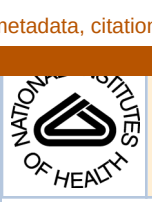

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Single and Multiple Dose Pharmacokinetics of Darunavir plus Ritonavir and Etravirine in Semen and Rectal Tissue of HIV-Negative Men

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Abstract

Background—Antiretroviral therapy (ART) has become a central component of combination HIV prevention efforts. Defining the individual exposure of commercially available ART in genital secretions and vulnerable mucosal tissues is paramount to designing future prevention interventions.

Methods—A pharmacokinetic study was performed in 12 HIV-negative men receiving darunavir 600mg, ritonavir 100mg, and etravirine 200mg orally twice daily for 8 days. Seven blood plasma (BP) samples were collected over 12 hours on Day 1 (PK1) and Days 7 and 8 (PK2). One rectal tissue (RT)sample from each subject was collected during PK1 and PK2. During PK1, two seminal plasma (SP)samples were collected from each subject. During PK2, six SP samples were collected from each subject over 2 days.

Results—Antiretrovirals were detected in SP and RT within 1 hour after a single dose. Over PK1 and PK2, SP exposures were lower than BP by 80–92% (DRV), 89–95% (RTV), 83–88% (ETR). However, protein binding in SP (14% for darunavir, 70% for ritonavir, and 97% for etravirine) was lower than in BP. RT AUCs were higher than BP by 39 to 155-fold for darunavir, 12 to 61-fold for ritonavir, and 20 to 40-fold for etravirine.

Conclusions—Lower SP protein binding resulted in higher pharmacologically active darunavir and etravirine concentrations compared to BP. High RT concentrations may also be favorable for suppressing viral replication in the gastrointestinal mucosa. The high protein-unbound exposures in SP and total exposures in RT support further investigations of darunavir+ritonavir and etravirine in secondary prevention.

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Conflicts of Interest: Kevin C Brown – none, Kristine B Patterson – has served on advisory panel for Janssen Therapeutics, Steven H Jennings – none, Stephanie A Malone – none, Nicholas J Shaheen – none, Heather M Asher Prince – none, Melissa Spacek – none, Myron S Cohen – none, Angela DM Kashuba – none

Flexible sigmoidoscopies and rectal tissue sampling were performed at UNC Hospitals GI Procedures and UNC Healthcare Meadowmont GI Clinic by Nicholas Shaheen, Ryan Madanick, and Evan Dellon and at Chapel Hill Internal Medicine GI Clinic by Nicholas Shaheen.

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Keywords

darunavir; ritonavir; etravirine; pharmacokinetics; semen; rectal; HIV

Introduction

The Joint United Nations Program on HIV/AIDS (UNAIDS) strategy aims to reduce the sexual transmission of HIV by one-half by 2015[1]. Disproportionate to the burden of disease, men who have sex with men (MSM) have limited access to prevention services other than barrier methods. As such, the number of new HIV infections in MSM in the US continues to increase[2]. In order to achieve this goal, a comprehensive prevention program utilizing antiretroviral therapy (ART) is being incorporated into this strategy.

Recently, the HTPN 052 trial in HIV sero-discordant heterosexual couples demonstrated that immediate initiation of antiretrovirals in the HIV-positive partner at a CD4+ T cell count of >350, compared to delayed therapy at a CD4+ cell count of <250, reduced HIV transmission to the uninfected sexual partner by 96%[3]. HIV transmission modeling has correlated increasing concentrations of HIV RNA in semen to an increasing probability of infection[4]. Despite suppression of HIV RNA in blood, HIV RNA can still be detected in genital secretions of up to 8% of HIV-infected men on antiretroviral therapy[5]. Using selected antiretrovirals to eliminate HIV replication in the genital secretions of HIV-infected men has implications in preventing transmission to sexual partners. Antiretrovirals that achieve high concentrations in colorectal tissues may also reduce HIV replication, and limit infectiousness. Additionally, selecting antiretrovirals that target vulnerable mucosal tissues may offer optimal protection from HIV acquisition when used in a post-exposure prophylaxis regimen. Characterizing genital tract and colorectal tissue antiretroviral pharmacokinetics is critical for informing the development of future prevention strategies. The current study was designed to define the exposure of darunavir plus ritonavir and etravirine in the seminal fluid and rectal tissue following single and multiple doses.

