PK/PD Results of CHAPS Oral Pre-exposure Prophylaxis Trial in Foreskin Tissue

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Introduction

On demand pre-exposure prophylaxis (PrEP) in msm has not been evaluated in Africa and the dosing requirement for insertive sex is unknown. The CHAPS trial (NCT03986970) aims to optimize on-demand PrEP dosing for insertive sex for young men in sub-Saharan Africa.

Materials and Methods

Phase 2 open-label, randomised controlled trial (RCT) 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 receiving F/TDF, F/TAF or no PrEP at 1 (2 tablets) or 2 (2+1 tablets) consecutive days with final dose 5 or 21h prior to VMMC (**Table 1**). Inner and outer foreskins explants were exposed to HIV-1_{BaL} at a high (HVT) or a more biologically relevant, low viral titre (LVT). Explants were further dosed ex vivo using the same oral PrEP drug 20 h post-challenge (**Figure 1**). Infection was assessed at different time points during 15 days of culture by measurement of p24 in culture supernatants. TFV-diphosphate (TFV-DP) and emtricitabine-triphosphate (FTC-TP) tissue levels were measured using LC-MS methods (LLQ = 0.04 pmol/sample). Parallel systemic PK/PD evaluation was performed in isolated PBMCs at VMMC. PK and PD parameters were log-transformed for comparison between trial groups using two-tailed unpaired *t* tests; $p \leq 0.05$ was considered statistically significant. We present data from South Africa.

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

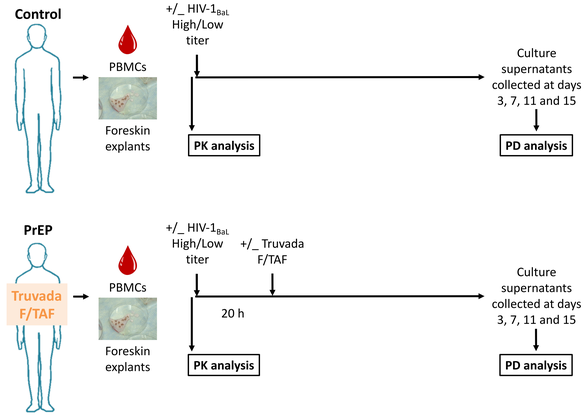

Figure 1. Specimen processing. Outer and inner foreskin tissues were cut into explants comprising both epithelium and stroma. An outer and an inner explant were immediately frozen for PK analysis. PD analysis was performed in triplicate (with an outer and an inner explant/well) for each condition of *ex vivo* viral challenge and *ex vivo* dosing with the same drug used for oral dosing. Explants were cultured for 15 days and p24 levels in supernatants were measured by antigen specific ELISA. Parallel PK/PD analysis was performed in PBMCs from blood obtained just before surgery.

