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Raltegravir Pharmacokinetics during Pregnancy

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Abstract

Objective—We evaluated the pharmacokinetics (pk) of raltegravir in HIV-infected women during pregnancy and postpartum.

Methods—IMPAACT 1026s is an on-going prospective study of antiretroviral pk during pregnancy (NCT00042289). Women receiving 400 mg raltegravir twice daily in combination antiretroviral therapy had intensive steady state 12-hour pk profiles performed during pregnancy and at 6–12 weeks postpartum. Targets were trough concentration above 0.035 µg/mL, the estimated tenth percentile in non-pregnant historical controls.

Results—Median raltegravir AUC was 6.6 µg*hr/mL for second trimester (n= 16), 5.4 µg*hr/mL for third trimester (n=41), and 11.6 µg*hr/mL postpartum (n= 38) (p=0.03 pp vs 2nd trimester, p=0.001 pp vs third trimester). Trough concentrations were above the target in 69%, 80%, and 79% of second trimester, third trimester and postpartum subjects respectively, with wide variability (<0.010–0.917 µg/mL), and no significant difference between third trimester and postpartum trough concentrations was detected. The median ratio of cord blood/maternal raltegravir concentrations was 1.5. HIV RNA levels were < 400 copies/mL in 92% of women at

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delivery. Adverse events included elevated liver transaminases in one woman and vomiting in one. All infants with known status are HIV-uninfected.

Conclusions—Median raltegravir AUC was reduced by approximately 50% during pregnancy; trough concentrations were frequently below target both during late pregnancy and postpartum. Raltegravir readily crossed the placenta. High rates of viral suppression at delivery and the lack of a clear relationship between raltegravir concentration and virologic effect in nonpregnant adults suggest that despite the decreased exposure during pregnancy, a higher dose is not necessary.

Keywords

HIV; pregnancy; raltegravir; pharmacokinetics

Introduction

Raltegravir, an integrase strand transfer inhibitor antiretroviral agent, is recommended as a preferred regimen for initial therapy in non-pregnant HIV-infected adults.¹ Because data are limited on its use in pregnancy, raltegravir is recommended for use in special circumstances in pregnancy, such as when women have resistance or intolerance to more commonly used agents.² Most reports are of raltegravir use in late pregnancy because of its rapid viral load reduction.^{3–6}

Data on drug exposure in pregnant women receiving raltegravir and placental transfer are currently very limited. Croci et al reported a trough level of raltegravir of 0.21 µg/mL in the third trimester in one patient, compared to median trough concentrations in a trial of non-pregnant adults of 0.029–0.118 µg/mL.⁷ Maternal plasma raltegravir at delivery was 0.19 µg/mL with cord:maternal ratio of 1.0.⁷ In another case report, the maternal trough level was 0.162 µg/mL, cord blood was 0.173 µg/mL and a cord:maternal ratio of 1.06.⁶ In a case series from London, maternal levels near delivery ranged from 0.022–0.493 µg/mL five to 13 hours after maternal dosing, and levels in infant blood one to three hours after delivery ranged from seven to nine times higher than concomitant maternal levels.⁵ In a recent presentation on 28 women treated with raltegravir during pregnancy, the drug was well tolerated and 81% had undetectable HIV RNA at delivery.⁸ Maternal levels in 16 women were 0.169 µg/mL (0.010–0.270 µg/mL) at delivery. Median cord blood levels were 0.198 µg/mL (0.005–0.198 µg/mL) with a cord:maternal ratio of 3.48.⁸

No systematic pharmacokinetic study of raltegravir in pregnant women has been reported. The purpose of this study was to describe the pharmacokinetics of raltegravir in the second and third trimesters of pregnancy compared to postpartum.

Methods

International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network Protocol 1026s is a multi-center, prospective opportunistic study to evaluate the pharmacokinetics of antiretrovirals among HIV-infected pregnant women from USA, Thailand, Brazil, Argentina, and Uganda ([Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00042289) identifier NCT00042289). This report includes women receiving raltegravir 400 mg twice daily.