Methods

Study Design and Subject Selection

This 8-day, open-label, pharmacokinetic (PK) study in healthy HIV-negative male volunteers was conducted between June 2009 and January 2010 at the University of North Carolina at Chapel Hill (UNC). Darunavir and etravirine tablets and ritonavir capsules were provided by Janssen Therapeutics. UNC Biomedical Institutional Review Board approved the study. All visits were conducted in The UNC Clinical and Translational Research Center (CTRC). The study was registered with the NIH clinical trial registry (NCT00855088). All subjects provided written informed consent before any procedures were performed.

Screening procedures occurred within 42 days of study drug dosing. Subjects were eligible to participate if they were healthy males 18 –49 years of age having a body mass index(BMI)between 18 and 30 kg/m^2, with intact genital and gastrointestinal tracts. Subjects were excluded if they had a history of regular alcohol consumption, were currently smoking more than 5 cigarettes per day, had a positive urine drug screen, or had a currently active sexually transmitted disease. Subjects were screened for gonorrhea, chlamydia, trichomonas, syphilis, herpes simplex virus-2, hepatitis B and C, and HIV. All testing was performed in the UNC Health Care McLendon Laboratories and in the UNC Sexually Transmitted Diseases Cooperative Research Center Microbiology Core Lab.

Subjects were excluded for any clinically significant abnormality in the laboratory results or physical examination deemed by the study physician to increase subject risk or compromise study results. Twelve-lead electrocardiogram (ECG) testing was performed on subjects that were greater than 35 years of age, and subjects were excluded if they exhibited a QTc >450 milliseconds. All prescription and non-prescription medications and supplements, with the exception of acetaminophen (up to 1g/day), were required to be discontinued at least 7 days prior to study drug dosing until study completion. Subjects were instructed to abstain from all sexual activity and use of intra-rectal products 72 hours prior to dosing until study discharge.

Safety laboratory monitoring was performed on the day prior to dosing, 6 days after initial dosing, and at follow-up. A full physical examination was performed at screening and at follow-up, and brief physical examinations were performed on the day prior to dosing and day 6. Urine toxicology screening was performed at screening, on the day prior to dosing, and on day 6.

Study Visits

Subjects received darunavir 600mg, ritonavir 100mg, and etravirine 200mg orally twice daily on days 1–7 and a single dose on the morning of day 8. Subjects followed a low fiber diet for 3 days prior, and a clear liquids diet the afternoon prior, to the flexible sigmoidoscopy to collect rectal tissue (RT). Subjects were admitted the evening before day 1 to the UNC CTRC and provided a baseline seminal plasma (SP) sample. Subjects fasted for 2 hours before and 4 hours after dosing on days 1, 7, and 8 and were provided a standardized meal with each dose (500kcal 20% fat). On day 1, blood plasma (BP) was obtained immediately pre-dose and then 1, 2, 3, 6, 8, and 12 hours after first dose. Each subject collected 2 semen specimens that were time-matched with two of the six post-dose BP samples. A total of four subjects were assigned to each time point. A single RT biopsy was obtained that was time-matched with one post-dose BP sample. Two subjects were assigned to each RT biopsy time point. Subjects recorded dosing times on days 2–6 while at home and were instructed to take doses with meals. Subjects were readmitted to the CTRC in the evening of day 6. On days 7 and 8, BP and RT PK sampling identical to day 1 were performed. However, each subject collected 6 semen specimens over days 7 –8 that were time-matched with BP samples. Subjects were discharged after the 12-hour PK sample collection on day 8 and returned for safety evaluations 7–10 days after the last dose of study medications.

Sample Collection and Processing

Whole blood was obtained using K_2EDTA collection tubes (BD Diagnostics, Franklin Lakes, NJ) and centrifuged at 1700g at 5°C for 10 minutes. Whole semen samples were allowed to liquefy at room temperature for at least 45 minutes, and then were centrifuged at 2500g at 10°C for 15 minutes. Prior to collection, rectal biopsy sites were rinsed with a solution containing simethicone 40mg (simethicone oral suspension 40mg/0.6ml, Major Pharmaceuticals, Livonia, Michigan) diluted in 500mL sterile water for irrigation. Ten single RT biopsies were collected using Radial Jaw® 4 Large Capacity Forceps (Boston Scientific, Natick, MA), pooled into a single cryovial, and snap frozen. All specimens were stored at −80°C until analysis.

