Pregnancy outcomes and pharmacokinetics in pregnant women living with HIV exposed to long-acting cabotegravir and rilpivirine in clinical trials

Parul Patel | Susan L. Ford | Mark Baker | Claudia Meyer | Louise Garside | Ronald D’Amico | Rodica Van Solingen-Ristea | Herta Crauwels | Joseph W. Polli | Ciara Seal | Itziar Yagüe Muñoz | Shanker Thiagarajah | Eileen Birmingham | William R. Sreen | Bryan Baugh | Jean van Wyk | Vani Vannappagari

1ViiV Healthcare, Durham, North Carolina, USA
2GlaxoSmithKline, Durham, North Carolina, USA
3ViiV Healthcare, Nyon, Switzerland
4GlaxoSmithKline, Brentford, UK
5PHASTAR, Macclesfield, UK
6Janssen Research & Development, Beerse, Belgium
7GlaxoSmithKline, Collegeville, Pennsylvania, USA
8Janssen Research & Development, Titusville, New Jersey, USA
9ViiV Healthcare, Brentford, UK

Correspondence
Parul Patel, ViiV Healthcare, 406 Blackwell Street, Suite 300, Durham, NC 27701, USA.
Email: parul.x.patel@viivhealthcare.com

Funding information
Janssen Research & Development; ViiV Healthcare

Abstract

Background: Limited data exist on pregnant women living with HIV exposed to cabotegravir + rilpivirine (CAB + RPV). Outcomes in pregnant participants exposed to CAB + RPV, and pharmacokinetic washout data in those exposed to CAB + RPV long-acting (LA) with live births, are presented.

Methods: Women exposed to one or more doses of CAB + RPV (oral/LA) from ViiV Healthcare-sponsored phase 2b/3/3b clinical trials and the compassionate use programme who became pregnant were included. Upon pregnancy in the trial programme, CAB + RPV was discontinued, an alternative antiretroviral regimen was initiated, and quarterly pharmacokinetic sampling for 52 weeks post-last injection was obtained. CAB + RPV continuation or alternative antiretroviral regimen initiation was decided by pregnant compassionate use programme participants and their treating physicians.

Results: As of 31 March 2021, 25 pregnancies following CAB + RPV exposure at conception were reported (five oral, 20 LA), including four who conceived during pharmacokinetic washout following treatment discontinuation. There were eight elective abortions, six miscarriages (five in first trimester), one ectopic pregnancy, and 10 live births (one oral, nine LA), including one infant born with congenital ptosis. Among participants exposed to CAB + RPV LA at conception with live births, plasma CAB and RPV washout concentrations during pregnancy were within the range of those observed in non-pregnant women.
**INTRODUCTION**

Globally, an estimated 1.3 million people living with HIV become pregnant annually [1]. In many areas of the world, HIV infection may be first diagnosed during pregnancy, including close to the time of delivery [2-5]. Pregnant people living with HIV require antiretroviral therapy (ART) to achieve and maintain an undetectable viral load, which has been associated with a reduced risk of maternal morbidity and mortality compared with pregnant people living with HIV not receiving ART [6-9]. Achieving viral suppression also significantly reduces the risk of perinatal HIV transmission [10, 11]; many regional and national health authorities recommend against breastfeeding to reduce the risk of mother–child HIV transmission through breastmilk [11-13]. In the past decade, ART use has increased from 45% to 85% in pregnant people living with HIV [1]. Despite this, understanding of the safety profiles of ART used in pregnant women is limited [14], and safety data may often come from post-marketing studies or antiretroviral drug registries, which can cause a delay in data accumulation from new ARTs. Given the maternal benefits of receiving ART [6-9] and the importance of reducing mother–child HIV transmission risk [10, 11], understanding ART safety and efficacy during pregnancy and postpartum is critical.

Cabotegravir (CAB) and rilpivirine (RPV) are two antiretrovirals for which long-acting (LA), intramuscular (IM) injection formulations, dosed monthly or every 2 months, have been approved for the maintenance of HIV-1 virological suppression [15-21]. Phase 2b/3/3b ViiV Healthcare-sponsored clinical trials demonstrated that IM CAB + RPV dosed every 4 weeks (Q4W) was noninferior to oral ART, and CAB + RPV dosed every 8 weeks (Q8W) was noninferior to Q4W dosing, in maintaining virological suppression [15-17, 22-24]. LA therapy may address some of the challenges associated with daily oral ART for people living with HIV, including HIV stigma and fear of inadvertent disclosure, anxiety related to adherence, and the daily reminder of HIV status [25].

ART dosed monthly or every 2 months averts the need for daily oral dosing, which may be an attractive option for pregnant people living with HIV. Pregnant people living with HIV with poor oral tolerability due to morning sickness, including nausea/vomiting, hyperemesis gravidarum (a pregnancy complication characterized by severe nausea, vomiting, malnutrition, and dehydration) [26], documented challenges maintaining adherence to daily oral ART, and/or experiencing life stresses, may benefit from LA therapy [27]. Also, an important consideration is the persistence of detectable plasma concentrations despite therapy discontinuation for pregnant women and those considering a future pregnancy. In the multinational HIV Prevention Trials Network (HPTN) 077 study, the median time from the last injection to an undetectable CAB concentration among females without HIV was 67 weeks and was prolonged for female participants with a body mass index (BMI) ≥27 kg/m² [28]. LA RPV concentrations were measurable for >18 months after a single-dose injection of 1200 mg in healthy adult women [29]. Thus, despite discontinuation of active dosing in the event of pregnancy, pregnant women will still be exposed to CAB and RPV due to the long CAB and RPV pharmacokinetic (PK) washout, in addition to any additional ARTs that may be started. Evaluating pregnancy outcomes and residual CAB and RPV concentrations in people living with HIV switching from CAB + RPV LA to another ART regimen for pregnancy may be useful in providing early safety information in pregnant women exposed to CAB + RPV at conception.

