EDURANT® (rilpivirine)
Use of EDURANT in Pregnancy

SUMMARY

- Total rilpivirine (RPV) exposures were generally lower during pregnancy compared to the postpartum period.[1]
- For pregnant patients who are already on a stable EDURANT regimen prior to pregnancy and who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) the recommended dosage in adults and pediatric patients weighing at least 25 kg is one 25 mg tablet once daily (QD) taken orally with a meal.[1]
- **Osiyemi et al (2018)**[2] evaluated the pharmacokinetics (PK) of total and unbound RPV in 19 HIV-1-infected pregnant women.
  - Total RPV exposure was 29-31% lower during pregnancy vs postpartum; differences were less pronounced for unbound RPV.
- The International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Protocol 1026s phase 4 study included a study arm of 32 women that received EDURANT during their pregnancy.[3,4]
  - The area under the plasma concentration time curve (AUC) target of 0.88 µg•hr/mL was achieved by 93% of women during the 2nd trimester, 93% during the 3rd trimester, and 89% postpartum.
  - The RPV concentration 24 hours post dose (C_{24}) was lower during the 2nd trimester of pregnancy compared to postpartum.
  - The AUC 24 hours post dose (AUC_{24}) and the C_{24} were decreased during the 3rd trimester of pregnancy compared to postpartum.
  - The median (range) RPV cord blood/maternal plasma ratio: 0.55 (range, 0.3-0.8).
- An arm of the IMPAACT Protocol 1026s phase 4 study described RPV concentrations in the genital tract in 24 pregnant and postpartum women.[5]
  - For all time points combined, median (interquartile range [IQR]) RPV concentrations were 70 (23-121) ng/mL in cervicovaginal fluid (CVF) and 92 (49-147) ng/mL in plasma.
  - The RPV CVF to plasma AUC from pre-dose concentration to 4 hours post-dose ($AUC_{[0-4]}$) ratios were significantly higher in the second (0.90, 90% confidence interval [CI]: 0.61-1.46) and third trimesters of pregnancy compared with postpartum (0.40, 90% CI: 0.19-0.87) (second trimester vs postpartum, *P*=0.02; third trimester vs postpartum, *P*=0.04).
  - Three of 189 (1.6%) plasma samples in 2 women were below the lower limit of quantification (LLQ) and the corresponding CVF concentrations were also below the LLQ (plasma LLQ= 10 ng/mL; CVF LLQ=1 ng/mL).
  - Seventeen of 189 (10.6%) additional CVF concentrations were below the LLQ in 13 patients.
- **Schalkwijk et al (2017)**[6] evaluated the PK of EDURANT in 16 HIV-1-infected pregnant women as part of the phase 4 ANtiretroviral agents in HIV-infected pregNAnt women (PANNA) study.
  - Geometric mean ratios of third trimester vs postpartum were 0.55 (90% CI: 0.46-0.66) for the 24-hour area under the concentration-time curve (AUC_{0-24h}), 0.65 (90% CI: 0.55-0.76) for the maximum concentration (C_{max}), and 0.51 (90% CI: 0.41-0.63) for the minimum observed concentration (C_{min}).
  - Four of 16 (25%) patients had C_{min} <0.04 mg/L in the third trimester of pregnancy.
  - There were no subtherapeutic levels observed postpartum.
  - The median cord/maternal plasma ratio (n=5): 0.5 (range, 0.35-0.81).
- In a human cotyldeon perfusion model, the fetal transfer rate (FTR) of RPV was 26%±8%.[7]

ANTIRETROVIRAL PREGNANCY REGISTRY

To monitor maternal-fetal outcomes of pregnant women exposed to EDURANT, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.[1]

PHARMACOKINETIC STUDIES

Osiyemi et al (2018)[2] evaluated the PK of total and unbound RPV in HIV-1-infected pregnant women (N=19).

