



Mucosal Tissue Pharmacokinetics of Maraviroc and Raltegravir in Women: Implications for Chemoprophylaxis

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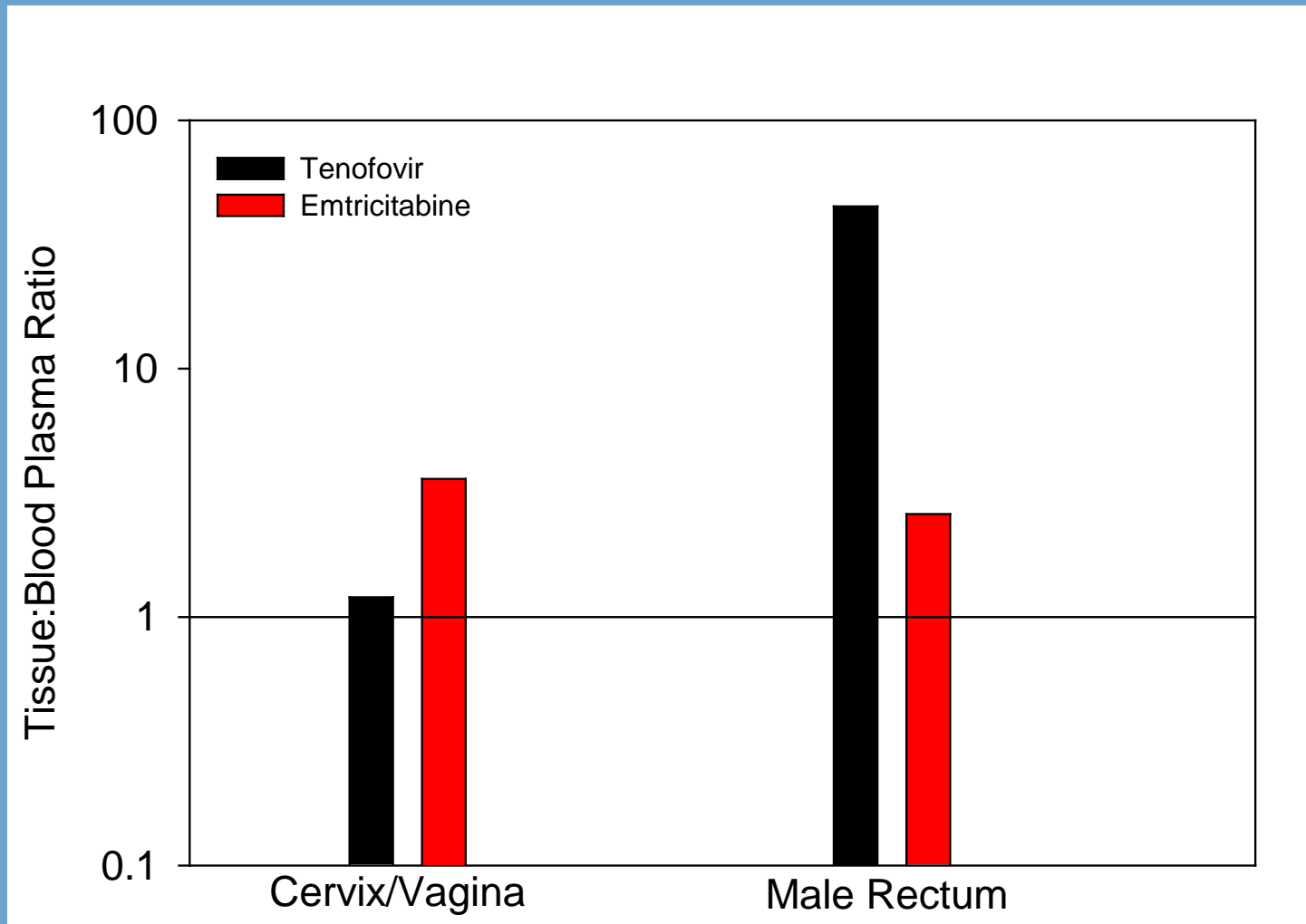
Once Daily PrEP May Not Be Feasible in Women

	Study Title	Study Population	Treatment(s)	Effect Size HR(95% CI)	PK Evidence of Recent Use
Protection	Partners PrEP	Serodiscordant Couples	Daily Oral TDF	0.33 (0.19,0.56)	>80%
	Partners PrEP	Serodiscordant Couples	Daily Oral TDF/FTC	0.25 (0.13, 0.45)	>80%
	iPrEx	MSM	Daily Oral TDF	0.56 (0.37, 0.85)	28%
	TDF2	Heterosexuals	Daily Oral TDF/FTC	0.38 (0.17, 0.84)	78%
	Bangkok TDF	IV Drug Users	Daily Oral TDF/FTC	0.51 (0.29, 0.91)	65%
	CAPRISA004	Women	BAT24 TFV Gel	0.63 (0.42, 0.94)	NA
Futility	FEM-PrEP	Women	Daily Oral TDF/FTC	Futile	<25%
	VOICE	Women	Daily Oral TDF	Futile	<30%
	VOICE	Women	Daily Oral TDF/FTC	Futile	<30%
	VOICE	Women	Daily TFV Gel	Futile	<30%

N Engl J Med. 2012 Aug 2;367(5):411-22; N Engl J Med. 2012 Aug 2;367(5):423-34; N Engl J Med. 2012 Aug 2;367(5):399-410; N Engl J Med. 2010 Dec 30;363(27):2587-99; Science. 2010 Sep 3;329(5996):1168-74; The Lancet, 2013 Jun 381 (9883): 2083 – 2090; Study (MTN003) 20th CROI. Atlanta, GA, March 3-6, 2013; NEMJ (2012) 367:411-22

FTC Emtricitabine, MSM men who have sex with men, TDF Tenofovir disoproxil fumarate, TFV Tenofovir

PrEP Adherence Requirement May Differ by Exposure Site



Phase I, single center, open-label, dose ranging single-dose Maraviroc and Raltegravir PK study

- Study Aims
 1. Determine if mucosal tissue concentrations are dose proportional
 2. Develop a predictive PK model of tissue distribution
- UNC IRB # 10-1393
- ClinicalTrials.gov: NCT01330199