Currently, prescribing information for CAB + RPV LA acknowledges that insufficient human data are available in pregnant people living with HIV to adequately assess the potential of drug-associated risk of birth defects and miscarriage [18, 30]. It is recommended that the benefit–risk profile of CAB + RPV LA be discussed on an individual basis, with consideration of the potential for foetal drug exposure during pregnancy, prior to initiating LA therapy in women of childbearing potential [18, 30].

**Conclusion:** In this first analysis of pregnancy outcomes following CAB + RPV exposure at conception, 10 live births, including one with congenital anomaly, were reported. Plasma CAB and RPV washout concentrations during pregnancy were within the range of those in non-pregnant women. Pregnancy surveillance within ViiV Healthcare-sponsored clinical trials is ongoing, with dedicated pregnancy studies planned.

**KEYWORDS**
cabotegravir, HIV-1, long-acting, pharmacokinetics, pregnancy, rilpivirine
Animal studies have demonstrated no teratogenic effects of oral CAB and RPV [18, 30, 31]. No birth defects were observed in preclinical reproductive toxicology studies in which 224 pregnant rat dams (2882 foetuses) and 88 pregnant rabbit does (600 foetuses) received oral CAB at exposures >28 times that of the oral recommended human dose (RHD) of 30 mg [32]. However, a delay in the onset of parturition and an increased number of stillbirths and neonatal deaths immediately after birth were observed in the pre- and postnatal assessment rat study [32]. At lower levels of CAB exposure in rats (~10 times the RHD), no association with delayed parturition, stillbirths, or neonatal mortality was observed [32]. There was no preclinical reproductive toxicology signal for adverse birth outcomes with RPV [31]. A moderate amount of data with oral RPV in pregnant women (over 550 pregnancy outcomes) indicate no malformative or foetal/neonatal toxicity of RPV [31, 33].

While CAB use in pregnant women has not been formally evaluated, studies with oral RPV in pregnant women have demonstrated reduced third trimester exposures compared with postpartum, without evidence of perinatal transmission [34–36]. These data supported the approval of once-daily oral 25 mg RPV for use during pregnancy, with intense viral load monitoring.

In ViiV Healthcare-sponsored phase 2b/3/3b CAB + RPV LA clinical trials, pregnancy was exclusionary and women of childbearing potential were required to use highly effective methods of contraception [15–17, 22]. Per protocol, upon pregnancy identification, CAB + RPV (oral/LA) was discontinued and an alternative ART regimen initiated. Following LA therapy discontinuation, participants entered long-term follow-up (LTFU) for 52 weeks post-last injection to monitor safety, viral load, and the decline of CAB and RPV concentrations. In the compassionate use (CU) programme, the decision to continue LA therapy or switch to an alternative oral ART regimen during pregnancy was made following consultation between the participant and their treating physician [37].

The primary aim of this analysis was to describe pregnancy outcomes in people living with HIV exposed to CAB + RPV at conception in clinical trials and within the CU programme. Additionally, CAB and RPV PK washout data in those exposed to LA therapy with subsequent live birth outcomes are reported.

**MATERIALS AND METHODS**

**Participants and study design**

Female participants exposed to one or more doses of CAB + RPV (oral/LA) who became pregnant during study conduct from four phase 2b/3/3b ViiV Healthcare-sponsored clinical trials or the CU programme through 31 March 2021 were included in this analysis. Demographic, exposure, and pregnancy and outcome data for pregnant participants were collated using the GlaxoSmithKline safety database, based on study investigator reports on all available pregnancy details and infant outcomes at delivery. In the CU programme, pregnant participants were identified via correspondence from their treating physicians to the sponsor. CAB + RPV LA was administered Q4W or Q8W in the phase 2b LATTE-2 and phase 3b ATLAS-2M studies, and Q4W in the phase 3 ATLAS and FLAIR studies and CU programme [15–17, 22]. Prior to receiving IM dosing, all clinical trial participants received oral CAB + RPV daily as lead-in therapy for approximately 4 weeks to assess individual tolerability before switching to LA dosing [15, 16]. Full details for each study design, evaluated dosing regimens, and eligibility/exclusion criteria have been published [15–17, 22].

Eligible women of childbearing potential were required to use highly effective contraception during clinical studies and for at least 52 weeks after the last injection, which may have included oral, intravaginal, transdermal combined (oestrogen- and progestogen-containing) hormonal contraception; injectable progestogen-only hormonal contraception; implantable progestogen-only hormonal contraception; mechanical intrauterine device; intrauterine hormone-releasing system; bilateral tubal occlusion; a vasectomized partner; or sexual abstinence. Urine pregnancy testing was assessed at baseline, prior to each injection, whenever a menstrual cycle was missed, or when pregnancy was otherwise suspected. Per clinical protocol, CAB + RPV was discontinued upon pregnancy detection, an alternative ART regimen initiated, and quarterly CAB and RPV PK sampling for 52 weeks post-last injection in LTFU was obtained. Women who were not exposed to LA therapy did not enter LTFU. In the CU programme, the decision to continue LA therapy or switch to an alternative oral ART regimen during pregnancy was made following consultation between the participant and their treating physician.