Study Design/Methods

- Phase 3b, multicenter, open-label study that assessed PK parameters of antiretrovirals (ARV), including EDURANT, as part of clinical care.
- Study patients received either EDURANT 25 mg QD as separate agents, or as part of a single-tablet regimen (EDURANT/emtricitabine [FTC]/tenofovir disoproxil fumarate [TDF]) in combination with other ARVs. EDURANT was taken with a meal.
- Inclusion criteria included:
  - 18 years of age or older in the second trimester of pregnancy, taking EDURANT 25 mg QD.
  - If receiving EDURANT as part of their first line of therapy: pretreatment viral load <100,000 copies/mL, no evidence of specific NNRTI mutations, and use of EDURANT in combination with 2 active nucleosides/tides.
  - If receiving EDURANT as part of the single-tablet, complete regimen EDURANT/FTC/TDF and treatment-experienced: no history of virologic failure, on first or second ARV regimen and virologically suppressed for ≥6 months prior to switching to EDURANT/FTC/TDF, and no current or past history of resistance to EDURANT, FTC, or TDF.
- The PK results from 15 women in the 2nd trimester (weeks 24-28 of gestation), 12 women in the 3rd trimester (weeks 34-38), and 11 women postpartum (6-12 weeks after giving birth) were available during the analysis.
- Twelve infants were born from the 12 women who remained in the study until after delivery and completed the study.
- Baseline characteristics included: 63% had viral load <50 copies/ml; 53% used FTC and TDF as part of their background regimen.

Results

Pharmacokinetics of EDURANT

- RPV exposure during 2nd and 3rd trimesters was less than exposure observed postpartum.
  - Total RPV during pregnancy of AUC_{24}: 29%-31% lower, C_{max}: 20%-21% lower, C_{min}: 35%-42% lower.
  - Total unbound RPV during pregnancy included AUC_{24}: 22%-25% lower, C_{max}: 10%-15% lower, C_{min}: 32%-36% lower.
- The median cord/maternal plasma ratio was available for 8 women. The data was collected the day of delivery: 0.55 (range 0.43 – 0.98).

Efficacy

- 10 infants had available data: none had perinatal viral transmission.
- Of the 12 women who were virally suppressed at baseline, 10/12 (83%) remained suppressed at the conclusion of the study (6-12 weeks postpartum).

Safety

- 9 of 19 (47%) experienced 1 or more adverse events (AEs).
  - None of the AEs were considered related to EDURANT and none led to discontinuation.
  - 1 case of premature labor (delivery at 34 weeks gestation).
- 4 of 19 (21%) experienced 1 or more serious AE (none related to EDURANT).
  - The serious AEs consisted of blurred vision, sepsis, chorioamnionitis, intrauterine death, preeclampsia, and premature labor.
  - One women experienced chorioamnionitis with related sepsis and intrauterine death of fetus (withdrawn from study because of terminated pregnancy).
- All infants AEs were of grade 1 or 2 in severity and none were considered by the investigator to be related to EDURANT.
- The most common AEs (occurring in >1 infant) were exomphalos (n=2 [17%]) and neonatal vomiting (n=2 [17%]).

IMPAACT Protocol 1026s

Mirochnick et al (2015)[3] **and Tran et al (2016)**[4] evaluated the PK of EDURANT during pregnancy and postpartum in the IMPAACT Protocol 1026s (N=32). **Eke et al (2018)**[5] described RPV concentrations in the genital tract in pregnant and postpartum women in the IMPAACT Protocol 1026s (N=24).

Study Design/Methods

- In the PK substudy:[3,4]
  - Study patients received combination ARV treatment, including EDURANT 25 mg QD as part of clinical care.
  - Plasma samples were collected from baseline to 24 hours post-dose.
  - The PK results from 19 women in the 2nd trimester, 31 women in the 3rd trimester, and 30 women postpartum were available during this analysis.
  - The target AUC was ≥0.88 µg•hr/mL.
- In the CVF substudy:[5]
  - CVF and plasma samples were collected predose and at 1, 2, and 4 hours post-dose during the second trimester, third trimester, and postpartum.
  - RPV CVF concentrations were measured by liquid chromatography-tandem mass spectrometry (LLQ=1 ng/mL). RPV plasma concentrations were measured by high-performance liquid chromatography with ultraviolet detection (LLQ=10 ng/mL).
  - A total of 24 women were included in the analysis. CVF and plasma concentration data were available for 10 women in the second trimester, 17 women in the third trimester, and 19 women postpartum.