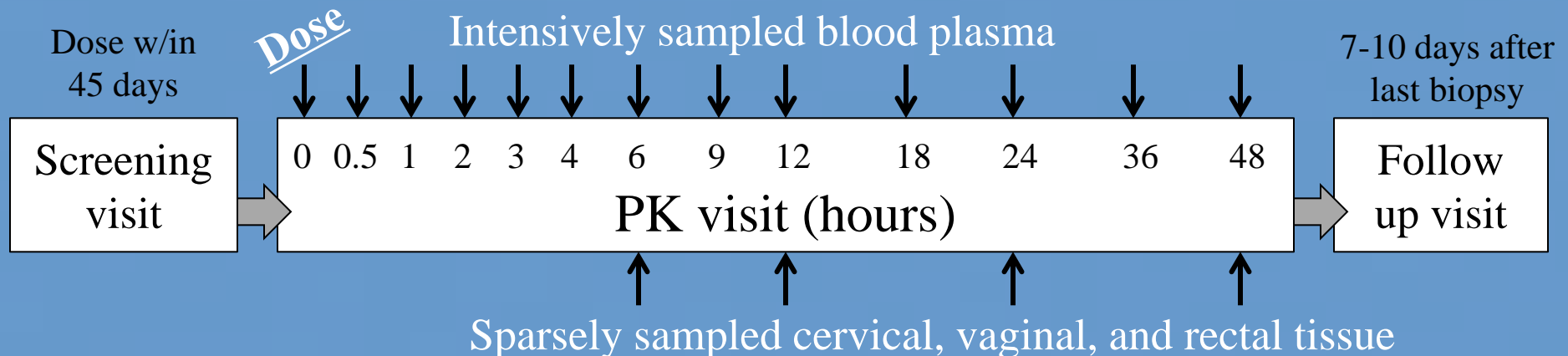
Study Design

Inclusion Criteria

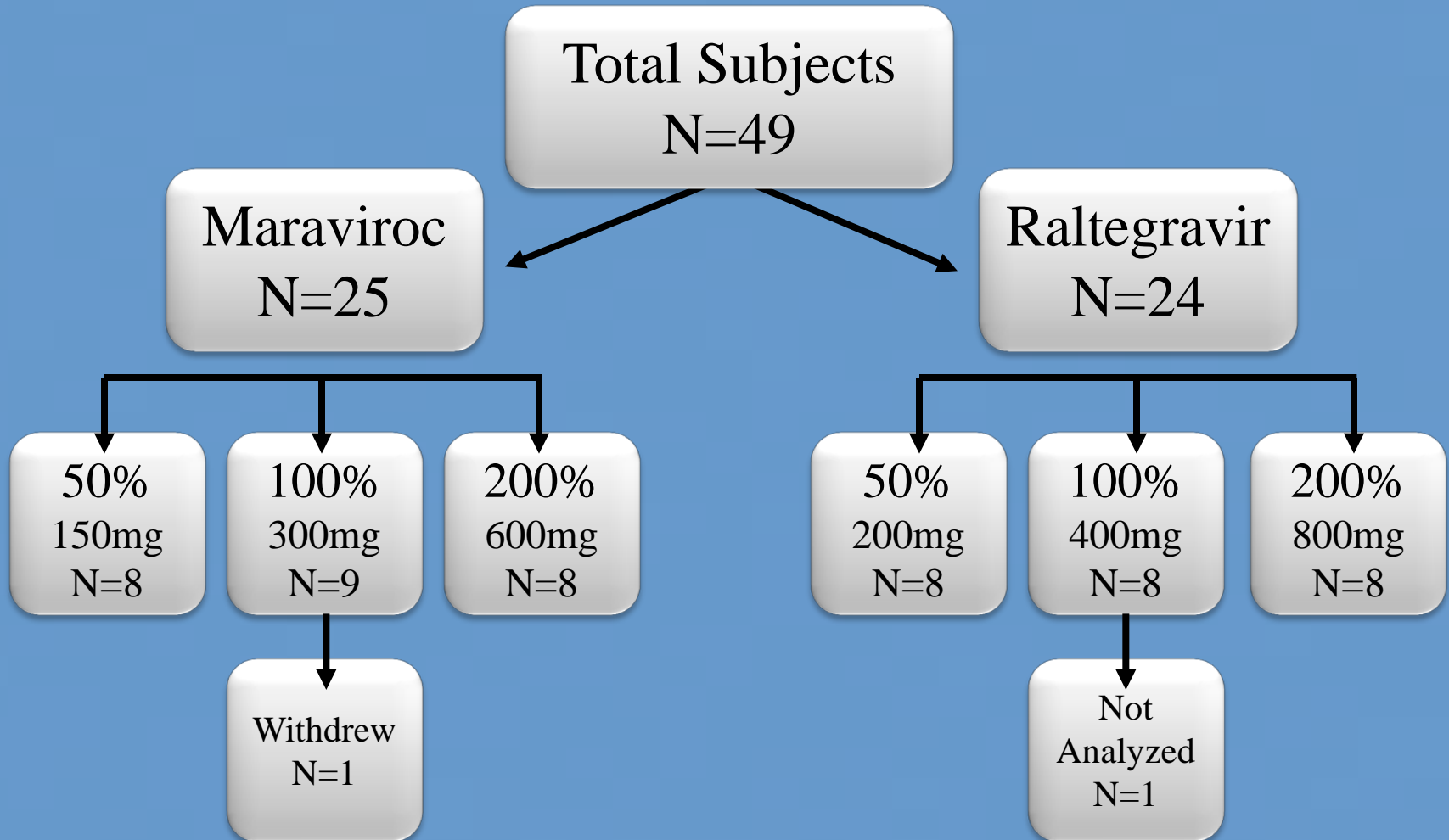
- Healthy, premenopausal women
- 18-49 years
- Intact gastrointestinal and genital tracts
- Regular menstrual cycles
- History of normal Pap smear

Exclusion Criteria

- Medication allergies
- Clinically significant medical conditions
- Abnormal laboratory tests
- Symptomatic bacterial vaginosis or any STI
- Pregnant or lactating
- Positive urine drug screen



Treatment Arms



Methods

- Sample Analysis – LC-MS/MS
 - Plasma calibration range: 5-5000ng/ml
 - Tissue homogenate calibration range: 0.02-20ng/ml
- Data Analysis - WinNonlin[®]
 - Individual plasma NCA
 - Composite tissue NCA
- Statistical Analysis
 - Dose proportionality
 - Power model equation¹: $AUC=e^{\beta_1} \cdot Dose^{\beta_2}$
 - Assumed if the 90% CI of slope (β_1) falls within: 0.64, 1.36
 - SigmaPlot[®] Mann-Whitney Rank Sum and Wilcoxon Signed Rank test, where appropriate
 - SigmaPlot[®] Linear regression

