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Effect of HIV Infection and Menopause Status on Raltegravir Pharmacokinetics in the Blood and Genital Tract

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Abstract

Background—This study describes first dose and steady state pharmacokinetics of raltegravir (RAL) in cervicovaginal fluid (CVF) and blood plasma (BP).

Methods—Three cohorts of women were enrolled sequentially in a single-site, open-label pharmacokinetic study of oral raltegravir 400 mg twice daily: HIV-negative premenopausal, HIV-infected premenopausal, and HIV-infected postmenopausal women. BP and CVF were collected over 12 hours after a single observed dose and at steady state. RAL concentrations were measured by HPLC-MS methods. Data are expressed as median (interquartile range [IQR]). The ANOVA rank sum test was used to evaluate between-group differences in steady state raltegravir exposure ($AUC_{0\text{-}12h}$).

Results—First dose PK was obtained in HIV-negative premenopausal women and HIV-infected postmenopausal women only. The median(IQR) BP $AUC_{0\text{-}12h}$ was 3099(985-5959) and 4239(2781-13695)ng*hr/mL and the median(IQR) CVF $AUC_{0\text{-}12h}$ was 1720(305-5288) and 13797(11066-19563)ng*hr/mL for HIV-negative premenopausal and HIV-infected postmenopausal women, respectively. All cohorts contributed to steady state pharmacokinetic profiles. Median(IQR) BP $AUC_{0\text{-}12h}$ did not differ between the groups: 8436(3080-10111), 5761(1801-10095) and 6180(5295-8282)ng*hr/mL in HIV-negative premenopausal, HIV-infected premenopausal, and HIV-infected postmenopausal women, respectively. There was a trend for lower CVF $AUC_{0\text{-}12h}$ among HIV-negative women 3164(1156-9540) compared to 11465(9725-17138) and 9568(4271-24306)ng*hr/mL HIV-infected premenopausal, and HIV-infected postmenopausal women, respectively, but this was not statistically significant (p=0.08). HIV-negative premenopausal women had a median(IQR) CVF:BP $AUC_{0\text{-}12h}$ ratio of 0.46(0.2-1.1),

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Disclosures

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whereas HIV-infected premenopausal and postmenopausal women had median(IQR) CVF:BP $AUC_{0\text{-}12h}$ ratio of 3.9(1.2-6.7) and 1.4(0.7-4.3), respectively.

Conclusions—This is the first study to investigate RAL exposure in BP and CVF in premenopausal HIV-negative and pre and postmenopausal HIV-infected women. These data indicate HIV and menopausal status may influence antiretroviral distribution into the female genital tract.

Keywords

Raltegravir; Female Genital Tract; Pharmacokinetics

Introduction

Worldwide, the incidence of HIV remains relatively stable despite improved global availability of potent antiretroviral therapy [1]. The primary route of transmission for new HIV infections is sexual contact [2]. Consistent suppression of plasma viral load with antiretroviral therapy reduces transmission [3]. However, sexual transmission of HIV infection on antiretroviral therapy can still occur[4] presumably due to persistent HIV replication in the genital tract of source patients [5,6]. Additionally, with emerging evidence suggesting that cells in tissues may continue to produce low levels of HIV despite suppression with antiretroviral therapy[7], eradicating virus from susceptible anatomical sites like the female genital tract may be an important goal for HIV cure.

The unique mechanism of action of integrase strand inhibitors (INSTI) may make this class particularly well suited to suppress HIV replication in the genital tract. Raltegravir (Isentress®, Merck Sharp & Dohme Corp, Whitehouse, NJ, USA), the first of three FDA approved INSTIs, is potent and well-tolerated [8]. We have previously demonstrated that raltegravir rapidly distributes to gut-associated lymphoid and rectal tissue with high exposure [9]. Characterizing the extent to which raltegravir penetrates into the female genital tract will assist in determining raltegravir's potential utility for primary and secondary HIV prevention and HIV eradication. This study aimed to characterize the first dose and steady state pharmacokinetics of raltegravir in cervicovaginal fluids (CVF) and blood plasma (BP) in three populations of female volunteers who would be candidates for primary and secondary HIV prevention and eradication: HIV-negative premenopausal women, HIV-infected premenopausal women, and HIV-infected postmenopausal women.