Results

Maternal Results

- In the PK substudy:[3,4]
  - Concomitant ARVs that were administered at some time during the pregnancy included TDF/FTC (n=32), zidovudine (n=5), and darunavir/ritonavir (n=1).
  - Of the 30 patients with postpartum results, 70% had HIV RNA levels ≤50 copies/mL and 90% had HIV RNA levels ≤400 copies/mL at delivery.
  - The median (range) CD4+ cell count (cells/µL) at specific time points were the following:
    - 593 (180-1080) during the 2nd trimester
    - 557 (151-1277) during the 3rd trimester
    - 550 (112-1149) at delivery
    - 716 (185-1427) postpartum

- In the CVF substudy:[5]
  - Maternal plasma HIV-1 RNA was ≤50 copies/mL in 7 of 10 (70%) patients during the second trimester, 13 of 17 (82%) patients during the third trimester, and 13 of 18 (72%) patients postpartum.
  - The median (IQR) CD4+ cell count (cells/mm^3) at specific time points were the following:
    - 565 (293-828) during the 2nd trimester
    - 554 (297-1147) during the 3rd trimester
    - 693 (185-1180) postpartum

Infant Results

- In the PK substudy, there were 21 (70%) infants that were uninfected and 9 (30%) that were indeterminate/pending.[3,4]
- In the CVF substudy, no congenital anomalies were identified, and no infants in the cohort were infected with HIV.[5]

Pharmacokinetics

- In the PK substudy:[3,4]
  - The median (range) C_{24} were lower (P<0.05) during the 3rd trimester (56 ng/mL [<10 to 181 ng/mL]) compared to postpartum (81 ng/mL [<10 to 299 ng/mL]), as was AUC_{24} (1.70 µg•hr/mL [0.56 to 4.31 µg•hr/mL] and 2.39 µg•hr/mL [0.19-6.74 µg•hr/mL]).
  - During the 2nd trimester, C_{24} were lower (63 ng/mL [36 to 225ng/mL]) compared to postpartum (P<0.05).
  - The AUC target was achieved by 93% of women during the 2nd trimester, 93% during the 3rd trimester, and 89% postpartum.
  - Maternal plasma samples and umbilical samples were available for 21 women:
    - Cord blood riplivirine levels (median) were 29.2 ng/mL (range, <10.0-101.5 ng/mL).
    - Maternal delivery plasma levels (median) were 55.2 ng/mL (<10.0-233.8 ng/mL).
    - Cord blood/maternal blood ratio was 0.55 (0.3-0.8).
- In the CVF substudy:[5]
  - Three of 189 (1.6%) plasma samples in 2 women were below the LLQ for RPV; the corresponding CVF concentrations were also below the LLQ for RPV.
  - Seventeen of 189 (10.6%) additional CVF concentrations were below the LLQ in 13 women.
  - When all time points were combined, median (IQR) RPV concentrations were 70 (23-121) ng/mL in CVF and 92 (49-147) ng/mL in plasma.
  - Median (IQR) RPV CVF and plasma $AUC_{(0-4)}$ and their ratio for the second trimester, third trimester, and postpartum visits are shown in Table: RPV CVF and Plasma PK.

