Cabotegravir plus Rilpivirine: Pregnancy Outcomes and Pharmacokinetic Considerations

Summary

- Limited information is available regarding the use of cabotegravir (CAB) and rilpivirine (RPV) during pregnancy.
- *Cabenuva* (long-acting cabotegravir and rilpivirine [CAB + RPV LA]) should only be used during pregnancy when the potential benefits outweigh the risk.[1]
- Among 25 pregnancies reported during phase 2 and 3 clinical trials of CAB + RPV LA, there were 10 live births and 15 non-live births.[2]
    - One congenital anomaly (ptosis) was reported among the live births.
- A real-world study described 31 pregnant individuals: there were 28 live births, 2 spontaneous abortions, and 1 stillbirth reported.[3]
- The Antiretroviral Pregnancy Registry (APR) reported data on 43 outcomes (42 pregnancies), which included 35 live births (1 twin birth), 1 stillbirth, 3 spontaneous abortions, and 4 induced abortions.[4]
- A maternal-fetal physiological-based pharmacokinetic (PBPK) model predicted a reduction in plasma concentrations in pregnancies who initiate CAB LA and RPV LA during the 2nd and 3rd trimesters.[5]
- Important Safety Information can be found in the Prescribing Information and can also be accessed from Our HIV Medicines.

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Cabotegravir[1]

CAB use in pregnant women has not been evaluated. CAB should be used during pregnancy only if the expected benefit justifies the potential risk to the pregnant woman and fetus.

CAB was not teratogenic when studied in pregnant rats and rabbits but caused a delay in delivery in rats that was associated with increased stillbirths and reduced neonatal viability at exposures higher than for therapeutic doses. The relevance to human pregnancy is unknown.

CAB has been detected in systemic circulation for up to 12 months or longer after an injection; therefore, consideration should be given to the potential for fetal exposure during pregnancy.

Rilpivirine[1]

Limited clinical data is available for pregnant patients taking RPV. Animal studies have shown no evidence of relevant embryonic or fetal toxicity or an effect on reproductive function. In offspring from rats and rabbits treated with RPV during pregnancy and lactation, there were no toxicologically significant effects on developmental endpoints.

RPV should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

RPV has been detected in systemic circulation for up to 12 months or longer after an injection; therefore, consideration should be given to the potential for fetal exposure during pregnancy.

PREGNANCY OUTCOMES FROM THE LONG-ACTING CABOTEGRAIVR PLUS RILPIVIRINE CLINICAL DEVELOPMENT PROGRAM

Pregnancy was an exclusion criterion in the phase 2 and 3 trials that evaluated the efficacy and safety of long-acting cabotegravir and rilpivirine (CAB + RPV LA).[6-9] Subjects who became pregnant were discontinued from the study, regardless of termination status of pregnancy. Pregnancy outcome information from these trials is shown below.

There were 325 women of childbearing potential who were exposed to CAB + RPV during clinical trials. Overall (through March 31, 2021), 25 pregnancies were reported: 20 pregnancies occurred following CAB + RPV LA exposure at conception, and 5 in women with only exposure to oral CAB + RPV and did not progress to LA therapy.[2]

A summary of live and non-live birth outcomes following CAB + RPV exposure can be found below in Tables 1 and 2, respectively.

Table 1. Summary of Live Birth Outcomes Following CAB + RPV Exposure[2]

Participant	CAB + RPV Regimen	Duration of Exposure Prior to Conception[a]	Pregnancy Outcome
1	Oral (daily)	< 1 week	Term, normal birth weight, no congenital anomaly
2	Q8W	87 weeks	Term, normal birth weight, no congenital anomaly
3[b]	Q4W	35 weeks	Term, normal birth weight, no congenital anomaly
4	Q4W	204 weeks	Term, normal birth weight, no congenital anomaly (via caesarean)
5	Q4W	37 weeks	Term, birth weight not documented, no congenital anomaly
6	Q4W	106 weeks	Term, normal birth weight, no congenital anomaly
7[c]	Q4W	34 weeks	Term, low birth weight, congenital ptosis (IUGR; multiple comorbidities)
8	Q4W (during LTFU)[d]	Last injection 10 weeks prior to LMP	Term, normal birth weight, no congenital anomaly
9	Q4W	36 weeks	Term, normal birth weight, no congenital anomaly
10	Q4W (during LTFU)[d]	Last injection 28 weeks prior to LMP	Preterm (induced at 36 weeks + 5), normal birth weight, no congenital anomaly

[a] Conception was estimated to be 14 days following last menstrual period. Duration of prior exposure to CAB + RPV LA includes at least 4 weeks of oral CAB + RPV as an oral lead-in prior to injectable treatment.