Methods

Study Design and Subject Selection

This was an open-label, single-center pharmacokinetic study of oral raltegravir 400mg dosed twice daily in three unique female cohorts: HIV-negative premenopausal women, HIV-infected premenopausal women, and HIV-infected postmenopausal women. Each of the three study protocols were approved by the UNC Biomedical Institutional Review Board, and registered on clinicaltrials.gov under the identifiers NCT00961272, NCT00746499, and NCT00666055, respectively. All study activities were carried out in accordance with the ethical standards of the International Conference on Harmonization E6 Good Clinical

Practice Guidance. Informed consent was obtained from all participants prior to any study activities. HIV-negative premenopausal women were enrolled between August and October 2008, HIV-infected premenopausal women were enrolled between July 2009 and January 2010, and HIV-infected postmenopausal women were enrolled between May 2008 and December 2010. At the time of study initiation, raltegravir was a newly approved "first in class" antiretroviral, which limited the number of women of childbearing potential receiving raltegravir for HIV treatment as well as providers willing to switch virologically-suppressed women to raltegravir. Therefore, to facilitate enrollment HIV-infected premenopausal women already on raltegravir as part of their HAART regimen were recruited. HIV-infected postmenopausal women were raltegravir naïve at the time of enrollment.

All subjects underwent intensive screening within 28 days prior to enrollment. Screening procedures consisted of a complete medical history review, physical examination, and comprehensive laboratory studies, including screening for sexually transmitted infections such as syphilis, gonorrhea, chlamydia and trichomoniasis. Subjects were excluded for any clinically relevant biochemical, physical or pelvic abnormalities, or other clinical condition deemed to increase subject risk or to potentially compromise study results. Additionally, women were excluded if they had an allergy to any component of the study product, were on a concomitant medication that had the potential to change the typical pharmacokinetic parameters by ≥30%, or were receiving hormone replacement therapy (ie oral, topical, or transdermal estrogen preparations or androgen replacement). Subjects were not eligible if they were unwilling or unable to remain abstinent from all sexual activity and insertion of all vaginal products starting 72 hours prior to enrollment until study completion, to limit alcohol consumption to <14 beverages per week, and to limit acetaminophen use to <1gm/day. Premenopausal subjects were eligible if they had a fully intact genital tract; documentation of a normal Pap smear within the previous year; screened negative for sexually transmitted diseases and bacterial vaginosis; and were willing to use at least one of the following forms of acceptable contraception for the duration of the study: abstinence, bilateral tubal ligation, condoms with spermicide or foam, stable male partner with vasectomy, female only partners, or oral hormonal contraception (started at least 3 months prior to enrollment).

Cohort-specific enrollment criteria were also defined. HIV-negative premenopausal women were required to be 18-49 years of age (inclusive at the date of screening), have regular menstrual cycles, and have a body mass index (BMI) of 18-30kg/m^2 with total body weight greater than 50kg. These women underwent anonymous HIV testing using a standard HIV 1/2 ELISA (Abbott Laboratories, Abbott Park, IL) with pooled HIV-1 PCR testing to confirm that they were HIV-negative. All HIV-infected women were required to have at least one positive HIV test or detectable plasma HIV RNA prior to, or during the screening process. HIV-infected premenopausal women were eligible if they were 18-49 years of age; had been receiving raltegravir 400mg twice daily for at least 3 weeks as part of their HAART regimen; and had missed ≤ 6 raltegravir doses in the month prior and no doses in the 3 days prior to the pharmacokinetic visit. HIV-infected postmenopausal women were eligible if they were 18 years or older and their last menstrual period occurred >12 months from the time of screening without another identifiable etiology for amenorrhea. Biochemical confirmation of menopause was performed at screening and defined as an

estradiol level <20 pg/mL with a follicle stimulating hormone level of > 35 mIU/mL. Postmenopausal subjects with hysterectomy and/or oophorectomy at least 6 months prior to enrollment were eligible. Lastly, HIV-infected postmenopausal women were eligible if they were raltegravir naïve and either initiating as part of their first regimen or changing to a new regimen containing raltegravir 400mg twice-daily.

