OPTIMIZING PRE-EXPOSURE PROPHYLAXIS WITH TDF-FTC and TAF-FTC for INSERTIVE SEX

00995

Carolina Herrera[1], Laura Else[2], Emily Webb[3], Azure-Dee AP. Pillay[4], Thabiso B. Seiphetlo[4], Limakatso Lebina[5], Jennifer Serwanga[6], Andrew Ssemata[6], Patricia Namubiru[6], Geoffrey Odoch[6], Clive Gray[4,7], Francesca Chiodi[8], Saye Khoo[2], Neil Martinson[5], Julie Fox[9] and on behalf of the CHAPS study team

[1]Imperial College London, London, UK; [2]The University of Liverpool, Liverpool, UK; [3]London School of Hygiene and Tropical Medicine, London, UK; [4]University of Cape Town, Cape Town, South Africa; [5]University of the Witwatersrand, Johannesburg, South Africa; [6]MRC/UVRI, Entebbe, Uganda; [7]Department of Biomedical Sciences, Stellenbosch University, Tygerberg, Cape Town, South Africa; [8]Karolinska Institute, Solna, Sweden; [9]Guys and St. Thomas' NHS Foundation Trust and King's College London, London, UK

Introduction

Simplifying pre-exposure prophylaxis (PrEP) dosing will facilitate implementation. On-demand PrEP has not been evaluated in sub-Saharan Africa, young adults nor using TAF-FTC. Dose needed for insertive sex remains unknown. The CHAPS trial (NCT03986970) addressed these gaps of knowledge and pre-clinically assessed post-exposure prophylaxis (PEP) in foreskin.

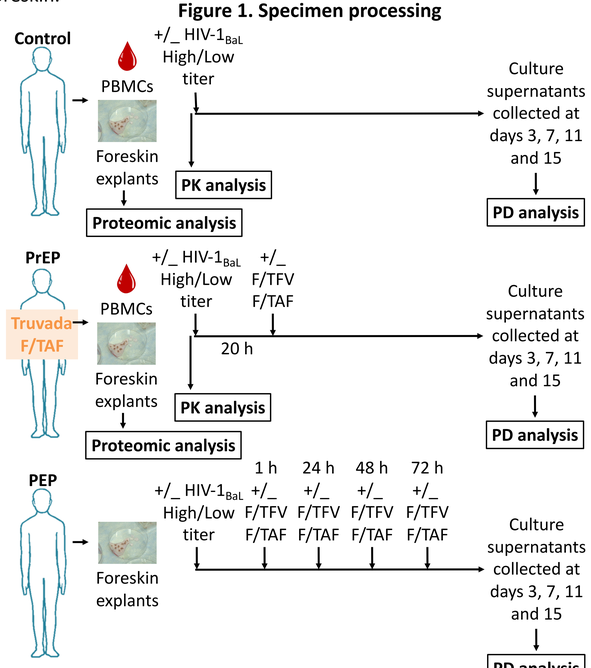
Materials and Methods

Phase 2 open-label, randomised controlled trial in Uganda and South Africa of 144 HIV negative men aged 13-24yrs, eligible for voluntary medical male circumcision (VMMC) and randomized to one of 9 arms (**Table** 1). Foreskin explants (inner and outer pooled) and PBMCs were exposed to HIV-1_{BaL} at high (HVT) or more biologically relevant, low viral titre (LVT); and further dosed *ex vivo* 20 h post-challenge (**Figure 1**). PEP without PrEP was evaluated in explants at different time points post-challenge. Infection was assessed by p24 ELISA of culture supernatants. TFV-diphosphate (TFVdp) and FTC-triphosphate (FTCtp) concentrations were measured using LC-MS in PBMCs, foreskin tissue and CD4$^+$T cells isolated from foreskin. PrEP effect on foreskin proteomics was assessed by western blot evaluation of tight junction proteins and inflammatory cytokines by Luminex.

Table 1. CHAPS randomization arms.

Arm	Drug	N	Dose 1	Dose 2 24 h later; (+/-1h)	Interval between last PrEP dose and VMMC (h) (+/-1h)
1	Control	16	-	-	-
2	F/TDF	16	2 tablets	-	5
3	F/TDF	16	2 tablets	-	21
4	F/TDF	16	2 tablets	1 tablet	5
5	F/TDF	16	2 tablets	1 tablet	21
6	F/TAF	16	2 tablets	-	5
7	F/TAF	16	2 tablets	-	21
8	F/TAF	16	2 tablets	1 tablet	5
9	F/TAF	16	2 tablets	1 tablet	21

Figure 1. Specimen processing



Results

Oral PrEP with F/TDF or F/TAF provides *ex vivo* protection; however, *ex vivo* modelling shows no added protection in foreskin with a PrEP+PEP regimen.

