Maraviroc Pharmacokinetics in Blood Plasma, Genital Tract Fluid and Tissue in Healthy Female Volunteers

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Background

- There is large variability in ARV exposure in the female genital tract. (Dumond et al. AIDS, 2007; Min et al. JAIDS, 2004)

- Discordance in exposure between the genital tract and blood plasma may lead to…
  - -Resistant variants in the genital tract
  - -Reseeding systemic compartment with resistant virus
  - -On-going genital shedding of HIV-1 and secondary transmission

- The concentration of ARV achieved in the genital tract is potentially important in developing strategies to prevent the sexual transmission of HIV.

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Maraviroc

- CCR5 antagonist
- Novel mechanism prevents cellular entry of R5 HIV-1
- The extent to which maraviroc penetrates into the female genital tract is not known

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Objectives

- **Primary**
  - To describe first dose (FD) and steady state (SS) PK of maraviroc (MVC) in cervicovaginal fluid (CVF) in HIV-negative women
- **Secondary**
  - To evaluate SS vaginal tissue (VT) concentrations of MVC
  - To assess the protein binding of MVC in CVF
  - To describe the terminal elimination of MVC in CVF and BP

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Methods

- Healthy HIV-negative women
  - Comprehensive sexually transmitted infection evaluation
- Single site, open-label trial
- Days 1-6: MVC 300 mg BID

  Day 7: MVC 300 mg single dose
- First dose administered within 7-10 days following onset of menses

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Pharmacokinetic Sampling

Blood Plasma (BP)

Cervicovaginal Fluid (CVF)

Vaginal Tissue (VT)

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Analyses

- Sample Analyses:
  - BP, CVF, and VT analyzed by validated methods using LC/MS/MS*
  - Quantitation range for maraviroc assay (LLQ-ULQ)
    - Plasma and CVF: 0.5 - 500 ng/mL
    - VT: 20 - 20,000 ng/g
  - Protein Binding determined by equilibrium dialysis on pooled samples
- Data Analyses:
  - Non-compartmental PK analysis
  - Summary statistics

*LC/MS/MS: Liquid chromatography with tandem mass spectrometry

Subject Demographics (mean, range)

N = 12

Age (yrs)	26.9 (20-40)
Race/Ethnicity	4 (33%) African American 6 (50%) Caucasian 1 (8%) Asian 1 (8%) Other
Weight (kg)	63.0 (54.3-79.8)
BMI (kg/m^2)	22.2 (18.7-25.3)