Study Visits

Vital signs, serum chemistries, and complete blood counts were performed at each study visit. Pregnancy tests were administered before each visit for all premenopausal women. Women were assessed for medication adherence and adverse events with a standardized daily questionnaire while on study. HIV-negative premenopausal and HIV-infected postmenopausal subjects demonstrating at least 80% compliance to study drug during the study period were eligible for the second PK visit. All adverse events were graded using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events [10].

The initial PK evaluation occurred within 5-7 days following the end of premenopausal subjects' menses. Study drug was provided by Merck Sharp & Dohme Corp (Whitehouse, NJ, USA) for the HIV-negative volunteers and self-supplied by HIV-infected volunteers. After confirming eligibility, subjects were admitted to the Clinical Translational Research Center (CTRC) the evening before each intensive pharmacokinetic (PK) evaluation. All doses immediately preceding pharmacokinetic sampling were observed by study staff. Premenopausal subjects received a standard 500 kcal, 20-25 gm fat meal 30 min before dosing, whereas postmenopausal subjects were fasting for a minimum of 8 hours before dosing.

Sample Collection and Processing

Nine paired BP and CVF samples were collected at pre-dose and at 0.5, 1, 2, 3, 4, 6, 8, and 12 hours post dose on Day 1 (first dose) and on Day 7 (steady state) from HIV-negative premenopausal women. Eight paired samples were collected at 0.5, 1, 2, 4, 6, 8, 10, and 12 hours post dose from HIV-infected premenopausal women already dosed to steady state conditions at the time of enrollment. Seven paired samples were collected at pre-dose and at 1, 2, 4, 6, 8, and 12 hours post dose on Day 1 (first dose) and Day 30 (steady state) from HIV-infected postmenopausal women.

Whole blood was collected using 3ml K_2EDTA tubes (BD Diagnostics, Franklin Lakes, NJ, USA) and centrifuged at 1300g at 4°C for 15 minutes. Approximately 1.5ml of BP from each sample was aliquoted into labeled cryovials and stored at −80°C until analysis. CVF was self-collected via direct aspiration with an aspiration device as previously described[11,12], transferred to labeled cryovials, and stored at −80°C until analysis.

Sample Analyses

BP and CVF were analyzed using high performance liquid chromatography with mass spectrometry detection (HPLC-MS) methods validated by the UNC Center for AIDS Research (CFAR) Clinical Pharmacology and Analytical Chemistry Core [13,14]. The

dynamic range for raltegravir in BP was 20-10,000ng/mL and in CVF was 50-10,000ng/mL with a minimum of 90% accuracy, and inter-and intra-day variability of 2.4-7.9% and 1.4-3.8%, respectively [15-17].

Statistical Analysis

The sample size for each cohort of women was pragmatically chosen to generate preliminary pharmacokinetic data adequate for understanding penetration of raltegravir into the female genital tract. Subject demographic information was collected, summarized descriptively and presented as median (range). Pharmacokinetic parameters were estimated using noncompartmental methods (Phoenix WinNonlin Pro 6.3; Certara, L.P., St. Louis, MO, USA). Maximum concentration (C_{max}), time at maximum concentration (T_{max}), and concentration 12 hours after dosing (C_{12h}) were determined by visual inspection of the subject profiles, and the log-linear trapezoidal method was used to calculate the area-under-the-concentration-time-curve over the 12-hour dosing interval ($AUC_{0\text{-}12h}$). Sample concentrations below the limit of quantification were imputed at 50% the lower limit of quantification. Sample concentrations below the limit of detection were assigned 0.1ng/ml. Descriptive statistics using SigmaPlot 11.0 Software (Systat Software Inc, San Jose, CA, USA) were performed. An ANOVA rank sum test with Bonferroni corrections for multiple comparisons were conducted for steady state $AUC_{0\text{-}12h}$. Pharmacokinetic data are presented as median (interquartile range [IQR]) for BP and CVF. Accumulation ratios were calculated utilizing the equation: steady state $AUC_{0\text{-}12h}$ ÷ first dose $AUC_{0\text{-}12h}$.