The trials included in this analysis were conducted in accordance with the Declaration of Helsinki [38], the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, Good Clinical Practice, and applicable country-specific requirements. The CU programme was conducted in accordance with local regulatory guidelines for Belgium, Canada, France, Italy, Portugal, South Korea, Spain, Switzerland, the Netherlands, the United Kingdom, and the United States (USA). Individuals in the CU programme provided written informed consent as required by
local regulations. All clinical trial participants provided written informed consent. The study protocols, any amendments, the informed consent, and other information that required pre-approval were reviewed and approved by a national, regional, or investigational centre ethics committee or institutional review board.

Outcomes and procedures

The objective of this analysis was to describe pregnancy outcomes, including the number of pregnancies, live births, spontaneous abortions, elective abortions, and stillbirths (babies who die after 28 weeks of pregnancy, before or during birth, per the World Health Organization [WHO] definition [39], dosing regimen (oral/LA) and frequency (daily, Q4W, or Q8W) at time of conception, the duration of CAB + RPV exposure, subsequent alternative ART regimen use, relevant past or current obstetric history, and HIV-1 RNA viral load. Neonatal outcomes included the detection of congenital anomalies, preterm births (gestational age of <37 weeks at delivery per the WHO definition [40]), low-birth-weight infants (<2500 g or <5.5 lb per the WHO definition [41]), and intrauterine growth restriction (IUGR).

Individual PK profiles from participants in LTFU with live births were plotted over time, beginning from the last trough assessment pre-conception, at/near time of pregnancy identification, during pregnancy, and post-partum, at approximately quarterly intervals after last injection, as available. Per protocol, plasma trough samples were collected pre-dose prior to each injection and 1, 3, 6, 9, and 12 months after last injection during LTFU. Pregnancy outcomes within the CU programme were collected via communication with the treating physicians. PK sampling was not part of the CU protocol, and thus PK sampling of pregnant women in the CU programme was obtained on the treating physician’s request.

RESULTS

Population characteristics and birth outcomes

Figure 1 shows the outcomes of all reported pregnancies. Through 31 March 2021, 23 pregnancies and their outcomes were reported for 21 women among 325 women of childbearing potential exposed to CAB + RPV in phase 2b/3/3b clinical trials, with two of the women reporting a pregnancy during active exposure to CAB + RPV LA, and a second pregnancy during PK washout. Additionally, one woman in the CU programme conceived two pregnancies during active CAB + RPV LA dosing. Of the 25 reported pregnancies, five had exposure to oral CAB + RPV only at time of conception and did not proceed to LA therapy. The duration of oral CAB + RPV exposure prior to conception ranged between <1 and 4 weeks. Twenty pregnancies occurred following CAB + RPV LA exposure at conception, including four conceived during PK washout following LA treatment discontinuation. The duration of CAB + RPV LA exposure prior to conception ranged between 3 and 210 weeks, with the majority (82%, n = 14/17) of participants on CAB + RPV LA receiving Q4W dosing.

Past obstetric history was recorded for 21 of the women who became pregnant, of whom 76% (n = 16) reported previous pregnancies, and 71% (n = 15) reported one or more live births prior to trial participation.

Summary of birth outcomes

Of the 25 reported pregnancies, there were 10 live births (Table 1). A total of 15 pregnancies did not result in live births (Table 2), including eight elective abortions, six spontaneous abortions, and one ectopic pregnancy managed surgically. No stillbirths were reported.

Summary of live birth outcomes with CAB and RPV exposure

Among 10 participants with subsequent live births, one pregnancy occurred during oral CAB + RPV exposure; six pregnancies resulting in live births were reported in participants receiving Q4W dosing, one in a participant receiving Q8W dosing, and two during PK washout following discontinuation of Q4W dosing. Alternate ART regimens switched to following CAB + RPV discontinuation are listed in Table 1.

Of the 10 live births, the majority (80%, n = 8/10) were reported to be healthy, full-term-weight infants at delivery. Although the delivery of one infant was complicated by chorioamnionitis (amniotic cavity infection), the event was not considered related to the study treatment, and delivery was at full term with no congenital abnormalities reported and an uncomplicated postpartum course. One pregnancy was induced at 36 weeks + 5 due to gestational hypertension with proteinuria, for which the mother was receiving labetalol. The infant was born healthy. One infant was born prematurely with low birth weight complicated by IUGR and unilateral congenital ptosis (participant 7, Table 2). The congenital ptosis was considered to be a random congenital anomaly by the treating physician, not associated with LA therapy. The
mother received CAB + RPV LA Q4W and continued LA dosing during pregnancy following consultation with her treating physician. Despite an initial reduction in viral load, she did not consistently achieve an undetectable viral load, with low-level viremia persisting prior to and throughout pregnancy. As a result of maternal low-level viremia, the infant received a 4-week triple regimen of zidovudine, lamivudine, and raltegravir. Infant HIV-1 RNA and DNA tests were negative at birth and 4 weeks of age, with continued follow-up. At the 4-month ophthalmology consult, congenital ptosis was resolving without treatment.