HIV-infected pregnant women receiving standard dose raltegravir as part of clinical care before the beginning of the 35th week of pregnancy were eligible. Exclusion criteria were: concurrent use of medications known to interfere with the absorption, metabolism or clearance of raltegravir (carbamazepine, phenobarbital, phenytoin, rifampin, esomeprazole, lansoprazole, omeprazole, rabeprazole), multiple gestation, or clinical or laboratory toxicity that would likely require a change in the medication regimen during the study. Local institutional review boards approved the protocol at all participating sites, and written informed consent was obtained from all subjects before participation. Subjects continued to take their prescribed medications throughout pregnancy. The choice of additional antiretrovirals was determined by the subject's physician, who prescribed all medications and remained responsible for clinical management throughout the study. Women continued on study until the completion of postpartum pharmacokinetic sampling.

For women enrolled during the second trimester of pregnancy, intensive raltegravir pharmacokinetics were determined in real time (within two weeks of receiving the samples in the pharmacology laboratory) between 20 and 26 weeks of gestation and repeated between 30 and 36 weeks of gestation. Women enrolling in the third trimester had pharmacokinetic sampling performed between 30 and 36 weeks of gestation. Pharmacokinetic sampling was repeated between six and 12 weeks postpartum. The observed raltegravir trough (C_{12h}) for each woman was compared to the raltegravir C_{12h} in non-pregnant adult populations.⁹ Each subject's physician was notified of the subject's plasma concentrations and C_{12h} within two weeks of sampling during pregnancy. If the C_{12h} was below the estimated tenth percentile in non-pregnant adult populations ($0.035 \mu\text{g/mL}$),⁹ the physician was offered the option of discussing the results and possible dose modification with a study team pharmacologist.

Clinical and Laboratory Monitoring

HIV-related laboratory testing was performed at each study visit if not available as part of routine clinical care. Maternal clinical data used for this analysis were: maternal age, ethnicity, weight, concomitant medications, CD4+ lymphocyte and HIV RNA assay results. HIV RNA assays were performed locally and had lower limits of detection ranging from 20 to 400 copies/mL. Maternal clinical and laboratory toxicities were assessed through clinical evaluations (history and physical examination) and laboratory assays (liver transaminases, creatinine, blood urea nitrogen, albumin, bilirubin, hemoglobin) on each pharmacokinetic sampling day, at delivery, and at 24 weeks postpartum. Infant birth weight, gestational age at birth, and HIV infection status were collected. Infants received physical examinations after birth; laboratory evaluations were done only if clinically indicated. The study team reviewed toxicity reports on monthly conference calls, although the subject's physician was responsible for toxicity management. The Division of AIDS (DAIDS)/NIAID Toxicity Table for Grading Severity of Adult Adverse Experience was used to grade adverse events for study subjects. (<http://rsc.tech-res.com/safetyandpharmacovigilance/gradingtables.aspx>) All toxicities were followed through resolution.

Sample Collection

Subjects were stable on their antiretroviral regimen for at least two weeks before pharmacokinetic sampling. Seven plasma samples were drawn at the second trimester, third trimester, and postpartum pharmacokinetic evaluation visits, including pre-dose, 1, 2, 4, 6, 8, and 12 hours after dosing. Women were required to fast for two hours before and two hours after the observed raltegravir dose to minimize the variability of the pharmacokinetic parameters. Information collected included the time of the two prior doses, the two most recent meals, and maternal height and weight. A single maternal plasma sample and an umbilical cord sample after cord clamping were collected at delivery.

Drug Assays

Raltegravir concentrations were measured at the University of California, San Francisco Clinical Pharmacology Laboratory using a validated, liquid chromatography tandem mass spectrometry method. The lower limit of quantitation (LLOQ) was 0.010 µg/mL. The interassay coefficient of variation (CV) was 7.12% at the LLOQ and ranged from 3.36% to 6.95% of CV for low, middle and high controls. Overall recovery from plasma was 96.3%.

