria, were documented in the code book to improve inter-coder reliability. Coders (JC and RO) assigned codes to sections of the text using NVivo 12. All transcripts were independently double-coded and coders compared and reconciled coding results with assistance from the lead qualitative investigator (EDL) in group meetings. Once transcripts were coded, principle sub-themes were identified within each code that reflected finer distinctions in the data. Matrices were used to display the data to highlight differences arising from different groups, including: adolescents versus parents and caregivers, age (older *vs* younger), sex, enrolment site, and long-acting cabotegravir versus long-acting rilpivirine. Relationships between themes and speakers were mapped to highlight and clarify similarities and differences in perspective.

This trial is registered at ClinicalTrials.gov, NCT03497676.

Role of the funding source

The Division of AIDS provided regulatory oversight. Representatives of the National Institutes of Health, ViiV Healthcare, and Janssen participated in study design, data interpretation, and manuscript writing. Funders had no role in data collection or data analysis.

Results

Between March 19, 2019, and Nov 25, 2021, 30 participants were assigned to receive long-acting cabotegravir and 25 to long-acting rilpivirine (table 1). Most adolescents expressed that they hoped someday to take medicine that does not require daily pills and that they are interested in research of new treatments; freedom from daily pills drove participation for 29 (55%) of the 53 participants who completed the reasons for switch questionnaire (table 2). Despite the high motivation to have non-pill regimens, 32 (60%) of 53 individuals indicated that they find it "easy" or "very easy" to take their pills every day as recommended by their doctor. At week 4, 43 (83%) of the 52 individuals who completed the questionnaire reported that the injection did not hurt or hurt a little bit (table 3). Total functioning was reported to be similar from baseline (median 91, IQR 84–96) to 16 weeks (94, 87–97; table 4). Perceptions of the injections were similar across time points. Most adolescents reported either having no injection-related symptoms or being only "a little" bothered by symptoms (table 5). Few adolescents reported being "moderately", "very", or "extremely" bothered by any injection-related symptoms. Pain during the injection was reported most commonly, with

	Cohort 1C (LA-cabotegravir)			Cohort 1R (LA-rilpivirine)			Total		
	Week 4 (n=29)	Week 8 (n=29)	Week 12* (n=8)	Week 4 (n=23)	Week 8 (n=23)	Week 12* (n=13)	Week 4 (n=52)	Week 8 (n=52)	Week 12* (n=21)
No hurt	12 (41%)	9 (31%)	6 (75%)	4 (17%)	3 (13%)	3 (23%)	16 (31%)	12 (23%)	9 (43%)
Hurts little bit	13 (45%)	15 (52%)	1 (13%)	14 (61%)	11 (48%)	4 (31%)	27 (52%)	26 (50%)	5 (24%)
Hurts little more	2 (7%)	4 (14%)	1 (13%)	1 (4%)	6 (26%)	4 (31%)	3 (6%)	10 (19%)	5 (24%)
Hurts even more	2 (7%)	1 (3%)	0	3 (13%)	2 (9%)	2 (15%)	5 (10%)	3 (6%)	2 (10%)
Hurts whole lot	0	0	0	1 (4%)	1 (4%)	0	1 (2%)	1 (2%)	0
Hurts worst	0	0	0	0	0	0	0	0	0

Data are n (%). Percentages might not sum to 100 due to rounding. Answers are verbatim quotations from the questionnaire. The pain during injection questionnaire used a face scale. LA=long-acting injectable. *Only participants enrolled in protocol version 2.0 received a week 12 injection.