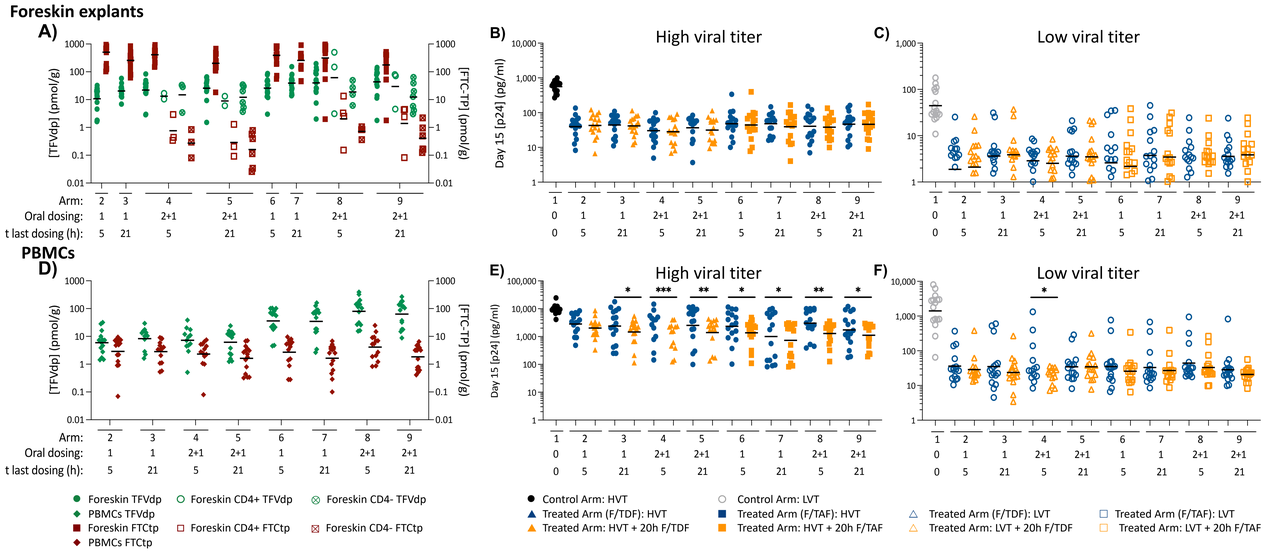


Figure 2. *Ex vivo* pharmacological profile. TFVdp and FTCtp levels in (**A**) foreskin explants and isolated CD4+/- cells and (**D**) PBMCs following oral dosing. Day 15 p24 levels in (**B**, **C**) tissue and (**E**, **F**) PBMCs, following *ex vivo* challenge with HVT or LVT, respectively. Symbols are means of triplicates for each condition for each participant. Lines are the geometric mean of each arm.

Ex vivo dosing 20 h post-challenge does not increase the inhibitory potency of *in vivo* dosing in foreskin explants

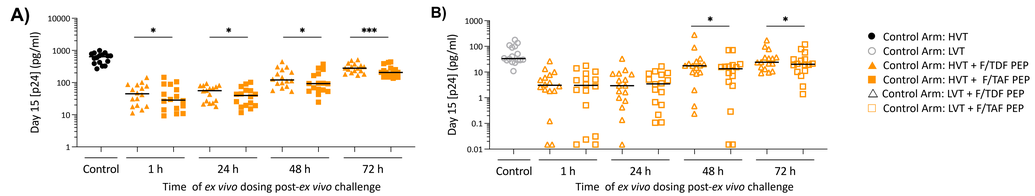


Figure 3. *Ex vivo* PEP activity of F/TFV and F/TAF. Day 15 p24 levels in foreskin explants following *ex vivo* challenge with (**A**) HVT or (**B**) LVT; and dosing with or without F/TFV and F/TAF at different post-challenge times. Symbols are means of triplicates for each condition for each participant. Lines are the geometric mean of each arm.

Safety profile of F/TDF and F/TAF as oral PrEP in foreskin tissue: modulation of cytokine profile and impact on tight junctions proteins as markers of epithelial integrity

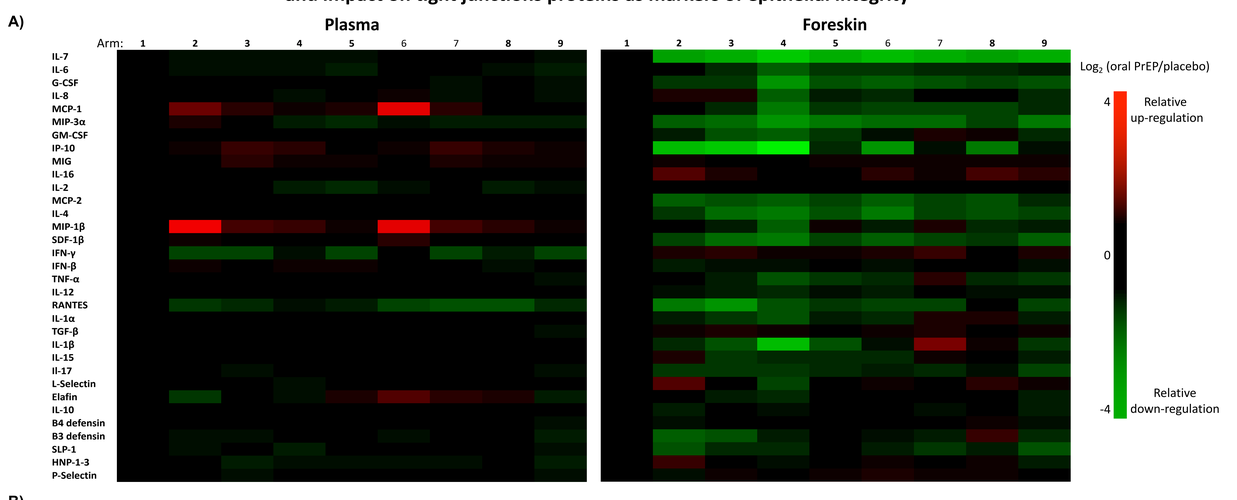


Figure 4. Proteomic analysis. (**A**) Heatmap of plasma and foreskin cytokines that are up- (red) or down-regulated (green) in each trial arm in comparison to the control arm 1. (**B**) Expression of tight junction proteins in foreskin explants. Lines are the geometric mean of each arm.

Summary:

- **Oral on-demand PrEP with F/TDF or F/TAF provides *ex vivo* protection of foreskin and PBMCs without inducing foreskin inflammation nor disrupting epithelial integrity.**
- **F/TAF provided higher TFVdp levels in foreskin and PBMCs, and better PEP activity than F/TDF in foreskin.**
- **PEP protection decayed after 48 h post-exposure.**