Darunavir, ritonavir, and etravirinein BP and SP were analyzed using a previously published method [6]. For the analysis of rectal tissue, approximately 25 mg of blank rectal tissue was spiked with 100μL of a known concentration of darunavir, etravirine, and ritonavirto make a calibration range of 10–10,000ng/mL (40–40,000ng/g). Quality controls (QCs) were prepared at 30, 750, and 7,500ng/mL (120, 3,000, and 30,000 ng/g). The samples were

placed in 2.8 mm Precellys metal bead kit vials (P/N 03961-1-008, Bertin Technologies, Villeurbanne, France)and homogenized (Precellys 24, Bertin Technologies, Villeurbanne, France). The subsequent sample preparation extraction steps were identical to the published method[6].

All three matrix concentrations were analyzed using validated methods on an Agilent 1100 series High Performance Liquid Chromatography System and an Agilent 1100 MSD (Agilent Technologies, New Castle, Delaware). The Agilent 1100 MSD instrument was used in positive ESI mode, with a source temperature of 350°C. Analytes were separated on an Agilent Zorbax XDB C-8 (3.0 × 50 mm, 1.8 m) PN#927975-306 with a frit (Agilent (4.6 mm, 0.2 μm) PN 5067-1562) using a gradient mobile phase method. Analysis was performed in SIM mode with the mass:charge ratio (m/z)being 309.0 for alprazolam (internal standard), 548.2 for darunavir, 721.3 for ritonavir, and 435.0 for etravirine. The quantification ranges of the assays were 2–2000 ng/mL for BP and SP and 40–40,000 ng/g for rectal tissue. Intra and inter-day accuracy and precision were ≤15% and ≤10%, respectively, for all matrices.

SP protein binding was determined by incubating 300 μL of SP pooled by subject from PK2 in duplicate at 37°C, 300rpm for 18 hours in rapid equilibrium dialysis cartridges (Rapid Equilibrium Dialysis Device System, Thermo Scientific, Pittsburg, Pennsylvania; Thermo Scientific RED Device Inserts, Thermo Scientific Part No: 89810; reusable Teflon base plate, Thermo Part No: 89811), followed by liquid extraction using methyl-tert-butyl-ether. Concentrations were analyzed using the same equipment and settings as previously stated. The quantification range of the assay was 2–10,000 ng/mL for SP binding. Intra and inter-day accuracy and precision were ≤15% for semen protein binding. All methods were validated as mandated by the industry guidance set by the US DHHS, FDA, and CDER[7].

Data Analysis

BP, SP and RT pharmacokinetic parameters were estimated using noncompartmental methods (Phoenix WinNonlin; Pharsight, Cary, NC). The maximum concentration (Cmax) was determined visually, and time to maximum concentration (Tmax)was defined at Cmax. Exact sample collection times were used in the analysis. The area under the plasma concentration-time curve within the dosing interval (AUC_{12h}) was estimated using the log-linear trapezoidal method, and visual curve stripping was performed to estimate terminal elimination slopes. Blood plasma concentrations 12 hours post-dose (C_{12h})were obtained from the intermediate output calculating AUC_{12h}. For PK2, individual time concentration profiles were created using the six samples collected on days 7 and 8, and by supposition, the concentration at 12 hours post-dose was used at time zero. Previous investigations have determined that sampling frequency does not affect SP concentrations of antiretrovirals[8]. To estimate SP PK parameters for PK1, and RT PK parameters for PK 1 and PK2, a composite approach was used by analyzing geometric mean concentrations. Composite profiles for PK1 SP, PK1 RT and PK2 RT were created using geometric mean concentrations and times at each time point, and samples were grouped using the closest nominal time. A rectal tissue density of 1.04 g/mL was used to convert ng/g to ng/mL[9]. To compare SP and RT exposure to BP, SP:BP and RT:BP AUC_{12h} ratios were calculated for days 1 and 7/8. To describe multi-dose accumulation in BP, SP, and RT, PK2:PK1 AUC_{12h} ratios were calculated.

Descriptive statistics were generated by SAS Institute, Inc. software version 9.1.3 (Cary, NC). Demographic data and pharmacokinetic parameters are presented as median (range). Geometric mean ratios (GMR) with 90% confidence intervals (90% CI) are presented for PK2 SP vs. BP. For the ratios that included a composite profile (PK1 SP vs. BP, PK1 RT vs. BP, and PK2 RT vs. BP), the composite parameter value was divided by the corresponding geometric mean BP.