Table 3: **Responses to pain during injection questionnaire**

	Cohort 1C (LA-cabotegravir)		Cohort 1R (LA-rilpivirine)		Total	
	Baseline (n=30)	Week 16 (n=29)	Baseline (n=25)	Week 16 (n=23)	Baseline (n=55)	Week 16 (n=52)
Physical functioning dimension	97 (94–100)	97 (91–100)	100 (97–100)	100 (94–100)	100 (94–100)	98 (91–100)
Emotional functioning dimension	90 (80–100)	95 (80–100)	90 (70–100)	95 (90–100)	90 (75–100)	95 (88–100)
Social functioning dimension	100 (90–100)	100 (95–100)	95 (90–100)	100 (95–100)	100 (90–100)	100 (95–100)
School functioning dimension	80 (70–90)	80 (65–90)	70 (60–88)	85 (80–95)	80 (65–90)	85 (70–90)
Psychosocial functioning dimension	90 (82–97)	92 (77–97)	83 (77–95)	92 (87–97)	90 (78–95)	92 (86–97)
Total functioning dimension	93 (87–97)	94 (83–97)	89 (84–96)	95 (90–98)	91 (84–96)	94 (87–97)

Data are median (IQR). LA=long-acting injectable.

Table 4: **Quality of life questionnaire summary scores**

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	Cohort 1C week 16 (LA-cabotegravir; n=8)	Cohort 1R week 16 (LA-rilpivirine; n=15)	Total week 16 (n=23)
Feel anxious about getting the injection before your last injection?			
Not at all	4 (50%)	9 (60%)	13 (57%)
A little	4 (50%)	5 (33%)	9 (39%)
Moderately	0	1 (7%)	1 (4%)
Very	0	0	0
Extremely	0	0	0
How bothered were you by pain during the injection?			
Not at all	3 (38%)	8 (53%)	11 (48%)
A little	3 (38%)	3 (20%)	6 (26%)
Moderately	2 (25%)	3 (20%)	5 (22%)
Very	0	1 (7%)	1 (4%)
Extremely	0	0	0
How bothered were you by pain in your butt (buttock)?			
Not at all	5 (63%)	5 (33%)	10 (44%)
A little	0	6 (40%)	6 (26%)
Moderately	1 (13%)	3 (20%)	4 (17%)
Very	2 (25%)	1 (7%)	3 (13%)
Extremely	0	0	0
How bothered were you by redness at the injection site?			
Not at all	8 (100%)	15 (100%)	23 (100%)
A little	0	0	0
Moderately	0	0	0
Very	0	0	0
Extremely	0	0	0
How bothered were you by swelling at the injection site?			
Not at all	8 (100%)	12 (80%)	20 (87%)
A little	0	3 (20%)	3 (13%)
Moderately	0	0	0
Very	0	0	0
Extremely	0	0	0
How bothered were you by itching at the injection site?			
Not at all	7 (88%)	15 (100%)	22 (96%)
A little	1 (13%)	0	1 (4%)
Moderately	0	0	0
Very	0	0	0
Extremely	0	0	0
How bothered were you by hardening (a bump) at the injection site?			
Not at all	8 (100%)	11 (73%)	19 (83%)
A little	0	4 (27%)	4 (17%)
Moderately	0	0	0
Very	0	0	0
Extremely	0	0	0
How bothered were you by bruising at the injection site?			
Not at all	5 (63%)	14 (93%)	19 (83%)
A little	2 (25%)	1 (7%)	3 (13%)
Moderately	1 (13%)	0	1 (4%)
Very	0	0	0
Extremely	0	0	0

(Table 5 continues in next column)

