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Raltegravir in HIV-1 Infected Pregnant Women: Pharmacokinetics, Safety and Efficacy

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Key points: Physiological changes during pregnancy can reduce antiretroviral drug exposure and may increase the risk of HIV transmission to the infant. Our findings support the use of raltegravir in standard dosages in HIV-infected pregnant women to prevent mother-to-child HIV transmission.

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Abstract

Background

The use of raltegravir in HIV-infected pregnant women is important in the prevention of mother-to-child HIV transmission (MTCT), especially in circumstances when a rapid decline of HIV RNA viral load is warranted or when preferred antiretroviral agents cannot be used. Physiological changes during pregnancy can reduce antiretroviral drug exposure. We studied the effect of pregnancy on the pharmacokinetics of raltegravir and its safety and efficacy in HIV-infected pregnant women.

Methods

An open-label, multi-centre, phase IV study in HIV-infected pregnant women receiving raltegravir 400 mg twice daily, was performed (PANNA Network). Steady state pharmacokinetic profiles were obtained in the third trimester and postpartum along with cord and maternal delivery concentrations. Safety and virological efficacy were evaluated.

Results

Twenty-two patients were included of which 68% started raltegravir during pregnancy. Approaching delivery 86% of the patients had an undetectable viral load (<50 copies/mL). None of the children were HIV-infected. Exposure to raltegravir was highly variable. Overall AUC and C_{12h} plasma concentrations in third trimester were on average 29% and 36% lower compared to postpartum:

Geometric mean ratios (90% confidence interval) were 0.71 (0.53-0.96) for $AUC_{0\text{-}12h}$ and 0.64 (0.34-1.22) for C_{12h}. The median (IQR) ratio of raltegravir cord/maternal blood was 1.21 (1.02-2.17; n=9).

Conclusions

Raltegravir was well tolerated during pregnancy. The pharmacokinetics of raltegravir showed extensive variability. The observed mean decrease in exposure to raltegravir during third trimester compared to postpartum is not considered to be of clinical importance. Raltegravir can be used in standard dosages in HIV-infected pregnant women.

Introduction

An estimated 1.4 million pregnant women infected with HIV give birth annually worldwide, of which the majority live in Sub-Saharan Africa.[1] Mother-to-child HIV transmission (MTCT) is the most common route of HIV-infection among infants and children. Each day, approximately 1,000 infants acquire HIV due to MTCT during pregnancy, delivery or breastfeeding.

Combination antiretroviral therapy (cART) is the standard of care for the prevention of perinatal transmission. The main goal of cART is maximal suppression of HIV replication. Its implementation together with other effective interventions has led to dramatic declines in the number of perinatally HIV-infected children from 15-40% to <2%. Absent or delayed prenatal care, acute primary infection in late pregnancy, and the continued increase in incidence of HIV infection in women of childbearing age are among the most important obstacles to fully eliminate perinatal transmission in the United States and other resource-rich countries.[2]

In current US and European treatment guidelines for HIV-1 infection in pregnancy, preferred combined antiretroviral agents include two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) in combination with the protease inhibitors (PIs) lopinavir or atazanavir boosted with ritonavir or the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine. Regimens including the HIV-1 integrase inhibitor raltegravir can be considered for use in special circumstances because information on the pharmacokinetics and the safety of raltegravir in pregnancy is limited. Examples of these special circumstances could be pregnant women who present late in care (>28 weeks gestational age) or whose HIV RNA load is not undetectable at third trimester.[2-4] HIV integrase inhibitors such as raltegravir have demonstrated to rapidly reduce HIV RNA load with shorter times to achieve virological suppression compared to agents from other drug classes.[5] Case reports and small case series suggest that raltegravir could play an important role when a rapid decline in maternal plasma HIV RNA is needed to prevent MTCT during delivery or as an alternative antiretroviral drug in complex treatment-experienced HIV-infected pregnant women.[6-17] In a pilot

study including 28 pregnant HIV-infected women, which was presented as abstract at a conference, the use of raltegravir seemed safe in both women and infants.[18]

Pregnancy is associated with considerable physiological changes such as changes in gastrointestinal, hepatic, and renal function as well as alterations in the expression and activity of transport proteins and metabolic enzymes. Pregnancy may influence the pharmacokinetic profile of antiretroviral agents and lead to decreased drug exposure. Suboptimal drug exposure can result in HIV RNA rebound, the selection of resistant virus and an increased risk of HIV-1 transmission to the infant.[19, 20] Published information on the pharmacokinetics of raltegravir during pregnancy is limited.[21, 22] Watts *et al*. describe a 50% reduction in median exposure to raltegravir during pregnancy compared to postpartum and a large variability in raltegravir pharmacokinetics. The authors report that 92% of women had an HIV RNA load of <400 copies/mL at delivery and none of the infants were confirmed to be infected. Additional well-controlled studies are needed to confirm that raltegravir can be used safely in this special patient population. We studied the effect of pregnancy on the pharmacokinetics of raltegravir and its safety and efficacy in pregnant HIV-infected women.