Results

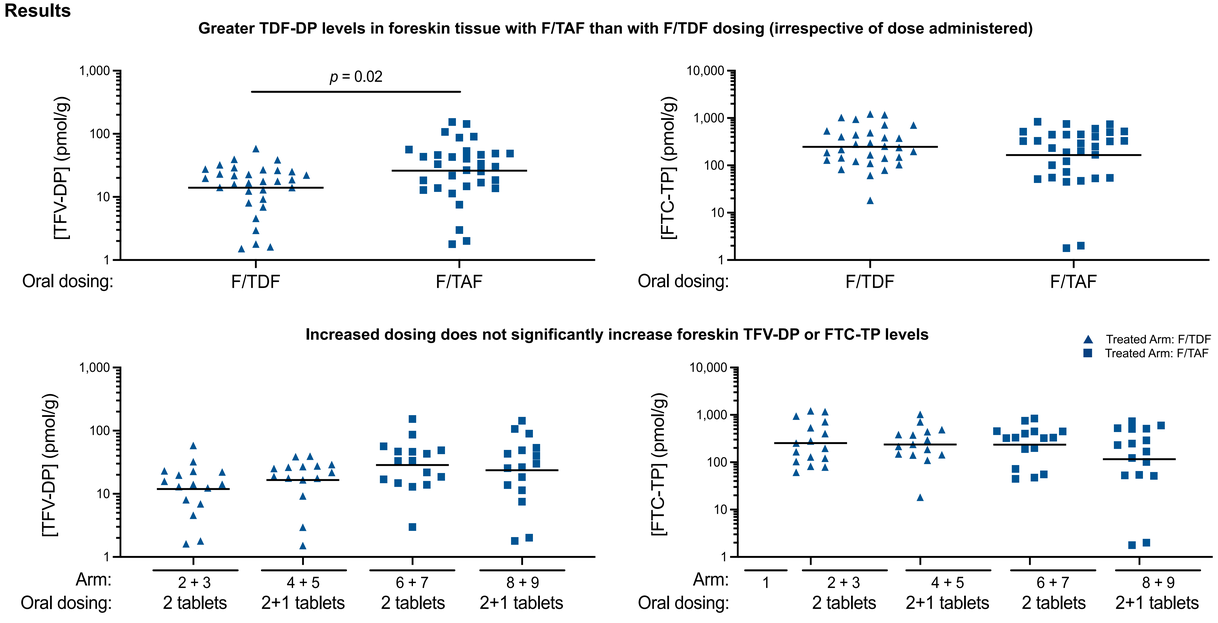

Figure 2. Quantification of active phosphorylated metabolites following oral dosing with F/TDF or F/TAF. A piece of outer and of inner foreskin tissues were cut and immediately frozen in the same tube upon arrival to the laboratory. Explants were homogenised in methanol and 20mM EDTA/EGTA (70:30 v/v). Metabolites were extracted with a mixture of acetonitrile:formic acid (100µL; 98:2 v/v) followed by further sample clean-up using polymeric reverse phase SPE [Strata-X 33µ (30mg/1mL)]. Symbols represent each participant. Lines are the geometric mean of each dosing.

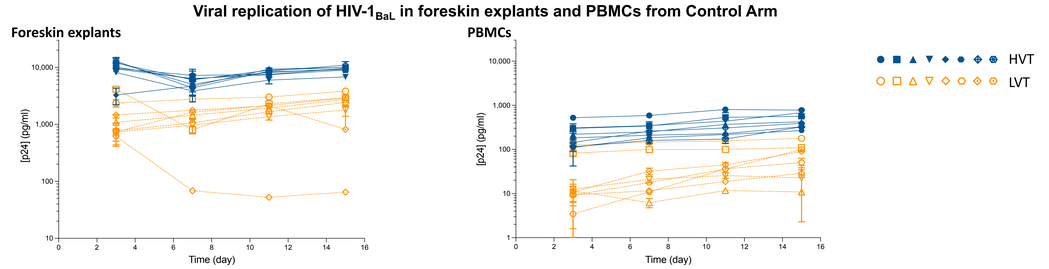

Figure 3. Viral replication kinetics. Foreskin explants and PBMCs were challenged overnight with HIV-1_{BaL} at a high (blue symbols) or at a low viral titre (orange symbols), washed four times in PBS, and cultured in fresh plates for 15 days. Supernatants were harvested at different time points, and p24 concentrations measured by ELISA. Data are means (± standard deviations) of triplicates for each participant from the control arm.