RPV CVF and Plasma PK[5]

Parameter Median (IQR)	Second Trimester	Third Trimester	Postpartum
CVF $AUC_{(0-4)}$ (ng•h/mL)	419 (176-578)	325 (185-491)	217 (61-456)
Plasma $AUC_{(0-4)}$ (ng•h/mL)	409 (263-627)	327 (185-646)	410 (238-738)
CVF:plasma $AUC_{(0-4)}$ratio	0.90 (0.61-1.46)[a]	0.74 (0.49-1.32)[b]	0.40 (0.19-0.87)

Abbreviations: $AUC_{(0-4)}$, area under the concentration time curve from pre-dose concentration to 4 hours post-dose; CVF, cervicovaginal fluid; IQR, interquartile range; PK, pharmacokinetic; RPV, rilpivirine.
[a]Second trimester vs postpartum (P=0.02).
[b]Third trimester vs postpartum (P=0.04).

Safety

- In the PK substudy:[3,4]
  - EDURANT was generally well tolerated.
  - Four maternal grade 3-4 AEs were reported: anemia (n=2), spinal headache (n=1), and tachycardia (n=1).
  - There were 2 AEs that were possibly attributed to EDURANT: oligohydramnios and grade 2 serum glutamic pyruvic transaminase elevation.
  - Infant AEs were reported in 5 of 30 infants included: high bilirubin (days 1-2 of life), probable sepsis, low absolute neutrophil count, low blood glucose, vomiting
  - Congenital anomalies and other findings were reported in 5 infants which included: Mongolian spot, polydactyly, labial fusion, genitourinary, testicular torsion and bilateral hydrocele.
- In the CVF substudy, no major safety concerns were noted.[5]

PANNA

Schalkwijk et al (2017)[6] evaluated the pharmacokinetics of EDURANT as part of the ongoing, phase 4, open-label, non-randomized, multicenter study (PANNA study) in HIV-1-infected pregnant women (N=16).

Study Design/Methods

- Patients 18 years of age or older and receiving EDURANT 25 mg QD for at least 2 weeks before the day of first PK evaluation were included in the study.
- PK blood sampling was performed in the third trimester and at least 2 weeks postpartum.
- Plasma samples were collected pre-dose and at intervals up to 24 hours post-dose.
- The PK results from 16 women were available during the analysis.
- All patients received a fixed-dose combination of EDURANT/TDF/FTC. One patient also received ritonavir-boosted lopinavir.
- 100% of patients had viral load <50 copies/mL.

Results

Pharmacokinetics of EDURANT

- In the third trimester of pregnancy, the RPV $AUC_{0\text{-}24h}$ and C_{min} were reduced by 45% and 49%, respectively, compared to postpartum.
  - This indicates a substantially lowered exposure during pregnancy.
- Geometric mean ratios of third trimester vs postpartum are shown in Table: Geometric Mean Ratios for EDURANT 25 mg QD PK Parameters in HIV-Infected Women – Third Trimester of Pregnancy vs Postpartum (N=15).
- Two of 16 (13%) patients had subtherapeutic C_{0h} and 4 of 16 (25%) patients had C_{min} <0.04 mg/L in the third trimester of pregnancy.
- There were no subtherapeutic levels observed postpartum.
- The median observed C_{24} were 0.07 (IQR, 0.03-0.13) mg/L and 0.08 (IQR, 0.05-0.13) mg/L in the third trimester of pregnancy (n=12) and postpartum (n=8), respectively.
- The median cord/maternal plasma ratio was available for 5 women. The data was collected at delivery: 0.50 (range 0.35-0.81).

Geometric Mean Ratios for EDURANT 25 mg QD PK Parameters in HIV-Infected Women – Third Trimester of Pregnancy vs Postpartum (N=15)[6]

Parameter	Geometric Mean Ratio, %	90% Confidence Interval
$AUC_{0\text{-}24h}$	55	46-66
C_{max}	65	55-76
C_{0h}	47	38-58

Parameter	Geometric Mean Ratio, %	90% Confidence Interval
C_{min}	51	41-63
CL_{ss}/F	184	154-220
Abbreviations: AUC_{0-24h},24-hour area under the concentration-time curve; C_{0h}, predose concentration; CL_{ss}/F, apparent clearance under steady-state conditions; C_{max}, maximum concentration; C_{min}, minimum observed concentration; PK, pharmacokinetic; QD, once daily.		