Among the 10 participants with live birth outcomes, viral load data were available for all nine participants who switched to an alternative ART regimen during pregnancy. All nine participants maintained virological suppression throughout pregnancy and postpartum, or the last available viral load assessment. The 10th participant remained on CAB + RPV LA during her pregnancy and had a live birth but experienced persistent low-level

FIGURE 1 Summary of pregnancy outcomes with cabotegravir + rilpivirine exposure through 31 March 2021 across phase 2b/3/3b ViiV Healthcare-sponsored clinical trials and within the compassionate use programme. *Of the 25 pregnancies, 22 were first pregnancies and three were second pregnancies during the trial period. †Reported by investigator as spontaneous abortion at 23 weeks gestational age with intrauterine growth restriction in a mother with multiple comorbidities

TABLE 1 Participant demographics

| Characteristic | Participants with a live birth outcome (n = 8) | Participants with non-live birth outcomes (n = 12) | Participants with a non-live and a live birth outcome (n = 2) | Total (n = 22) |
|----------------|-----------------------------------------------|-----------------------------------------------|-------------------------------------------------|---------------|
| Age at conception, median (range) years | 34 (26–42) | 36 (26–45) | 22 (21–22) | 33 (21–45) |
| ≥30 years, n (%) | 6 (75) | 9 (75) | 0 | 15 (68) |
| Baseline BMI, median (IQR) kg/m² | 21.8 (15.3–34.8) | 27.5 (19.4–39.1) | 32.5 (25.0–40.0) | 27.1 (15.3–40.0) |
| ≥30 kg/m², n (%) | 3 (38) | 5 (42) | 1 (50) | 9 (41) |
| Time on ART, median (range) years | 0.42 (0–6.33) | 3.29 (0.42–10.67) | 0 (0) | 2.25 (0–10.67) |
| Time on CAB + RPV (oral and/or LA) at conception, median (range) weeks | 92 (<1–210) | 35 (1–195) | 35 (3–35) | 47 (<1–210) |
| Viral load at/near conception, copies/ml | <50 | <50 | <40 | <50 |

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CAB, cabotegravir; CU, compassionate use; IQR, interquartile range; LA, long-acting; LMP, last menstrual period; LTFU, long-term follow-up; PK, pharmacokinetic; RPV, rilpivirine.

*Age at conception was estimated using date or year of birth and estimated date of conception (based on LMP). Age at conception was not included for one participant with a non-live birth outcome, as neither LMP nor date of spontaneous abortion were reported (pregnancy I; Table 3).

†Time on ART and viral load data at/near time of conception were not available for participant 7 (Table 2), who received CAB + RPV LA as part of the CU programme.

Two participants had pregnancies detected during the LTFU after study completion. CAB + RPV LA discontinued 10 weeks prior to LMP (participant 8; received CAB + RPV [including oral and LA dosing] for 96 weeks) and 28 weeks prior to LMP (participant 10; received CAB + RPV [including oral and LA dosing] for 210 weeks) (Table 2). Two participants became pregnant during active exposure to CAB + RPV LA, with second pregnancies during PK washout. Pregnancy O was conceived 38 weeks after CAB + RPV LA discontinuation (CAB + RPV [including oral and LA dosing] for 35 weeks prior to first pregnancy [participant 3 in Table 2]), and pregnancy N was conceived 38 weeks after CAB + RPV LA discontinuation (CAB + RPV [including oral and LA dosing] for 92 weeks prior to first pregnancy [pregnancy M in Table 3]).
viremia prior to and throughout her pregnancy. There were no instances of perinatal HIV transmission at delivery or during the LTFU period.

Summary of non-live birth outcomes

A summary of the 15 non-live birth outcomes reported for 14 women is shown in Table 2, including relevant prior obstetric history. A total of eight elective abortions were reported, all of which occurred within the first trimester. One participant had a laparotomy during the first trimester for ectopic pregnancy. No stillbirths were reported. Of the six spontaneous abortions reported, five occurred within the first trimester. One participant had a spontaneous abortion at 23 weeks gestational age, with postmortem findings suggestive of IUGR and placental insufficiency. A full case history has previously been reported [42].

Among the 14 participants with non-live birth outcomes, 13 switched to an alternative ART regimen during pregnancy and maintained virological suppression...
TABLE 3  Summary of non-live birth outcomes following CAB + RPV exposure

| Non-live birth | CAB + RPV dosing regimen | Study or CU programme | Duration of exposure prior to conception* | Relevant past obstetric history | Pregnancy outcome |
|----------------|--------------------------|-----------------------|------------------------------------------|-------------------------------|-------------------|
| A              | Oral (daily)             | Study participant     | 1 week                                   | Two full-term normal births, two induced abortions | Elective abortion (first trimester; ~8 weeks GA) |
| B              | Oral (daily)             | Study participant     | 3 weeks                                   | 10 previous pregnancies (five preterm births, two full-term normal births, three spontaneous abortions) | Spontaneous abortion (first trimester; ~8 weeks GA) |
| C              | Oral (daily)             | Study participant     | 2 weeks                                   | One premature birth, one spontaneous abortion | Elective abortion (first trimester) |
| D              | Oral (daily)             | Study participant     | 4 weeks                                   | Two prior children (details unknown) | Spontaneous abortion (first trimester)* |
| E              | Q4W                      | Study participant     | 71 weeks                                  | Two full-term normal births | Elective abortion (first trimester; ~7 weeks GA) |
| F              | Q4W                      | Study participant     | 11 weeks                                  | One full-term normal birth, three preterm births, one stillbirth, two induced abortions | Elective abortion (first trimester; ~5 weeks GA) |
| G              | Q4W                      | Study participant     | 12 weeks                                  | Two full-term normal births, one elective abortion | Elective abortion (first trimester; ~6 weeks GA) |
| H              | Q4W                      | Study participant     | 110 weeks                                 | Two full-term normal births, two elective abortions | Spontaneous abortion (first trimester; ~8 weeks GA) |
| I              | Q4W                      | Study participant     | 57 weeks                                  | No previous pregnancies | Spontaneous abortion (first trimester)* |
| J              | Q4W                      | Study participant     | 189 weeks                                 | One elective abortion | Spontaneous abortion (first trimester; ~4–5 weeks GA) |
| K              | Q4W + oral ARTd          | CU programme          | 3 weeks                                   | No previous pregnancies | Spontaneous abortion (23 weeks GA, IUGR, multiple comorbidities) |
| L              | Q8W                      | Study participant     | 195 weeks                                 | Two full-term births | Laparotomy for ectopic pregnancy (first trimester; ~5 weeks)* |
| M              | Q8W                      | Study participant     | 92 weeks                                  | One full-term normal birth | Elective abortion (first trimester; ~8 weeks GA) |
| N              | Q8W (PK washout)g        | Study participant     | Last injection 38 weeks prior to conception | One full-term normal birth, one elective abortion | Elective abortion (first trimester)* |
| O              | Q4W (PK washout)g        | Study participant     | Last injection 54 weeks prior to conception | One full-term normal birth | Elective abortion (first trimester; ~10 weeks) |

