# Cabotegravir (CAB)

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## Summary

- Pharmacokinetic (PK) data are insufficient to make dosing recommendations for oral cabotegravir (CAB) or long-acting (LA) injectable cabotegravir (CAB-LA) during pregnancy or breastfeeding.
- Clinical data are insufficient to characterize the risk for congenital anomalies associated with *in utero* exposure to CAB. No reproductive toxicity or teratogenicity concerns were identified in animal studies.
- Long-acting CAB and rilpivirine (RPV) (LA CAB/RPV) is U.S. Food and Drug Administration (FDA) approved for HIV treatment.
- CAB-LA is FDA approved for HIV pre-exposure prophylaxis (PrEP).

## Human Studies in Pregnancy

### Pharmacokinetics

Prospective CAB PK data during pregnancy and postpartum are largely limited to preliminary data from the HIV Prevention Trials Network (HPTN) 084 protocol open-label extension (OLE)[1] in which, upon diagnosis of pregnancy, HIV-negative participants were given the choice of continuing the current regimen (either CAB-LA or tenofovir disoproxil fumarate [TDF]/emtricitabine [FTC]) or switching to a self-selected regimen (CAB-LA or TDF/FTC) for HIV PrEP. Monthly PK sampling was performed among a subset of 75 participants; preliminary PK data from the first 50 participants, all of whom were continuing on CAB from before pregnancy (median number of CAB-LA intramuscular injections before conception was 6, range 4–7), found that concentrations decreased in pregnancy but were largely maintained above the protocol-defined exposure target of four times the protein-adjusted 90% inhibitory concentration of 0.664 µg/mL. No PK data are reported on CAB-LA initiation in pregnancy.

Additional PK data were published on 27 pregnancies among participants who received CAB-LA in the blinded portion of HPTN 084.[2] Among these pregnancies, median prepregnancy CAB-LA exposure was 342 days (interquartile range [IQR] 192–497). Upon diagnosis of pregnancy, participants were unblinded and switched to open-label TDF/FTC for the duration of pregnancy and breastfeeding. To evaluate pregnancy associated differences in terminal-phase half-life estimates (adjusted $R^2$ of ≥ 0.85), terminal-phase half-life was compared between 17 participants HPTN 084 with three or more CAB PK measurements after confirmation of pregnancy and 35 nonpregnant women from HPTN 077 who received at least one injection of 600 mg CAB-LA; differences in terminal decay were not statistically significant between cohorts. Pregnancy-associated changes in weight or body mass index did not influence terminal CAB-LA PK.

A case report of a single pregnancy on bimonthly LA CAB/RPV reported that CAB concentrations were comparable to those in nonpregnant individuals.[3] No other prospective PK data on LA CAB/RPV for HIV treatment during pregnancy and postpartum exist. Earlier clinical trial PK data are limited to pregnant women who stopped receiving CAB injections for the treatment of HIV once pregnancy was recognized and began an alternative oral antiretroviral (ARV) regimen throughout the remainder of their pregnancies.[4]

### Placental and Breast Milk Passage

Median (IQR 25–75) CAB maternal-to-fetal concentration ratio assessed using an *ex vivo* dually perfused human cotyledon model was 10% (IQR 5–16), suggesting low placental transfer.[5] No data are available describing breast milk passage of CAB in humans.[6] See Rilpivirine for data about RPV.

### Teratogenicity/Adverse Pregnancy Outcomes

The Antiretroviral Pregnancy Registry (APR) provides updated birth defect data for CAB and other ARV drugs twice a year through an interim report released in June and December. The APR has not monitored sufficient numbers of first-trimester exposures to CAB to report on the risk of overall birth defects.