The percent protein-unbound was calculated by subtracting the percent protein-bound from 100%. The unbound exposure and trough concentration of drug in SP was calculated by multiplying the total exposure and trough concentration by the percent protein-unbound derived from the RED cartridge analytical method. The protein-unbound GMRs were calculated similarly by using the reported unbound fraction in BP(darunavir: 5%, ritonavir: 3%, etravirine: 0.1%).

Results

Subject Demographics, Disposition, and Safety

Eighteen men screened for this study: 13 were enrolled, and 12 completed. Of the 13 subjects, one subject withdrew due to schedule conflicts. This subject did not contribute demographic or pharmacokineticdata. Median (range) age of the 12 participants was 27 (21–36) years, weight was 78.6 (68.4–108.1) kg, and BMI was 25.5 (20–29.9) kg/m^2. Six(50%) subjects were Caucasian, 1 (8%)was Hispanic Caucasian and 5 (42%)were African American.

Subjects tolerated the study medications well. Most adverse events (AEs) were mild, and no serious AEs were reported. The most frequently reported AE was GI disturbance including loose stools or diarrhea (69%). Other AEs included fatigue(15%), decreased concentration (15%), and headache (15%). Grade 2 rash was experienced by one participant approximately 1–2 hours after leaving his PK2 study visit and resolved in 7 days. One subject reported sustained sensations of urinary urgency; resolution could not be assessed since subject was lost to follow up. RT sampling was well tolerated. A single subject reported spotting on toilet tissue and a small amount of blood on stool immediately following the procedure, which resolved within a few hours.

BP, Semen and Rectal Tissue Pharmacokinetics

Figures 1, 2 and 3 depict the BP, SP, and RT concentrations for all 12 subjects at day 1 (PK1) and days 7/8 (PK2), respectively. After the first dose, darunavir(Fig 1a), ritonavir (Fig 2a) and etravirine (Fig 3a)were detected in all biological matrices. Table 1 summarizes the PK parameters for each matrix. After single and multiple doses, median AUC_{12h}, and C_{12h} were highest in RT and lowest in SP for all three drugs. Table 2 summarizes the relative exposures of each drug in SP and RT versus BP and the PK2:PK1 accumulation ratios.

Seminal Plasma—After the first dose, darunavir exposures in SP were 82–92% lower than in BP and were detected 1 hour post-dose. After multiple doses, darunavir exposures in SP were 80–85% lower than in BP. Using C_{12h} and AUC_{12h} as measures of exposure, darunavir accumulated (PK2:PK1) in SP by 2–2.8 fold upon multiple dosing.

Ritonavir was not detected in SP until 2 hours after the first dose, and peak exposures were not reached until 8 hours post-dose. After the first dose, ritonavir exposures in SP were 89–95% lower than in BP. After multiple doses, ritonavir exposures in SP were 93% lower than in BP. Ritonavir accumulated (PK2:PK1) in SP by 1.4–2.3 fold with multiple dosing.

Etravirine was detected in SP 2 hours after the first dose. Etravirine exposures in SP were 83–87% lower than in BP after the first dose, and 85–88% lower than in BP after multiple dosing. Etravirine accumulated (PK2:PK1) in SP by 3.6–5.2 fold with multiple dosing.

Seminal Plasma Protein Binding—The median (IQR)protein binding in SP was 14.0% (10.1–18.4%) for darunavir. This is much lower than darunavir's protein binding in blood plasma, which is approximately 95%[10]. Based on these data, the protein-free AUC_{12h} and

C_{12h} in SP were 3.4 and 2.5-fold higher than in BP, respectively. For ritonavir the median (IQR)protein binding in SP was 70.3% (66.9–73.3%). Ritonavir's protein binding in blood plasma is reported to be 98%[11]. Based on these data, the protein-free AUC_{12h} and C_{12h} in SP were similar (within 2%) to BP. For etravirine, the median (IQR) protein binding in SP was 96.7% (95.2–99.0%). Etravirine's protein binding in blood plasma is reported to be 99.9%[12]. Based on these data, the protein-free AUC_{12h} and C_{12h} in SP were 4.8 and 3.8-fold higher than in BP, respectively.