	Cohort 1C week 16 (LA-cabotegravir; n=8)	Cohort 1R week 16 (LA-rilpivirine; n=15)	Total week 16 (n=23)
(Continued from previous column)			
How much were you bothered when you were trying to fall asleep?			
Not at all	5 (63%)	10 (67%)	15 (65%)
A little	1 (13%)	3 (20%)	4 (17%)
Moderately	1 (13%)	1 (7%)	2 (9%)
Very	1 (13%)	1 (7%)	2 (9%)
Extremely	0	0	0
How much were you bothered when you were rolling over or moving during sleep?			
Not at all	5 (63%)	8 (53%)	13 (57%)
A little	2 (25%)	5 (33%)	7 (30%)
Moderately	0	1 (7%)	1 (4%)
Very	1 (13%)	1 (7%)	2 (9%)
Extremely	0	0	0
How much were you bothered when you were walking?			
Not at all	2 (25%)	9 (60%)	11 (48%)
A little	4 (50%)	2 (13%)	6 (26%)
Moderately	1 (13%)	3 (20%)	4 (17%)
Very	0	1 (7%)	1 (4%)
Extremely	1 (13%)	0	1 (4%)
How much were you bothered when you were sitting?			
Not at all	3 (38%)	11 (73%)	14 (61%)
A little	4 (50%)	2 (13%)	6 (26%)
Moderately	0	1 (7%)	1 (4%)
Very	1 (13%)	1 (7%)	2 (9%)
Extremely	0	0	0
How much were you bothered when you were exercising, playing or lifting heavy objects?			
Not at all	5 (63%)	9 (60%)	14 (61%)
A little	1 (13%)	3 (20%)	4 (17%)
Moderately	1 (13%)	1 (7%)	2 (9%)
Very	1 (13%)	1 (7%)	2 (9%)
Extremely	0	1 (7%)	1 (4%)
How much pain did you feel when you were trying to fall asleep?			
Not at all	5 (63%)	12 (80%)	17 (74%)
A little	1 (13%)	1 (7%)	2 (9%)
Moderately	1 (13%)	1 (7%)	2 (9%)
Very	1 (13%)	1 (7%)	2 (9%)
Extremely	0	0	0
How much pain did you feel when you were rolling over or moving during asleep?			
Not at all	5 (63%)	9 (60%)	14 (61%)
A little	0	5 (33%)	5 (22%)
Moderately	2 (25%)	0	2 (9%)
Very	1 (13%)	1 (7%)	2 (9%)
Extremely	0	0	0

(Table 5 continues in next column)

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	Cohort 1C week 16 (LA-cabotegravir; n=8)	Cohort 1R week 16 (LA-rilpivirine; n=15)	Total week 16 (n=23)
(Continued from previous column)			
How much pain did you feel when you were walking?			
Not at all	4 (50%)	9 (60%)	13 (57%)
A little	2 (25%)	2 (13%)	4 (17%)
Moderately	0	3 (20%)	3 (13%)
Very	1 (13%)	0	1 (4%)
Extremely	1 (13%)	1 (7%)	2 (9%)
How much pain did you feel when you were sitting?			
Not at all	3 (38%)	10 (67%)	13 (57%)
A little	4 (50%)	2 (13%)	6 (26%)
Moderately	0	2 (13%)	2 (9%)
Very	1 (13%)	0	1 (4%)
Extremely	0	1 (7%)	1 (4%)
How much pain did you feel when you were exercising, playing or lifting heavy objects?			
Not at all	4 (50%)	9 (60%)	13 (57%)
A little	2 (25%)	3 (20%)	5 (22%)
Moderately	0	2 (13%)	2 (9%)
Very	1 (13%)	1 (7%)	2 (9%)
Extremely	1 (13%)	0	1 (4%)
How acceptable was/were the reaction(s) you had to the injection?			
Totally acceptable	3 (38%)	8 (53%)	11 (48%)
Acceptable	1 (13%)	3 (20%)	4 (17%)
Moderately acceptable	4 (50%)	2 (13%)	6 (26%)
A little acceptable	0	1 (7%)	1 (4%)
Not at all acceptable	0	1 (7%)	1 (4%)
How acceptable was your pain?			
Totally acceptable	2 (25%)	6 (40%)	8 (35%)
Acceptable	0	2 (13%)	2 (9%)
Moderately acceptable	5 (63%)	6 (40%)	11 (48%)
A little acceptable	0	1 (7%)	1 (4%)
Not at all acceptable	1 (13%)	0	1 (4%)
How satisfied were you with the needle and syringe that were used to give you the injection?			
Very satisfied	2 (25%)	3 (20%)	5 (22%)
Satisfied	4 (50%)	5 (33%)	9 (39%)
Neither satisfied nor dissatisfied	1 (13%)	6 (40%)	7 (30%)
Dissatisfied	0	1 (7%)	1 (4%)
Very dissatisfied	1 (13%)	0	1 (4%)
(Table 5 continues in next column)			
(Continued from previous column)			
How anxious do you feel about getting your next injection?			
Not at all	1 (13%)	5 (33%)	6 (26%)
A little	3	1 (7%)	4 (17%)
Moderately	1 (13%)	1 (7%)	2 (9%)
Very	1 (13%)	1 (7%)	2 (9%)
Extremely	0	0	0
Not applicable	2 (25%)	7 (47%)	9 (39%)
If you were not involved in this study, would you want to receive your medicine as injections?			
Yes, definitely	4 (50%)	11 (73%)	15 (65%)
Yes, probably	4 (50%)	1 (7%)	5 (22%)
I don't know	0	1 (7%)	1 (4%)
Probably not	0	2 (13%)	2 (9%)
Definitely not	0	0	0
How much more likely would you be to want to receive your medicine as injections if you could receive the injections every 8 weeks instead of every 4 weeks?			
Much more likely	7 (88%)	11 (73%)	18 (78%)
A little bit more likely	1 (13%)	2 (13%)	3 (13%)
Neither more likely nor less likely	0	2 (13%)	2 (9%)

