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ORAL FTC/TAF COMBINATION PREVENTS VAGINAL SHIV INFECTION IN PIGTAIL MACAQUES

Epidemiology/Public Health:
(T) Prevention Interventions

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Background: Tenofovir alafenamide (TAF) is a novel tenofovir prodrug with improved properties relative to tenofovir disoproxil fumarate (TDF) that makes it an attractive candidate for PrEP. We recently showed that the combination of TAF and emtricitabine (FTC) was highly effective in preventing rectal simian HIV (SHIV) infection in rhesus macaques. Here we investigated the efficacy of FTC/TAF against vaginal SHIV infection
Methods: The pharmacokinetic profile of TAF was studied at first dose. Tenofovir (TFV) was measured in plasma and vaginal and rectal secretions. Intracellular tenofovir di-phosphate (TFV-DP) and FTC-triphosphate (FTC-TP) were measured in PBMCs and/or rectal and vaginal biopsies. The efficacy of FTC/TAF in preventing vaginal infection was investigated using an established model of vaginal SHIV exposure consisting of up to 16 once-weekly virus challenges with 50 TCID50 of SHIV162p3. Six macaques received FTC/TAF (20 and 1.5 mg/kg, respectively) orally 24h before and 2h after each weekly virus exposure and 5 received placebo. Infection was monitored by serology and RT-PCR.
Results: As observed in humans, plasma TFV levels with 1.5 mg/kg of TAF were low (Cmax = 17 [5-42] ng/ml). In PBMCs, TFV-DP concentrations peaked at 5-24 hr (median = 154 [34-295] fmol/106cells) and gradually declined with a half-life of 38 (33-122) hr. TFV exposure in vaginal fluids (AUC0-24h = 2,001 [216-11,569] ng*h/mL) was lower than in rectal fluids (17,205 [216-313,122] ng*h/mL) although the difference was not statistically significant (p = 0.38). 24h after dosing, TFV-DP levels in vaginal and rectal tissues were similar (9 [6-10] and 11 [7-19]) fmol/mg, respectively, p = 0.25). All 5 untreated controls exposed vaginally to SHIV were infected after a median of 5 [2-14] exposures. In contrast, 5 of the 6 animals that received FTC/TAF remained uninfected after 16 virus challenges (p = 0.012 log-rank test). All the protected animals had detectable TFV-DP and FTC-TP in PBMCs (median = 237 [123-829] and 1837 [1256-2653] fmols/106 cells, respectively) at the time of virus exposure. In contrast, the PrEP breakthrough animal only had detectable FTC-TP (median=1499 fmols/106 cells).
Conclusion: A clinically equivalent dose of FTC/TAF administered orally to macaques 24h before and 2h after vaginal SHIV exposure prevented infection to a degree similar to that previously observed with FTC/TDF. These results support the evaluation of FTC/TAF for PrEP against vaginal HIV infection.