Pharmacokinetic Analyses

The pre-dose concentrations ($C_{\text{pre-dose}}$), maximum plasma concentration (C_{max}), corresponding time (T_{max}), minimum plasma concentration (C_{min}), and 12 hour post-dose concentration ($C_{12\text{h}}$) were determined by direct inspection. For concentrations below the assay limit of detection, a value of one-half of the detection limit was used in summary calculations. AUC_{0-12} during the dose interval (from time 0 to 12 hours post-dose) was estimated using standard non-compartmental methods. Apparent clearance (CL/F) from plasma was calculated as dose divided by AUC_{0-12} . The terminal slope of the curve (λ_Z) was estimated from the last two measurable and declining concentrations between 8 and 12 hours post-dose. Half-life was calculated as dose divided by λ_Z , and apparent volume of distribution (V_d/F) was determined by CL/F divided by λ_Z .

Statistical Analyses

Target enrollment was at least 12 second trimester subjects and 25 third trimester subjects with evaluable pregnancy and postpartum raltegravir pharmacokinetic assessments. To prevent ongoing enrollment of subjects receiving potentially inadequate dosing, early stopping of enrollment was to be considered if six of the first 25 study subjects had third trimester raltegravir C_{12} below the estimated tenth percentile for the non-pregnant historical controls. The statistical rationale for this early stopping criterion has been previously described.¹⁰

Descriptive statistics were calculated for pharmacokinetic parameters of interest during each study period. Raltegravir pharmacokinetic parameters during the second trimester versus third trimester and postpartum and during the third trimester versus postpartum were compared at the paired, within-subject level using the Wilcoxon signed-rank test, with a p-value <0.05 considered to indicate statistical significance. The Spearman rank correlation test was used to evaluate the relationship between covariates, such as weight, with

raltegravir AUC. The Wilcoxon signed-rank test was used to compare raltegravir AUC between ethnic groups.

Results

Forty-two women were enrolled, with 16 completing second trimester sampling between 20 and 26 weeks of gestation, 41 completing third trimester sampling between 34 and 41 weeks, and 38 completing sampling at 3 to 14 weeks postpartum. The clinical characteristics of the women and their pregnancy outcomes are shown in Table 1. The majority of the women were of African descent and from the USA. Half of the women were on regimens of two or more nucleoside reverse transcriptase inhibitors only with raltegravir, while the remaining women were on regimens including drugs from at least three classes of antiretrovirals. Sixteen (94%) of the 17 women on raltegravir with only nucleosides were on their first antiretroviral regimen compared to nine (39%) of 23 on regimens with drugs from three or more classes ($p < 0.001$). Two women were taking concomitant ritonavir-boosted atazanavir, which can increase raltegravir exposure. At least 90% of women had HIV RNA levels below 400 copies/mL in the third trimester and at delivery. All infants were at least 36 weeks of gestation at delivery. None of the infants were confirmed to be infected; thus far, 34 are HIV-uninfected and eight are indeterminate or pending further testing. Seven infants had congenital anomalies, but no major anomalies were judged to be related to raltegravir use based on timing of exposure and family history.

Raltegravir was well tolerated, with grade 3 or 4 toxicities noted in four women, including fever in one, hypertension and shortness of breath in one, gum pain and face/scalp rash in one, and elevated amylase, drainage from the abdominal cesarean delivery incision, uterine pain, and vaginal bleeding in another. None of these were judged to be treatment related. Moderate (grade 2) possibly treatment-related findings included transient liver transaminase elevations in one subject and intermittent vomiting in another subject.

Raltegravir Exposure

Raltegravir pharmacokinetic parameters at each sampling interval are presented in Table 2, and raltegravir concentrations versus time at each interval are shown in Figure 1. Six (38%) of 16 women in the 2nd trimester, 13 (32%) of 41 women in the 3rd trimester, and 5 (13%) of 38 women postpartum had delays in absorption of raltegravir, defined as a 1-hour post dose concentration lower than the pre-dose concentration. C_{max} ranged from 0.365–5.960 $\mu\text{g/mL}$ in the second trimester, from 0.315–7.820 $\mu\text{g/mL}$ in the third trimester, and from 0.312–12.600 $\mu\text{g/mL}$ postpartum. Eleven (69%) of 16 subjects studied during the second trimester exceeded the target raltegravir C_{12h} of at least 0.035 $\mu\text{g/mL}$, compared with 33 (80%) of 41 third trimester subjects, and 30 (79%) of 38 postpartum subjects. The trough concentration was significantly lower in the second trimester compared to postpartum, and the peak concentration was significantly lower in the third trimester compared to postpartum. C_{12h} and other pharmacokinetic parameters were quite variable, and their variability increased from second to third trimester and into the postpartum period. C_{min} during the second trimester ranged from below the quantifiable limit (BQL)—0.162 $\mu\text{g/mL}$, in the third trimester from BQL–0.607 $\mu\text{g/mL}$, and from BQL–0.917 $\mu\text{g/mL}$ postpartum. No significant

differences were found between the second and third trimester parameters in a paired comparison including 16 women with sampling at both times.