[b] First pregnancy; second pregnancy corresponds to participant O in Table 2 below.

[c] Second pregnancy; first pregnancy corresponds to participant K in Table 2 below. Participant 7 had 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.

[d] Pregnancy detected during LTFU. 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).

CAB = cabotegravir; RPV = rilpivirine; Q4W = every 4 weeks; Q8W = every 8 weeks; IUGR = intrauterine growth restriction; PK = pharmacokinetic; GA = gestational age; LMP = last menstrual period; LTFU = long term follow-up

Table 2. Summary of Non-Live Birth Outcomes Following CAB + RPV Exposure[2]

Participant	CAB + RPV Regimen	Duration of Exposure Prior to Conception[a]	Relevant Past Obstetric History	Pregnancy Outcome
A	Oral	1 week	2 full-term normal births, 2 induced abortions	Elective abortion (1st trimester, ~8 weeks GA)
B	Oral	3 weeks	10 previous pregnancies (5 preterm births, 2 full-term normal births, 3 spontaneous abortions)	Spontaneous abortion (1st trimester. ~8 weeks GA)

Participant	CAB + RPV Regimen	Duration of Exposure Prior to Conception[a]	Relevant Past Obstetric History	Pregnancy Outcome
C	Oral	2 weeks	1 premature birth, 1 spontaneous abortion	Elective abortion (1st trimester, ~7 weeks GA)
D	Oral	4 weeks	2 prior children (details unknown)	Spontaneous abortion (1st trimester)[b]
E	Q4W	71 weeks	2 full-term normal births	Elective abortion (1st trimester, ~7 weeks GA)
F	Q4W	11 weeks	1 full-term normal birth, 3 pre-term births, 1 still-birth, 2 induced abortions	Elective abortion (1st trimester, ~5 weeks GA)
G	Q4W	12 weeks	2 full-term normal births, 1 elective abortion	Elective abortion (1st trimester, ~6 weeks GA)
H	Q4W	110 weeks	2 full-term normal births, 2 elective abortions	Spontaneous abortion (1st trimester, ~8 weeks GA)
I	Q4W	57 weeks	No previous pregnancies	Spontaneous abortion (1st trimester)[b]
J	Q4W	189 weeks	1 elective abortion	Spontaneous abortion (1st trimester, ~4-5 weeks GA)
K[c]	Q4W + oral ART[d]	3 weeks	No previous pregnancies	Spontaneous abortion at 23 weeks GA, IUGR. Multiple maternal risk factors
L	Q8W	195 weeks	2 full-term births	Laparotomy for ectopic pregnancy (1st trimester, ~5 weeks GA)[e]
M	Q8W	92 weeks	1 full-term normal birth	Elective abortion (1st trimester, ~8 weeks GA)
N[f]	Q8W (PK tail)[g]	Last injections 38 weeks prior to conception	1 full-term normal birth, 1 elective abortion	Elective abortion (1st trimester)[h]
O[i]	Q4W (PK tail)[g]	Last injections 54 weeks prior to conception	1 full-term normal birth	Elective abortion (1st trimester, ~10 weeks GA)

Participant	CAB + RPV Regimen	Duration of Exposure Prior to Conception[a]	Relevant Past Obstetric History	Pregnancy Outcome

[a] Conception was estimated to be 14 days following las menstrual period. Duration of prior exposure to CAB + RPV LA includes at least 4 weeks of oral CAB + RPV as an oral lead-in prior to injectable treatment.

[b] Ultrasound was unable to confirm intrauterine pregnancy despite initial positive β-hCG test, indicating early spontaneous abortion of pregnancies (participants D and I)

[c] 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 1. This patient was exposed to CAB + RPV LA during the compassionate use program.

[d] Cobicistat/darunavir/emtricitabine/tenofovir alafenamide

[e] Classified in medical database as an elective abortion

[f] Pregnancy N is a 2nd pregnancy, 1st pregnancy corresponds to participant M

[g] 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 1]), 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 2]).