* MVC-related AEs: nausea, fatigue and headache

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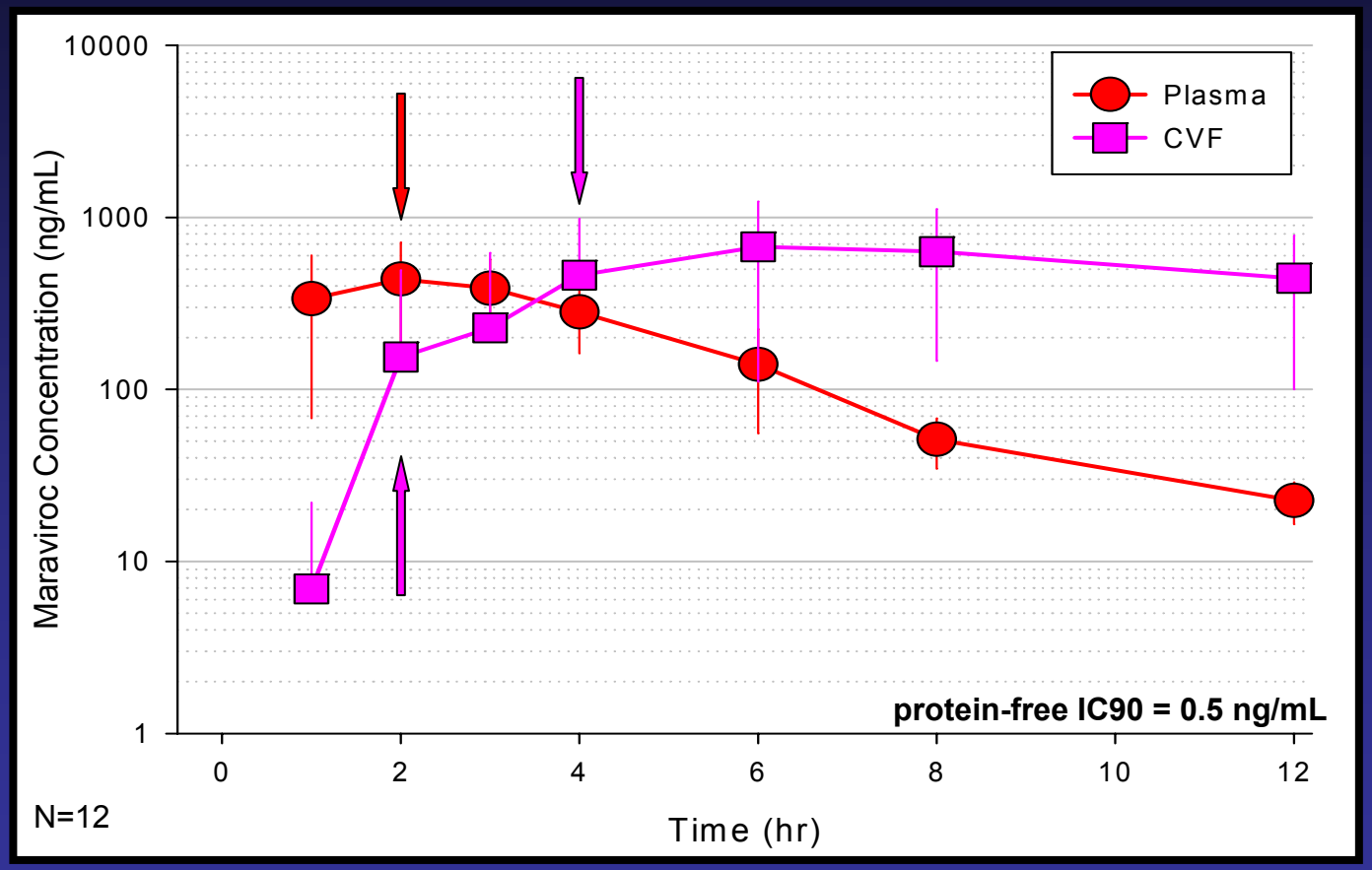
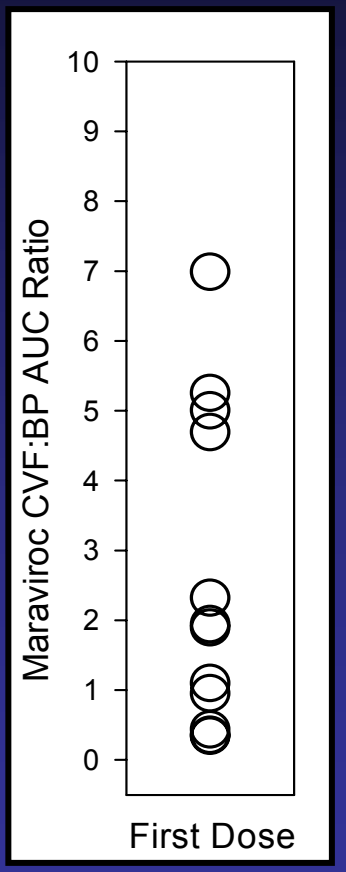
Pharmacokinetic Results

First Dose

mean (SD)