Data are n (%). Percentages might not sum to 100 due to rounding. Questions and answers are verbatim quotations from the questionnaire. Only US, English-speaking and Spanish-speaking participants were included in the perceptions of injections questionnaire. LA=long acting injectable. PIN=perceptions of injection.

Table 5: **Responses to revised PIN questionnaire**

26% being "a little", 22% "moderately", and 4% being "very" bothered by pain during the injection at week 16. Three (38%) of the eight participants in the long-acting cabotegravir group who completed the PIN questionnaire reported being a little or moderately bothered by bruising at the injection site while one (7%) of the 15 responders in the long-acting rilpivirine group reported being "a little" bothered by bruising. At least a little pain with sitting was reported by five (63%) of the responders in the long-acting cabotegravir group compared with five (33%) of responders in the long-acting rilpivirine group. Overall, adolescents receiving long-acting rilpivirine rated their pain and reactions to the injections as more acceptable than adolescents receiving long-acting cabotegravir. However, two adolescents (one in the long-acting rlpivirine arm and one in the long-acting cabotegravir arm) rated their pain or reactions as "not at all acceptable". PedsQL scores were similar between baseline (pre-injection) and week 16 (appendix p 3).

Although our final few interviews did not elicit any new themes, we are not confident that thematic saturation was reached for younger adolescents. Only three participants aged 12 years or 13 years were eligible for in-

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depth interviews. In the interviews with US-based participants, the participants overwhelmingly indicated that they found the long-acting formulations to be desirable. However, they also highlighted practical concerns about switching from oral to injectable long-acting ART. The codes that were most represented in the interview data are summarised by CFIR domain (appendix p 4). Themes related to not having to remember to take pills and avoiding the stress of monitoring adolescents' daily medication-taking and not having to worry about hiding pills from peers dominated discussions of the relative advantage of long-acting versus pill-based regimens. However, the ability to maintain a routine injection schedule when busy with school, extracurricular activities, and work, particularly for those planning to move to college, was a coexisting common concern.

When stratified by participants' age, sex, enrolment site, and whether they received long-acting cabotegravir or long-acting rilpivirine, no consistent differences in themes emerged. However, perspectives of adolescents receiving the long-acting medications and their parents or caregivers differed in several key respects. Pre-study disagreements between adolescents and their consenting parents or caregivers regarding whether the adolescent should initiate long-acting ART were described. Both adolescents and parents or caregivers had positive assessments of their experience with the long-acting formulations (appendix pp 5–8). They agreed that adaptability is a key advantage of the long-acting formulations. However, parents and caregivers had many more concerns than their children regarding the strength and quality of evidence supporting the use of the long-acting products. For those who verbalised the most hesitancy, their trust in their health-care providers played a key role in their ultimately agreeing to let the adolescent try the long-acting formulation. Parents and caregivers expressed having greater initial fear about the process of ensuring safety and practical follow-up needs. However, all interviewed parents and caregivers reported being reassured after experiencing the process with the first dose. For example, the mother of a male participant aged 14 years noted: "I really was scared that he wouldn't be able to go to school, but he went to school the next day." After experiencing what it was like for her child to receive the injection, she said: "My advice to other parents is that I think, on my own part, that the injection is better [than daily pills]."

