Ex vivo HIV suppression in foreskin tissue after oral dosing of F/TDF and F/TAF in young African males

EPA065

Carolina Herrera[1], Laura Else[2], Emily Webb[3], Azure-Dee AP. Pillay[4], Thabiso B. Seiphetlo[4], Limakatso Lebina[5], Jennifer Serwanga[6], Christian Callebaut[7], Robin Shattock[1], Francesca Chiodi[8], Clive Gray[4], 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]Gilead Sciences, Foster City, CA, USA; [8]Karolinska Institute, Solna, Sweden; [9]King's College London, London, UK

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 (Uganda and South Africa). We present data from South Africa.

Materials and Methods

Phase II open-label, randomized controlled trial of 144 HIV negative men aged 13-24 yrs, 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**). Explants were exposed to HIV-1_{BaL} at a high (HVT) or a more biologically relevant, low viral titre (LVT). Explants were further dosed or not using the same oral PrEP drug 20 h post-challenge (**Figure 1**). Infection was assessed by measurement of p24 in culture supernatants via ELISA. TFV-diphosphate (TFV-DP) and emtricitabine-triphosphate (FTC-TP) tissue levels were measured using LC-MS methods (LLQ = 0.04 pmol/sample). Parallel PK/PD evaluation was performed in PBMCs. PrEP effect on foreskin tight junctions was assessed by western blot.

Table 1. CHAPS randomization arms.

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

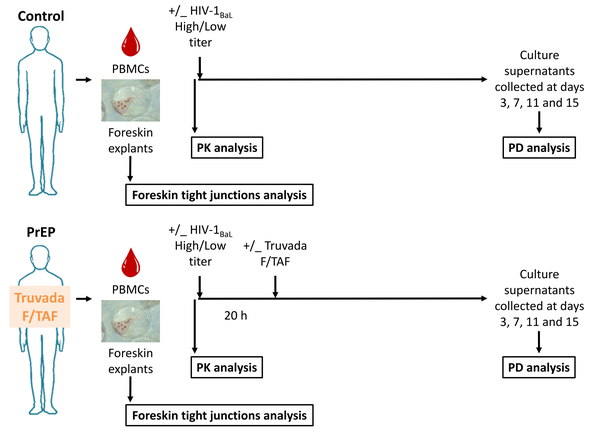


Figure 1. Specimen processing. Outer and inner foreskin tissues were cut into explants comprising both epithelium and stroma. A set of outer and inner explants were frozen for PK analysis and another set for tight junctions analysis. PD analysis was performed in triplicate (with an outer and an inner explant/well) for each condition. Parallel PK/PD analysis was done in PBMCs from blood obtained just before surgery.

Results

Oral PrEP with F/TDF or F/TAF does not affect integrity of foreskin epithelium

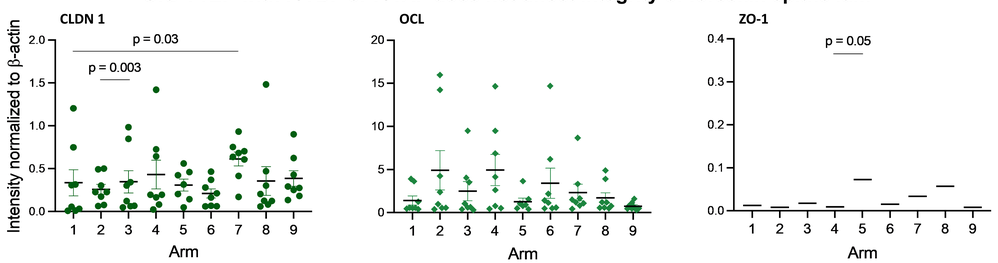


Figure 2. Analysis of foreskin tight junctions following oral PrEP. Explants were lysed and claudin-1 (CLDN 1), occluding (OCL) and zonula occludens-1 (ZO-1) levels analyzed by western blot. Densitometry values were normalized towards β-actin levels for each sample. Symbols represent each participant. Lines: geometric mean.

Greater TDF-DP levels with F/TAF than with F/TDF dosing

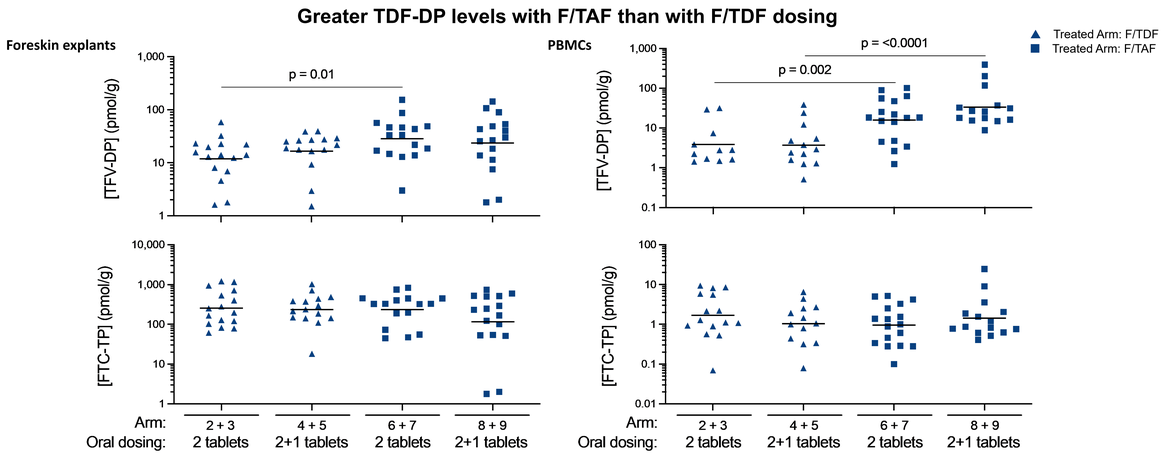


Figure 3. Quantification of active metabolites following oral dosing with F/TDF or F/TAF. Samples were homogenized in methanol and 20 mM EDTA/EGTA (70:30 v/v). Metabolites were extracted with a mixture of acetonitrile:formic acid (98:2 v/v) followed by further sample clean-up using polymeric reverse phase SPE [Strata-X 33µ (30mg/1mL)]. Symbols represent each participant. Lines: geometric mean.