Abbreviations: β-hCG, beta-human chorionic gonadotropin; ART, antiretroviral therapy; CAB, cabotegravir; GA, gestational age; IUGR, intrauterine growth restriction; LA, long-acting; LMP, last menstrual period; PK, pharmacokinetic; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

*Conception was estimated to be 14 days following documented LMP. Duration of prior LA exposure includes ≥4 weeks of CAB + RPV oral lead-in dosing prior to CAB + RPV LA.

*Ultrasound was unable to confirm intrauterine pregnancy despite initial positive β-hCG test, indicating early spontaneous abortion of pregnancies D and I.

*Pregnancy K experienced prior sagittal venous sinus thrombosis, for which she self-administered prescribed prophylactic low-molecular-weight heparin during the pregnancy, and had low-level viremia prior to and throughout pregnancy: Pregnancy K is the first of two pregnancies; second pregnancy corresponds to participant 7 in Table 2.

*Cobicistat/darunavir/emtricitabine/tenofovir alafenamide.

*Classified in medical database as an elective abortion.

*Pregnancy N is a second pregnancy; first pregnancy corresponds to participant M in Table 3.

*Pregnancy detected during LTFU after CAB + RPV LA was discontinued. Pregnancy O was conceived 38 weeks after CAB + RPV LA discontinuation (CAB + RPV [including oral and LA dosing]) for 35 weeks prior to first pregnancy (participant 3 in Table 2), and pregnancy N was conceived 38 weeks after CAB + RPV LA discontinuation (CAB + RPV [including oral and LA dosing]) for 92 weeks prior to first pregnancy (pregnancy M in Table 3).

*GA at pregnancy outcome was not reported for pregnancy N, as at the time of data cut-off the pregnancy was ongoing, with an elective abortion planned.

*Pregnancy O is a second pregnancy; first pregnancy corresponds to participant 3 in Table 2.
through pregnancy and postpartum, or the last available viral load assessment. The remaining participant received CAB + RPV LA Q4W and continued LA dosing throughout the duration of the pregnancy following consultation with her treating physician.

**Maternal CAB and RPV washout concentrations during pregnancy and postpartum following CAB + RPV LA discontinuation**

Plasma CAB and RPV concentrations were available for seven of the nine participants exposed to CAB + RPV LA therapy with live birth outcomes (Figure 2). Plasma CAB and RPV concentrations during pregnancy were within the range of concentrations observed in non-pregnant women within the treatment programme who discontinued LA therapy [43, 44]. Observed CAB and/or RPV concentrations during LTFU may have been impacted by metabolic induction or the inhibition propensity of the subsequent alternative ART regimen that participants were switched to after LA discontinuation. For example, participant 5's more rapid CAB + RPV plasma clearance may have been affected by induction from efavirenz, participant 3's RPV concentration may have been increased via CYP3A-mediated inhibition of plasma RPV clearance by darunavir/ritonavir-containing ART, and participant 10's RPV concentration appeared increased because the subsequent ART received after stopping CAB + RPV LA contained oral RPV.

**DISCUSSION**

This analysis is the first to collate pregnancy outcomes among CAB + RPV LA clinical trials and CU participants and describe CAB and RPV PK washout during pregnancy in the presence of alternative oral ART among participants who had live births.

All women exposed to CAB + RPV (oral/LA) who discontinued CAB + RPV therapy with subsequent live birth outcomes maintained virological suppression from conception through pregnancy and postpartum, or the last available viral load assessment following a switch to alternative ART. The participant in the CU programme with a live birth who elected to continue CAB + RPV LA during pregnancy had low-level viremia prior to and throughout her pregnancy (the infant's HIV-1 RNA and DNA tests were negative at birth and at 4 weeks of age).

Plasma CAB and RPV concentrations among those discontinuing CAB + RPV LA due to pregnancy were within the range of concentrations observed among non-pregnant women within the treatment programme who discontinued LA therapy and switched to comparable ART regimens. It is important to note that the choice of alternative ART regimen has the potential to impact residual CAB and RPV concentrations, depending on the
propensity for the regimen to either induce or inhibit systemic metabolism of CAB and/or RPV. A previous investigation found that alternative ART with metabolic induction or inhibition potentially minimally impacts the duration of change in plasma CAB and/or RPV concentrations following LA discontinuation, given the elimination of plasma concentrations after an LA injectable is primarily dependent on absorption rate and is without reported efficacy or safety concerns [45]. These observations are limited and not sufficient to establish dosing or any potential need for dose adjustment during active CAB + RPV LA dosing.