Adolescents' most consistent concern was about the location of the injection. Many expressed wanting a shot that could be given somewhere other than the buttocks. Nevertheless, all interviewed adolescents expressed that they would recommend long-acting formulations to their peers. The idea that the long-acting regimens would relieve them of the hassle and internalised stigma associated with daily pill-taking was seen as compelling. As one female participant aged 12 years summarised: "Take the shot once a month, be over with it and you can actually live a normal life instead of taking pills in front of people every day or looking at yourself like you're not a real human or something." However, although some participants saw the ability to avoid daily reminders of their HIV status (ie, through taking pills) as a positive, a few noted that more frequent clinic visits could add to their stress related to living with HIV-1. A male participant aged 14 years expressed that: "Especially for that teenager who's already not liking to be reminded that they're HIV positive. Then actually having to go to the clinic every month would not be necessarily a positive experience for them."

Discussion

Through both quantitative assessments asked of all adolescent participants and in-depth interviews of US-based adolescents and parents or caregivers enrolled in cohort 1 of the MOCHA study, we established that acceptability and tolerability of long-acting cabotegravir or rilpivirine injections was high. The MOCHA study data provide timely evidence for the high acceptability and tolerability of these injections, given that the long-acting cabotegravir and long-acting rilpivirine regimen has been approved by the US Food and Drug Administration for treatment of adolescents aged 12 years and older and weighing at least 35 kg, including an optional oral lead-in (for tolerability) and an every-2-months dosing option.[16] A previous study[17] including five individual interviews with parents of children living with HIV-1 in the USA showed that parents' interest in long-acting ART varied according to their child's age and sensitivity to injections. However, a survey of 303 youth living with HIV aged 13–24 years at four US clinical sites revealed high enthusiasm, with 88% reporting that they were probably or definitely willing to use long-acting ART.[18] Data from this study suggest that individuals aged 12–17 years are likely to maintain their enthusiasm after receiving this treatment method. Adolescents in this phase of the study were required to continue their oral ART. When able to stop their oral ART, their enthusiasm could be higher. However, tolerability in adolescents after receiving both injections over a longer period still needs to be evaluated. The ongoing MOCHA Study cohort 2 will provide some of these data.

A particularly notable aspect of the qualitative data from the current study is the initial discordance between parental and adolescent attitudes about long-acting ART, with the interviewed adolescents showing less hesitancy. This might be due to parents' overall higher risk aversion when making decisions for their adolescents.[19] However, the convergence of positive views of long-acting ART after receipt suggests that both participant-reported and parent-reported outcomes after use of the combined long-acting cabotegravir and long-acting rilpivirine without pre-study oral ART could be similar to the high acceptability in adult treatment studies.[4,11,20]

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Although minor consent laws in the USA allow adolescents to consent for their own HIV treatment,[21] parental consent was required for study participation. Therefore, adolescents whose parents had recalcitrant hesitancy might have been excluded from this study. The generalisability of our findings might also be limited by the data being primarily from US sites. Social desirability bias might also have led to participants reporting more favourable views of the study products. Questionnaires were completed with support from site staff who were generally known to the participants. Although having staff ask the questions was efficient and avoided missing data issues, participants might have been less willing to give negative assessments directly to site staff. We attempted to minimise the risk of social desirability bias in the in-depth interviews by conducting interviews in a private space over the phone. Interviewers who were not known to participants connected from a distant site and ensured participants that information identifying individual participant views would not be shared with site staff. The major limitation of the interviews was that we did not conduct as many as initially planned due to the study opening to international sites without approval being granted for in-depth interviews of non-US participants. Since we were unable to sample to thematic saturation for younger adolescents, we cannot say whether developmental issues of early adolescence might raise unique concerns with regards to long-acting ART.

It is notable that the reported desire to use long-acting ART was strong in participating adolescents despite most reporting that they do not find it difficult to take pills daily. Individuals enrolling in clinical trials are frequently a lower-risk population than those in larger real-world populations.[22] Desire for the long-acting ART option might be stronger among adolescents with current struggles with adherence to pill-based regimens.

