STROMAL FIBROBLASTS FROM FEMALE GENITAL TRACT DIMINISH THE IN VITRO EFFICACY OF PrEP

00213

Ashley F. George[1, 2], Matthew McGregor[1, 2], Jason Neidleman[1, 2], Warner C. Greene[1, 3], and Nadia R. Roan[1, 2]

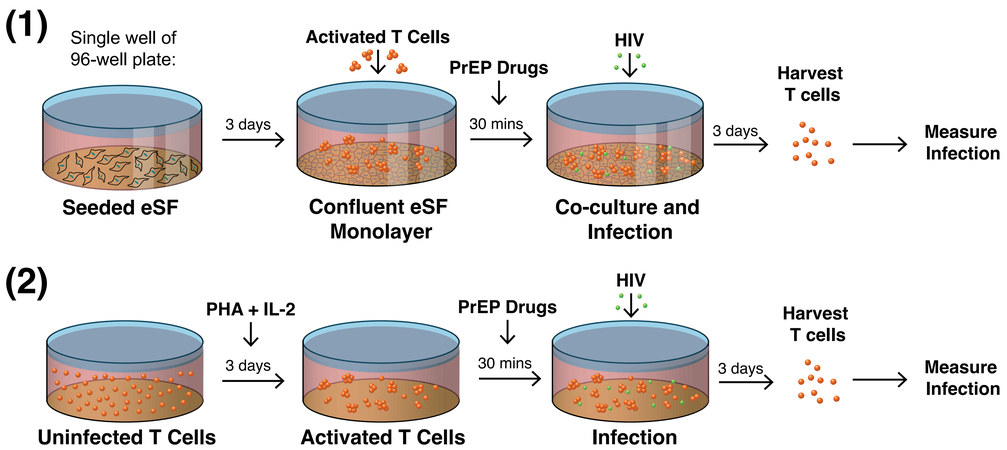
[1]Gladstone Institute of Virology, University of California, San Francisco, USA [2]Department of Urology, University of California, San Francisco, USA. [3]Departments of Medicine and Microbiology and Immunology, University of California, San Francisco, USA.

BACKGROUND

- Sexual intercourse is the most common means of HIV transmission, and young women account for the majority of new worldwide cases of infections.
- While pre-exposure prophylaxis (PrEP) has been effective in preventing HIV transmission in MSM, it has proven to be less effective in women.
- Contributing factors as to why PrEP has been less effective in women include lower adherence due to socioeconomic factors, composition of the vaginal microbiome, and reduced drug concentrations within the female reproductive tract (FRT).
- Our prior studies (*Neidleman et al., 2017*) have demonstrated that fibroblasts from the lower and upper FRT can markedly enhance HIV infection of CD4+ T cells (by up to 100-fold).
- Given the current testing of cabotegravir and dapivirine regimens as candidate PrEP agents for women, we set out to determine using *in vitro* assays whether endometrial stromal fibroblasts (eSF) isolated from the FRT may also affect the anti-HIV activity of these PrEP drugs.