Methods

Study design and participants

This multi-centre, phase IV study was designed as a non-randomised, open-label trial in HIV-infected pregnant women and coordinated by the PANNA network study group. The PANNA network is a European network of 19 hospitals in seven countries with the primary aim to collect pharmacokinetic data during pregnancy on antiretroviral agents for which no or limited data are available (www.pannastudy.com). We enrolled HIV-infected pregnant women (aged ≥18 years) who were on a cART regimen containing raltegravir 400 mg twice daily. Patients were eligible for inclusion if they were on raltegravir treatment for at least two weeks prior to the first pharmacokinetic assessment in the third trimester of pregnancy. Exclusion criteria were a medical history or current condition that might interfere with drug absorption, distribution, metabolism or excretion (such as renal failure or

hepatic failure), and grade III/IV anaemia (i.e. Hb <4.6 mmol/L or <7.4 g/dL). The study was conducted in compliance with the principles of the "Declaration of Helsinki". Informed consent was obtained from each participant before undergoing any protocol-specified procedures. The study was approved by the appropriate medical ethical committee of each centre and by the national authorities where applicable. The trial is registered at ClinicalTrials.gov, number NCT00825929.

Procedures

Inclusion screening consisted of clinical evaluations (medical history and physical examination) and laboratory assays (serum biochemistry, haematology, qualitative urinalysis, HIV-1 RNA load and CD4 cell count). Blood samples for safety and efficacy assessments were obtained on pharmacokinetic sampling days and analysed at local laboratories. Adverse events were recorded at each visit and graded according to the Division of AIDS (DAIDS) toxicity table (2004). Infant birth weight, gestational age at birth, congenital abnormalities and HIV infection status were collected. Safety outcomes were maternal adverse events and congenital abnormalities. Efficacy outcomes were an undetectable HIV RNA load (<50 copies/mL) measured at or prior to delivery, and infant HIV infection status measured by HIV DNA Polymerase Chain Reaction test.

Pharmacokinetic assessment took place in the third trimester (approximately at week 33) and at least two weeks postpartum (approximately 4-6 weeks postpartum). Blood samples for pharmacokinetic assessment were collected during a 12-hour period at 0 (pre-dose), 0.5, 1, 2, 3, 4, 6, 8, 12 hours after observed intake of 400 mg of raltegravir after a standard breakfast (650kCal; 30g fat). Where possible umbilical cord blood (CB) and matching maternal blood samples were obtained at delivery to assess placental transfer. Plasma was separated and stored at ≤-18°C until shipment on dry ice to the laboratory of the Pharmacy of the Radboud University Medical Center (Nijmegen, The Netherlands). Concentrations of raltegravir in plasma were analyzed using validated reversed phase high-pressure liquid chromatography (HPLC) with fluorescence detection. The linear calibration ranges in plasma were 0.014-10.0 mg/L with a lower limit of quantification (LLOQ) of 0.014 mg/L. The

raltegravir assay was externally validated through the International Interlaboratory Quality Control Program for Measurement of Antiretroviral Drugs in Plasma as well as by the Proficiency Testing program of the ACTG/IMPAACT group.[16, 23]

Statistical analysis

Pharmacokinetic parameters were determined using a non-compartmental model in WinNonlin/Phoenix version 6.3 (Pharsight Corporation, CA, USA). Based on the individual plasma concentration-time data, the following pharmacokinetic parameters of raltegravir were determined: the area under the plasma concentration-time curve from 0 to 12 hours after intake using the trapezoidal rule ($AUC_{0\text{-}12h}$), the trough concentration (C_{12h}) defined as the sample taken at 12 hours, the maximum plasma concentration of the drug (C_{max}), the time to reach C_{max} (T_{max}), the apparent volume of distribution (V/F), the apparent oral clearance being the dose divided by $AUC_{0\text{-}12h}$ (CL_{ss}/F) and the apparent elimination half life (T_{half}). Patients from whom a curve was taken during pregnancy were included in demographic, safety analyses and descriptive statistics of the pharmacokinetic parameters. Pharmacokinetic parameters are reported as geometric means with 95% confidence intervals (CI). We calculated geometric means ratios (GMRs) and 90% CI of raltegravir pharmacokinetic parameters of third trimester versus postpartum using a mixed effects model in WinNonlin/Phoenix. Cord blood/maternal blood plasma concentration ratios were determined and described.

