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ENEMA DELIVERED MICROBICIDE, A POTENTIAL ALTERNATIVE TO PREP

Francois Villinger[1], Peng Xiao[1], Sanjeev Gumber[2], Mark A Marzinke[3], Abhijit A Date[3], Thuy Hoang[3], Laura M Ensign[3], Lisa Rohan[4], Edward J Fuchs[3] and Craig Hendrix[3]

[1]University of Louisiana at Lafayette, USA
[2]Emory University, USA
[3]Johns Hopkins University School of Medicine, USA
[4]University of Pittsburgh, USA

Oral PrEP (tenofovir disoproxil fumarate/emtricitabine) has been approved for pre-exposure prophylaxis of HIV-1 transmission, but is associated with high costs and issues of adherence. Protection from receptive anal transmission of HIV using topical microbicides using methods more congruent with sexual behavior offers the promise of improved adherence. However, there are limited data evaluating the pharmacokinetic (PK) and pharmacodynamic effects of topical prevention. We compared the PK and ex vivo efficacy of iso-osmolar (IOsm) and hypo-osmolar (HOsm) rectal enema formulations of tenofovir (TFV) in a macaque model. Single-dose PK of IOsm or HOsm high (5.28 mg/mL) and low (1.76 mg/mL) dose formulations of TFV enemas were evaluated for systemic uptake in blood, colorectal biopsies and rectal CD4+ T cells. Markedly higher TFV concentrations were observed in plasma as well as in tissues after administration of the HOsm high dose formulation than all other formulations tested. TFV and TFV diphosphate (TFV-DP) concentrations in tissue were highly correlated for the HOsm high dose formulation (1 h: r=0.8986, p=0.0333; 24 h: r=0.9411, p=0.0167), demonstrating rapid uptake and transformation of TFV to TFV-DP in tissues. TFV-DP concentrations in colorectal tissues collected at 1 hour (4783.77±1390.85 fmol/mg) and 24 hours (2407.26±762.89 fmol/mg) were 7 and 5 fold higher, respectively (p<0.01) compared to the same high dose formulated as IOsm enema. HOsm high dose (5.28 mg/mL) formulation was safe and highly effective in preventing SHIV162p3 and SIVmac251 infection in ex vivo challenges of rectal tissues collected at 1, 24 and 72 hours after the intrarectal dosing, whereas the same TFV dose formulated as IOsm enema was less effective. Thus, rectally applied HOsm high dose formulation of TFV enema promotes far more rapid TFV uptake and TFV-DP transformation to achieve colon tissue protective target drug concentrations compared to IOsm formulation of the same TFV dose.

fvillin@emory.edu