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MODERATE EFFICACY OF ORAL SINGLE-AGENT TAF AGAINST VAGINAL SHIV INFECTION IN MACAQUES
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Background:
Tenofovir alafenamide (TAF) is a prodrug of TFV that is under evaluation as oral PrEP in combination with emtricitabine (FTC), and as a long-acting single agent delivered from implants. We recently showed that oral TAF in combination with FTC was highly effective in preventing vaginal simian HIV (SHIV) infection in female pigtailed macaques. Here we investigated if TAF alone is sufficient for preventing vaginal SHIV infection.

Methods:
The efficacy of single agent TAF in preventing vaginal infection was investigated in an established model of vaginal SHIV exposures consisting of up to 15 once-weekly virus challenges with SHIV162p3. Nine pigtail macaques received a clinically equivalent dose of TAF (1.5 mg/kg) orally 24h before and 2h after each weekly virus exposure. Infection outcome was compared with 21 placebo animals (6 real-time and 15 historical controls). TFV-diphosphate (TFV-DP) and dATP levels in PBMCs were measured once a week at the time of virus challenge. Kaplan-Meier survival analysis and a log-rank test was used to compare time to infection in TAF-treated animals relative to controls. Infection rates were compared using the fisher exact test. TFV-DP levels were measured in vaginal and rectal biopsies from a separate group of 9 macaques.

Results:
Infection rates and time to SHIV RNA detection were similar in real time and historical controls (p=0.500 and p=0.319, respectively). Two of the 9 TAF-treated animals did not metabolize TAF (TFV-DP level of 15 and 16 fmols/106 cells) and were excluded from the analysis. Three of the remaining 7 TAF-treated and 19/21 control animals became infected (p=0.021). Infection in TAF-treated animals was also delayed relative to controls (p=0.036). TFV-DP levels in the 3 animals infected during TAF PrEP (median=351 fmols/106 cells; range=143-1,568) were similar to those seen in the 4 uninfected macaques (median=331; range = 236-584; p=0.359). dATP/TFV-DP ratios were also similar among infected and protected animals (median=0.685 and 1.045, respectively, p=0.982). After a single oral dose, TFV-DP was detected in 5/9 vaginal and 9/9 rectal biopsy specimens (5 and 7.9 fmols/mg, respectively).

Conclusion:
A clinically equivalent dose of single agent TAF administered orally 24h before and 2h after virus exposure without FTC conferred moderate protection against vaginal SHIV infection in female macaques. These data highlight the importance of defining the PBMC TFV-DP concentrations associated with complete vaginal protection from single agent TAF.