Results

Demographics

A total of 18 women (7 HIV-negative premenopausal; 6 HIV-infected premenopausal; and 5 HIV-infected postmenopausal) underwent intensive pharmacokinetic sampling. Demographic information for the three groups of women is summarized in Table 1. The age of HIV-negative premenopausal women, HIV-infected premenopausal women, and HIV-infected postmenopausal women ranged from 19-46, 29-45, and 45-68 years, respectively. While 100% of HIV-negative women were white, the majority of both HIV-infected groups were black. HIV-infected premenopausal women had a median BMI that was 24-33% higher. The majority of HIV-infected women were on a regimen that included either raltegravir with tenofovir disoproxil fumarate plus emtricitabine (TDF/FTC, Truvada®, Gilead Sciences, Foster City, CA) or raltegravir with TDF/FTC and a protease inhibitor (PI). One HIV-infected participant's regimen included a PI with maraviroc, a CCR5 antagonist, and etravirine, a non-nucleoside reverse transcriptase inhibitor (NNRTI). The average time on raltegravir for HIV-infected premenopausal women was approximately one year prior to pharmacokinetic evaluation. Two of the 5 HIV-infected postmenopausal women were HAART-naïve prior to enrollment.

Pharmacokinetic Analysis

First Dose Conditions

First dose PK was obtained in HIV-negative premenopausal women and HIV-infected postmenopausal women only. The concentration-time profiles in BP and CVF of these two groups of women are graphically depicted in Figure 1. Raltegravir demonstrated rapid absorption following oral administration. Within 1 hour of dosing, all subjects in both groups had detectable concentrations of raltegravir in BP.

In CVF, only 2 of 7 subjects from the HIV-negative group had quantifiable raltegravir concentrations by 4 hours post-dose with a median T_{max} of 8 hours. Additionally, HIV-negative women exhibited relatively low exposure [median (IQR) $AUC_{0\text{-}12h}$=1720 (305-5288) hr*ng/mL]. Raltegravir CVF concentrations were detected as early as 1 hour after the first dose for 3 of the 5 HIV-infected postmenopausal women with a median T_{max} of 12 hours. We observed relatively high exposure [median (IQR) $AUC_{0\text{-}12h}$=13797 (11066-19563) hr*ng/mL] in the CVF of HIV-infected postmenopausal women. The pharmacokinetic estimates and CVF:BP $AUC_{0\text{-}12h}$ ratios of raltegravir are shown in Table 2. There was a large degree of variability around the point estimates for both groups. The median CVF:BP ratio was 0.4 (0.07-2.0) in HIV-negative premenopausal women and 4 (1.0-5.4) in HIV-infected postmenopausal women.

Steady State Conditions

All three groups of women contributed to steady state pharmacokinetic profiles. The steady state BP and CVF concentration time profiles are graphically depicted in Figures 2A and 2B, respectively. There were no significant differences in BP $AUC_{0\text{-}12h}$ between any of the groups (Table 3). The C_{12h} appeared to be highest in the CVF of HIV-infected postmenopausal women [958 (313-1252) ng/mL] compared to HIV-negative premenopausal women [0.1 (0.1-798) ng/mL] and HIV-infected premenopausal women [447 (181-546) ng/mL]. The median (IQR) CVF $AUC_{0\text{-}12h}$ appeared lower in HIV-negative premenopausal women [3164 (1156-9540) ng*hr/mL] compared to the HIV-infected premenopausal women [11465 (9725-17138) ng*hr/mL], and HIV-infected postmenopausal women [9568 (4271-24306) ng*hr/mL]. However, this trend was not statistically different (p=0.08).

At steady state, the HIV-negative women demonstrated a median CVF:BP $AUC_{0\text{-}12h}$ ratio of 0.46 (0.2-1.1). In contrast, HIV-infected premenopausal women and postmenopausal women demonstrated median ratios of 3.9 (1.2-6.7) and 1.4 (0.7-4.3), driven primarily by differences in CVF pharmacokinetics. With repeated dosing, HIV-negative premenopausal women exhibited a 1.5- and 3-fold increase in raltegravir CVF and plasma exposure, respectively. CVF and BP exposure was nearly equivalent (1.3-fold and 0.9-fold change with repeated dosing) in HIV-infected postmenopausal women.