Efficacy

- No virologic breakthrough was seen in the study.
- All newborns tested negative for HIV.

Safety

- One serious AE, hospital admission due to irregular contractions, was determined not to be related to EDURANT.
- A total of 13 AEs were reported by 8 patients, including anemia (n=3), gestational diabetes (n=3), rectal molluscum pendulum, duodenitis, urinary tract infection, preeclampsia, hemorrhagic delivery, irregular contractions, and urticaria. None were related to study medication.
- There were no birth defects reported.

IN VITRO DATA

Human Cotyledon Perfusion Model

Mandelbrot et al (2015)[7] evaluated the placental transfer of RPV in 8 *ex vivo* perfused human cotyledon with full term delivery in mothers that were seronegative for HIV, hepatitis B, hepatitis C, and were not receiving medication.

Study Design/Methods

- This study utilized the placentas from uncomplicated pregnancies.
  - Eight procedures were validated.
- EDURANT 25 mg tablets were crushed and perfused into the placentas.
- The FTR was the ratio of fetal to maternal RPV levels.

Results

- The RPV concentration (mean±standard deviation [SD]) was 401±31 ng/mL in the maternal compartment and 101±38 ng/mL in the fetal compartment.
  - These drug levels exceeded the 50% effective concentration (EC_{50}) against wild-type HIV-1 of 0.27 ng/mL.
- The FTR for RPV was 26%±8%.

Reproduction and Toxicity Study

Desmidt et al (2009)[8] assessed the potential effects of EDURANT 25 mg on embryo-fetal development in rats and rabbits.

Study Design/Methods

- EDURANT was administered by oral gavage at doses of up to 400 mg/kg/day to pregnant Sprague-Dawley rats and up to 20 mg/kg/day in pregnant New Zealand white rabbits during the period of organogenesis (gestation days 6–17 in rats and days 6–19 in rabbits) to determine the maternal and embryo-fetal toxicity and teratogenic potential.

Rat Results

- At the 120 and 400 mg/kg doses, indications of moderate maternal toxicity were noted (reduced food consumption and body weight gain, and increased thyroid weight).
- No teratogenic effect was seen and there was no effect of treatment on pregnancy parameters in any group.
- The only finding on embryo-fetal development was an increase in the incidence of a visceral variant of dilated renal pelvis, at the 120 and 400 mg/kg doses.
- The maternal and embryo-fetal embryo-fetal no-observable-adverse-effect levels (NOAEL) in rats was 40 mg/kg/day, associated with a maternal $AUC_{0\text{-}24h}$ value of 37 µg•h/mL.

Rabbit Results

- There was no maternal toxicity up to 20 mg/kg/day.
- No teratogenic effect was seen and there was no effect of treatment on pregnancy parameters in any group.
- The only finding on embryo-fetal development was a slight increase in the incidence of fetuses exhibiting minor variations of the left subclavian artery originating from the aorta and of hypoplastic interparietal bone in the group given 20 mg/kg/day.
- The maternal toxicity and NOAELs in the rabbit were 20 and 10 mg/kg/day, respectively, associated with maternal $AUC_{0\text{-}24h}$ values of 232 and 170 µg•h/mL.
- Exposures in rats were up to 63 times higher than those in HIV-infected patients receiving EDURANT 25 mg QD at steady-state, and exposure in rabbits were up to 97 times higher
    - $AUC_{0–24h}$: 2.8 µg•h/mL in adult humans (phase 2b TMC278-C204 study)

LITERATURE SEARCH

A literature search of MEDLINE®, EMBASE®, BIOSIS Previews®, and DERWENT® pertaining to this topic was conducted on 18 January 2024. Summarized in this response are relevant data from clinical studies. Additional data from beyond these parameters are available upon request.

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