$AUC_{CVF:BP}$



AUC_{BP}: 1,991 (518) ng*hr/mL

AUC_{CVF}: 4,655 (3,661) ng*hr/mL

$CVF:BP\ AUC\ Ratio_{mean} = 2.6$

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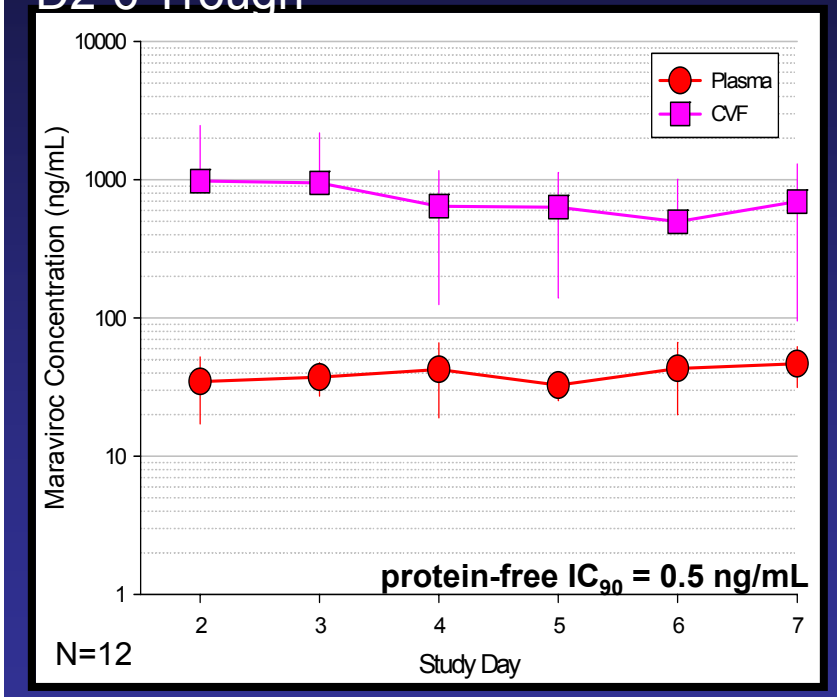
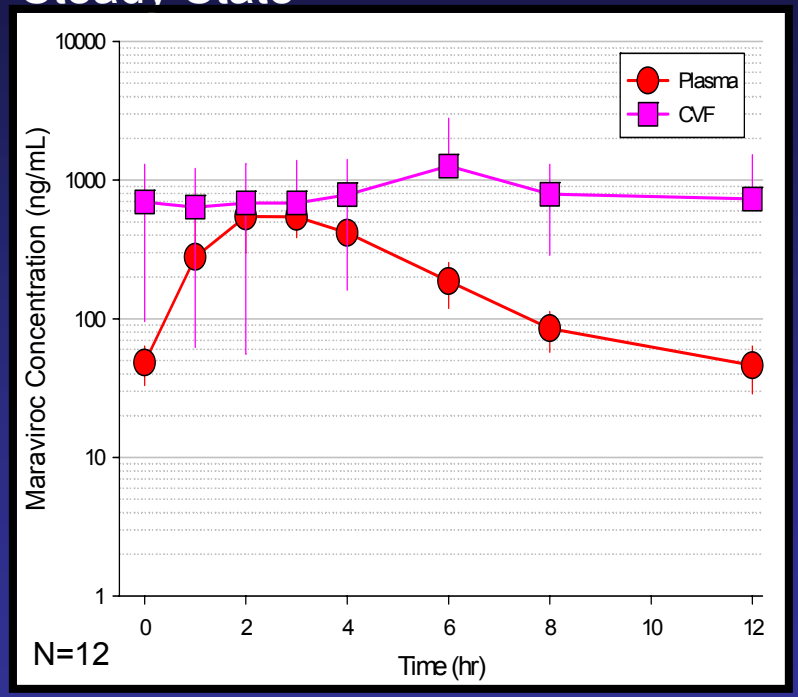
Pharmacokinetic Results

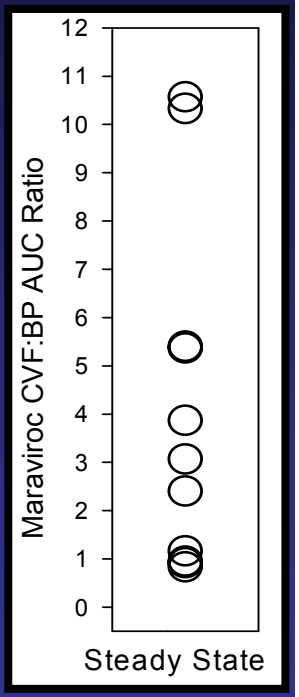
Steady State mean (SD)