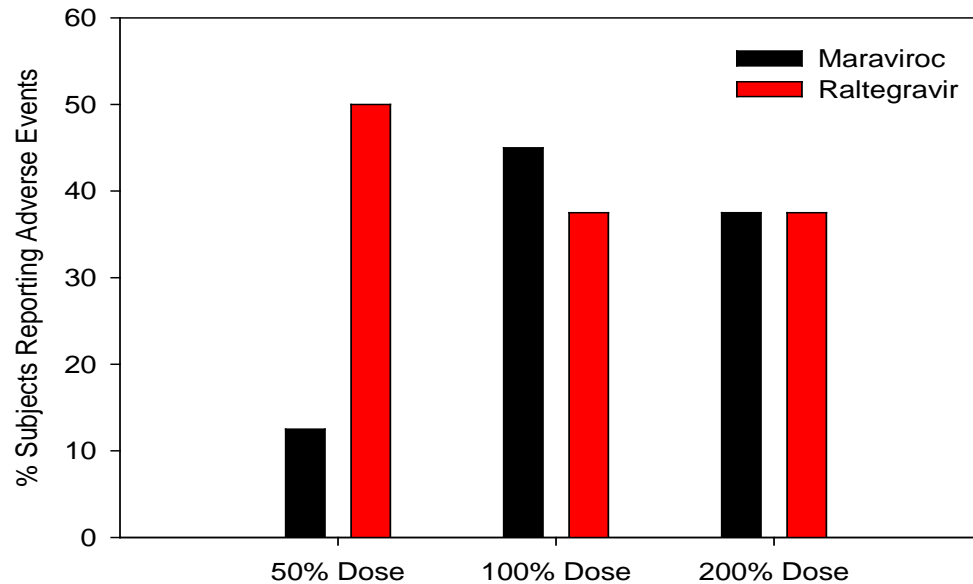
¹Holder et. al. A Method For Estimating And Testing Area Under The Curve In Serial Sacrifice, Batch, And Complete Data Designs. Journal of Biopharmaceutical Statistics 9(3), 451-464 (1999)

Sample Demographics

Variable	MRV (n=24)	RAL (n=24)
	<i>Number (%)</i>	
Female	24 (100)	24 (100)
Race		
Caucasian	16 (67)	18 (75)
African American	7 (29)	4 (17)
Asian American	1 (4)	1 (4)
American Indian	0 (0)	1 (4)
	<i>Median (IQR)</i>	
Age (years)	27 (22-31)	22 (21-27)
Weight (kg)	67 (60-76)	63 (58-72)
BMI (kg/m ²)	24.1 (21.5-26.3)	22.5 (20.8-26.5)

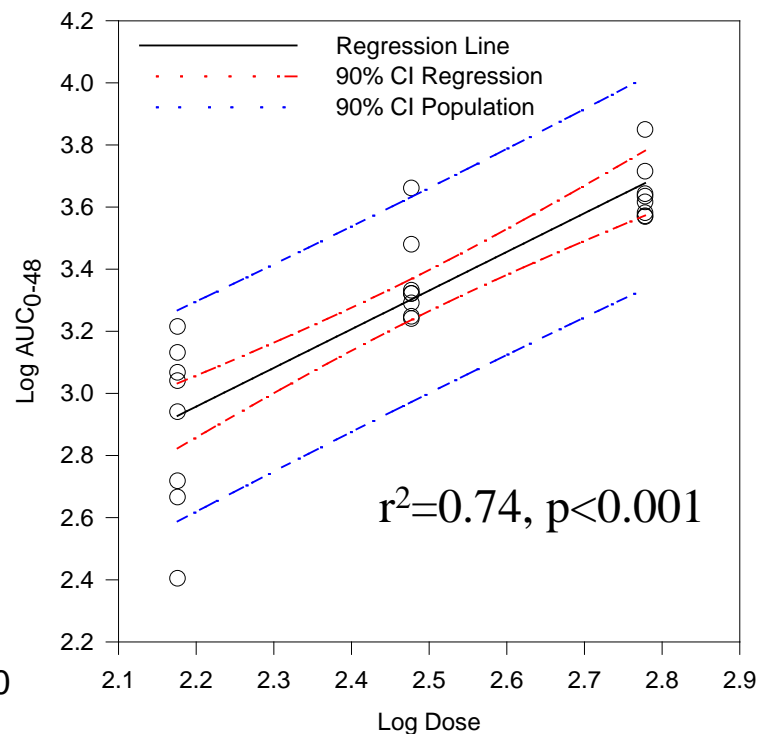
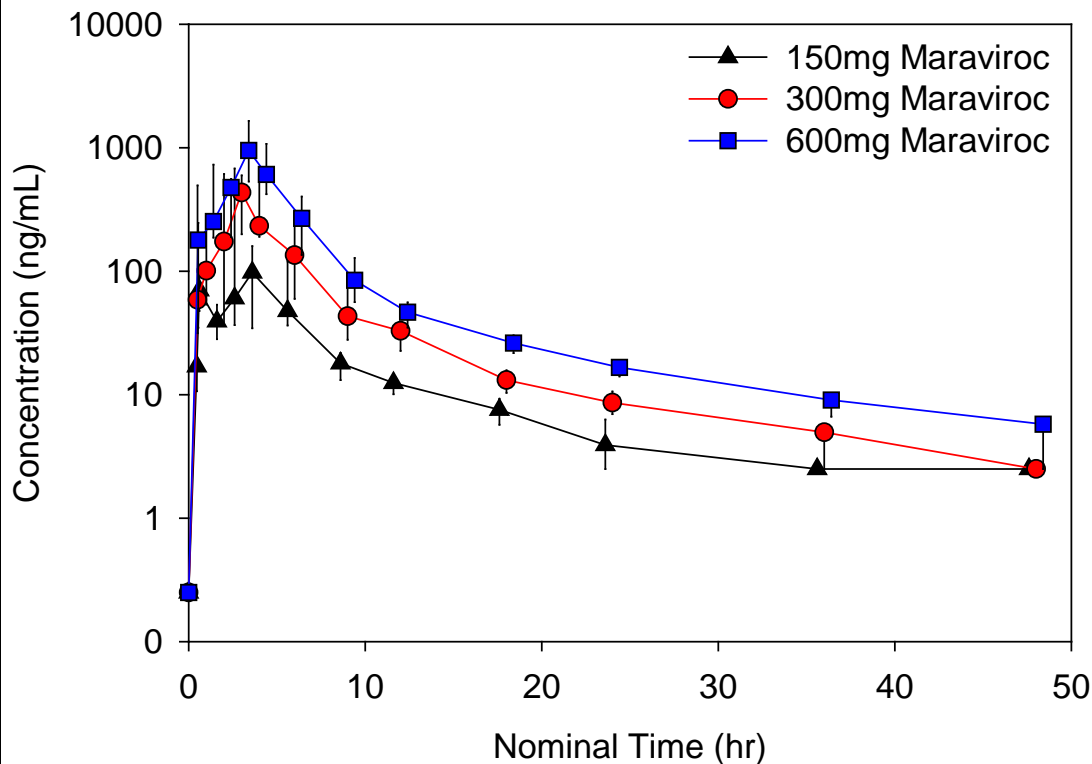
Safety