Viral replication of HIV-1_{BaL} in foreskin explants and 'resting' PBMCs from Control Arm

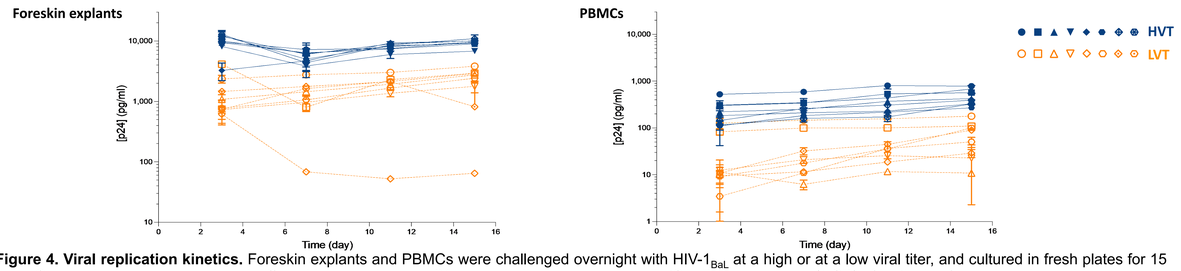
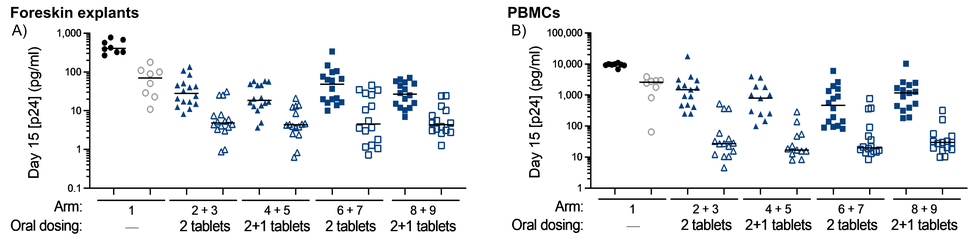


Figure 4. Viral replication kinetics. Foreskin explants and PBMCs were challenged overnight with HIV-1_{BaL} at a high or at a low viral titer, and cultured in fresh plates for 15 days. Supernatants were harvested at different time points, and p24 concentrations measured by ELISA. Data are means (± SD) of triplicates for each participant.

Oral PrEP with F/TDF or F/TAF protects against *ex vivo* challenge with HIV-1_{BaL}



Foreskin explants and PBMCs:

Comparison (viral titer)	*p* value
Any Treated arm vs. Control (HVT)	<0.001
Any Treated arm vs. Control (LVT)	<0.001

Ex vivo dosing 20 h post-challenge does not increase the inhibitory potency of oral PrEP

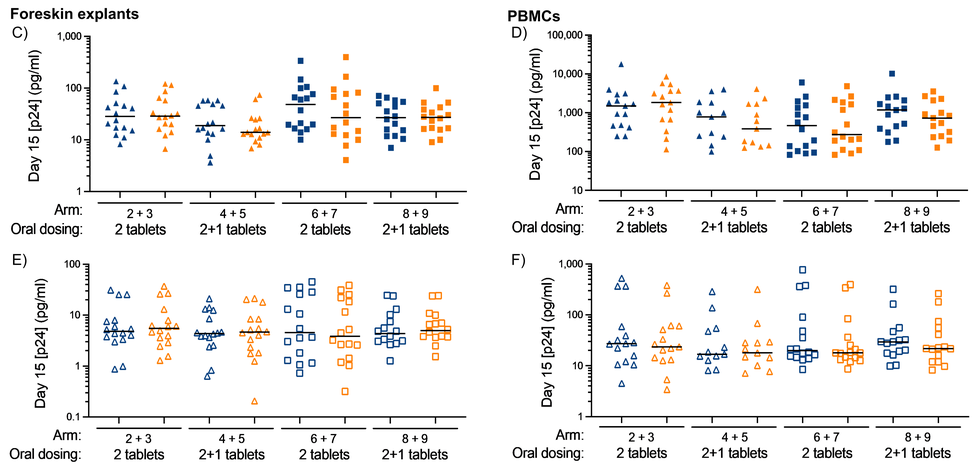


Figure 5. *Ex vivo* pharmacodynamic profile following oral and *ex vivo* dosing. (A-F) Foreskin explants and PBMCs obtained from participants in control and treated arms were challenged overnight with HIV-1_{BaL} at a high or at a low viral titer. (**C-F**) Twenty hours after addition of virus, explants from treated arms were dosed or not for 2 h with the same drug administered orally to the participant. Symbols are means of triplicates for each condition for each participant. Lines: geometric mean.

Summary:

- **Dosing with F/TAF results in higher TDF-DP levels in foreskin tissue and PBMCs 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 tends to increase with 2 + 1 dosing.**
- **Post-exposure *ex vivo* dosing does not increase the inhibitory potency obtained with oral PrEP.**
- **Oral dosing with F/TDF or F/TAF does not significantly affect the expression level of tight junction proteins analyzed.**
- **- *Ex vivo* challenge studies in human foreskin explants may facilitate dosing requirements and evaluation of new drugs for PrEP.**