Discussion

This study characterizes raltegravir exposure in the genital tract of HIV-negative premenopausal women and HIV-infected postmenopausal women following a single dose. With the first dose of raltegravir, we observed a high degree of penetration into the genital

tract of HIV-infected postmenopausal women with a (median CVF:BP AUC=4). In HIV-negative premenopausal women exhibited only a modest degree of penetration into the genital tract with a (median CVF:BP AUC=0.4). Although not statistically significant (p=0.08), steady state exposure in the female genital tract appeared to be lowest in HIV-negative premenopausal women suggesting altered mechanisms of drug distribution. These findings are important considerations as antiretrovirals are evaluated for prevention strategies such as pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) in HIV-negative individuals, as well as treatment as prevention (TasP) in HIV-infected individuals.

In the clinical setting, raltegravir exhibits large inter- and intra-individual variability in plasma pharmacokinetics, which does not impact systemic virologic outcomes in HIV-infected individuals receiving 400mg twice daily [18]. Raltegravir is primarily eliminated by glucuronidation via uridine-diphosphate glucuronosyltransferase (UGT)1A1 and, to a lesser extent, renally excreted [19]. Differences in UGT1A1 polymorphisms and glomerular filtration rates may account for the wide inter-individual variability in plasma raltegravir exposure observed in this and other studies. Similarly wide variability in raltegravir exposure was observed in genital secretions following single or multiple doses (Figures 1 and 2).

Under steady state conditions, CVF exposure between HIV-negative premenopausal women, HIV-infected premenopausal women, and HIV-infected postmenopausal women exhibited a non-significant trend towards lower exposure in HIV-negative premenopausal women. Normalizing the genital tract exposure to BP exposure did not correct this trend, suggesting local influences within the vaginal and cervical mucosa. Recently, the expression of drug transporters within the vaginal and cervical mucosa has been investigated. Our group[20] and others[21] have identified high expression of drug efflux transporters (including p-glycoprotein) in the female genital tract. P-glycoprotein expression in the female genital tract negatively correlates with age and, in one study, was decreased by 17% in postmenopausal women compared to premenopausal women [20]. Given that raltegravir is a p-glycoprotein substrate[23], our finding that raltegravir exposure in the female genital tract is 4 and 1.4-fold higher than the BP after single and repeated doses for postmenopausal women is consistent with decreased p-glycoprotein expression and activity.

The expression of p-glycoprotein and other MDR1 transporters is also regulated by inflammatory cytokines released during pro-inflammatory states through complex modulation pathways [24,25]. For example, the pro-inflammatory cytokines, IL-6 and IL-1β, have been shown to modestly attenuate p-glycoprotein and BCRP expression, whereas TNF-alpha strongly augments p-glycoprotein and attenuates BCRP [26]. Although beyond the scope of the current investigation, it is possible that low-grade inflammation in the female genital tract of HIV-infected women results in attenuated p-glycoprotein expression and subsequently increased raltegravir exposure. In support of this notion, higher raltegravir exposure in the CVF compared to the BP has been previously observed in women with bacterial vaginosis [27]. In our study, 2 of 5 postmenopausal women were provided a full course of treatment for bacterial vaginosis but not rescreened prior to enrollment. Additionally, genital HIV RNA positively correlates with IL-6 and IL-1β in the female genital tract[28] and has been observed in women on antiretroviral therapy despite

undetectable plasma HIV RNA [5]. Thus, the trend towards increased raltegravir exposure in HIV-infected women vs negative women may be due to attenuated p-glycoprotein efflux transporter expression secondary to inflammation in the genital tract. Finally, the inter-individual variability of raltegravir exposure in the genital tract may be reflecting the differential hormonal and inflammatory states in our participants.