D2-6 Trough



Steady State





AUC_{BP}: 2,648 (798) ng*hr/mL

AUC_{CVF}: 9,629 (7,819) ng*hr/mL

CVF:BP AUC Ratio $_{mean}$ = 4.1

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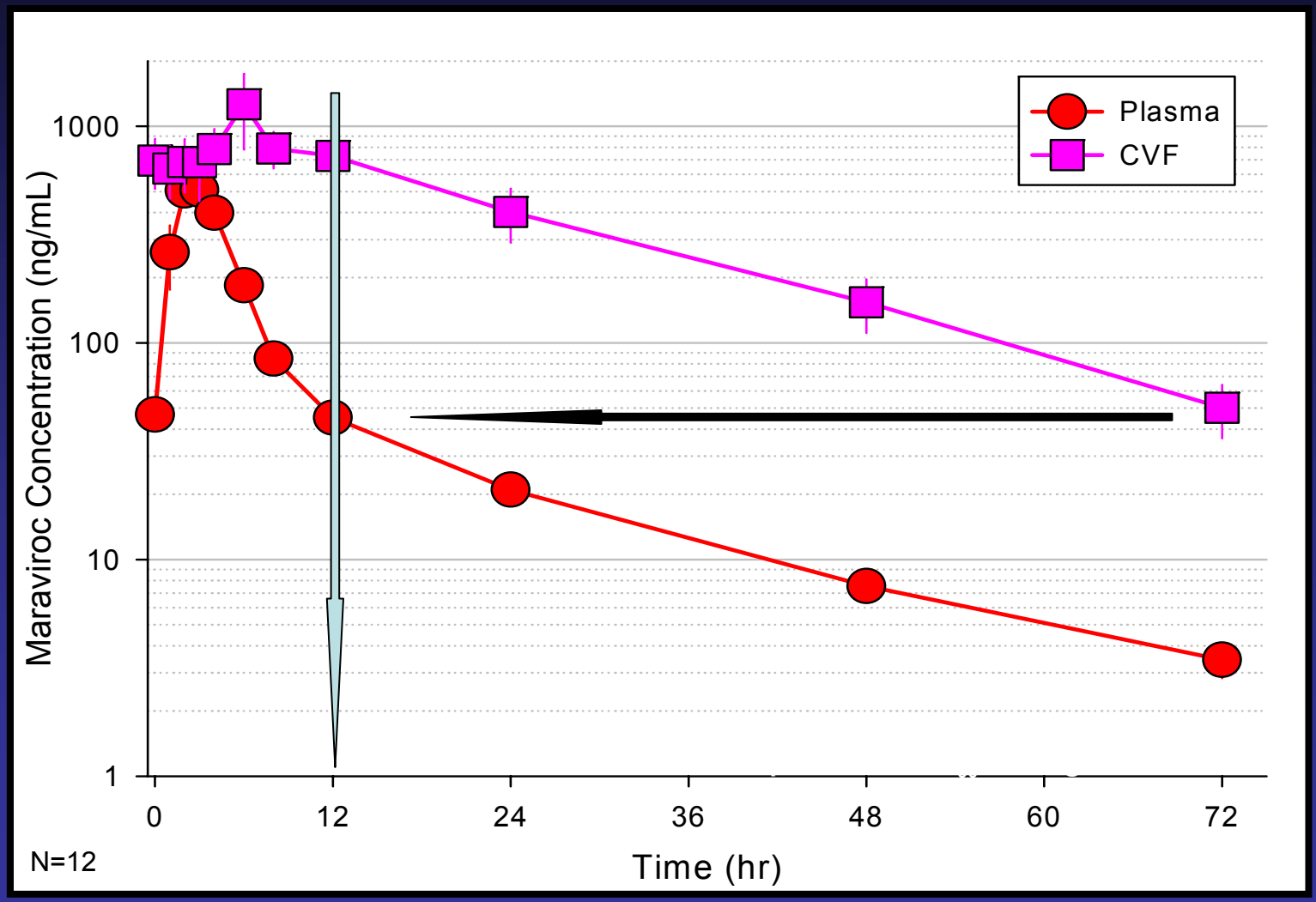
Pharmacokinetic Results

Terminal Elimination



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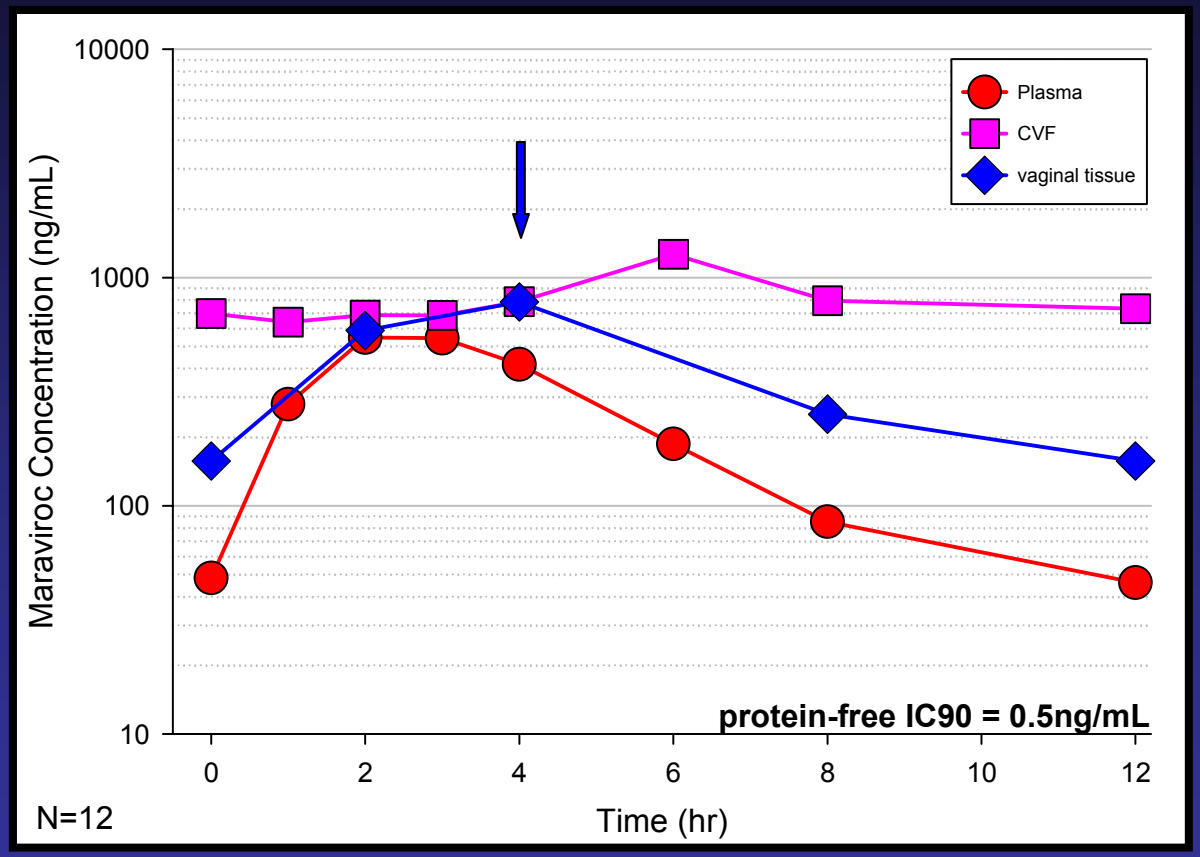
Pharmacokinetic Results