Rectal Tissue—After the first dose, darunavir exposures in RT were 1.1 to 1.2-fold higher than in BP, and were detected 1 hour post-dose. Tmax occurred 2.4 hours after peak plasma concentrations. After multiple doses, darunavir exposures in RT were 2.3 to 2.7-fold higher than in BP. Darunavir accumulated (PK2:PK1) in RT by 3.3 to 4-fold with multiple dosing. After the first dose, ritonavir exposures in RT were 5.8 to 12-fold higher than in BP, and were detected 1 hour post-dose. Tmax occurred 4.9 hours after peak plasma concentrations. After multiple doses, ritonavir exposures in RT were 13 to 27-fold higher than in BP. Ritonavir accumulated in RT by 3.7 to 5.2-fold with multiple dosing. After the first dose, etravirine exposures in RT were 15 to 16-fold higher than in BP and were detected 1 hour post dose. Tmax occurred 4.9 hours after peak plasma concentrations. After multiple doses, etravirine exposures in RT were 7.5 to 9.7-fold higher than in BP. Etravirine accumulated in RT by 2 to 3.6-fold with multiple dosing.

Discussion

Despite strong implementation of behavioral interventions, the incidence of HIV in the United States has not substantially declined over the past 15 years[2]. Therefore, combination prevention, the use of antiretroviral agents to prevent HIV transmission in conjunction with behavior modification and barrier methods, appears to be the most effective strategy to date. For example, HPTN 052 demonstrated that transmission to sero-discordant heterosexual partners was reduced by 96% by offering potent antiretroviral therapy to the HIV-infected partner[3]. The most likely means by which transmission was prevented in this study was through the reduction in systemic, and thus genital tract, viremia[4]. This study was performed to characterize the pharmacokinetics of DRV and ETR in SP and RT, informing their role in reducing HIV replication at these sites, as well as being used in a PEP regimen where colorectal tissue was exposed to HIV.

Whether specific antiretroviral regimens are more effective in offering protection from HIV acquisition or preventing HIV transmission is unknown. Drugs that reach high concentrations quickly at sites of transmission and infection would be favorable in antiretroviral-based post-exposure prophylaxis. Antiretrovirals that achieve high exposures in genital secretions and can limit local HIV replication may be favorable for decreasing the infectivity of the HIV-infected person. Therefore, defining the antiretroviral exposures in biological compartments that are vulnerable to acquisition and are sources of infection, such as rectal tissue and semen, could assist in selecting regimens for HIV prevention.

Darunavir, ritonavir, and etravirine total drug concentrations in SP were 80–93% lower than in blood plasma. This is consistent with other antiretrovirals, in which higher BP protein binding results in lower SP concentrations[13]. As BP protein binding decreases, there is a greater amount of protein-unbound drug available to cross cellular membranes and distribute into physiological compartments. However, the drug-binding proteins albumin and alpha-1-acid glycoprotein (AAG) are approximately 97% lower in SP thanin BP[14]. We measured the protein-unbound concentrations in SP and confirmed that lower protein binding exists for all three antiretroviralsin this compartment. Darunavir binds primarily to alpha-1-acid glycoprotein. Unbound darunavir concentrations in SP were approximately 2.5 fold higher

than BP concentrations. Our measured protein-unbound trough concentration (230ng/mL) was 150-fold higher than the unbound EC_{90} measured in vitro(1.5ng/mLor 2.7nM[15]). The relatively low fraction of protein-bound darunavir in SP is likely due to the very low concentrations of AAG in SP, and the resulting high protein-unbound concentration of darunavir relative to its EC_{90} could be favorable in suppressing viral replication in the male genital tract and in reducing infectivity. Etravirine binds to both albumin and alpha-1-acid glycoprotein. This investigation determined that unbound etravirine concentrations in SP were approximately 3.8 fold higher than BP concentrations, and the unbound etravirine trough concentration (1.2ng/mL) was similar to the protein-free EC_{90} (1.3ng/mL or 2.9nM[16]).

Understanding antiretroviral RT pharmacokinetics is essential to developing appropriate strategies to reduce viral replication in this highly vascularized compartment rich in lymphoid tissue and to select optimal antiretrovirals for post-exposure prophylaxis regimens. Compared to BP, RT exposures of darunavir, ritonavir, and etravirine were 1.3, 5.8, and 15.7 times higher after a single dose and 2.7, 12.8, and 7.5 times higher after multiple doses, respectively. All drugs were detected in the rectal mucosa within 1 hour after dosing. The quick penetration of these drugs into the rectal tissue may be due to a highly vascularized mucosa and protein binding in interstitial fluid[17].