[h] 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

[i] Pregnancy O is a second pregnancy; first pregnancy corresponds to participant 3 in Table 1

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; RPV = rilpivirine; Q4W = every 4 weeks; PK = pharmacokinetic; Q8W = every 8 weeks

REAL-WORLD DATA[3]

Short, et al. conducted a multicenter, retrospective chart review of 31 pregnant individuals prescribed CAB + RPV LA in the US at anytime during pregnancy between January 2021 and April 2024.

The median (interquartile range [IQR]) age at delivery was 29 (6, 34) years and 81% were Black/African American. The median (IQR) time since HIV diagnosis was 14 (9, 24) years and 39% had perinatally acquired HIV. At the first prenatal visit, the median (IQR) gestational age was 9 (8, 11) weeks and median (IQR) body mass index was 29 (22, 35) kg/m^2. Comorbidities included psychiatric illness (42%), hypertension (19%), active substance use (16%), and diabetes mellitus (3%).

Most patients (n = 23, 74%) were on CAB + RPV LA prior to pregnancy. Of these, 61% received CAB + RPV LA every 2 months. Seven patients switched off CAB + RPV LA during pregnancy; all switched to bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF). Median (IQR) gestational age at switch off CAB + RPV LA was 22 (17, 28) weeks. Three patients had their CAB + RPV LA dose changed during pregnancy. Eight patients initiated CAB + RPV LA (all monthly dosing) during pregnancy at a median (IQR) gestational age of 22 (17, 28) weeks. Regimens prior to switch included BIC/FTC/TAF (n = 6), dolutegravir + FTC/TAF (n = 1), and BIC/FTC/TAF + darunavir/cobicistat + doravirine (n = 1).

HIV-1 RNA at initial visit was: < 20 copies/mL (n = 23/31 [75%]), 20–200 copies/mL (n = 2/31 [6%]), 201–1000 (n = 1/31 [3%]), and > 1000 (n = 5/31 [16%]). Virologic, delivery, and neonatal outcomes are summarized in Table 2. Data on the occurrence of congenital abnormalities was not reported.

Table 2. Virologic, Delivery, and Neonatal Outcomes[3]

	Overall cohort (N = 31)
HIV-1 RNA at delivery, copies/mL, n (%)	
< 20	25 (81)
20–200	4 (13)
201–1000	0
> 1000	2 (6)
Birth Outcome, n (%)	
Live birth	28 (90)
Spontaneous abortion	2 (7)
Stillbirth	1 (3)
Mode of delivery, n (%)	
Vaginal	14 (52)
Cesarean[a]	13 (48)
Gestational age at delivery, weeks, median (IQR)	37 (36, 39)
Birth weight, grams, median (IQR)	2750 (2275, 2910)
Negative neonatal HIV status at Month 4, %	100
Method of infant feeding, n (%)	
Formula	26 (84)
Breast/chest	5 (16)

[a] All but one were for obstetrical indications

IQR = interquartile range

PREGNANCY EXPOSURE REGISTRY[4]

To monitor maternal-fetal outcomes of pregnant women, an Antiretroviral Pregnancy Registry (APR) has been established (http://www.apregistry.com). This is a voluntary prospective, exposure-registration, cohort study designed to collect and evaluate data on the outcomes of pregnancy exposures to antiretroviral products.

Limited data for CAB + RPV are available from the APR. Through July 2024, 42 pregnancies of individuals exposed to CAB LA have been reported. The indication for most was HIV treatment (n = 32/42 [76%]); the remaining 10 individuals received CAB LA for HIV pre-exposure prophylaxis. Half were reported from the US. Birth outcomes were not stratified by indication.

The median (range) maternal age at conception was 29 (21–39) years. For those not on CAB at time of conception, 27 (64%) were exposed 0–6 months prior to conception and 12 (29%) were exposed 6–12 months prior. For those first exposed during pregnancy, earliest exposures were at: first trimester (n = 1), second trimester (n = 1), and third trimester (n = 1).

Of the 43 total outcomes reported: 35 were live births (1 twin birth), 1 stillbirth, 3 spontaneous abortions, and 4 induced abortions. Neonatal outcomes are summarized in Table 3.