Results

Twenty-two HIV-infected pregnant women receiving raltegravir 400 mg twice daily were enrolled in 10 European hospitals during 2010 to April 2014. The characteristics of the study population are presented in table 1. Four patients (18%) were diagnosed with HIV after conception at 12, 16, 18 and 23 weeks of gestational age respectively. Of the 18 pregnant women who were already aware of their HIV-positive status, 14 were on cART at the time of conception with a median duration of

approximately five years (257 weeks). Seven patients (32%) were using raltegravir 400 mg twice daily prior to conception. If not used prior to conception raltegravir was started mainly during the second (27%) and third (32%) trimester of the pregnancy. Only two patients (9%) started a raltegravir-based regimen during the first trimester, of which one patient was still unaware of her pregnancy at that time. Various indications for raltegravir in this special patient population were presented: Raltegravir was started either as part of the first cART regimen to obtain a rapid decline in HIV RNA viral load with raltegravir as 4th agent; or added to the current regimen to optimize or intensify treatment in patients with a detectable viral load; or used as alternative to a preferred antiretroviral agent due to side effects (gastro-intestinal or hyperbilirubinemia). Concomitant HIV and non-HIV medication which could possibly influence raltegravir exposure was the use of ritonavir boosted atazanavir in four patients, the use of acid reducing agents (ranitidine 150 mg twice daily or sodium alginate as needed) in two patients, the use of a calcium carbonate supplement in two patients, and the use of a magnesium supplement (in combination with atazanavir) in one patient. All potential drug-interacting agents were used during both pharmacokinetic assessments, limiting its influence on the comparison between the exposure in third trimester versus postpartum.

Pharmacokinetic assessment in third trimester took place at a median (IQR) gestational age of 33 (32-35) weeks. A total of 21 evaluable raltegravir pharmacokinetic curves were obtained. One pharmacokinetic profile sampling was stopped at 3 hours at the volunteer's request and these plasma concentrations could only be partly included in the analysis. Pharmacokinetic assessment postpartum took place at a median (IQR) of 5 (4-6) weeks and a minimum of 3 weeks after delivery in 18 evaluable pharmacokinetic postpartum curves. Four patients did not have a postpartum curve because they withdrew consent. The mean plasma concentration-time profile of raltegravir in the third trimester and postpartum are presented in figure 1 and summary statistics of the pharmacokinetic parameters are listed in table 2.

Exposure to raltegravir, which is expressed as $AUC_{0\text{-}12h}$, was 29% lower in the third trimester compared to postpartum by intrasubject comparison. C_{max} and C_{12h} were on average 18% and 36%

lower during pregnancy. The apparent elimination half-life of raltegravir did not appear to be influenced by pregnancy. One patient in the third trimester (and none postpartum) had a C_{12h} plasma concentration below the suggested threshold of 0.020 mg/L which was associated with failure to achieve an undetectable HIV RNA load in treatment-naive patients in QDMRK.[24] Raltegravir pharmacokinetics was highly variable which is best seen in the large 90% confidence intervals around the GMR in table 1 and graphically in figure 2. Figure 2 shows the individual changes in $AUC_{0\text{-}12h}$ (A) and C_{12h} (B) of raltegravir in the third trimester of the pregnancy compared to postpartum. Although a mean decrease in raltegravir exposure (29%) and C_{12h} plasma concentrations (36%) in the third trimester was observed, considerable variation in the amount and direction of the effect is seen as well as variation between individual patients. Eleven out of 17 patients with complete paired pharmacokinetic curves (65%), showed a decrease in raltegravir exposure in third trimester compared to postpartum.

Nine umbilical cord blood (CB) samples were collected with matching maternal blood samples. The median (IQR) time between the reported last dose and CB sampling if available was 10 h (7-11 h); the median (IQR) time between CB sample and maternal sample was 0 minutes (0-4 min). The median (IQR) ratio of raltegravir CB/maternal blood was 1.21 (1.02-2.17; n=9).

No congenital abnormalities were reported. Five patients reported a total of ten adverse events which were considered not or unlikely related to the cART given. Seven events were grade 1 or 2. Grade 3 neuropatic pain was reported as a serious adverse event not related to the use of raltegravir. Other grade 3 adverse events were severe anaemia due to haemorrhagic delivery and varicella lesions.