The multiple-dose accumulation of both darunavir and ritonavirin RT was approximately 2-fold greater than in BP (4.0 vs. 1.8 for darunavir, 5.2 vs. 2.3 for ritonavir). These high exposures may in part be due to the elimination pathway of these drugs. Forty-one percent of darunavir and 34% of ritonavir is fecally eliminated as unchanged drug, allowing for local colorectal drug exposure. Mucus trapping of drug is another potential factor in the accumulation in RT[18]. Conversely, the accumulation of etravirine in RT after multiple dosing was only 50% that in BP (2.0 vs. 4.2). The long blood plasma half-life of etravirine explains the high blood plasma accumulation ratio. Additionally, more etravirine (86%) is fecally eliminated as unchanged drug than DRV or RTV.[19,20]. Since we found etravirine to reach multiple-dose concentrations in the RT by 6 hours after the first dose, it may be possible that the relatively larger amount of the fecally eliminated etravirine “saturates” the tissue after the first dose. Therefore any accumulation of etravirine in blood plasma contributes less to the rectal tissue concentrations than the fecal concentrations.

The RT pharmacokinetic profiles of these drugs are similar to previous data that we have reported for maraviroc. Maraviroc also had detectable concentrations 1 hour after the first dose, and the accumulation ratio with multiple dosing was 4.0. The relative exposure of maraviroc in RT compared to BP was 26-fold, which is higher than what was seen with DRV (2.7), RTV (12.8) and ETR (7.5)[21]. Rectal concentrations of tenofovir and emtricitibine were measured 24hr after a single dose by Patterson et al. Tenofovir rectal concentrations at the end of the dosing interval were 46-fold higher than BP, which is higher than DRV (1.1), RTV (12.3) and ETR (15.4). Emtricitibine rectal concentrations were 2.6-fold higher than BP, which is lower than RTV and ETR, but higher than DRV.[22] Furthermore, these high exposures in rectal tissue indicate that these drugs are penetrating a suspected HIV tissue reservoir, thus minimizing the possibility of HIV replication.[23] Data from Kelley et al and Lampinen et al demonstrating rectal HIV RNA shedding is rare, even in the face of sexually transmitted infections, when HIV RNA is below quantification in blood plasma, provides indirect evidence that high rectal antiretroviral concentrations are providing strong activity at this site[24,25].

One potential limitation of this study is that it characterized the pharmacokinetics of these antiretrovirals in unperturbed rectal mucosa. Bowel preparations were not used prior to the biopsy procedure, since hyperosmolar enemas can shift a significant amount of water into

the lumen of the colon and cause epithelial sloughing[26]. Future studies assessing the impact of bowel preparations may be important, as they are commonly (up to 60% of MSM) used prior to anal intercourse[27] and may increase the risk of HIV transmission[28].

In summary, we evaluated combination antiretroviral exposure in RT and defined exposure and protein binding in SP. These data provide pharmacologic plausibility for the use of darunavir plus ritonavir and etravirinein secondary HIV prevention, in both infected and uninfected individuals. The quick penetration and sustained concentrations of darunavir and etravirinein the rectal mucosa are desirable characteristics for prevention of HIV acquisition. The unbound concentrations in semen are higher than in blood and could be effective in suppressing HIV replication in the male genital tract. Future investigations will determine if these concentrations in rectal tissue and semen can fully suppress viral shedding. Despite intensive sampling and scheduling challenges for multiple precisely timed rectal biopsies and semen samples, our data also demonstrate that these studies can be performed efficiently and safely.

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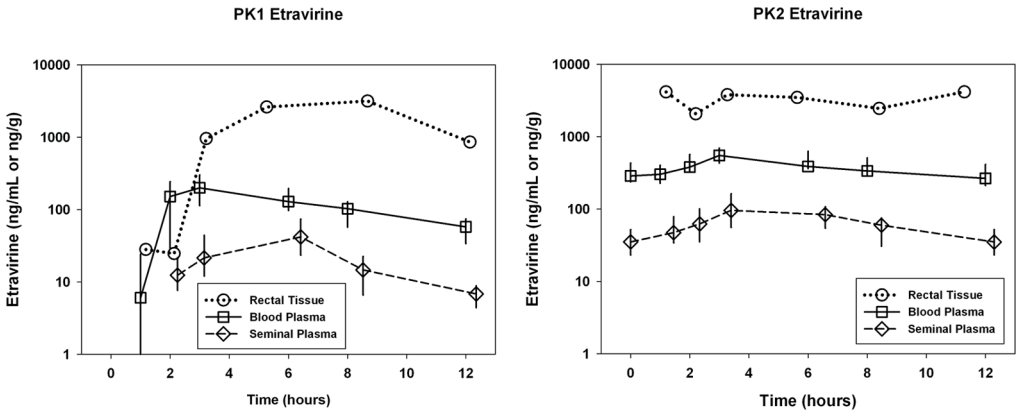

Figure 1.