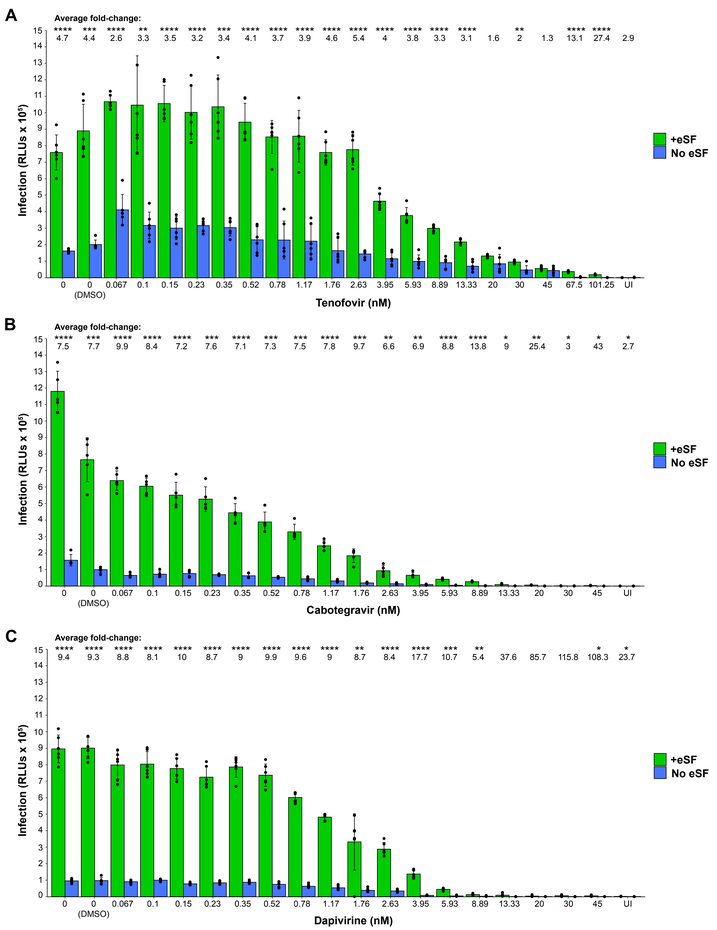
METHODS

- eSFs were isolated from endometrial biopsies and expanded in culture.
- Activated PBMCs from HIV-seronegative individuals were incubated with escalating concentrations of tenofovir, cabotegravir, or dapivirine, in the absence or presence of eSF.
- Cells were then infected with a HIV luciferase reporter virus and infection levels were monitored 3 days later by luminescence.



RESULTS

Tenofovir, cabotegravir, and dapivirine lose antiviral activity in the presence of endometrial stromal fibroblasts.

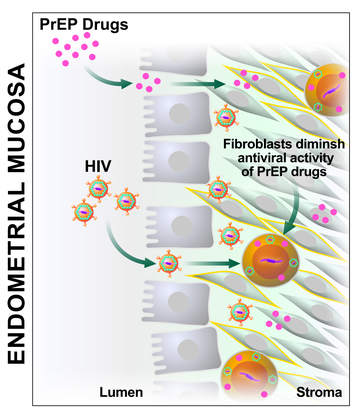


Infection rates of PBMCs exposed to increasing concentrations of (A) tenofovir, (B) cabotegravir, or (C) dapivirine are shown. Activated PBMCs treated with the indicated drug were mock-treated or inoculated with a CCR5-tropic HIV luciferase reporter virus, in the absence (blue) or presence (green) of eSF. Mean luciferase activities ± SD derived from sextuplet infections are shown (RLU/s, relative light units per second).

Consistent with previous data, eSF enhanced HIV infection rates in PBMCs. The presence of tenofovir, cabotegravir, and dapivirine inhibited HIV infection in a dose-dependent manner both in the absence and presence of eSF, but in the presence of eSF infection rates were on average 9.60-fold higher (range 5.5-19.5) for tenofovir, 3.40-fold higher (range 2.3-4.81) for cabotegravir, and 6.06-fold higher (range 2.54-18.44) for dapivirine. (*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 by 2-tailed t test). At high drug concentrations (>3.95 mM), we observe no infection with PBMCs alone, but significant infection rates with eSFs.

CONCLUSIONS

- These data suggest that the antiviral activity of clinically-relevant PrEP drugs are diminished by mucosal fibroblasts abundant in FRT, and suggest that *in vitro* infection assays testing PrEP using T cells in isolation may overestimate effectiveness relative to what occurs in the FRT.
- Supplementing PrEP with inhibitors targeting the ability of FRT fibroblasts to enhance HIV infection may increase PrEP efficacy, particularly under limiting drug concentration conditions.



Funding:

- UCSF AIDS Research Institute 2021 Strategic Support Award (to AFG).
- NIH R01 AI127219 (to NRR)