HIV Pre-exposure Prophylaxis: PK-PD Studies on Anti-HIV Drugs Maraviroc, Raltegravir and Tenofovir in a Humanized Mouse Model

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Background/Objective
Strategies utilizing anti-retroviral drugs for Pre-exposure prophylaxis (PrEP) show considerable promise for HIV prevention. However there is insufficient pharmacokinetic and pharmocodynamic (PK-PD) data on the required protective concentrations of the drug that needs to be reached at the vaginal and rectal mucosal tissues to confer full protection. Here our goal is to derive PK-PD data on three leading drugs, the RT inhibitor tenofovir (TFV) and CCR5 inhibitor maraviroc (MVC) and integrase inhibitor raltegravir (RAL) both individually and in various combinations.

Method
A new generation humanized mouse model that permits HIV mucosal transmission was used in these studies. Mice were orally administered with human equivalent doses of the drugs and later challenged with HIV vaginally to determine the drug efficacy. In PK studies, plasma and various tissue matrixes were collected for assaying the drug concentrations

Result
Each of the drugs showed significant protection against viral challenge. In PK studies, each of the drug could be detected in the vaginal, rectal and intestinal tissues. The drug exposures (AUC24hr) were found to be higher in vaginal tissue compared to plasma with even higher levels detected in rectal and intestinal tissues. Results obtained confirmed favorable PrEP profile of TFV. While RAL and MVC showed efficacy, mucosal drug levels indicated that PrEP doses would need to be higher than therapeutic ones to allow for once a day dosing. In combinatorial TFV/RAL and TFV/MVC oral application studies, increase in the active form of TFV (Tenofovir diphosphate, TFV-DP) accompanied by agonistic effect for the second drug in combination was observed.

Conclusion
The overall general trends of drug concentrations seen in humanized mice reflect those seen in the human thus establishing the utility of this model for future pre-clinical evaluations of promising HIV PrEP drug candidates.