Twenty-two infants were born and they were all tested HIV-negative. Three infants (14%) were small for gestational age (below 10th percentile of fetal-infant growth chart by Fenton[25]), which is higher than observed in the US for children born from HIV-infected women (7.3%).[26] Other pregnancy outcomes are shown in table 1 as well as the results of the maternal HIV RNA viral load measurements. In summary 3/22 patients (14%) failed to achieve an undetectable HIV RNA viral load

(<50 copies/mL) close to delivery (144, 242 and 290 copies/mL) when measured with a median (IQR) of 3 (0-4) weeks before delivery. The patient with a C_{12h} level below the threshold of 0.020 mg/L in third trimester had an HIV RNA viral load of 74 copies/mL measured in third trimester and an undetectable viral load on the day of delivery. Adherence, based on self-reporting, was good in all patients.

Discussion

In this study we evaluated the effect of pregnancy on the pharmacokinetics of raltegravir and its safety and efficacy in 22 HIV-infected women. In the third trimester of pregnancy systemic exposure (AUC) to raltegravir was on average 29% lower compared to postpartum. However, pharmacokinetics of raltegravir was highly variable and exposure was not consistently decreased in third trimester compared to postpartum. Of the 17 women with paired pharmacokinetic curves six (35%) had a higher $AUC_{0\text{-}12h}$ in third trimester. A similar effect of pregnancy on C_{12h} plasma levels was observed, leading to an average decrease of 36 % of the plasma levels seen postpartum. The magnitude of the observed effect is not considered to be of clinical importance. Similar effects of drug-interacting agents on the pharmacokinetics of raltegravir are described in the product information leaflet without special recommendation to adjust the dosage of raltegravir.[27] Viral suppression was good in our population with an HIV RNA load <400 copies/mL in all women and <50 copies/mL in 84% of women prior to delivery. The women (14%) who failed to have an undetectable viral load prior to delivery had adequate C_{12h} levels in third trimester. Only one patient had a C_{12h} level below 0.020 mg/L in third trimester, which is considered to be too low for adequate virological response in treatment-naive patients.[24] She had an undetectable viral load on the day of delivery.

The decrease in AUC (29%) in third trimester compared to postpartum was in line with the observations in a previous study with intensive pharmacokinetics of raltegravir during pregnancy from Watts *et al*..[21] They describe a more pronounced decrease of approximately 50% in AUC in third trimester compared to postpartum. Given the high rate of viral suppression at delivery and the

lack of a clear pharmacokinetic/pharmacodynamic relationship in non-pregnant adults, the authors suggest that a higher dose of raltegravir is not necessary during pregnancy. Watts *et al.* reported a median AUC of 5.4 h*mg/L (n=41) in third trimester, which is comparable to the geometric mean AUC in third trimester (5.00 h*mg/L) found in our study. The postpartum median AUC reported by Watts *et al.* was higher than the AUC we found: 11.6 h*mg/L (n=38) measured 3-14 weeks postpartum versus 7.11 h*mg/L. This difference probably causes the more pronounced decrease between third trimester and postpartum found by Watts *et al.*. Raltegravir C_{12h} levels in third trimester were comparable: 0.064 mg/L reported by Watts et al. and 0.077 mg/L in our study. The postpartum curves in our study are consistent with intensive pharmacokinetic profiles in non-pregnant HIV-infected patients in the twice daily treatment arm of the QDMRK study.[24] Geometric mean AUC and C_{12h} (n=20) of raltegravir are 5.84 h*mg/L and 0.114 mg/L respectively in the QDMRK study compared to 7.11 h*mg/L and 0.120 mg/L postpartum (n=18) in our study. This would suggest that the pharmacokinetic parameters collected at a median of 5 weeks postpartum in our study can be used as reference for the non-pregnant situation. The large inter- and intra-subject variability in raltegravir pharmacokinetics observed in our study is well recognised by others in non-pregnant populations.[28, 29] Inter-subject variability in our study might have been caused by drug-drug interactions and differences in patient characteristics. These factors together with the time of postpartum pharmacokinetic assessment could also have contributed to the differences in pharmacokinetic parameters of raltegravir postpartum between Watt *et al.* and our study.