Adverse Event (\leq Grade 1)	Maraviroc [n (%)]	Raltegravir [n (%)]
Total	8 (32)	10 (42)
Headache	1 (4)	5 (21)
Nausea	2 (8)	0
Fatigue	1 (4)	0
Bowel disturbances	1 (4)	1 (4)
Elevated transaminases	0	1 (4)
Pelvic cramps	0	1 (4)
Vaginal dryness	0	1 (4)



Maraviroc Plasma Exposure and Dose Proportionality

Median \pm IQR (N=24)

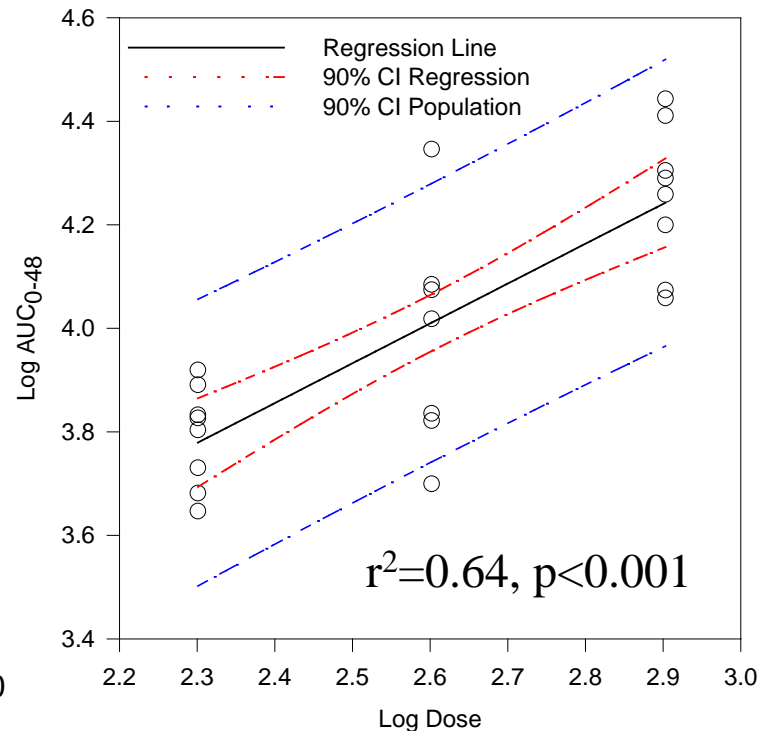
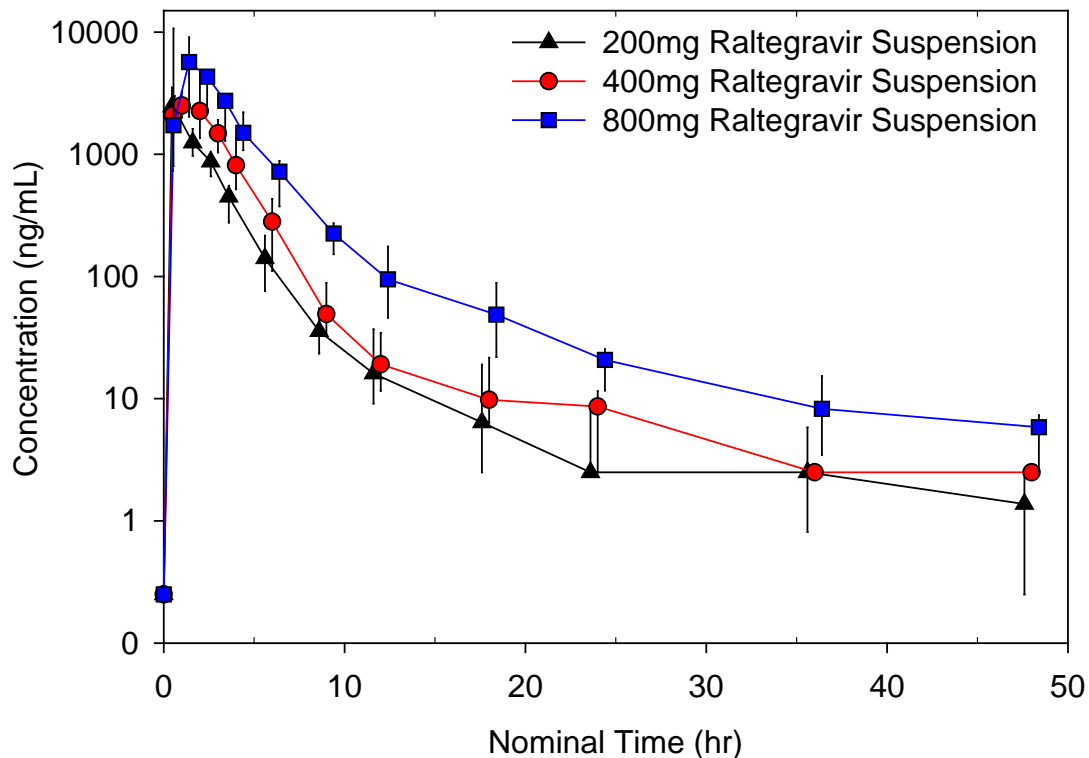


β_1 (90% CI) = 1.14 (0.88, 1.4)

Prespecified range= (0.64, 1.36)

Raltegravir Plasma Exposure and Dose Proportionality

Median \pm IQR (N=23)