The qualitative data from MOCHA cohort 1 revealed adolescent-specific issues that could have implications on a successful long-acting ART treatment rollout for the adolescent population. Sustainable effective implementation of long-acting ART for adolescents will need to consider the implementation determinants stressed by participants in the MOCHA cohort 1 in-depth interview's including the need for adolescent-friendly and comprehensive family-centered clinical environments for delivery, flexible options for adolescents going away to college, and supporting attendance for the more frequent clinic visits required with an in-clinic monthly or every-2-months injection dosing regimen.

Contributors

EDL, JC, and RO had full access to all qualitative interview data for the study. KB, RM, SW, JH, BH, and JK had full access to all questionnaire data in the study. EDL, JC, KC, RMVS-R, CCM, CB-M, and AHG formulated the overarching research goals and aims. EDL, JC, BH, CCM, JK, and SB reviewed, interpreted, and maintained research data. EDL, JC, RO, KB, AA, JH, RM, and SW assisted with analysis plans and analysed and synthesised study data. CCM assisted with acquiring the financial support for the project leading to this publication. EDL, JC, ALA, CS-A, AC-G, JD'A, AB, CB-M, and AHG implemented the study and collected data. EDL, JC, KC, RMVS-R, CCM, AA, HC, CB-M, and AHG developed the protocol. JC, KC, DEY, ALA, CH, CCM, VC, HC, SB, CB-M, and AHG managed and coordinated research activity, planning, and execution. EDL, JC, KC, BH, SB, CB-M, and AHG developed and provided study materials and resources. EDL, KC, BH, AA, VC, CB-M, and AHG oversaw and led research activity planning and execution. EDL, JC, RO, KB, SW, and RM monitored results to verify validity and reproducibility and accessed and verified the data. EDL, JC, KB, SW, RM, and AHG prepared the visualisation and data presentation of the manuscript. EDL led the initial manuscript writing. All authors contributed to the manuscript development and review, had full access to the data, and had final responsibility for the decision to submit for publication.

Declaration of interests

KC, SB, and DEY received grant funding from the National Institutes of Health (NIH) to support work on this protocol. JC received support to travel and attend a meeting from the IMPAACT Network. AHG's institution has Clinical Trial agreements with ViiV to support work on this study and has a Clinical Trial agreement with Janssen to support other studies; and AHG received payment from ViiV Healthcare to attend a Pediatric Advisory Board meeting. KB, RM, and SW had funds paid to their institution by ViiV Healthcare related to their work on this manuscript. HC and RMVS-R are employees of Janssen and have stock and stock options with Johnson & Johnson. ALA is site principal investigator for multi-site Gilead and Merck studies, a Gilead expert advisory board attendee, a Merck consultant, expert advisory board attendee for ViiV, presenter at a workshop supported by ViiV, part of the Speaker's Bureau for the Simply Speaking HIV Prevention Series, an expert witness, an unpaid Advocates for Youth Board Chair, an unpaid member of the Well Project Board, and an unpaid HIVMA Vice Chair. AC-G is a ViiV Healthcare consultant and has received funds from Merck and Janssen. CCM, VC, and CH are employees at ViiV Healthcare. CCM and VC own GSK stock or stock options. DEY was previously an unpaid technical advisor for the following non-profit institutions: Cover the Globe and Maipelo Trust. JH is an employee at GSK. DEY is an employee of NIH. AA, AB, EDL, RO, CB-M, CS-A, BH, JK, and JDA 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 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) for quantitative data and to the corresponding author for in-depth-interview data, following formal agreement of the IMPAACT Network.

Acknowledgments

The authors thank the study participants and their families for their contributions to this study. Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (ie, IMPAACT) was provided by the National Institute of Allergy and Infectious Diseases (ie, NIAID) with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (ie, NIMH), all components of the National Institutes of Health (NIH), under award numbers UM1AI068632 (IMPAACT LOC), UM1AI068616 (IMPAACT SDMC), and UM1AI106716 (IMPAACT LC), and by NICHD contract number HHSN275201800001I. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. We thank Vani Shanker for scientific editing support.

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