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PROTECTION AGAINST VAGINAL SHIV INFECTION WITH AN INSERT CONTAINING TAF AND EVG
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Background:
On-demand topical PrEP for HIV prevention has several advantages over a daily oral PrEP regimen, including reduced costs, limited drug toxicity, decreased risk of resistance, and potential to increase adherence. Inserts containing tenofovir alafenamide fumarate (TAF) in combination with elvitegravir (EVG) are being developed by CONRAD/EVMS for flexible, on-demand vaginal or rectal pericoital use. We recently found in a dose-ranging pharmacokinetic assessment in macaques that vaginal administration of inserts containing 20 and 16 mgs of TAF and EVG, respectively, resulted in rapid accumulation of EVG and durable levels of tenofovir diphosphate (TFV-DP) in mucosal tissues at concentrations associated with in vivo protection. Here we used a macaque model of vaginal SHIV transmission to investigate the protective efficacy of TAF/EVG inserts.

Methods:
Normal cycling pigtail macaques (n=14) were exposed vaginally to SHIV162P3 once a week for up to 13 weeks. Six macaques received inserts containing a fixed-dose combination of TAF/EVG (20 mg/16 mg) and 8 received matching placebo inserts. Inserts were placed in the posterior vagina near the cervix 4 hours before each SHIV exposure. Infection was monitored weekly by serology and RT-PCR amplification of SHIV RNA in plasma. A Kaplan-Meier survival analysis was used to compare the survival distribution between the two groups and efficacy was calculated as 1-(p1 / p0), where p1 and p0 denote the proportion of infections per total challenges for TAF/EVG and placebo controls, respectively.

Results:
Of the 8 macaques that received placebo inserts, 7 became SHIV infected while 1 remained SHIV negative following 13 weekly challenges. The median number of challenges to infect macaques treated with placebo inserts was 3 (range 2-13). In contrast, 5 of 6 macaques that received TAF/EVG inserts remained protected after 13 challenges resulting in an estimated efficacy of 92%. Survival analysis demonstrate at least a 9-fold reduction in risk of infection in macaques that received TAF/EVG compared to placebo inserts (p=0.007; log-rank).

Conclusion:
Vaginal administration of inserts containing TAF and EVG was highly effective in preventing SHIV infection in a macaque model that mimics vaginal transmission of HIV in women. The data support the clinical development and first-in-human testing of TAF/EVG inserts for on-demand topical prophylaxis against vaginally acquired HIV infection.