A Translational Approach to Predicting the Efficacy of Maraviroc-based Regimens as HIV Pre-exposure Prophylaxis

Supplementary material

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Running Title: Maraviroc Pop-PK Model for PrEP efficacy

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Supplementary Material

Determination of protein binding in the female genital tract and rectal tissue of adult rhesus macaques:

Protein binding of Maraviroc (MVC) was determined in female genital tract and rectal tissues of six adult rhesus macaques by homogenizing individual tissue samples using 1 mL of 0.9% NaCl. Following homogenization, a Thermo scientific rapid equilibrium dialysis (RED) system, utilizing 300µL of homogenate sample and 500 µL of 0.01M HCL (buffer), was used. After a 16-hour incubation in the RED system (Thermomixer plate 37°C at 300rpm), a volume of tissue homogenate sample (red well) and buffer sample (white well) were extracted by protein precipitation with a stable-labelled internal standard (IS) for MVC (MVC-d6).

Chromatographic separation of was achieved using reverse-phase chromatography on a Waters Xterra MS C18 (50 x 2.1mm, 3.5µm) analytical column. With detection on an AB Sciex API-5000 triple quadrupole mass spectrometer using electrospray ionization in the positive ion mode.

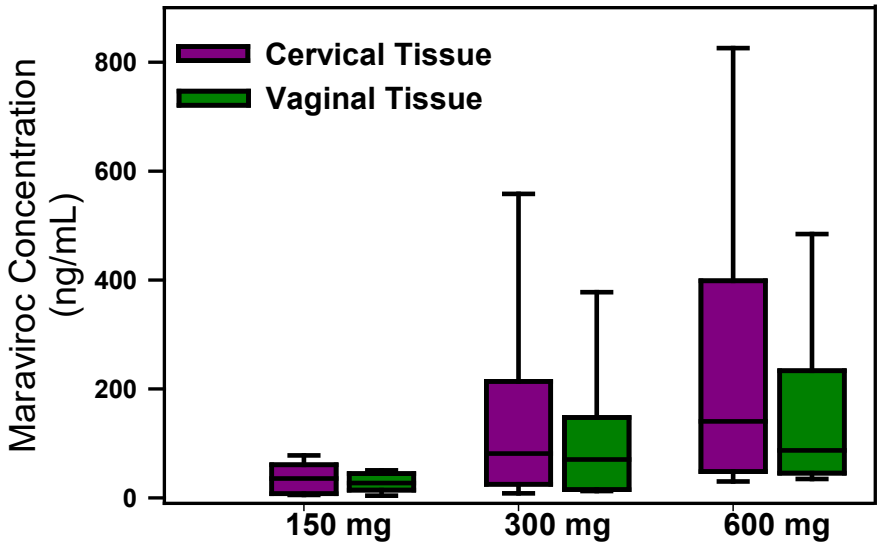
Data were collected using the Sciex Analyst Software. MVC was quantified against its internal standard using a linear regression algorithm with 1/x2 weighting.

Supplementary Table 1: Table of PK parameters for the final maraviroc population PK model

Parameter	Value	Inter-individual Variability (CV%)	Relative Standard Error (%)
Ka (1/hr)	0.216	-	10
V2 (L)	217	108%	34
V3 (L)	792	-	30
Clt (L/hr)	189	36%	17
Cl23 (L/hr)	20	-	29
V4 (L)	0.1 FIXED	-	-
Cl24 (L/hr)	0.027	-	35
Clfgt (L/hr)	0.01	-	19
Kg (1/hr)	0.036	37%	21
V5 (L)	0.17 FIXED	-	-
Cl25 (L/hr)	0.94	-	26
Clr (L/hr)	0.08	-	21
Residual variability in plasma = 77%			
Residual variability in FGT = 45%			
Residual variability in rectal tissue = 17%			

PK parameters are reported for the final population PK model

Supplementary Figure 1: Boxplots for the maraviroc concentrations in the vaginal tissue and cervical tissue at various dose levels. Wilcoxon signed rank test indicated that there was no statistically significant difference (p=0.07) between the vaginal and cervical tissue concentrations.



Supplementary Figure 2: Diagnostic plots for the maraviroc population pharmacokinetic model. Individual prediction versus observation plots are shown for the (a) plasma, (d) female-genital tract and (g) rectal tissue compartments. Conditional-weighted residual plot versus the time after last dose are shown for the (b) plasma, (e) female-genital tract and (h) rectal tissue compartments and visual predictive checks are shown as an overlay of maraviroc concentrations over the 5th, 25th, median, 75th and 95th percentiles of the model concentration predictions for the (c) plasma, (f) female-genital tract and (i) rectal tissue compartments. All diagnostic plots indicated that the model fit the data reasonably well.