The Pharmacokinetics and Pharmacodynamics of Oral and Topical Maraviroc: The CHARM-03 Study.

[1,2]Ian McGowan, [1,2]Rhonda M. Brand, [2]Jarret C. Engstrom, [2]Aaron Siegel, [2]Ashley Myerski, [2]Cindy Jacobson, [3]Mark A. Marzinke, [3]Craig W. Hendrix, [4]Alex Reinhart,

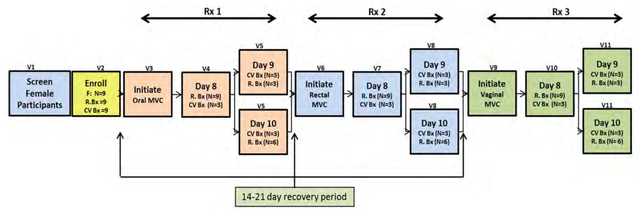
[5]John Steytler, [1,2]Charlene S. Dezzutti, [6]Nicola Richardson-Harman, [7]Hans M.L. Spiegel, [1]Ross Cranston, and the CHARM-03 team.

[1]University of Pittsburgh School of Medicine, Pittsburgh, PA, [2]Magee Womens Research Institute, Pittsburgh, PA, [3]Johns Hopkins University School of Medicine Baltimore, MD, [4]ViiV Healthcare, Research Triangle Park, NC, [5]International Partnership for Microbicides Silver Springs, MD, [6]Alpha StatConsult LLC, Damascus, MD, [7]Kelly Government Solutions, Contractor to National Institute of Allergy and Infectious Diseases, Department of Health and Human Services, Rockville, MD.

Introduction

- Maraviroc (MVC), a CCR5 receptor antagonist, is being evaluated as an HIV-1 PrEP agent.
- In non-human primate models, oral MVC did not provide protection from SHIV162p3 rectal challenge, whereas topically applied rectal MVC was protective.
- Phase 1/2 studies have not demonstrated significant viral inhibition in the *ex vivo / in vitro* colorectal explant challenge model.
- **The purpose of the CHARM-03 study was to characterize the safety, acceptability, pharmacokinetic (PK), and pharmacodynamic profile of MVC following oral, vaginal, and rectal administration.**

Methods



Rx= Treatment; F= Female; R= Rectal; Bx= Biopsies & CV= Cervical; N = number of participants having rectal or cervical biopsies
Participants will be randomized to product sequence and mucosal sampling schedule at Visit 2 (Enrollment)

- Participants were given 300 mg oral MVC and 1% MVC rectal gel for 8 consecutive days. Female participants (N=9) also received daily vaginally administered MVC 1% gel for 8 consecutive days.
- Blood and tissue (cervical and rectal) were collected prior to and +2, +24 or +48 hours after the final dose of study product.
  - Pharmacodynamic efficacy was determined in the explant challenge model by using tissue biopsies that were that incubated *ex vivo* with HIV-1_{BaL} for 2 hours, as previously described (McGowan I et al. Lancet HIV 2016).
  - To address potential drug disassociation from the tissue, one biopsy was snap frozen for PK and a second biopsy was incubated in culture medium for 2 hours before being snap frozen for PK.