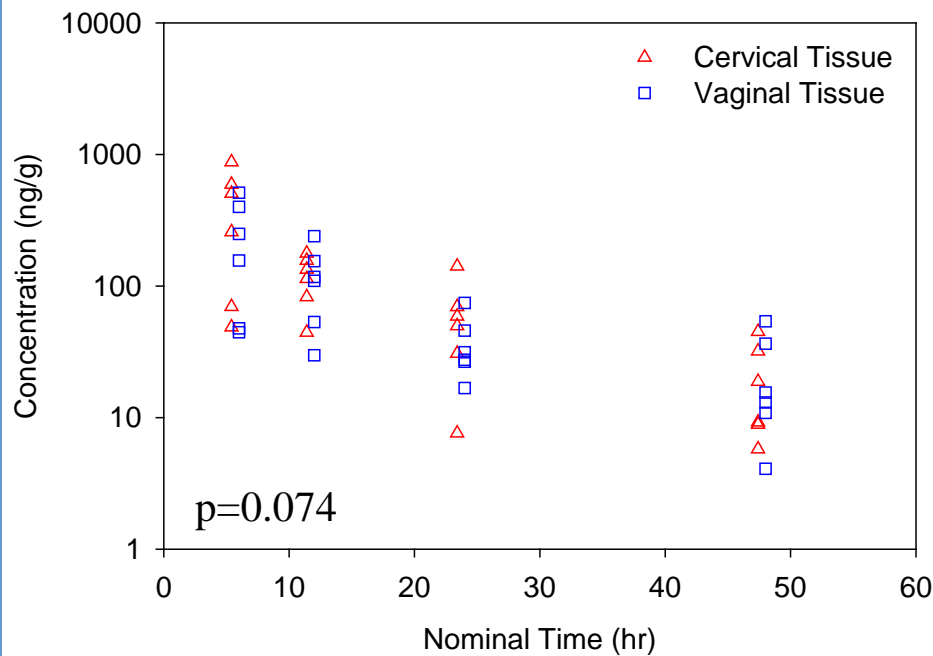


$$\beta_1 \text{ (90\% CI) = } \mathbf{0.79 \text{ (0.56, 1.02)}}$$

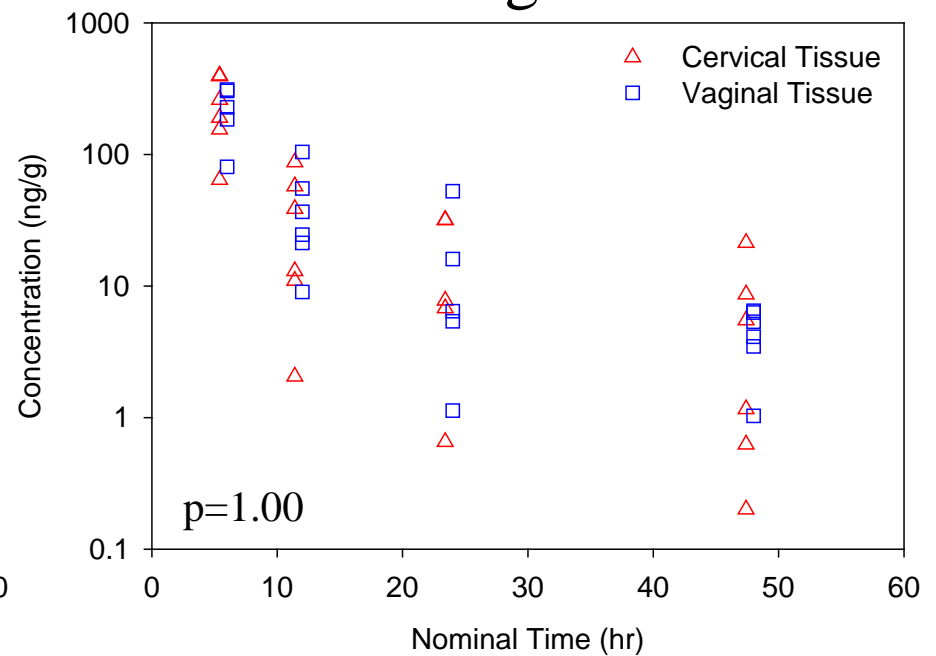
Prespecified range= (0.64, 1.36)