The present dataset is too small to make definitive conclusions on the frequency of birth defects, pregnancy outcomes, and neonatal outcomes for live births. Of the 10 live births, one congenital anomaly (congenital ptosis) was reported. In US populations, the majority of congenital ptosis cases are idiopathic; however, this abnormality may also arise from autosomal dominant inheritance or genetic or chromosomal defects [46]. In this analysis, the congenital ptosis occurred in an infant born to a mother in the CU programme with multiple comorbidities and was considered to be a random congenital anomaly by the treating physician, and not associated with LA therapy. In the most recent Antiretroviral Pregnancy Registry (APR) report covering the period between 1 January 1989 and 31 January 2021, congenital defects were reported in ~3% of live births following in utero exposure to ARTs during any trimester [33]. Owing to the recency of CAB + RPV LA approval in the USA, there are very few APR reports for this novel drug combination to date. In the HPTN 077 and HPTN 084 studies evaluating use of CAB LA as pre-exposure prophylaxis among adults without HIV-1, no congenital abnormalities were observed among live births (n = 2 and n = 13, respectively) [28, 47].

The rate of spontaneous abortions of 24% (n = 6/25) observed in this analysis may have been a result of frequent pregnancy testing (Q4W or Q8W prior to LA injection), which may have identified early pregnancies that ordinarily would not have been detected or reported in real-world settings. A previous study investigating the risk of early pregnancy loss in 221 healthy women attempting to conceive points to higher rates of pregnancy detection when frequent pregnancy monitoring is used [48]. Of the 221 pregnancies in the study, 28% were reported to have been terminated early, compared with 10%–15% reported in the general population following standard testing [48, 49]. The majority (69%, n = 43/62) of the early spontaneous abortions in the study occurred before clinical detection was possible [48]. The rate of spontaneous abortions in our study (24%) was also similar to that observed in the HPTN 084 study, in which participants were tested for pregnancy prior to CAB LA injections administered Q8W (n = 1641) [47]. Of the 18 pregnancies occurring in the HPTN 084 study, 28% (n = 5/18) resulted in spontaneous or elective abortions [47].

Although a systematic review has shown that people living with HIV on ART (n = 12 636) have higher adverse birth outcomes, including preterm birth, low birthweight, and being small for gestational age, compared with women without HIV (n = 7 812 115) [50], limited data exist specifically assessing the risk of spontaneous abortions among pregnant women on ART compared with women without HIV.

Pregnancy surveillance within clinical trial and CU programme participants continues, with an amendment of ongoing trial protocols allowing pregnant participants to remain on CAB + RPV LA where possible. Studies are planned to evaluate the safety and efficacy of continued LA dosing in pregnancy. This, along with continued surveillance of birth defects via the APR, will further our understanding of safety following CAB + RPV exposure during pregnancy.

**LIMITATIONS**

This analysis has several limitations. The number of pregnancies was too small to allow for a definitive assessment of safety in mothers and infants following exposure to CAB + RPV LA at conception. Since oral CAB + RPV was only used as an oral lead-in, data regarding pregnancy outcomes following longer exposures to oral CAB + RPV therapy were very limited. Despite a similar pattern of CAB and RPV plasma concentration decline following LA treatment discontinuation between pregnant and non-pregnant women, these data are in a limited number of pregnant participants and do not directly confirm expected CAB + RPV PK during continued LA dosing in pregnancy. Furthermore, as this is a retrospective analysis of pregnancy outcomes rather than a clinical trial, there were no data evaluating the prospective efficacy and PK of CAB + RPV LA during active dosing in pregnant women. Additionally, every effort was made to enter participants into the LTFU if they withdrew from or discontinued the study after receiving at least one dose of CAB + RPV PK. Participants were monitored by primary care providers and/or obstetrics and gynaecology once pregnancy was confirmed. Safety data related to pregnancy were collected at the discretion of the treating provider. Furthermore, cord blood samples, allowing assessment of placental transfer, and infant washout were not assessed.

Monitoring of birth defects and other outcomes within the APR and other pregnancy studies will
continue, though it may be several years before pregnancy outcomes are reported in sufficient numbers to draw meaningful conclusions.

CONCLUSIONS

This is the first analysis evaluating pregnancy outcomes in women exposed to CAB + RPV (oral/LA) at conception. The data set is too small to make definitive conclusions on the frequency of birth defects and pregnancy/neonatal outcomes. Among 10 live births there was one congenital anomaly (congenital ptosis) reported in an infant born to a mother in the CU programme with multiple comorbidities. A spontaneous abortion rate of 24% observed in this analysis may be explained by frequent pregnancy testing detecting very early pregnancies. All those exposed to CAB + RPV (oral/LA) who discontinued CAB + RPV therapy, for whom viral load data were available (n = 8/9), maintained virological suppression from conception through pregnancy and postpartum, or the last available viral load assessment following a switch to alternative ART. Plasma CAB and RPV concentrations during pregnancy among those with subsequent live births were within the range of concentrations observed in non-pregnant women within the treatment programme who discontinued LA therapy [43, 44]. Ongoing surveillance within ViiV Healthcare-sponsored clinical trials and the APR will further elucidate our understanding of safety following exposure to CAB + RPV during pregnancy.