There are many physiological changes during pregnancy that could alter distribution, metabolism and clearance of antiretroviral drugs used in pregnancy.[19, 20] During pregnancy the apparent volume of distribution increases with subsequent decreases in peak plasma concentrations, which was observed in our study as well. Alterations in drug elimination clearance during pregnancy can affect steady state concentrations. Raltegravir is primarily metabolized by uridine diphosphate glucuronosyltransferase (UGT)1A1. The potential effect of pregnancy on UGT1A1 activity has been evaluated and is believed to be increased during pregnancy.[19, 30] Jeong *et al*. suggest that the

induction of UGT1A1 expression by rising progesterone levels in pregnant women may be responsible for the increase in clearance of UGT1A1 substrates.[31] This hypothesis is not supported by our study in which the apparent elimination half-life of raltegravir in the third trimester was similar to postpartum.

Raltegravir was well tolerated during pregnancy and all of the children were tested HIV-negative. Only nine babies were exposed to raltegravir during the first trimester, with no birth defects reported. To assess prevalence rates of birth defects in infants exposed to raltegravir compared to non-exposed infants, more experience of raltegravir in human pregnancy is needed. Placental transfer of raltegravir is efficient with a median raltegravir CB/maternal plasma ratio of 1.21 in agreement with previous reports.[12, 13, 21, 32, 33] Unfortunately the collection of neonatal blood samples to describe the washout pharmacokinetics and safety of in utero exposure to raltegravir was not part of this study. UGT1A1 neonatal enzyme activity is still immature after birth and leads to prolonged elimination of raltegravir post-delivery. In newborns whose mothers were exposed to raltegravir during pregnancy raltegravir is slowly metabolized with an elimination half life that is highly variable.[9, 12, 33]

In conclusion, raltegravir was well tolerated during pregnancy in our study population. Raltegravir pharmacokinetics showed extensive inter- and intra-individual variability. Our findings show a mean decrease in exposure to raltegravir during third trimester compared to postpartum which is not considered to be of clinical importance. Raltegravir in combination with other antiretroviral agents was effective in preventing MTCT by reducing and/or maintaining HIV RNA viral load at an undetectable (<50 copies/mL) or low level (<400 copies/mL). Our data support the use of raltegravir in standard dosages in HIV-infected pregnant women for the prevention of MTCT.

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Potential conflicts of interest

AH has received honoraria from Abbvie, Bristol-Myers Squibb, Gilead, Janssen, Merck Sharp & Dohme Corp, Viiv. JM has received research funding, consultancy fees, and lecture sponsorships from and has served on advisory boards for Merck Sharp & Dohme Corp, Abbvie, Boehringer Ingelheim, Gilead Sciences, Viiv, Janssen-Cilag and Bristol-Myers Squibb. AG reports personal fees from Merck Sharp & Dohme Corp, Boehringer Ingelheim, Bristol-Myers Squibb. DB has received honoraria and/or study grants from Tibotec, Merck Sharp & Dohme Corp, Abbott, Bristol-Myers Squibb, Roche, Gilead and GlaxoSmithKline. GT has received honoraria from Abbvie. CG has received honoraria and lecture sponsorships from Viiv Healthcare, GlaxoSmithKline, Gilead Sciences and Sanofi Pasteur MSD. ME has served on advisory boards for Merck Sharp & Dohme Corp. All other authors report no potential conflicts of interest.

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Table 1. Patient characteristics and pregnancy outcomes.

Characteristics (n=22)	
Age at delivery (years)	33 (29-36)
Race/ethnicity	
White	9 (41%)
Black	12 (55%)
Other	1 (5%)
Smoking	0 (0%)
Alcohol use	0 (0%)
Drug use	0 (0%)
ARV treatment at start of pregnancy	14 (64%)
Median ARV treatment duration before pregnancy (weeks)	257 (110-440)
Start raltegravir	
Before conception	7 (32%)
1st trimester	2 (9%)
2nd trimester	6 (27%)
3rd trimester	7 (32%)
Concomitant ARVs	
NRTI	15 (68%) [11 (50%) tenofovir + emtricitabine; 3 (14%) tenofovir; 1 (5%) zidovudine + lamivudine]
Protease inhibitors‡	13 (59%) [8 (36%) DRV/r; 3 (14%) ATV/r; 2 (9%) LPV/r]
NNRTI	2 (9%) etravirine
Entry inhibitor	2 (9%) maraviroc

Third trimester (n=22)	
Gestational age (weeks)	33 (32-35)
Weight (kg)	73 (67-79)
HIV RNA detectable >50 copies/mL	3 (14%) [74 copies/mL; 144 copies/mL; 242 copies/mL]
CD-4 count (copies/uL)#	622 (240-756)
Delivery (n=22)	
Gestational age (weeks)	38 (38-39)
Caesarian section#	11 (52%)
HIV RNA detectable closest to delivery >50 copies/mL	3 (14%) [144 copies/mL; 242 copies/mL; 290 copies/mL]
Time between HIV RNA measurement and delivery (weeks)	3 (0-4)
Postpartum (n=18)	
Time after delivery (weeks)	5 (4-6)
Weight (kg)	64 (59-72)
HIV RNA detectable >50 copies/mL†	2 (12%) [99 copies/mL; 650 copies/mL]
CD-4 count (cells/uL)	585 (266-806)
Pregnancy outcomes	
Birth weight (grams) (n=22)	3115 (2628-3360)
Small for gestational age‡	3 (14%)
Infant HIV DNA PCR test negative	22 (100%)