Our previous work has demonstrated marked differences in penetration of antiretrovirals both within and between therapeutic drug classes in the female genital tract [11,29]. Pertinent to this study, the second-generation INSTI, dolutegravir, has relatively low distribution in the female genital tract when compared to BP with a CVF:BP AUC ratio of 0.07 [30]. In comparison, raltegravir exposure in all three groups of women was considerably higher (eg, ≥ 0.4). In the HIV-infected pre- and postmenopausal women, raltegravir genital tract exposure is 1.4- to 4-fold higher than BP, respectively. Given this relatively high penetration, coupled with the recent reformulation to facilitate once daily dosing [31], raltegravir may be well-suited for primary and secondary prevention.

All women undergo alterations in endogenous hormones across the lifespan yet studies exploring the effect of hormones on antiretroviral pharmacokinetics have focused on pregnancy and contraception [32,33]. Observational data suggests exogenous hormones administered for contraception may affect HIV acquisition and transmission[34] theoretically due to changes in the female genital tract environment. As the population of aging women infected with, or susceptible to, HIV continues to increase[35], quantifying antiretroviral pharmacokinetics and pharmacodynamics in older women will become increasingly important. Previous studies have not compared genital tract exposure of antiretroviral agents in HIV-negative and HIV-infected women or women of different menopausal status. These data indicate HIV infection and menopausal status may influence local raltegravir disposition and potentially other antiretroviral pharmacokinetics. Taken together, these findings illustrate the complexity and unpredictability of antiretroviral pharmacokinetics in the female genital tract.

The lack of any statistically significant differences in steady state $AUC_{0\text{-}12h}$ may be a consequence of the small sample size as suggested by the lower exposure in HIV-negative premenopausal women. Despite this limitation, these data provide reasonable estimates of central tendency that support the need for larger clinical studies to confirm our findings. The lack of first dose pharmacokinetics in HIV-infected premenopausal women does not allow for full pharmacokinetic comparisons of the three cohorts. Additionally, the lack of an HIV-negative postmenopausal cohort makes discerning the effect of HIV infection vs menopausal status on raltegravir pharmacokinetics difficult. The differing proportion of black women among our cohorts are unlikely to confound the pharmacokinetic data presented herein, given that the Raltegravir early therapy in African-Americans living with HIV (REAL) study did not identify any raltegravir plasma pharmacokinetic differences based on race[15]. Finally, in our study premenopausal women received raltegravir in the fed state while postmenopausal women were in the fasted state. Administration of a moderate fat meal results in clinically insignificant changes in raltegravir AUC, C_{max}, and C_{12h}, which are increased by 13%, 5%, and 66%, respectively[19]. Given that our fasted postmenopausal group tended to exhibit higher raltegravir PK parameters, it is unlikely that the

pharmacokinetic findings reported herein can be attributed to these methodological differences.

In summary, these data indicate that HIV and menopausal status may be important influencers of the distribution of antiretrovirals into the female genital tract. HIV-negative premenopausal women had the lowest relative penetration (0.46) of raltegravir into the CVF of all three groups of women in our study. In comparison, raltegravir exposure in the genital tract of HIV-infected women was 3.9-fold and 1.4-fold higher than BP for pre and postmenopausal women, respectively. Given that genital tract penetration was enhanced in both groups of HIV-infected women, raltegravir may be a favorable option when choosing an INSTI-containing regimen for women such as those in an HIV serodiscordant relationship. While the concentrations of raltegravir necessary to suppress HIV in the female genital tract have yet to be determined, our findings indicate raltegravir effectively penetrates the site most commonly associated with HIV acquisition and transmission in women worldwide. The prospect of a once daily formulation may support raltegravir as a preferred INSTI for various prevention strategies such as TasP, PrEP and PEP.