In HPTN 084 OLE,[7] there were 495 confirmed pregnancies, with 435 live births. Pregnancy-related Grade 2+ maternal adverse event incidence was 42 (95% confidence interval [CI], 32–55), 35 (95% CI, 17–70), and 24 (95% CI, 11-54) per 100 person-years among those using CAB-LA during pregnancy, using CAB-LA starting before pregnancy, or no CAB-LA use, respectively. Adverse pregnancy outcome rates were similar across groups and consistent with background rates. Two major congenital anomalies (i.e., omphalocele, trisomy 21) were observed among those using CAB-LA during pregnancy, and were not considered related to CAB-LA exposure.[8]

Among the 57 pregnancies (30 on CAB-LA, 27 on TDF/FTC) previously reported in the blinded phase of HPTN 084, 58 pregnancy outcomes were reported, including one set of twin births and one loss to follow-up. Neither the incidence of Grade ≥2 maternal adverse events nor the rate of composite poor pregnancy outcomes differed between study arms. The majority of pregnancies (81%) resulted in live births (25 CAB-LA vs. 22 TDF/FTC). No congenital anomalies were observed.[2]

In earlier Phase 2b/3/3b trials of CAB and RPV, 25 of 325 women of reproductive potential became pregnant while exposed to CAB and RPV (5 oral, 20 LA injectable), resulting in 8 elective abortions, 6 spontaneous abortions (5 in the first trimester), 1 ectopic pregnancy, and 10 live births (1 oral, 9 LA injectable). Of the 10 live births, 1 case of congenital ptosis was reported in a preterm infant with intrauterine growth restriction, and 1 late preterm birth occurred due to induction of labor.[4] See Rilpivirine for additional information about RPV.

## Animal Studies

### Carcinogenicity

CAB was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Long-term carcinogenicity studies of CAB in mice did not show any carcinogenic potential at systemic exposures that were sevenfold (in females) or eightfold (in males) greater than human exposure at the recommended dose. In rats, no drug-related increases in tumor incidence were observed at CAB exposures up to approximately 26 times higher than those in humans at the recommended dose.[9]

CAB was not genotoxic in the bacterial reverse mutation assay, mouse lymphoma assay, or *in vivo* rodent micronucleus assay.[10] See Rilpivirine for data about RPV.

### Reproduction/Fertility

In rats, no effects on fertility were observed at CAB exposures at least 20 times greater than the exposure in humans at recommended doses. See Rilpivirine for data about RPV.

## Teratogenicity/Adverse Pregnancy Outcomes

Studies in pregnant rats showed that CAB crosses the placenta and can be detected in fetal tissue. Treatment of rat dams with CAB during pregnancy and postpartum had no effects on fetal viability, although a minor decrease was observed in fetal body weight with exposures 28 times those seen in humans at the recommended dose. No drug-related fetal toxicities were observed with rat dam exposures approximately 13 times those seen in humans at the recommended dose, and no fetal malformations were observed at any rat dam dose. A delay in the onset of parturition and increases in the number of stillbirths and neonatal deaths were seen with exposure of rat dams to CAB at 28 times the human exposure with recommended doses, but not with exposure at 13 times the human exposure with recommended doses.

No drug-related fetal toxicities were observed after CAB exposures of rabbit dams of up to approximately 0.7 times those seen in humans at the recommended dose.[10]

A recent study in mouse models demonstrated decreased human embryonic stem cell counts and pluripotency and induced dysregulation of genes involved in early differentiation at subtherapeutic levels of CAB.[11] Additionally, a study of zebrafish found that although CAB did not cause gross morphological defects at low doses, pericardial edema, uninflated swim bladder, decreased heartbeats, growth delay, and decreased hatching rate were observed at the highest concentrations. At subtherapeutic doses, decreased locomotion was observed, suggesting alterations of nervous system integrity.[12] Clinical data and clinical trials data in humans are insufficient to refute or corroborate these findings.

See Rilpivirine for data about RPV.

## Placental and Breast Milk Passage

Studies in lactating rats and their offspring indicate that CAB is present in rat milk. See Rilpivirine for data about RPV.