The Effect of MVC on HIV Infection of Mucosal Tissue

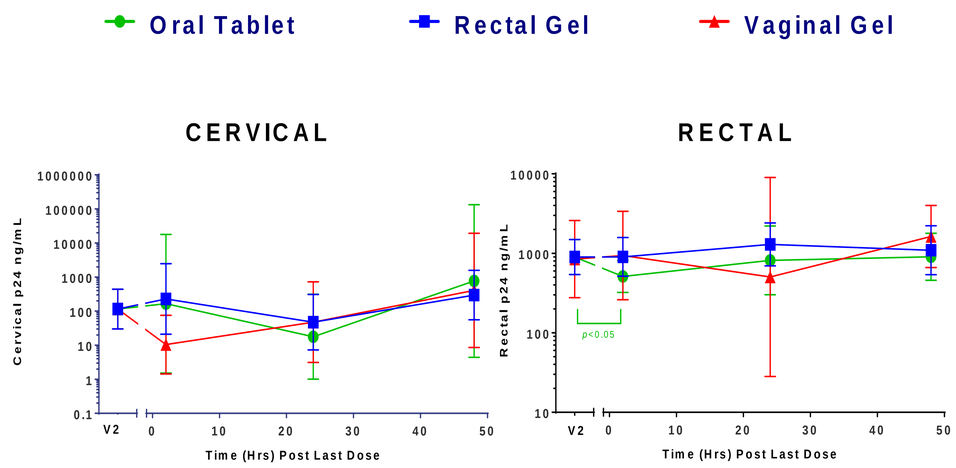


Figure 1: ***Oral MVC dosing inhibits HIV infection in the colorectal but not cervical explant challenge model.*** Prevention was only observed at 2 hrs post-dose ($p<0.05$). No inhibition was observed in either tissue after rectally or vaginally applied gels. V2 is a baseline challenge with no product present.

Table 1: PK comparison between plasma and rectal tissue at time of tissue collection. MVC levels recorded in ng/mL.

CHARM-03 Compartmental PK Comparison						
	Oral dosing		Rectal dosing		Vaginal dosing	
	mean	SD	mean	SD	mean	SD
Plasma (ng/mL)	512.5	73.3	11.3	1.3	2.8	0.9
Rectal tissue (ng/mL)	7.9	7.2	29.2	36.5	0.1	0.1

Table 2: Twenty-five adverse events (AE) were reported in 11 participants.

Product administration location					
AE (R=Related or NR=Not Related)					
	On Study	Oral	Rectal	Vaginal	Pre-Rx
Grade 1	24	3 (0R, 3NR)	14 (3R, 11NR)	4 (1R, 3NR)	3 (0R, 3NR)
Grade 2	1	0	1 (NR)	0	0
Grade 3	0	0	0	0	0
Grade 4	0	0	0	0	0
Grade 5	0	0	0	0	0
Total	25	3	15	4	3

Dissociation of MVC from Tissue During the 2 Hour HIV Incubation Used in the Explant Challenge Model

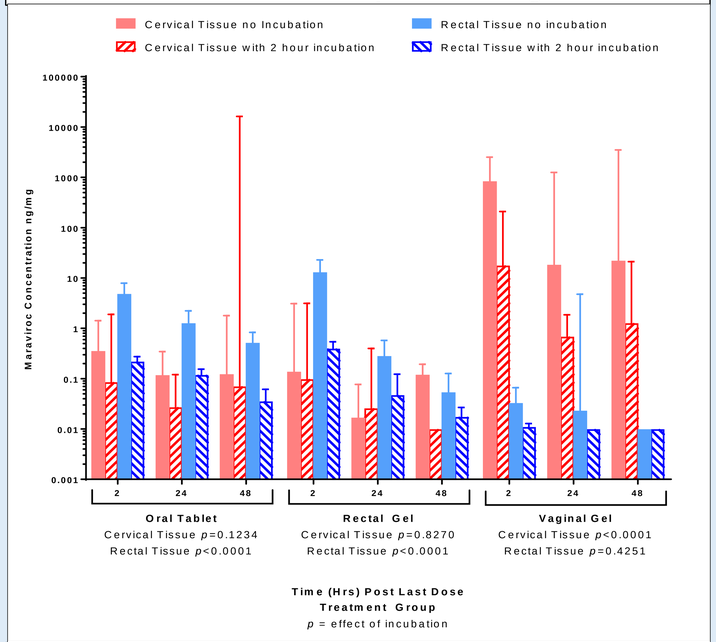


Figure 2: ***Tissue MVC levels demonstrated that MVC dissociated from tissue for all formulations tested***. MVC given in the oral or gel formulations dissociated from rectal tissue when stored in media for 2-hours ($p<0.0001$). Dissociation was also observed in cervical tissue after vaginal gel application ($p<0.0001$).

Conclusions

- Oral and topical MVC were safe and well tolerated.
- Oral MVC was associated with modest colorectal explant viral inhibition.
- MVC disassociated from explant tissue during incubation which may account for the absence of viral suppression after rectal and vaginal gel exposure.

Acknowledgments

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See Poster #1056- "Gender-specific rectal proteome changes with oral and topical Maraviroc use as PrEP" for additional results from the CHARM-03 study

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