Table 3. Neonatal Outcomes with Prenatal Exposure to CAB LA

		Earliest Exposure (during pregnancy)			Earliest Exposure (pre-conception only)	
	Overall	**1st Trimester**	**2nd Trimester**	**3rd Trimester**	**0–6 Months Prior to Conception**	**6–12 Months Prior to Conception**
Live, singleton newborns without defects, n	33	1	1	1	23	7
Gestational age, n (%)						
≥ 37 weeks	27 (82)	1 (100)	1 (100)	1 (100)	20 (87)	4 (57)
< 37 weeks (preterm)	5 (15)	0	0	0	3 (13)	2 (29)
Missing	1 (3)	0	0	0	0	1 (14)
Birth weight, n (%)						
≥ 2500 grams	22 (67)	1 (100)	1 (100)	1 (100)	16 (70)	3 (43)
< 2500 grams (LBW)	3 (9)	0	0	0	2 (9)	1 (14)
< 1500 grams (VLBW)	3 (9)	0	0	0	2 (9)	1 (14)
Missing	5 (15)	0	0	0	3 (13)	2 (29)

LBW = low birth weight; VLBW = very low birth weight

One birth defect (congenital ptosis) was reported among the live births (see participant 7 in Table 1 above): earliest CAB exposure was 6–12 months prior to conception. Other antiretroviral drug exposures included RPV (prior to conception) and darunavir/cobicistat/emtricitabine/tenofovir alafenamide (unknown time of earliest exposure).

PHYSIOLOGICALLY-BASED PHARMACOKINETIC (PBPK) MODELS[5]

PBPK models offer the ability to incorporate physiologic pregnancy-associated changes and drug specific characteristics to predict the concentration exposure during pregnancy before concentration measurements are made.

The ratio of simulated to observed PK parameters in nonpregnant individuals are shown in Table 3.

Table 3. Ratio of simulated vs. observed PK parameters in non-pregnant cisgender women[5]

	Rilpivirine		**Cabotegravir**				
	25 mg Oral Steady State	**1200 mg IM + 900 mg IM**	**30 mg Oral**	**100 mg IM**	**200 mg IM**	**400 mg IM**	**800 mg IM**
$AUC_{0\text{-}t}$ (mg*hr/L) Simulated/observed (ratio)	2.31/2.25 (0.92)	218/206 (1.06)	194/126 (1.54)	785/820 (0.96)	1570/1240 (1.27)	3430/2870 (1.2)	6010/6150 (0.98)
C_{max} (mg/L) Simulated/observed (ratio)	0.18/0.15 (1.2)	0.16/0.15 (1.07)	2.62/3.48 (0.75)	0.26/0.24 (1.08)	0.52/0.31 (1.68)	1.04/0.68 (1.53)	2.08/3.83 (0.54)
T_{max} (hr) Simulated/observed (ratio)	170/172 (0.99)	682/792 (0.86)	5.25/2.21 (2.47)	294/210 (1.4)	294/815 (0.36)	294/1663 (0.18)	294/133 (2.21)

AUC_{0-t} = area under the concentration versus time curve from 0 to 24 hours; C_{max} = maximum concentration; IM = intramuscular; PK = pharmacokinetic; T_{max} = time to C_{max}.

Simulation results showed that the trough concentrations after the 1st injection (loading dose) were 29.5% lower for CAB LA and 23% lower for RPV LA during pregnancy compared to outside of pregnancy. The trough concentrations after the 6th injection were 31.1% and 29.2% decreased for CAB LA and RPV LA, respectively.

ADDITIONAL INFORMATION: PREGNANCY OUTCOMES WITH LONG ACTING CABOTEGRAVIR WHEN USED FOR PREP

HPTN 084 is a double-blind, placebo-controlled, phase 3, superiority trial evaluating the safety and efficacy of long-acting injectable cabotegravir compared to daily oral TDF/FTC for pre-exposure prophylaxis in HIV-uninfected cisgender women.[10]

For additional information on pregnancy outcomes with long-acting cabotegravir in the HPTN 084 study, please click here.

This information is scientific and non-promotional in nature and is not intended for further distribution.

This information is not intended to offer recommendations for using this product in a manner inconsistent with its approved labeling. Please consult the Prescribing Information. For ViiV Healthcare to monitor the safety of our products, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 877-844-8872.

Selection of references follows principles of evidence-based medicine and, therefore, references may not be all inclusive.

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