Darunavir Concentrations after a Single Dose (PK1)[a] and Multiple Doses (PK2) [b] – Median (IQR) darunavir concentrations in rectal tissue (circles), BP (squares), and SP (diamonds). Median sampling times are used for SP and RT. RT lack error bars due to N=2 at each time point.

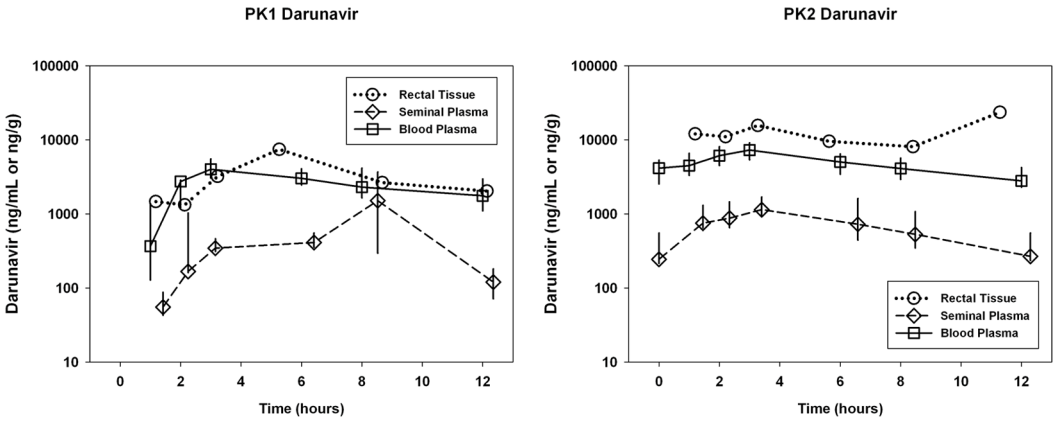

Figure 2.

Ritonavir Concentrations after a Single Dose (PK1)[a] and Multiple Doses (PK2) [b] – Median (IQR) ritonavir concentrations in rectal tissue (circles), BP (squares), and SP (diamonds). Median sampling times are used for SP and RT. RT lack error bars due to N=2 at each time point.

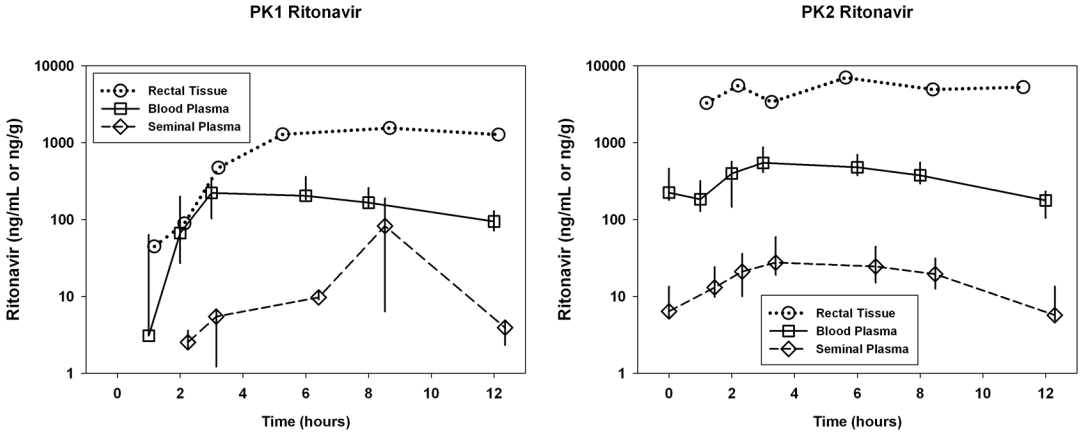

Figure 3.

Etravirine Concentrations after a Single Dose (PK1)[a] and Multiple Doses (PK2) [b] – Median (IQR) etravirine concentrations in rectal tissue (circles), BP(squares), and SP (diamonds). Median sampling times are used for SP and RT. RT lack error bars due to N=2 at each time point.