Data are n(%) or median and interquartile range (IQR)

ARV, antiretroviral; ATV/r, atazanavir/ritonavir; DRV/r, darunavir/ritonavir; LPV/r, lopinavir/ritonavir; (N)NRTI, (non)nucleoside reverse transcriptase inhibitor; PCR, polymerase chain reaction.

ǂ One subject stopped DRV/r before delivery and one subject switched from LPV/r to ATV/r during pregnancy (prior to pharmacokinetic assessments); Available for: #21 patients, † 17 patients

‡ Small for gestational age was determined as below the 10th percentile of the fetal-infant growth chart by Fenton (reference).

Table 2. Pharmacokinetic parameters raltegravir during third trimester of pregnancy and postpartum

	Third trimester[a] (n=21)		Postpartum[a] (n=18)		GM ratio (90% CI) of third trimester : postpartum (n=17)	
$AUC_{0\text{-}12h}$ (h*mg/L)	5.00	(3.56-7.01)	7.11	(4.91-10.30)	0.71	(0.53-0.96)
C_{max} (mg/L)	1.43	(0.93-2.22)	1.76	(1.10-2.80)	0.82	(0.55-1.23)
T_{max} (h)	1.98	(0-11.3)	2.03	(0-7.97)		
C_{12h} (mg/L)	0.077	(0.043-0.137)	0.120	(0.074-0.193)	0.64	(0.34-1.22)
t_{half} (h)	2.55[b]	(1.88-3.45)	2.53[c]	(1.91-3.36)	1.04	(0.73-1.47)
CL_{ss}/F (L/h)	80.1	(57.0-112)	56.2	(38.8-81.4)	1.41	(1.04-1.90)
V/F (L)	311[b]	(159-607)	205[c]	(115-367)	1.24	(0.67-2.27)

AUC, area under the curve; CI, confidence interval; GM, geometric mean.

[a]All values are GM (95% CI) except for Tmax [median (minimum–maximum)].

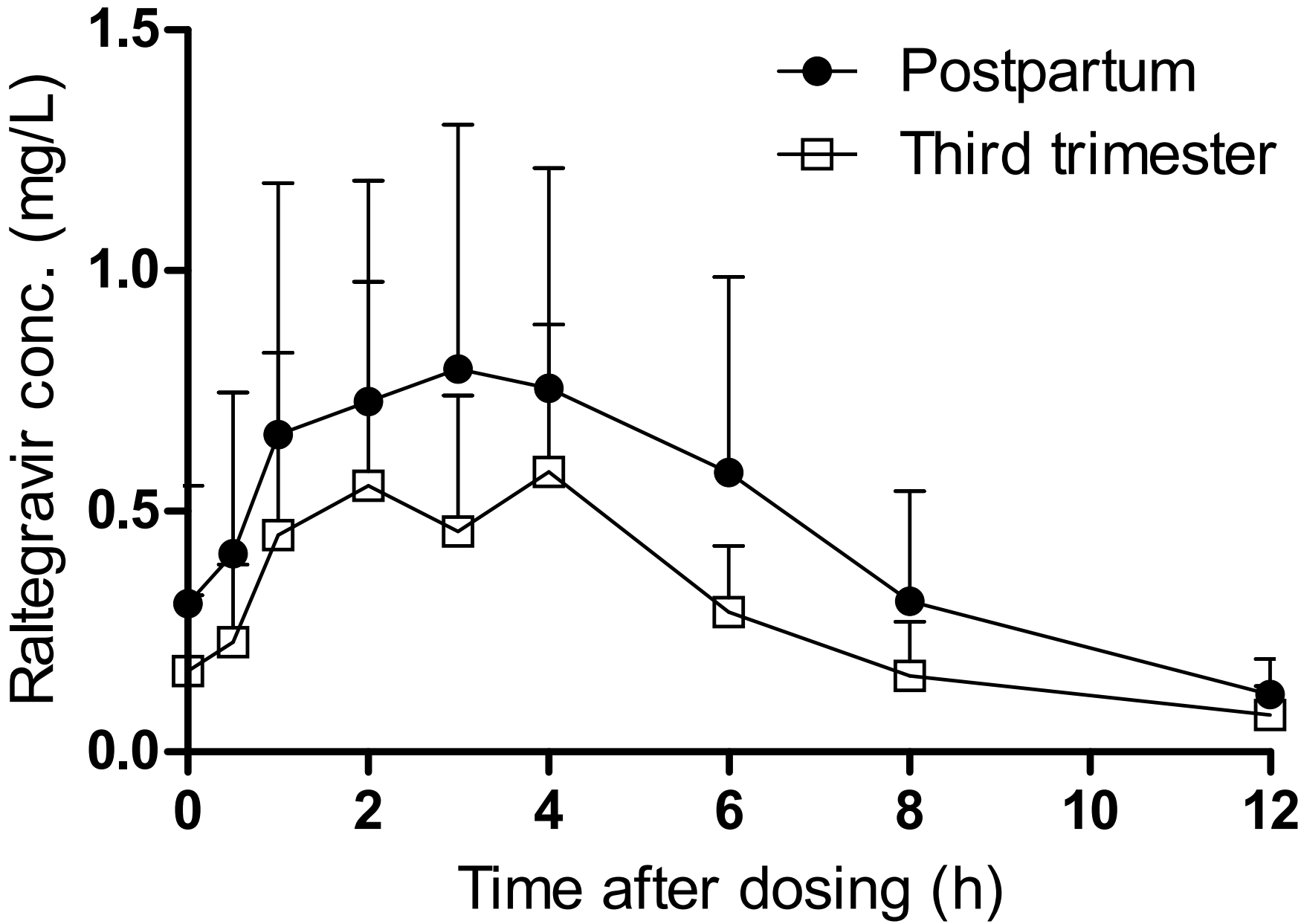
[b]Available for 15 patients; [c]Available for 14 patients.