Similar Exposure between the Vaginal and Cervical Tissue

Maraviroc

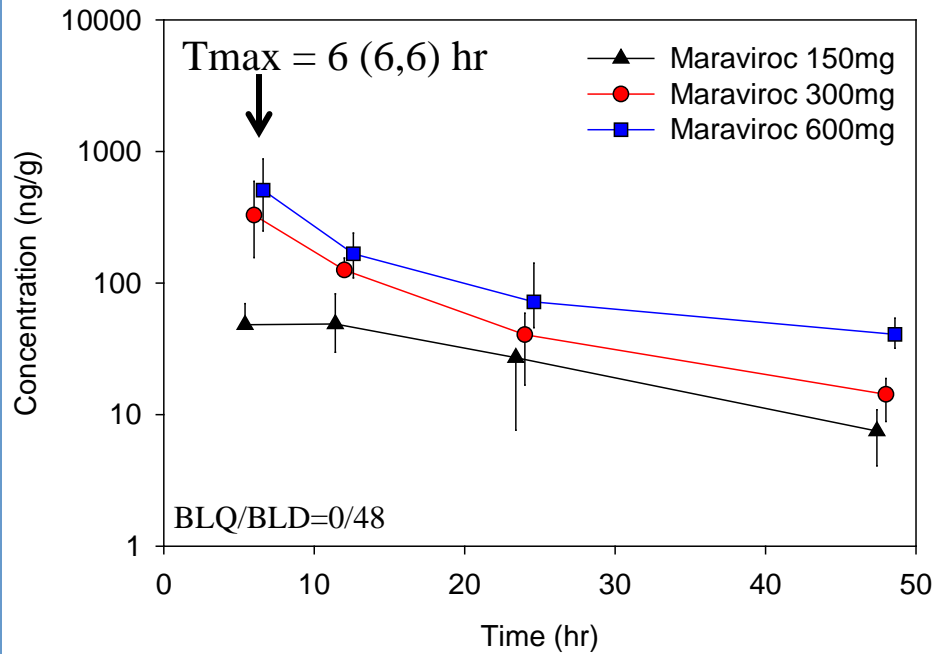


Raltegravir

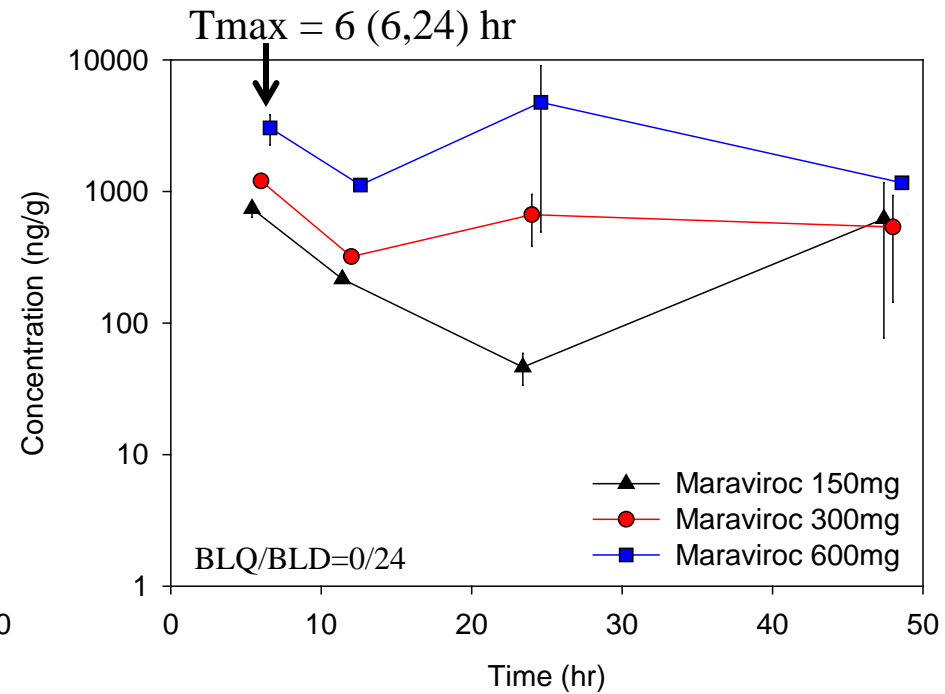


Maraviroc Pharmacokinetics in Tissue (Median \pm Range)

Cervical/Vaginal Tissue

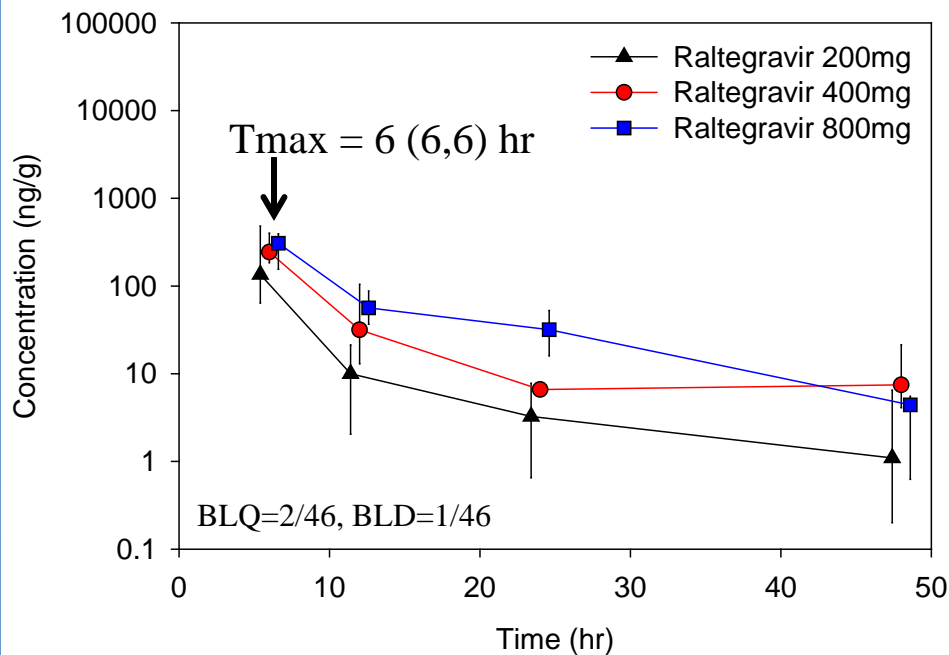


Rectal Tissue

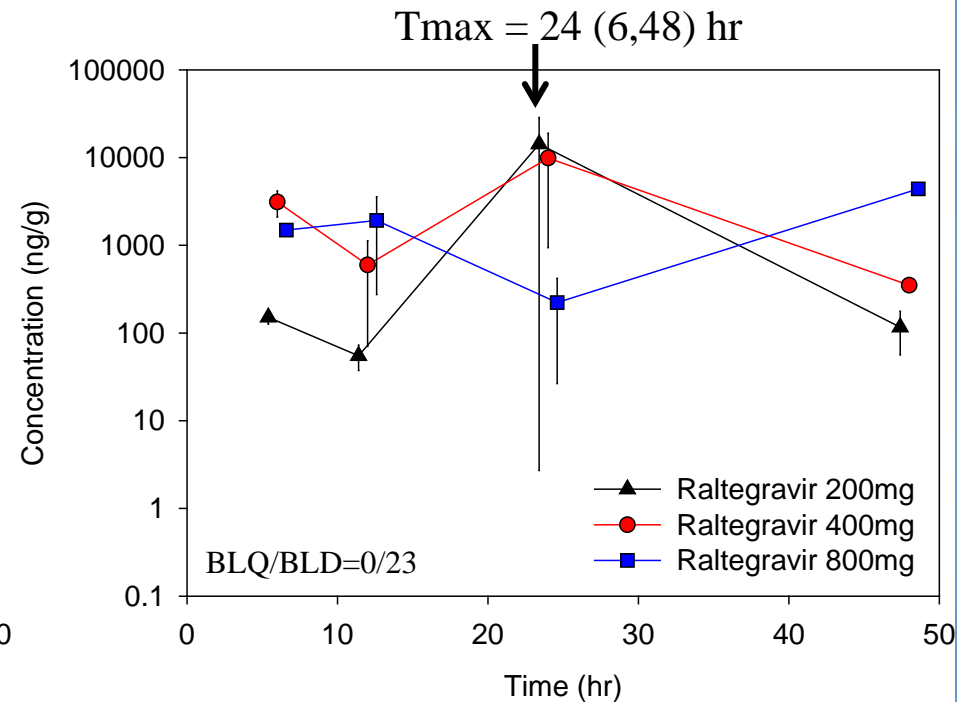


Raltegravir Pharmacokinetics in Tissue (Median \pm Range)

