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Single-dose Maraviroc Provides High Drug Levels in All Sites; No Gender Differences

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BACKGROUND

Oral pre-exposure prophylaxis (PrEP) is an effective prevention strategy against HIV-1 transmission. It is not known what drug level in plasma or tissue is requiered to provide protection for HIV. Maraviroc (MVC) 300mg stat showed no protection from HIV using ex vivo [CROI 2105]. Understanding the drugs levels achieved by stat dosing which failed to show ex vivo protection will help to inform future clinical trials of daily or "on demand" MVC PrEP.

We present drug levels in all HIV acquisition sites extended out to 72 hours following 300mg stat dose of MVC.

METHODS

56 healthy adult female (n=26) and male participants (n=30) were randomized to a control arm (Arm A n=6 with tissue samples taken at two time points one month apart) or to one of 4 intervention arms (n=12 per arm) where a single oral MVC 300 mg dose was taken at two time points prior to sampling, one month apart (Arm B: first sampling 2 h post first dose and second sampling 24 h post second dose; Arm C: 4 h and 36 h; Arm D: 6 h and 48 h; Arm E: 12 h and 72 h). Sampling to determine MVC concentrations included blood, saliva and rectal fluid (RF) for all subjects. In addition, men provided a urethral swab and rectal tissue (RT) and women provided cervico-vaginal fluid (VF) and vaginal tissue (VT). MVC drug concentrations were measured by validated LC-MS/MS.

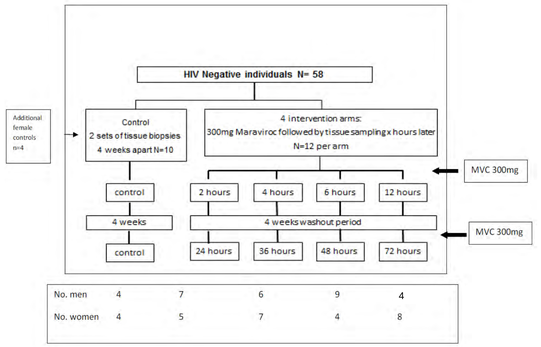
RESULTS

Baseline Characteristics

	Total N:56
Demographics	
Age in years mean (SD	32 (10.66)
Gender, n (%)	
Female	28 (48%)
Male	30(52%)
Ethnicity n (%)	
White	38 (65%)
Black	16 (27%)
Other	4 (8%)
Weight (kg) mean (SD)	73.84 (14.44)
BMI kg/m^2 mean (SD)	24.73 (4.00)

SD: Standard deviation
Baseline characteristics were summarised as the mean and standard deviation (continuous normally distributed variables), median and interquartile range (non-normally distributed variables), and as frequency and percentage (categorical variables)

