Supplemental Digital Content.

Table: Sensitivity analyses: Reversibility of eGFR decline after study drug discontinuation, according to treatment group

	Sensitivity analysis (n=4360)		
A: Mean eGFR			
Study visit	**FTC-TDF (n=1445)** *Mean eGFR (mL/minute/1.73 m^2); p-value*	**TDF (n=1436)** *Mean eGFR (mL/minute/1.73 m^2); p-value*	**Placebo (n=1479)** *Mean eGFR (mL/minute/1.73 m^2)*
Enrollment	129.1 (128.3, 130.0); p=0.19	129.8 (128.9, 130.7); p=0.27	129.0 (120.2, 129.8)
Last on-treatment	128.5 (127.7, 129.4); p=0.04	129.4 (128.6, 130.3); p=0.59	129.7 (128.9, 130.6)
First post-drug visit	130.7 (129.8, 131.5); p=0.86	131.4 (130.6, 132.2); p=0.21	131.6 (130.8, 132.4)
Proportion of participants with a post-study drug eGFR >75% of baseline level; p-value placebo			
Time after the last on-study drug date	**FTC-TDF (n=1445)** *No. at risk; Cum. probability† (95%CI)*	**TDF (n=1436)** *N0. at risk; Cum. probability† (95%CI)*	**Placebo (n=1479)** *N0. at risk; Cum. probability† (95%CI)*
4 weeks	1384; 74% (71, 76);	1376; 74% (72, 76);	508; 84% (83, 86)
8 weeks	197; 91% (89, 92);	194; 91% (90, 92);	118; 94% (93, 95)
12 weeks	93; 95% (94, 96);	82; 96% (95, 97);	60; 97% (96, 98)

Sensitivity analysis considered all participants with any serum creatinine measurement obtained after the last on-study drug date (i.e., regardless of whether the post-study drug phase creatinine was taken within 12 weeks of the last on-study drug date visit).

**Median follow time on study drug was 33 months and resulting annualized eGFR decline attributable to PrEP versus placebo of mL/min/1.73m^2 per year*

ǂMedian duration to the first post-study drug creatinine measurement was 4 weeks (IQR 3-5), similar across treatment groups.

†Cumulative probability of eGFR resolution (i.e > 75% of baseline level) after study drug discontinuation level. Median time for eGFR to return to >75% of baseline was 4 weeks (IQR 3-4) overall, quicker in those assigned placebo compared to those assigned active PrEP: 4 weeks (IQR 4-5) for PrEP vs 3 weeks (IQR 3-4) for placebo group; p <0.05.
P- values are for Wald tests, testing for the null hypothesis of no difference between active PrEP versus placebo.
eGFR estimated glomerular filtration rate; FTC emtricitabibe; TDF tenofovir disoproxil fumarate

Sensitivity analysis: Description of characteristics of participants with a <75% eGFR return to baseline level after drug discontinuation.

Participant #1

34 year old female in the placebo arm with baseline eGFR of 139 mL/min/1.73m^2 (serum creatinine: 0.60 mg/dL). Participant completed protocol defined on-study drug follow-up at month 33 with the last on-study drug eGFR of 124 mL/min/1.73m^2 (serum creatinine: 0.72 mg/dL). Final off-study drug creatinine clearance was 103 mL/min/1.73m^2 (serum creatinine: 0.84 mg/dL) at month 2 post-study drug visit. Serum phosphate, bicarbonate, and transaminases were all normal with no reported history of use known nephrotoxic medication.

Participant #2

27 year old male in the placebo arm with baseline eGFR 136 mL/min/1.73m^2 (serum creatinine: 0.88 mg/dL). Participant completed follow-up at month 25 with the last on-study drug eGFR of 101 mL/min/1.73m^2 (serum creatinine: 1.13 mg/dL). Final off-study drug eGFR was 92 mL/min/1.73m^2 (serum creatinine: 1.29 mg/dL) at month 2 post-study drug visit. Serum phosphate, bicarbonate, and transaminases were all normal with no reported history of use known nephrotoxic medication.

Participant #3

22 year old female in the placebo arm with baseline eGFR 150 mL/min/1.73m^2 (serum creatinine: 0.60 mg/dL). She had >1.5 increase in serum creatinine (eGFR: 94 mL/min/1.73m^2) at month 6 visit and study drug was discontinued per protocol specification. eGFR was 102 mL/min/1.73m^2 at the last observed visit (serum creatinine: 0.92 mg/dL). Serum phosphate, bicarbonate and transaminases were all normal with no reported history of use of known nephrotoxic medication.

Participant #4

46 year old male in the TDF group with baseline eGFR of 117 mL/min/1.73m^2 (serum creatinine: 0.6 mg/dL). Participant was diagnosed with acute HIV seroconversion at month 11 of study follow-up and had eGFR of 36 mL/min/1.73m^2 (serum creatinine 2.4 mg/dL, a >2 fold increase in serum creatinine from baseline) with history of herpes zoster and anemia in the preceding months. Study drug was permanently discontinued at this visit. Protocol did not require creatinine measurement post- HIV seroconversion.