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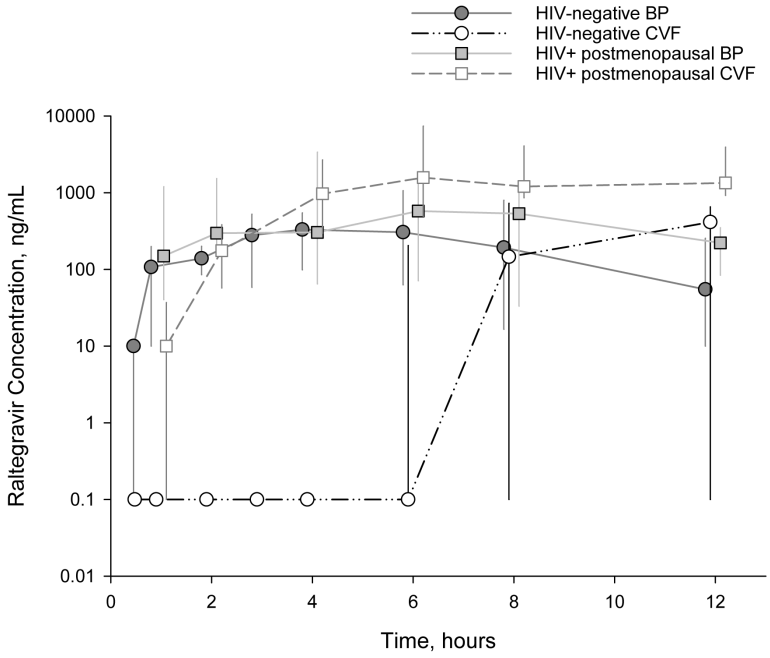

Figure 1.

Median (IQR) raltegravir concentrations over time in the blood plasma (BP) and cervicovaginal fluid (CVF) following a single dose of raltegravir in HIV-uninfected women and HIV-infected postmenopausal women

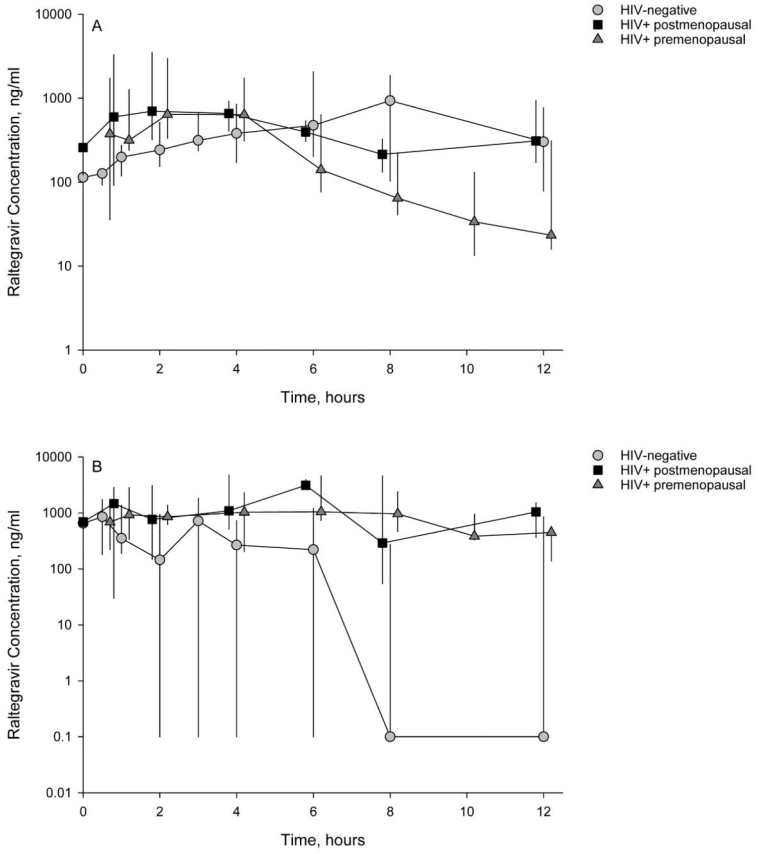

Figure 2.

Median (IQR) raltegravir concentrations over time in the (A) blood plasma (BP) and (B) cervicovaginal fluid (CVF) at steady state in HIV-uninfected women, HIV-infected premenopausal women and HIV-infected postmenopausal women.