Median AUC_{0-12} was significantly lower in the second ($6.6 \mu\text{g}\cdot\text{hr}/\text{mL}$) and third trimester ($5.4 \mu\text{g}\cdot\text{hr}/\text{mL}$) of pregnancy compared to postpartum ($11.6 \mu\text{g}\cdot\text{hr}/\text{mL}$). AUC_{0-12} showed wide variability, ranging from $2.1-18.5 \mu\text{g}\cdot\text{hr}/\text{mL}$ during the second trimester, $1.4-35.6 \mu\text{g}\cdot\text{hr}/\text{mL}$ during the third trimester and $1.6-39.9 \mu\text{g}\cdot\text{hr}/\text{mL}$ postpartum. No significant difference in oral clearance, half-life and volume of distribution between pregnancy and postpartum sampling was detected.

One subject taking concomitant atazanavir/ritonavir had trough concentrations above the target in the third trimester and postpartum. The other subject taking atazanavir/ritonavir had trough concentrations above the target in the second trimester and postpartum, but below the target during the third trimester. Weight inversely correlated with raltegravir AUC during the third trimester (spearman's $\rho = -0.490$, $p = 0.002$) and postpartum (spearman's $\rho = -0.346$, $p = 0.033$) but not significantly during the second trimester (spearman's $\rho = -0.365$, $p = 0.164$). No significant difference in raltegravir AUC was detected when the two largest ethnic groups represented in our sample, Black non-Hispanic subjects ($n=22$) and Hispanic subjects ($n=16$), were compared.

The median maternal raltegravir level at delivery was $0.140 \mu\text{g}/\text{mL}$, and the median cord blood level was $0.154 \mu\text{g}/\text{mL}$. The median cord/maternal ratio was 1.5. Maternal delivery and cord blood raltegravir concentrations and their ratio are plotted as a function of the time interval between maternal dosing and delivery in Figure 2.

Discussion

Raltegravir was well-tolerated in pregnancy with no treatment-related grade 3 or 4 adverse events. While numbers are too limited to rule out uncommon adverse events, ours is the largest series to date of raltegravir use in pregnancy. Previous reports have been generally reassuring,^{7,8} although one case report of markedly elevated liver transaminases in a pregnant woman started on raltegravir in late pregnancy suggest that until larger experience is gained with use in pregnancy, women should be monitored frequently for symptoms and laboratory abnormalities when starting raltegravir.¹¹ Half of the women in our study were on raltegravir with only two nucleoside agents as concomitant therapy, almost exclusively on their first antiretroviral regimen. Raltegravir may have been chosen in these cases for its tolerability in nonpregnant adults or because of the need for concomitant therapy such as rifampin that would interact with protease inhibitors.² In the other half of subjects, women were on multiclass regimens including drugs from at least three classes of agents, usually having been treated with prior regimens, and raltegravir was being used to provide an additional novel mechanism of activity. Even including women with multiple prior treatments, 92% of all women had undetectable HIV RNA levels at delivery.