Table 1

Median (range) Pharmacokinetic Parameters in Blood Plasma, Seminal Plasma, and Rectal Tissue after Single (PK1) and Multiple Dosing (PK2)

	Blood Plasma	Seminal Plasma	Rectal Tissue
Darunavir			
PK1 (Single Dose)			
C_{12h} (μg/mL or μg/g)	1.71 (0.88–3.82)	0.152[a]	2.05[a]
AUC_{12h} (μg*hr/mL or μg*hr/g)	29.7 (18.8–63.5)	5.67[a]	39.1[a]
PK2 (Multiple Dose)			
C_{12h} (μg/mL or μg/g)	2.80(1.17–6.91)	0.267 (0.116–5.25)	6.73[a]
AUC_{12h} (μg*hr/mL or μg*hr/g)	54.4(34.2–101.2)	7.46(2.37–217.7)	155.0[a]
Ritonavir			
PK1 (Single Dose)			
C_{12h} (μg/mL or μg/g)	0.0942 (0.0579–0.256)	0.0052[a]	1.28[a]
AUC_{12h} (μg*hr/mL or μg*hr/g)	1.68 (1.24–4.72)	0.223[a]	11.7[a]
PK2 (Multiple Dose)			
C_{12h} (μg/mL or μg/g)	0.1784(0.095–0.477)	0.0061 (0.0044–0.2338)	4.72[a]
AUC_{12h} (μg*hr/mL or μg*hr/g)	4.53 (2.68–10.1)	0.22(0.12–5.1)	60.8[a]
Etravirine			
PK1 (Single Dose)			
C_{12h} (μg/mL or μg/g)	0.0577 (0.0153–0.483)	0.0073[a]	0.901[a]
AUC_{12h} (μg*hr/mL or μg*hr/g)	1.29 (0.358–6.01)	0.215[a]	20.0[a]
PK2 (Multiple Dose)			
C_{12h} (μg/mL or μg/g)	0.264(0.161–1.25)	0.0364 (0.0115–0.181)	3.23[a]
AUC_{12h} (μg*hr/mL or μg*hr/g)	4.47(3.18–15.4)	0.792(0.258–2.92)	39.9[a]

PK1 seminal plasma, PK1 rectal tissue, and PK2 rectal tissue data were analyzed as composite concentration-time profiles. Blood plasma and saliva parameters for PK2 were calculated using data from study day 8. Seminal plasma and rectal tissue parameters for PK2 were calculated using data from study days 7 and 8.

[a] composite profiles

Table 2

Relative Exposure of Darunavir, Ritonavir, and Etravirine in Seminal and Rectal Tissue to Blood Plasma and Day 8:Day 1 Accumulation Ratios(GMR ±90% CI)

	Blood Plasma	Seminal Plasma	Rectal Tissue
Darunavir			
PK1 (Single Dose)			
C_{12h}	ref	0.084[a]	1.14[a]
AUC_{12h}	ref	0.182[a]	1.26[a]
PK2 (Multiple Dose)			
C_{12h}	ref	0.148 (0.083–0.262)	2.32[a]
AUC_{12h}	ref	0.202 (0.110–0.368)	2.70[a]
PK2 : PK1			
C_{12h}	1.61 (1.41–1.83)	2.83[a]	3.28[a]
AUC_{12h}	1.84 (1.65–2.06)	2.04[a]	3.96[a]
Ritonavir			
PK1 (Single Dose)			
C_{12h}	ref	0.050[a]	12.3[a]
AUC_{12h}	ref	0.110[a]	5.77[a]
PK2 (Multiple Dose)			
C_{12h}	ref	0.069 (0.037–0.127)	27.2[a]
AUC_{12h}	ref	0.067 (0.038–0.118)	12.8[a]
PK2 : PK1			
C_{12h}	1.67 (1.35–2.06)	2.32[a]	3.69[a]
AUC_{12h}	2.34 (1.98–2.77)	1.42[a]	5.21[a]
Etravirine			
PK1 (Single Dose)			
C_{12h}	ref	0.125[a]	15.4[a]
AUC_{12h}	ref	0.168[a]	15.7[a]
PK2 (Multiple Dose)			
C_{12h}	ref	0.116 (0.091–0.147)	9.74[a]
AUC_{12h}	ref	0.146 (0.118–0.181)	7.47[a]
PK2 : PK1			
C_{12h}	5.67 (4.20–7.67)	5.23[a]	3.58[a]
AUC_{12h}	4.18 (3.25–5.39)	3.64[a]	2.00[a]

Composite profiles ratios are calculated using the parameter values for PK1 SP, RT, and the geometric mean for BP.

[a] composite profile