Study Design

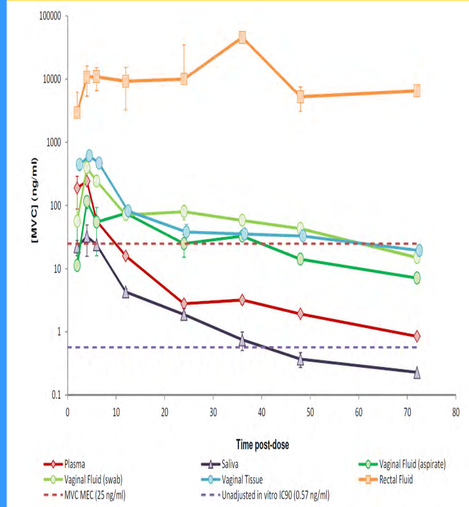


Male and Female pharmacokinetics

	Male				Female			
Compartment	**AUC_{0-72} (ng.h/ml)**	**se**	**Ratio (vs. plasma)**	**p value (z test)**	**AUC_{0-72} (ng.h/ml)**	**se**	**Ratio (vs. plasma)**	**p value (z test)**
Plasma	1212	195			1353	243		
Saliva	220	25	0.18	**<0.0001**	285	75	0.21	**<0.0001**
Rectal Fluid	991868	303656	818.51	**<0.01**	996496	320763	736.75	**<0.01**
Rectal Tissue	53950	11703	44.52	**<0.0001**				
Urethra	173965	39597	143.56	**<0.0001**				
Vaginal Fluid (aspirate)					2182	495	1.61	>0.05
Vaginal Fluid (swab)					5134	694	3.80	**<0.0001**
Vaginal Tissue					6537	758	4.83	**<0.0001**
Compartment	**C_{max} (ng/ml)**	**se**	**Ratio (vs. plasma)**	**p value (z test)**	**C_{max} (ng/ml)**	**se**	**Ratio (vs. plasma)**	**p value (z test)**
Plasma	141	48			242	101		
Saliva	30	9	0.21	<0.05	32	6	0.13	<0.05
Rectal Fluid	26165	13170	185.78	<0.05	45654	24682	188.40	>0.05
Rectal Tissue	1174	202	8.33	**<0.0001**				
Urethra	22156	10287	157.32	<0.05				
Vaginal Fluid (aspirate)					115	58	0.48	>0.05
Vaginal Fluid (swab)					395	107	1.63	>0.05
Vaginal Tissue					611	86	2.52	**<0.01**

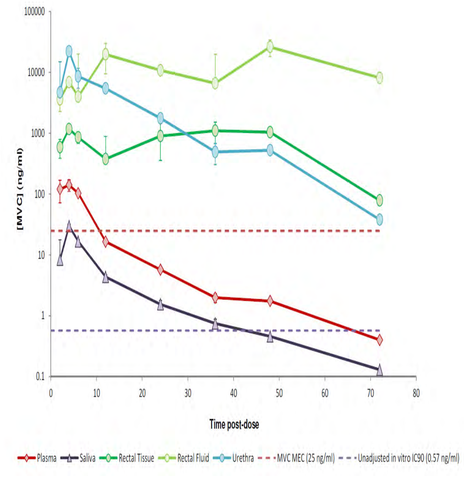
Male and female pharmacokinetic parameters in all compartments following a stat dose of maraviroc 300 mg. P values in bold type are significantly different to the plasma compartment.

Pharmacokinetics in HIV-negative females



Pharmacokinetic profile in plasma, saliva, genital tract (urethra) and rectum (rectal fluid and tissue) of HIV-negative females following a stat dose of maraviroc 300 mg orally. Data are expressed as mean (sem).

Pharmacokinetics in HIV-negative males



Pharmacokinetic profile in plasma, saliva, genital tract (urethra) and rectum (rectal fluid and tissue) of HIV-negative males following a stat dose of maraviroc 300 mg orally. Data are expressed as mean (sem).

Main Findings

Maraviroc maximum concentration (C_{max}) was reached within four hours post-dose in all compartments, except for rectal fluid where C_{max} maraviroc was achieved >35 hours, suggesting drug accumulation in this compartment.
Plasma C_{max} exceeded the suggested MEC and protein-binding adjusted IC90. At all other sites, C_{max} was well above the unadjusted in vitro IC90 and highest levels were achieved in rectal fluid.

Maraviroc concentrations at 72 hours were above the in vitro IC90 for rectal fluid (8095 ng/ml), rectal tissue (79 ng/ml) and urethral fluid (38 ng/ml) in males and for rectal fluid (6549 ng/ml), vaginal fluid (aspirate: 7 ng/ml, swab: 15 ng/ml) and vaginal tissue (19 ng/ml) in females.

No gender differences in AUC_{0-72} or C_{max} were observed for plasma, saliva or rectal fluid

CONCLUSIONS

MVC concentrations greater than the IC90 occurred in multiple sites of HIV acquisition after single oral 300mg MVC. This suggests that MVC may be a suitable candidate for PrEP. However, the lack of inhibition in rectal and vaginal tissue suggests that either the *ex vivo* challenge model for MVC requires further validation or that higher levels of MVC than previously thought are needed to prevent infection from HIV. The high levels in rectal fluid and urethra may partially reflect excretion of unchanged drug in urine and faeces, and therefore cannot be used as surrogate markers of tissue levels.