Raltegravir exposure was reduced during pregnancy, with median AUC being approximately 50% lower during the second and third trimesters than in the same women postpartum. The C_{12h} of raltegravir was below the target level in more than 10% of women at each sampling

time, including postpartum. Further, in about a third of women during pregnancy, the raltegravir concentration continued to decline after a dose (indicating an absorption lag), compared to about 10% of women postpartum. However, the C_{12h} was also quite variable, ranging from 0.0114 to 1.340 $\mu\text{g/mL}$. This finding is consistent with raltegravir pharmacokinetic data in non-pregnant adults. In the REAL study, Wohl et al found the median concentration at 12 hours after dosing to be 0.091 $\mu\text{g/mL}$ with a range of 0.010–1.386 $\mu\text{g/mL}$.¹² Despite the wide variability, 95% of subjects had an HIV RNA level below 200 copies/mL by week four of treatment.¹² In the QDMRK trial comparing once daily to twice daily dosing, the trough level with twice daily dosing was 0.128 $\mu\text{g/mL}$ with a range of 0.015–1.074 $\mu\text{g/mL}$.¹³ In this trial, trough levels correlated with virologic response with once daily dosing, but not with twice daily dosing. Analysis of pharmacokinetic and viral response data from the BENCHMRK 1 and 2 trials also showed considerable variability in raltegravir plasma concentrations and little relationship between raltegravir concentrations and virologic response.¹⁴ Given the high rate of virologic response in the current study, the large variability in raltegravir plasma concentrations seen in non-pregnant adults, and the lack of a clear relationship between raltegravir concentrations and virologic effect, we do not recommend a change in dosing from the 400 mg twice daily standard dose in non-pregnant adults.

Women in this study were on a wide range of concomitant antiretroviral agents, with 49% on protease inhibitors, usually with ritonavir boosting. Raltegravir is primarily metabolized by uridine diphosphate glycosyltransferase (UGT) 1A1. Its pharmacokinetics are minimally affected by concomitant administration of ritonavir, a potent inhibitor of cytochrome P450 3A enzymes, and efavirenz, an inducer of cytochrome P450 enzymes.¹⁵ In contrast, raltegravir concentrations have been shown to be modestly increased when administered to patients receiving atazanavir, a known inhibitor of UGT1A1 activity.¹⁶ In our study, 2 women received atazanavir in addition to raltegravir and their raltegravir exposures were not out of the range seen in the other subjects.

Median cord blood raltegravir concentrations were higher than concomitant maternal concentrations at delivery, with a median ratio of 1.5, suggesting high placental transfer. Previous studies of one to 16 subjects have found ratios of 1.0–3.48.^{6–8} In a study evaluating maternal levels near delivery and infant levels one to three hours after delivery, infant levels were seven to nine times higher than maternal levels.⁵ The high placental transfer suggests that raltegravir could provide pre-exposure prophylaxis against HIV exposure in the fetus before and during delivery.

Based on these data and other reports, raltegravir offers another option for treatment of HIV-infected pregnant women. For pregnant women requiring medications such as rifampin with significant interactions with protease inhibitors, raltegravir offers a significant advantage. For pregnant women with resistance or incomplete virologic response to non-nucleoside reverse transcriptase inhibitors or protease inhibitors, raltegravir offers an attractive alternative or additional drug. In addition, studies have demonstrated more rapid decrease in HIV RNA levels with raltegravir compared to efavirenz, suggesting that raltegravir may be advantageous for rapidly reducing viral load prior to delivery in HIV-infected women who start antiretroviral therapy late in pregnancy.¹⁷ A study (IMPAACT P1081,

[ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01618305) Identifier: NCT01618305) comparing viral decay with initiation of raltegravir, lopinavir/ritonavir and efavirenz regimens in the third trimester of pregnancy is underway. As experience with raltegravir use in pregnancy increases, this agent may become a recommended first line agent for pregnant women.

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Figure 1. Median raltegravir concentration-time curves during the second trimester, third trimester and postpartum. The dashed line represents the expected (50th percentile) concentration-time profile in nonpregnant adults.

Figure 2.

Maternal delivery raltegravir concentrations, cord blood raltegravir concentrations and their ratio plotted against the time between maternal dosing and delivery. Filled circles represent maternal plasma raltegravir concentration at delivery, open circles represent cord blood raltegravir concentrations and filled diamonds represent the ratio of cord blood to maternal delivery raltegravir concentration.