## Excerpt From Table 14

**Note:** When using fixed-dose combination (FDC) tablets, refer to other sections in Appendix B and Table 14 in the Perinatal Guidelines for information about the dosing and safety of individual drug components of the FDC tablet during pregnancy.

| **Generic Name** (Abbreviation) *Trade Name* | **Formulation** | **Dosing Recommendations[a]** | **Use in Pregnancy** |
|---|---|---|---|
| **Cabotegravir** (CAB)<br>*Vocabria (oral)*<br>*Apretude (injection for HIV pre-exposure prophylaxis)*<br>(CAB and RPV)<br>*Cabenuva*<br>**Note:** CAB and RPV is a two-drug co-packaged product for IM injection. | **CAB (Vocabria)**<br>• CAB 30-mg tablets for oral administration<br>**CAB (Apretude)**<br>• CAB 200-mg/mL suspension for IM injection<br>**CAB and RPV (Cabenuva)**<br>• CAB 200-mg/mL suspension for IM injection<br>• RPV 300-mg/mL suspension for IM injection | **Pregnancy**<br>*PK in Pregnancy*<br>• No published PK studies in human pregnancy<br>*Dosing in Pregnancy*<br>• Insufficient data to make dosing recommendations<br>For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., RPV).<br>**Standard Adult Doses**<br>*Oral Lead-in Therapy (Optional)*<br>• CAB (Vocabria)<br>o One 30-mg tablet once daily **in combination with RPV** (Edurant) 25 mg once daily taken with a meal for 4 weeks<br>• CAB (Apretude)<br>o Initiation<br>▪ CAB 600-mg (3 mL) injections given 1 month apart for 2 consecutive months (on the last day of an oral lead-in, if used, or within 3 days)<br>o Continuation Therapy<br>▪ CAB 600-mg (3 mL) injections every 2 months thereafter<br>• CAB and RPV (Cabenuva)<br>o Initiation<br>▪ CAB 600 mg (3 mL) and RPV 900 mg (3 mL), given as two separate injections in separate ventrogluteal sites for 2 consecutive months (on the last day of an oral lead-in, if used) | No human data are available regarding placental passage.<br>Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.<br>**Note:** Please see FDA label for full list of drugs with potential interactions and drugs for which administration with CAB is contraindicated. |

## Excerpt From Table 14

| Generic Name (Abbreviation) *Trade Name* | Formulation | Dosing Recommendations[a] | Use in Pregnancy |
|---|---|---|---|
| | | o Continuation Therapy<br>▪ *Monthly:* CAB 400 mg (2 mL) and RPV 600 mg (2 mL), given as two separate injections in separate ventrogluteal sites once a month with allowance for a +/- 7-day administration window<br>▪ *Every 2 months:* Starting in Month 4, CAB 600 mg (2 mL) and RPV 900 mg (3 mL), given as two separate injections in separate ventrogluteal sites once a month with allowance for a +/- 7-day administration window<br>**Note:** For all CAB IM injections, patients should be monitored for approximately 10 minutes for postinjection reactions. A 23-gauge, 1.5-inch IM needle is recommended for the injection and is provided in the packaging. Longer, 2-inch needles should be used in patients with BMIs >30 kg/m$^2$.<br>*Changing Dosing Frequency and Managing Missed Doses*<br>• Refer to the package insert for instructions about changing the frequency of continuation doses and managing missed doses (see Apretude and Cabenuva). | |

[a] Individual ARV drug doses may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Antiretroviral Guidelines, Appendix B).

[b] Placental transfer categories are determined by mean or median cord blood–to–maternal delivery plasma drug ratio:

**High:** >0.6
**Moderate:** 0.3–0.6
**Low:** <0.3

**Key:** ARV = antiretroviral; BMI = body mass index; CAB = cabotegravir; IM = intramuscular; PK = pharmacokinetic; RPV = rilpivirine

## References


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