Table 1

Subject Demographics

Characteristic[a]	HIV-negative Premenopausal (n=7)	HIV-infected Premenopausal (n=6)	HIV-infected Postmenopausal (n=5)
Age, years	21 (19-46)	42 (33-45)	54 (45-68)
Race/Ethnicity[b]			
Black	0 (0)	5 (83)	3 (60)
White	7 (100)	1 (17)	2 (40)
Weight, kg	65 (52-73)	98 (73-115)	71 (62-83)
BMI, kg/m^2	23.5 (20.8-27.1)	35.4 (27.4-44.2)	26.8 (23.9-28.5)
Other ART[c]			
TDF/FTC	N/A	2 (33)	2 (40)
TDF/FTC + PI	N/A	4 (67)	1 (2)
NNRTI + PI + MVC	N/A	0 (0)	1 (2)
PI	N/A	0 (0)	1 (2)
HIV diagnosis, years	N/A	15 (2-18)	13.4 (4-20)

ART=antiretroviral therapy; FTC=emtricitabine; MVC=maraviroc; NNRTI=non-nucleoside reverse transcriptase inhibitors; PI=protease inhibitors; TDF=tenofovir disoproxil fumarate

[a]Median (range)

[b]Number (%)

[c]Antiretrovirals (in addition to raltegravir): PI=darunavir/ritonavir, lopinavir/ritonavir, and atazanavir/ritonavir; NNRTI=etravirine

Table 2

First Dose Raltegravir Non Compartmental Analysis

PK Estimate[a]	HIV-negative PreMW (n=7)		HIV-infected PostMW (n=5)	
	BP	CVF[b]	BP	CVF
C_{max}, ng/mL	790 (263-2123)	607 (109-1253)	1664 (511-2803)	4778 (1432-6683)
T_{max}, hr	6 (3-6)	12[c] (8-12)	8 (4-9)	8 (6-12)
C_{12}, ng/mL	54 (10-225)	415 (57-643)	222 (116-311)	1288 (602-2245)
AUC $_{0\text{-}12h}$, hr*ng/mL	3099 (985-5959)	1720 (305-5288)	4239 (2781-13695)	13797 (11066-19563)
CVF:BP AUC	0.4 (0.07-2.0)		4 (1.0-5.4)	

[a] Median (IQR)

[b] 75% of first dose CVF samples collected post dose were BLD, and all samples collected over the dosing interval for two subjects were BLD. BLD PK parameters were imputed as 0.1 ng/ml for statistical analysis.

[c] Excludes PK estimates for two subjects who exhibited undetectable CVF samples for entire dosing interval BP=blood plasma; CVF=cervicovaginal fluid; IQR=interquartile range; PreMW=premenopausal women; PostMW=postmenopausal women

Table 3

Steady State Raltegravir Non Compartmental Analysis

PK Estimate[a]	HIV-negative PreMW (n=7)		HIV-infected PreMW (n=6)		HIV-infected PostMW (n=5)		P value	
	BP	CVF[b]	BP	CVF	BP	CVF	BP	CVF
C_{max}, ng/mL	1874 (587-2166)	1272 (885-1804)	1975 (650-4384)	1924 (1166-5888)	1173 (1034-4073)	2841 (326-4430)		
T_{max}, hr	8 (6-11)	3 (0.8-3)	3 (0.5-4)	5 (1-6)	3 (2-6)	8 (5-8)		
C_{12}, ng/mL	303 (101-680)	0.1 (0.1-798)	23 (18-226)	447 (181-546)	310 (243-520)	958 (313-1252)		
AUC $_{0\text{-}12h}$, hr*ng/mL	8436 (3080-10111)	3164 (1156-9540)	5761 (1801-10095)	11465 (9725-17138)	6180 (5295-8282)	9568 (4271-24306)	0.9	0.08
CVF:BP AUC	0.46 (0.2-1.1)		3.9 (1.2-6.7)		1.4 (0.7-4.3)			
Accumulation Ratios	3.0 (1.4-3.2)	1.5[c] (0.6-2.6)	N/A	N/A	0.9 (0.4-4.6)	1.3 (0.7-1.5)		

[a] Median (IQR)

[b] 27% of CVF samples collected were BLD. BLD PK parameters were imputed as 0.1 ng/ml for statistical analysis. BP=blood plasma; CVF=cervicovaginal fluid; IQR=interquartile range; PreMW=premenopausal women; PostMW=postmenopausal women