Table 1

Clinical characteristics and pregnancy outcome data

Characteristic	N (%)	Median (range)
Age at delivery (years)	42	30 (19–43)
Weight at delivery (kg)	38	76 (59–131)
Weight postpartum (kg)	38	73 (52–122)
Duration of raltegravir use at 2 nd trimester pk	15	88 weeks (2–182)
Duration of raltegravir use at 3 rd trimester pk	39	56 weeks (2–225)
Race/ethnicity		
Black, non-Hispanic	22 (52%)	
Hispanic (regardless of race)	16 (38%)	
White, non-Hispanic	3 (7%)	
Mixed race	1 (2%)	
Country		
USA	36 (86%)	
Brazil	4 (10%)	
Argentina	2 (5%)	
Concomitant antiretrovirals in third trimester		
Two or more NRTI's only	20 (49%)	
NRTI's plus NNRTI	1 (2%)	
NRTI's plus PI	17 (41%)	
NRTI/NNRTI/PI	2 (5%)	
PI/Maraviroc	1 (2%)	
Second trimester HIV RNA (copies/mL)	17	50 (20–59,800)
< 400 copies/mL	14 (82%)	
Third trimester HIV RNA (copies/mL)	39	< 48 (20–6800)
< 400 copies/mL	35 (90%)	
Delivery plasma HIV RNA (copies/mL)	39	< 48 (20–52066)
< 400 copies/mL	36 (92%)	
Second trimester CD4+ lymphocyte count (cells/ μ L)	17	430 (72–977)
Third trimester CD4+ lymphocyte count (cells/ μ L)	41	510 (71–1153)
Delivery CD4+ lymphocyte count (cells/ μ L)	40	518 (74–1568)
Gestational age at delivery (weeks)	42	38.4 (36.6–42.4)
Birth weight (grams)	42	3090 (2200–4425)

NRTI= nucleoside reverse transcriptase inhibitor, NNRTI= non-nucleoside reverse transcriptase inhibitor

Table 2

Raltegravir median (range) non-compartmental pharmacokinetic parameters with p values for comparison to postpartum

Parameter	2 nd trimester (2T) (n=16)	2T vs PP*	3 rd trimester (3T) (n=41)	3T vs PP**	Postpartum (PP) (n=38)
AUC ₀₋₁₂ (µg*hr/mL)	6.6 (2.1–18.5)	0.03	5.4 (1.4–35.6)	0.001	11.6 (1.6–39.9)
C _{12h} (µg/mL)	0.0621 (0.0128–0.438)	0.02	0.064 (0.0114–0.607)	0.3	0.0797 (0.0199–1.340)
C _{min} (µg/mL)	0.047 (<0.01–0.162)	0.03	0.057 (<0.01–0.607)	0.66	0.0474 (<0.01–0.917)
C _{max} (µg/mL)	2.250 (0.365–5.960)	0.09	1.770 (0.315–7.820)	0.003	3.035 (0.312–12.600)
T _{min} (hr)	12.0 (0–12.0)	0.91	12.0 (0–12.0)	0.67	12.0 (0–12.0)
T _{max} (hr)	4.0 (1.0–8.0)	ND	2.0 (0–12.0)	ND	2.0 (0–8.0)
CL/F (L/hr)	60.6 (21.6–190.5)	0.36	74.8 (11.2–285.7)	0.21	34.8 (10.0–250.0)
V _d /F (hr)	264.1 (36.4–11228.5)	0.08	329.4 (71.8–10183.2)	0.16	238.8 (42.9–3032.4)
T _{1/2} (hr)	2.9 (1.2–85.6)	0.26	3.7 (1.1–211.7)	0.57	3.6 (1.1–30.5)
Number (%) above C _{12h} 10 th percentile nonpregnant	11/16 (69%)	0.49	33/41 (80%)	1.0	30/38 (79%)

AUC₀₋₁₂ = area under the plasma concentration-time curve; C_{12h} = concentration 12 hours after last dose; C_{min} = minimum concentration; C_{max} = maximum concentration; T_{min} = time post-dose of minimum concentration; T_{max} = time post-dose of maximum concentration; ND = not done; CL/F = oral clearance; V_d/F = apparent volume of distribution; t_{1/2} = half-life

* paired comparison using the Wilcoxon signed rank test, n=14

** paired comparison using the Wilcoxon signed rank test, n=37

Changes between the second and third trimester were also compared using the Wilcoxon signed rank test (n= 16); no significant differences were found.