Vaginal Tissue Concentration



CVF Protein Binding*

(mean, range)

7.6 % (3.7-13.6%)

BP Protein Binding ~ 76%

*4 pooled samples

AUC_{VT}: 4,992 ng*hr/mL

AUC_{BP}: 2,648 (798) ng*hr/mL

AUC_{CVF}: 9,629 (7819) ng*hr/mL

$VT:BP\ AUC\ Ratio_{mean} = 1.9$

$CVF:BP\ AUC\ Ratio_{mean} = 4.1$

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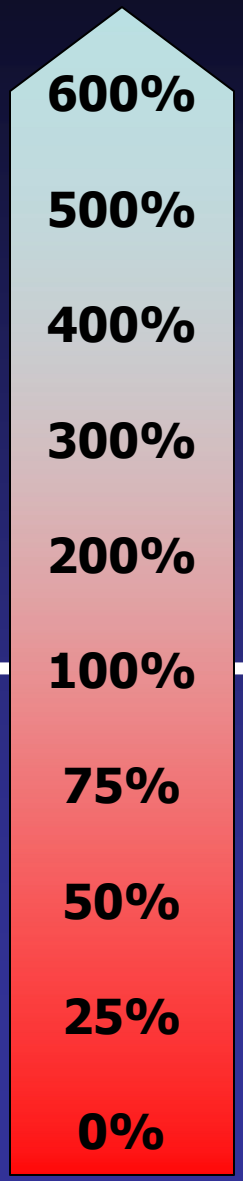
Cervicovaginal Fluid Exposure

(mean percent of blood plasma)



N(t)RTIs

- 3TC (400%)
- FTC (375%)
- ZDV (235%)
- TDF (110%)
- ddI (21%)
- ABC (8%)
- d4T (5%)

NNRTI

- NVP (80%)
- DLV (20%)
- EFV (0.4%)

PI

- IDV (200%)
- APV (50%)
- RTV (26%)
- ATV (18%)
- LPV (8%)
- SQV (ND)

Entry Inhibitors

- MVC (410%)

GT AUC : BP AUC

Min et al. JAIDS 2005
Dumond et al. AIDS 2007
Dumond et al. CROI 2008

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Conclusions

- Maraviroc concentrations in the female genital tract were 10-fold higher than IC_{90} in all subjects by 2hrs
- Maraviroc exposure in the female genital tract:
  - 2 (FD) and 4-fold (SS) higher AUC in CVF than BP
  - 72 hours after dosing CVF concentrations were similar to BP 12 hours post dose
  - Vaginal tissue (SS) ~2-fold higher than BP
  - Protein-binding in CVF 10-fold lower than BP
- First time terminal elimination, VT concentrations and protein binding has been measured in FGT

Maraviroc achieves one of the highest female genital tract exposure relative to BP of all ARVs evaluated to date. Additional work is needed to fully understand the implications of this finding.

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