Cervical/Vaginal Tissue

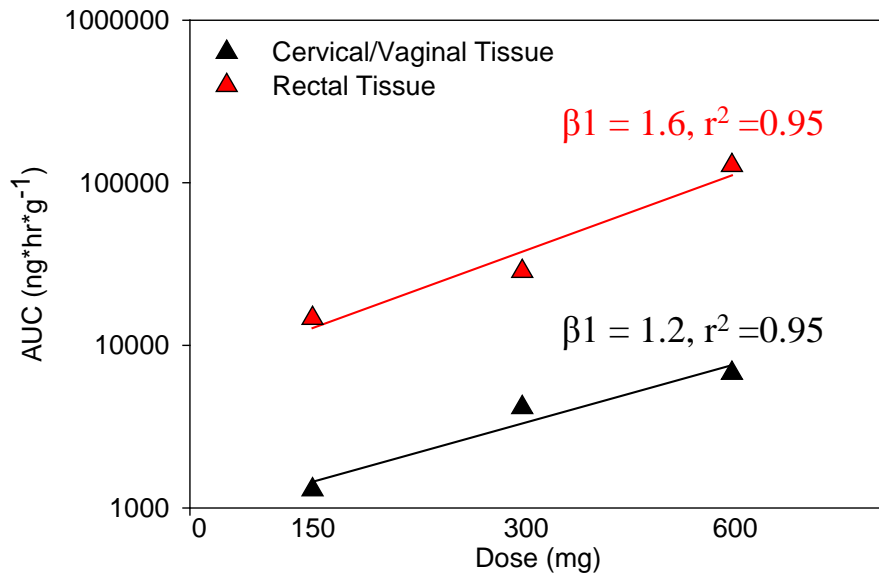


Rectal Tissue

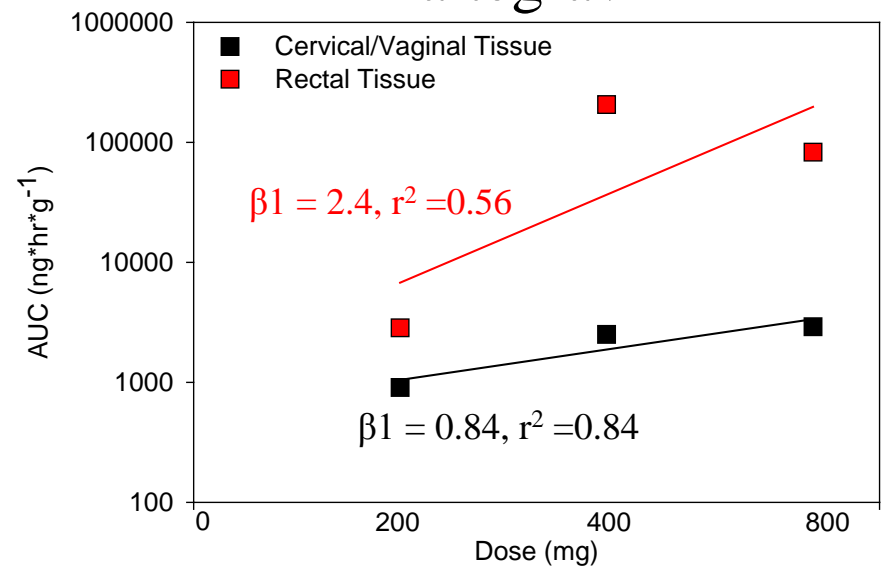


Linearity and Dose Proportionality in Tissue

Maraviroc



Raltegravir



CT/VT β_1 (90% CI) = 1.19 (0.9, 1.47)

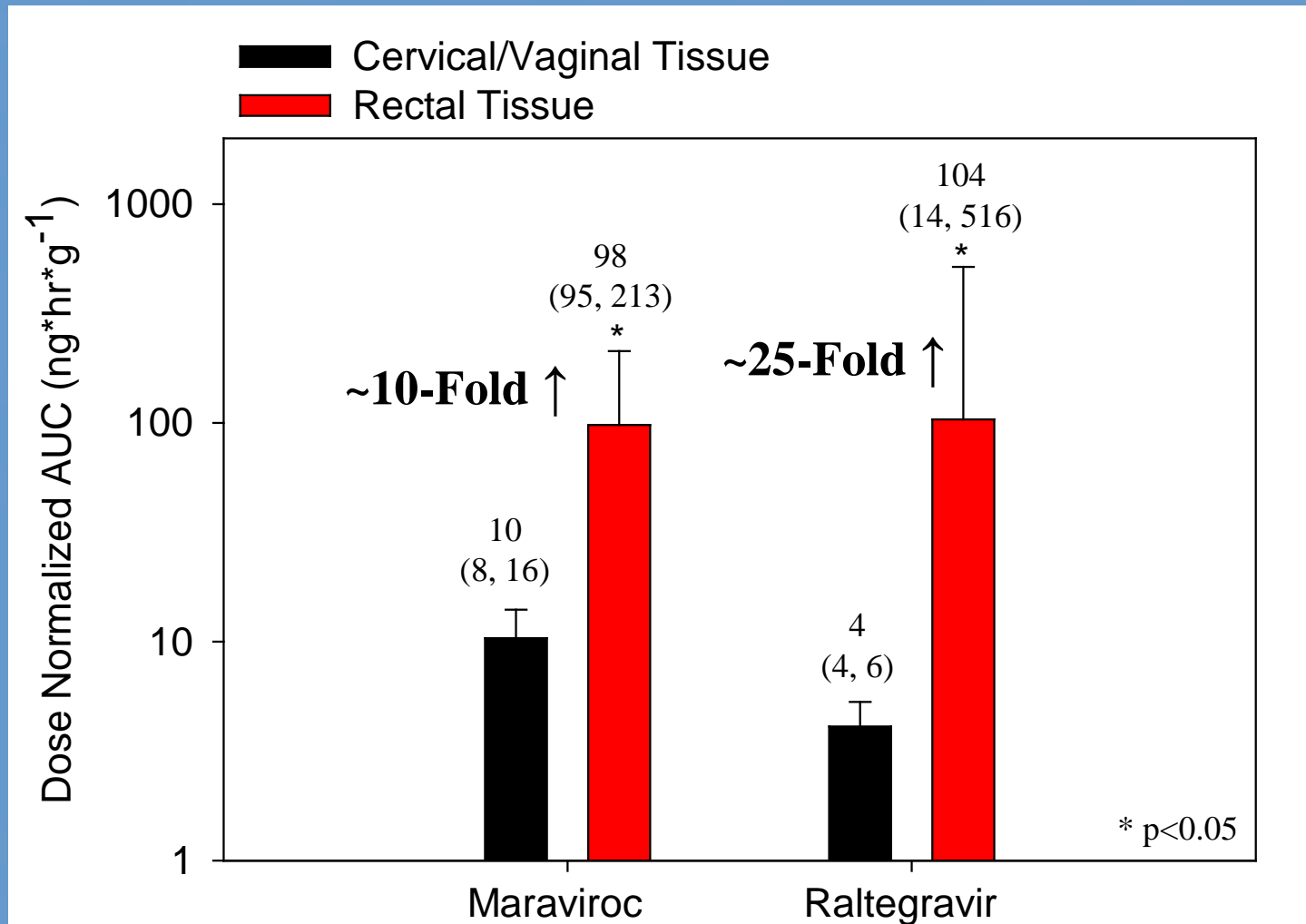
CT/VT β_1 (90% CI) = 0.78 (0.34, 1.24)