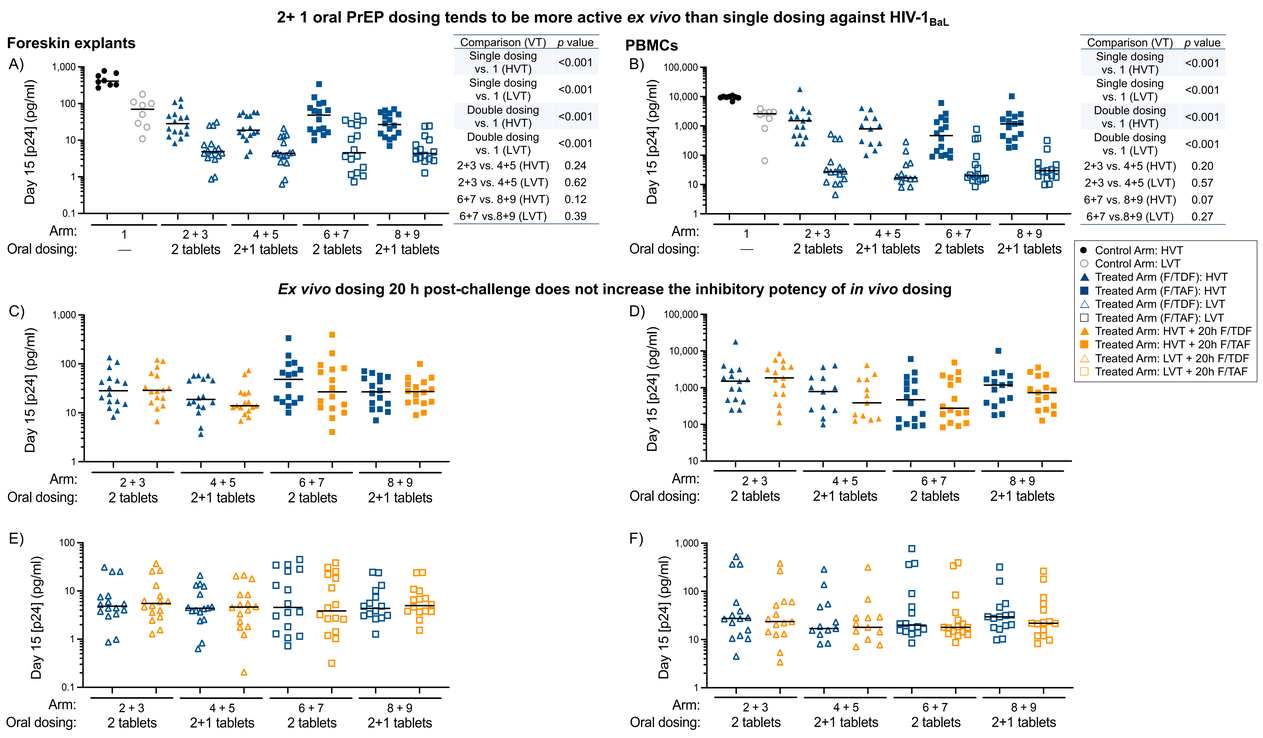

Figure 4. *Ex vivo* pharmacodynamic profile following oral and *ex vivo* dosing. (**A-F**) Foreskin explants and PBMCs obtained from participants in control and treated arms were challenged overnight with HIV-1_{BaL} at a high (blue symbols) or at a low viral titre (orange symbols). (**C-F**) Twenty hours after addition of virus, explants from treated arms were dosed or not for 2 h with the same drug administered orally to the participant. Explants were then washed four times in PBS and cultured in fresh plates for 15 days. Supernatants were harvested at different time points, and p24 concentrations measured by ELISA. Symbols are means of triplicates for each condition for each participant. Lines are the geometric mean of each arm.

Summary:

- **Dosing with F/TAF results in higher TDF-DP levels in foreskin tissue than dosing with F/TDF.**
- **Oral on demand PrEP dosing with 2 tablets of F/TDF or F/TAF from 5 to 21 h before HIV-exposure provides *ex vivo* protection of foreskin tissue which increases with 2 + 1 dosing.**
- **Post-exposure *ex vivo* dosing does not increase the inhibitory potency obtained with oral PrEP.**
- ***Ex vivo* challenge studies in human foreskin explants may facilitate dosing requirements and evaluation of new drugs for PrEP.**