AUTHOR CONTRIBUTIONS

Parul Patel, Susan L. Ford, Mark Baker, Claudia Meyer, Ronald D’Amico, Rodica Van Solingen-Ristea, Herta Crauwels, Joseph W. Polli, Ciara Seal, Shanker Thiagarajah, Eileen Birmingham, William R. Spreen, Jean van Wyk, and Vani Vannappagari are employees of ViiV Healthcare and stockholders of GlaxoSmithKline. Susan L. Ford, Claudia Meyer, Ciara Seal, Itziar Yagüe Muñoz, and Shanker Thiagarajah are employees and stockholders of GlaxoS–SmithKline. Louise Garside is an employee of PHASTAR and a stockholder of GlaxoSmithKline. Rodica Van Solingen-Ristea, Herta Crauwels, Eileen Birmingham, and Bryan Baugh are employees and stockholders of Janssen, Pharmaceutical Companies of Johnson & Johnson.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

ORCID

Herta Crauwels https://orcid.org/0000-0002-4516-8830

REFERENCES

1. UNICEF. Reimagining a resilient HIV response for children, adolescents and pregnant women living with HIV. http://www.childrenandaidsofsites/default/files/2020-12/2020%20World%20AIDS%20Day%20Report.pdf. Published 2020. Accessed November 10, 2021.
2. Chetty T, Vandormael A, Thorne C, Coutsoudis A. Incident HIV during pregnancy and early postpartum period: a population-based cohort study in a rural area in KwaZulu-Natal, South Africa. BMC Pregnancy Childbirth. 2017;17(1):248.
3. Drake AL, Wagner A, Richardson B, John-Stewart G. Incident HIV during pregnancy and postpartum and risk of mother-to-child HIV transmission: a systematic review and meta-analysis. PLoS Med. 2014;11(2):e1001608.
4. Machekano R, Tiam A, Kassaye S, et al. HIV incidence among pregnant and postpartum women in a high prevalence setting. PLoS ONE. 2018;13(12):e0209782.
5. Yee LM, Miller ES, Statton A, et al. Sustainability of statewide rapid HIV testing in labor and delivery. AIDS and Behav. 2018; 22(2):538-544.
6. Liotta G, Mancinelli S, Nielsen-Saines K, et al. Reduction of maternal mortality with highly active antiretroviral therapy in a large cohort of HIV-infected pregnant women in Malawi and Mozambique. PLoS One. 2013;8(8):e71653.
7. Li N, Matchi E, Spiegelman D, et al. Maternal mortality among HIV-infected pregnant women in Tanzania. Acta Obstet Gynecol Scand. 2014;93(5):463-468.
8. Marazzi MC, Palombi L, Nielsen-Saines K, et al. Extended antenatal use of triple antiretroviral therapy for prevention of mother-to-child transmission of HIV-1 correlates with favorable pregnancy outcomes. *AIDS*. 2011;25(13):1611-1618.

9. Chilaka VN, Konje JC. HIV in pregnancy - an update. *Eur J Obstet Gynecol Reprod Biol*. 2021;256:484-491.

10. National Institutes of Health. General Principles Regarding Use of Antiretroviral Drugs during Pregnancy. https://clinicalinfo.hiv.gov/en/guidelines/perinatal/overview?view=full. Published 2020. Accessed November 19, 2021.

11. European AIDS Clinical Society. Guidelines Version 11.0. October 2021. https://www.eacsociety.org/media/final2021eacsguidelinesv11.0_oct2021.pdf. Accessed November 19, 2021.

12. British HIV Association. British HIV Association guidelines for the management of HIV in pregnancy and postpartum 2018 (2020 third interim update). https://www.bhiva.org/file/5f1a1ab9aaba/BHIVA-Pregnancy-guidelines-2020-3rd-interim-update.pdf. Accessed November 19, 2021.

13. Centers for Disease Control and Prevention. Breastfeeding: Human Immunodeficiency Virus (HIV). https://www.cdc.gov/breastfeeding/breastfeeding-special-circumstances/maternal-or-infant-illnesses/hiv.html. Accessed November 19, 2021.

14. Gilleece Y, Krankowska D. ART in pregnant women living with HIV. *Lancet*. 2021;397(10281):1240-1241.

15. Orkin C, Arasteh K, Gorgolas Hernández-Mora M, et al. Long-acting cabotegravir and rilpivirine after oral induction for HIV-1 infection. *N Engl J Med*. 2020;382(12):1124-1135.

16. Overton ET, Richmond G, Rizzardini G, et al. Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2 M), 48-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study. *Lancet*. 2021;396(10267):1994-2005.

17. Swindells S, Andrade-Villanueva JF, Richmond GJ, et al. Long-acting cabotegravir and rilpivirine for maintenance of HIV-1 suppression. *N Engl J Med*. 2020;382(12):1112-1123.

18. Viiv Healthcare. Cabenuva PI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212888s000lbl.pdf. Published 2021. Accessed September, 2021.

19. Saag MS, Gandhi RT, Hoy JF, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2020 recommendations of the International Antiviral Society-USA panel. *JAMA*. 2020;324(16):1651-1669.

20. U.S. Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/whats-new-guidelines. Published 2021. Accessed September, 2022.

21. European Medicines Agency. Vocabria PI. https://www.ema.europa.eu/en/documents/product-information/vocabria-epar-product-information_en.pdf. Published 2021. Accessed February 24, 2022.

22. Margolis DA, Gonzalez-Garcia J, Stellbrink HJ, et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. *Lancet*. 2017;390(10101):1499-1510.

23. Jaeger H, Overton ET, Richmond G, et al. Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2 M), 96-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study. *Lancet HIV*. 2021;8(11):e679-e689.

24. Swindells S, Lutz T, Van Zyl L, et al. Week 96 extension results of a phase 3 study evaluating long-acting cabotegravir with rilpivirine for HIV-1 treatment. *AIDS*. 2022;36(2):185-194.

25. De Los Rios P, Young B, Marcotullio S, et al. 1329. Experiences and emotional challenges of antiretroviral treatment (ART)—findings from the Positive Perspectives study. *Open Forum Infect Dis*. 2019;6(Suppl 2):S481.

26. Hyperemesis Education and Research Foundation. About Hyperemesis Gravidarum (HG). https://www.hyperemesis.org/about-hyperemesis-gravidarum/. Published 2022. Accessed February 24, 2022.