RT β_1 (90% CI) = 1.56 (0.67, 2.46)

RT β_1 (90% CI) = 2.35 (0.81, 3.89)

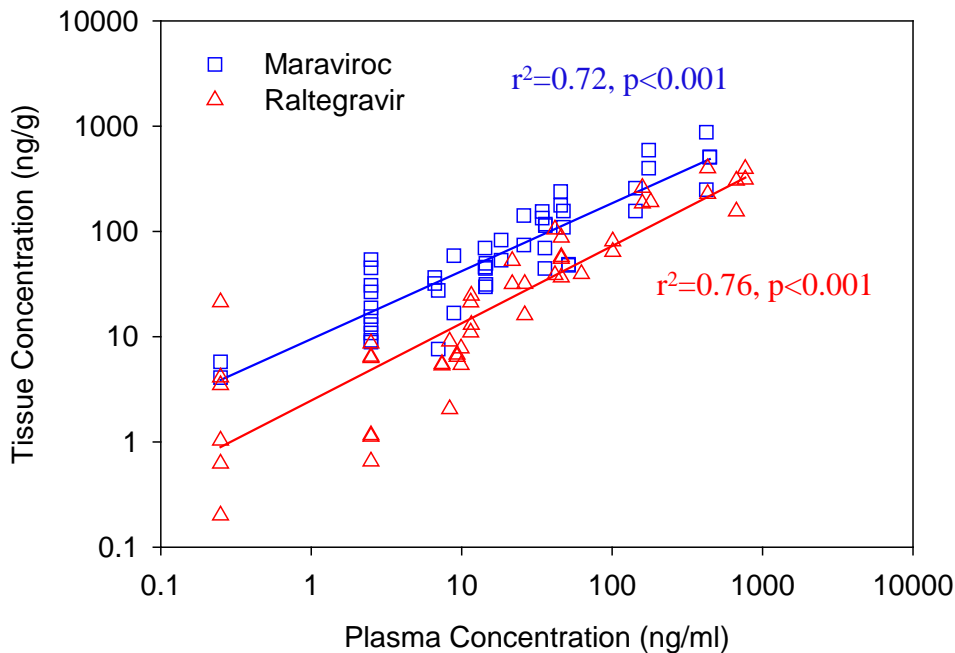
Prespecified range = (0.64, 1.36)

Exposure is Higher in the Rectal Tissue than Cervica/Vaginal Tissue [Median (\pm Range)]

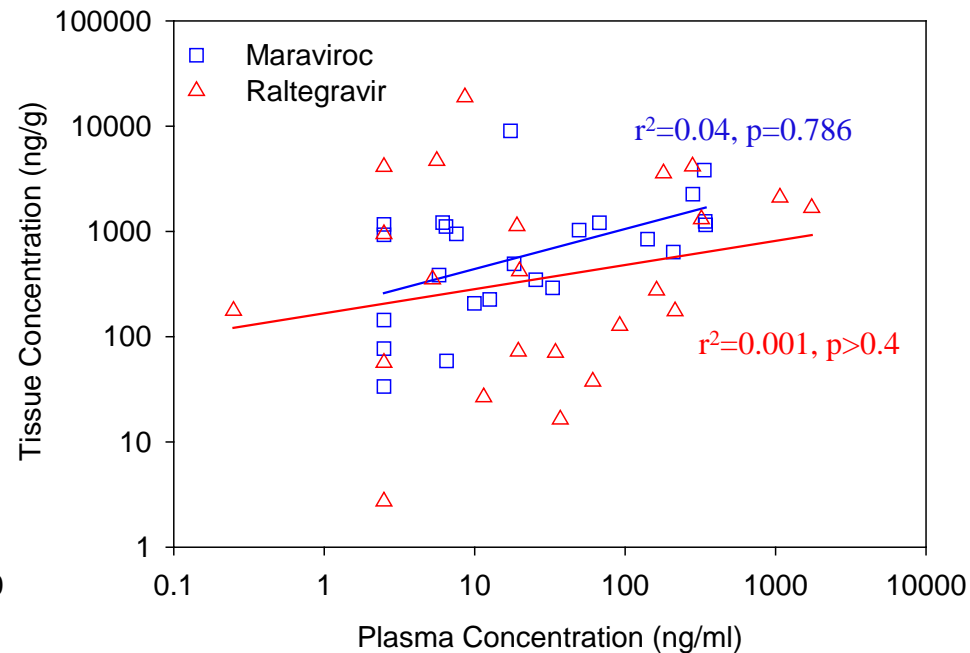


Plasma Concentrations Correlate with Cervical/Vaginal but not Rectal Tissue

Cervical/Vaginal Tissue



Rectal Tissue



Conclusions

- Rapid distribution
 - CT/VT: T_{max} ~6hr
 - RT: T_{max} ~ 6hr for maraviroc and ~24hr for raltegravir
- No difference between CT and VT concentrations
- Maraviroc tissue exposure vs dose
 - ↑ 4 fold [CT/VT] and 8-fold [RT] across dosing range
 - Linear trend; Not dose proportional
- Raltegravir tissue exposure vs dose
 - ↑ 2 fold [CT/VT] and 28-fold [RT] across dosing range
 - Linear trend in CT/VT but not RT; Not dose proportional
- 10-25-fold higher concentration in RT than in the CT/VT
- Plasma concentrations correlate with CT/VT but not RT
- **Future directions:** Predictive PK/PD modeling of concentrations achieved by various dosing schemes

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