A penile model in rhesus macaques to assess pharmacokinetics in penile tissues following oral or topical antiretroviral prophylaxis

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Background: The clinical development of systemic and topical antiretroviral prophylaxis for HIV prevention has benefited from preclinical macaque models of vaginal and rectal transmission, both of which have provided invaluable efficacy and pharmacokinetic (PK) data. There is increasing interest in developing penile PK and transmission models to extend assessment of interventions against this important route of infection. Here we report PK methods to examine drug exposures in various penile tissues and describe drug distribution following oral and topical tenofovir (TFV) dosing.

Methods: Drug exposures in penile tissues were assessed in rhesus macaques following topical or oral dosing with either 1% TFV gel or tenofovir disoproxil fumarate (TDF), respectively. Intact penile tissues were collected at necropsy 2 hours after 1ml application of 1% TFV gel (n=3) or 24 hours after oral TDF (22mg/kg) (n=7). Intracellular TFV di-phosphate (TFV-DP) levels (fmol/10^6 cells) were measured by mass spectrometry in lymphocytes isolated from urethral and foreskin tissues by enzymatic tissue digestion. We additionally tested biopsies and determined TFV-DP concentrations per mg of tissue collected from glans, foreskin, corpus, and urethra (1-6cm) tissues of one macaque sacrificed 2hr after penile application of 1% TFV gel.

Results: Median TFV-DP concentrations in lymphocytes at 2h from foreskin and urethra were 1,607 (range 558-3,652) and 2,491 (range 1,964-3,018) fmol/10^6 cells in animals dosed with TFV gel compared to 221 (range 1-1,249) and 161 (range 19-756) fmol/10^6 cells at 24 h in animals dosed with oral TDF, respectively. In one animal dosed with TFV gel, TFV-DP concentrations were high in biopsies collected from glans, corpus, and foreskin (43, 30, and 99 fmol/mg, respectively). Likewise, TFV-DP exposure was high in urethral tissue sections collected at 1, 3, 4, 5, and 6 cm from the prepuce (39, 138, 288, 78 and 98 fmol/mg, respectively).

Conclusion: Data document TFV dosing in urethral and foreskin lymphocytes, two relevant cell populations for HIV transmission. Similar to rectal and vaginal gel dosing, topical penile drug dosing also resulted in ~10-fold higher) mucosal drug levels compared to oral dosing. TFV-DP levels detected in urethral and foreskin lymphocytes were in range with those reported in vaginal and rectal lymphocytes that were also highly protective against SHIV transmission. These data support using this model to evaluate PK of next-generation antiretroviral prophylaxis products.