27. Nachega JB, Uthman OA, Anderson J, et al. Adherence to antiretroviral therapy during and after pregnancy in low-income, middle-income, and high-income countries: a systematic review and meta-analysis. *AIDS*. 2012;26(16):2039-2052.

28. Landovitz RJ, Li S, Eron JJ Jr, et al. Tail-phase safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir in HIV-uninfected adults: a secondary analysis of the HPTN 077 trial. *Lancet HIV*. 2020;7(7):e472-e481.

29. McGowan I. Persistence of Rilpivirine Following Single Dose of Long-Acting Injection. Presented at: 21st International AIDS Conference; July 18–22, 2016; Durban, South Africa.

30. European Medicines Agency. Vocabria Product Information. https://www.ema.europa.eu/en/documents/product-information/vocabria-epar-product-information_en.pdf. Published 2021. Accessed February 24, 2022.

31. Janssen Pharmaceuticals. Edurant PI. https://www.janssenslabels.com/package-insert/product-monograph/prescribing-information/EDURANT-pi.pdf. Published 2021. Updated 2021. Accessed January 25, 2022.

32. Stanislaus DJ, Ziejewski MK, Romach EH. Cabotegravir: Absence of reproductive and developmental toxicity in animal studies. Presented at: 10th International Workshop on HIV & Women; March 6–7, 2020; Boston, MA, USA. Poster 75.

33. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry international interim report for 1 January 1989–31 January 2021. http://www.apregistry.com/forms/interim_report.pdf. Published 2021. Accessed November 11, 2021.

34. Schalkwijk S, Colbers A, Konopnicki D, et al. Lowered Rilpivirine exposure during the third trimester of pregnancy in human immunodeficiency virus type 1-infected women. *Clin Infect Dis*. 2017;65(8):1335-1341.

35. Osiyemi O, Yasin S, Zorrilla C, et al. Pharmacokinetics, antiviral activity, and safety of rilpivirine in pregnant women with HIV-1 infection: results of a phase 3b, multicenter, open-label study. *Infect Dis Ther*. 2018;7(1):147-159.

36. Tran AH, Best BM, Stek A, et al. Pharmacokinetics of rilpivirine in HIV-infected pregnant women. *J Acquir Immune Defic Syndr*. 2016;72(3):289-296.

37. D’Amico R, Moodley R, Van Landuyt E, et al. Compassionate use of long-acting (LA) cabotegravir (CAB) and rilpivirine (RPV) for patients in need of parenteral antiretroviral therapy. Presented at: 23rd International AIDS Conference; July 6–10, 2020; Virtual. Poster PEB0263.
38. World Medical Association. World Medical Association declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191-2194.
39. World Health Organization. Stillbirth. https://www.who.int/health-topics/stillbirth#tab_1. Published 2022. Accessed February 24, 2022.
40. World Health Organization. Pre-term birth fact sheet. https://www.who.int/news-room/fact-sheets/detail/preterm-birth. Published 2018. Accessed November 11, 2021.
41. World Health Organization. Low birth weight fact sheet. https://www.who.int/data/nutrition/nlis/info/low-birth-weight. Published 2021. Accessed November 11, 2021.
42. D’Amico R, Cenoz Gomis S, Moodley R, et al. Compassionate use of long-acting cabotegravir plus rilpivirine for people living with HIV-1 in need of parenteral antiretroviral therapy. HIV Med. 2022. Online ahead of print. doi:10.1111/hiv.13370
43. Delany-Moretlwe S, Hughes J, Guo X, et al. Evaluation of CAB-LA Safety and PK in Pregnant Women in the Blinded Phase of HPTN 084. Presented at: 29th Conference on Retroviruses and Opportunistic Infections (CROI); February 12–16, 2022; Virtual. Poster 00700.
44. Crauwels H, Rice D, Neyens M, et al. Rilpivirine long-acting pharmacokinetic tail and pregnancy. E-poster presented at: 11th International Workshop on HIV & Women Virtual; April 26–28, 2021. Virtual Meeting. Poster 14. 2021.
45. Ford S, Crauwels H, Han K, et al. Cabotegravir and rilpivirine PK following long-acting HIV treatment discontinuation. Abstract presented at: Conference on Retroviruses and Opportunistic Infections (CROI); March 8–11; 2020.
46. American Academy of Ophthalmology. Congenital Ptosis. https://eyewiki.aao.org/Ptosis_Congenital#Etiology Published 2021. Accessed November 11, 2021.
47. Delany-Moretlwe S, Hughes JP, Bock P, et al. Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial. Lancet. 2022;399(10337):1779-1789.
48. Wilcox AJ, Weinberg CR, O’Connor JF, et al. Incidence of early loss of pregnancy. N Engl J Med. 1988;319(4):189-194.
49. March of Dimes. Miscarriage. https://www.marchofdimes.org/complications/miscarriage.aspx#:~:text=For%20women%20who%20know%20they%20to%205%20percent%20pregnancies. Published 2017. Accessed January 25, 2022.
50. Shinar S, Agrawal S, Ryu M, et al. Perinatal outcomes in women living with HIV-1 and receiving antiretroviral therapy—a systematic review and meta-analysis. Acta Obstet Gynecol Scand. 2022;101(2):168-182.

How to cite this article: Patel P, Ford SL, Baker M, et al. Pregnancy outcomes and pharmacokinetics in pregnant women living with HIV exposed to long-acting cabotegravir and rilpivirine in clinical trials. HIV Med. 2023;24(5):568-579. doi:10.1111/hiv.13439