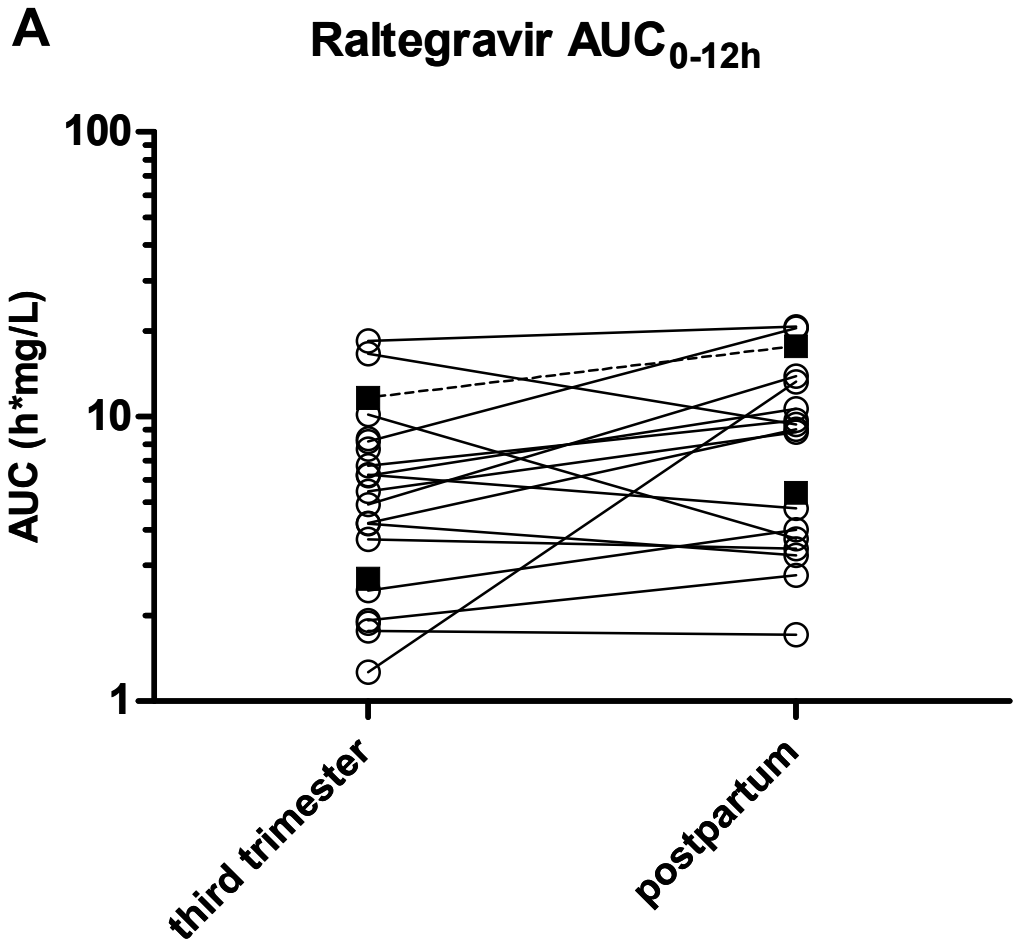
Figure legends

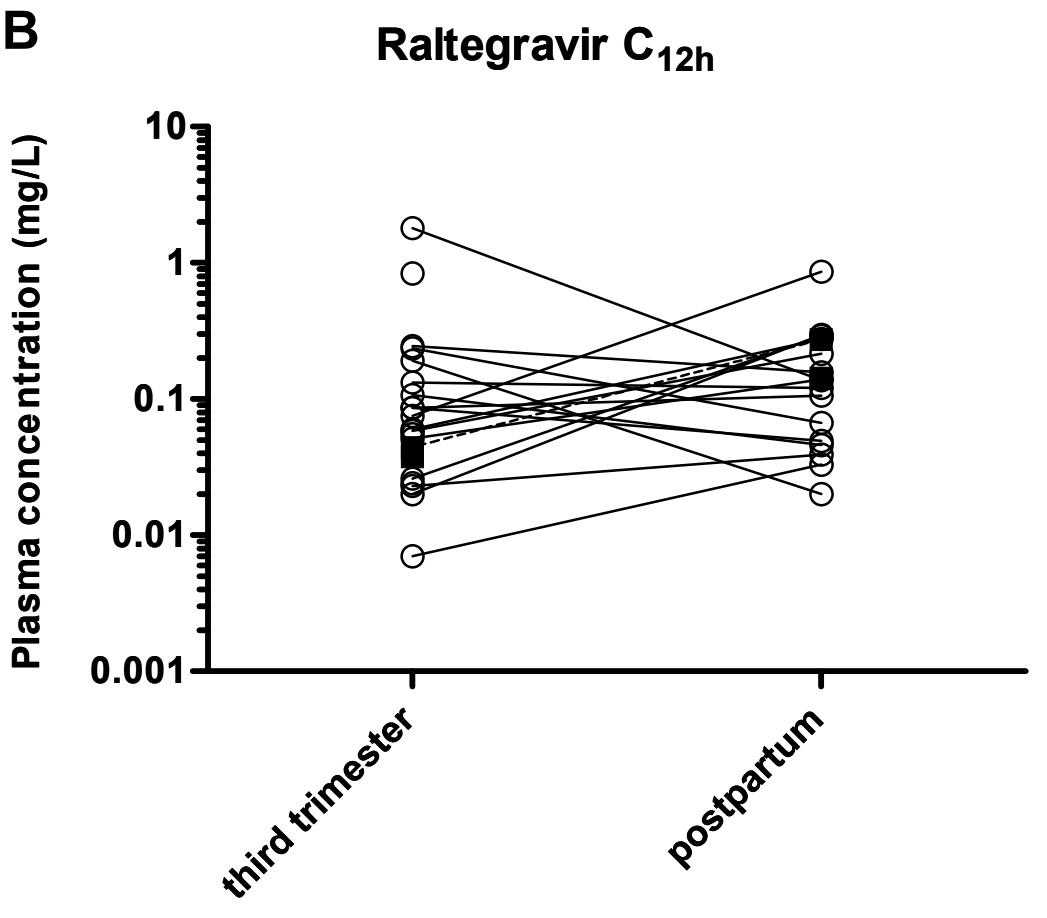
Figure 1: Geometric mean (+upper 95% confidence interval) raltegravir concentration-time profiles during the third trimester of pregnancy (open squares) and postpartum (filled circles).

Figure 2: Individual raltegravir $AUC_{0\text{-}12h}$ (A) and C_{12h} (B) parameters during the third trimester of pregnancy and postpartum

Symbols: Filled square ■ is a detectable (≥50 copies/mL) and an open circle ○ is an undetectable (<50 copies/mL) HIV RNA load close to delivery.


Postpartum
Third trimester
Raltegravir conc. (mg/L)
1.5
1.0
0.5
0.0
0
2
4
6
8
10
12
Time after dosing (h)


A
Raltegravir AUC0-12h
100
10
1
AUC (h*mg/L)
third trimester
postpartum


B
Raltegravir C_{12h}
Plasma concentration (mg/L)
10
1
0.1
0.01
0.001
third trimester
postpartum