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Changes in Renal Function After Switching from Emtricitabine/Tenofovir Disoproxil Fumarate to Emtricitabine/Tenofovir Alafenamide Fumarate for HIV Pre-exposure Prophylaxis (PrEP): A Real-World Study

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Conclusions

- This study used linked medical and prescription claims data to assess changes in renal function among individuals before and after switching from using emtricitabine/tenofovir disoproxil fumarate (F/TDF) to emtricitabine/tenofovir alafenamide (F/TAF) for HIV-1 pre-exposure prophylaxis (PrEP)
- In this real-world analysis, a decrease in estimated glomerular filtration rate (eGFR) was observed while individuals were receiving F/TDF but not after switching to F/TAF
- eGFR increased immediately after switching to F/TAF in modeled projections based on eGFR trajectories during F/TDF and F/TAF use
  - Sub-analyses suggest this increase in eGFR was likely driven by individuals with low baseline eGFR (<90 mL/min/1.73 m^2)
- These real-world data support results from the DISCOVER trial demonstrating improved renal endpoints in the F/TAF arm, compared with F/TDF
- To further understand the impact of switching PrEP regimens, future analyses should aim to characterize individuals in the low versus high baseline eGFR groups and examine renal function and other outcomes in individuals switching from F/TAF to F/TDF

Plain Language Summary

- Medications for HIV prevention are very effective at stopping people from getting HIV when used as prescribed
- HIV-prevention medications that are taken every day as a pill include emtricitabine/tenofovir disoproxil fumarate (also called “F/TDF”) and emtricitabine/tenofovir alafenamide (also called “F/TAF”)
- While most people can take these daily medications without serious problems, research has shown that some people who use F/TDF have problems with how well their kidneys work
- This study used medical and pharmacy records to look at how well peoples’ kidneys were working while they were taking F/TDF and after they switched to taking F/TAF
- While people were taking F/TDF, their kidney function tended to get worse; this was especially true for people who already had low kidney function at the start of the study
- When people with low kidney function switched from F/TDF to F/TAF, their kidney function started to improve
- For people who had high kidney function at the beginning of the study, switching to F/TAF did not change how well their kidneys were working
- The results from this study may help people and their doctors understand how switching HIV-prevention medication may affect their kidney function

Background

- The daily oral HIV-1 PrEP medications F/TDF and F/TAF are highly effective at preventing HIV-1 acquisition when used as prescribed[1]
- Although oral PrEP is well tolerated, studies have shown F/TDF may cause renal impairment due to proximal renal tubular dysfunction[2,3]
- In the Phase 3, randomized, double-blind, non-inferiority DISCOVER trial (NCT02842086), F/TAF showed a more favorable renal safety profile compared with F/TDF[3,4]
  - All prespecified renal biomarker secondary endpoints showed statistical superiority of F/TAF over F/TDF after 48 weeks and at 96 weeks[4]
- Existing evidence on renal safety of F/TAF versus F/TDF in real-world settings is limited and complicated by potential biases, including confounding by indication
- In this retrospective analysis, medical and pharmacy claims data were used to understand real-world renal function in people who switch from F/TDF to F/TAF; this crossover design reduces the potential for confounding by indication at the individual level

Objective

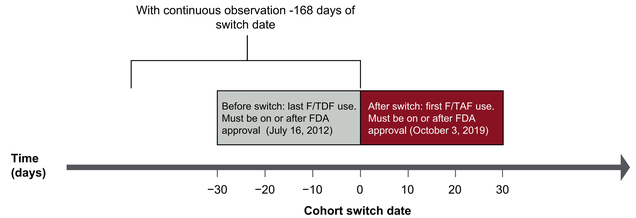
- To evaluate changes in eGFR in individuals before and after switching from F/TDF to F/TAF using a crossover study design

Methods

Study Design and Participants

- We conducted a retrospective, observational analysis using data from Optum® Clinformatics®; this database was selected based on data and sample availability
  - The crossover design evaluated renal safety by examining within-individual change in eGFR before and after switch from F/TDF to F/TAF (**Figure 1**)
- Eligible individuals were males who initiated F/TDF between July 2012 and May 2023, switched to F/TAF, and had ≥1 eGFR measurement within 1 year pre- and post-switch
  - Participants with a first F/TAF use within 30 days of their last F/TDF use were included

Figure 1. Crossover Study Design Included Individuals Who Switched from F/TDF to F/TAF



FDA, Food and Drug Administration; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate.

Assessment of Changes in eGFR

- Baseline eGFR categories were defined based on the first eGFR measurement available after F/TDF initiation and were categorized as low (<90 mL/min/1.73 m^2) or high (≥90 mL/min/1.73 m^2)
- The expected change in eGFR after switching from F/TDF to F/TAF was estimated using an interrupted time series analysis with segmented regression comparing changes in eGFR pre- and post-switch across all individuals and by baseline eGFR category
- Mixed-effects models were used to estimate individual-level effects

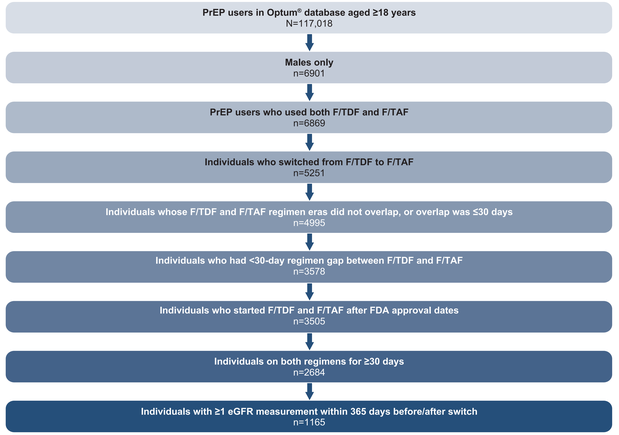
Adherence to PrEP

- Adherence to PrEP regimen was described using the proportion of days covered (PDC)
- PDC was calculated as number of days on regimen divided by the number of days in the study period, with a maximum study period of 365 days for F/TDF and F/TAF each

Results

- Overall, data from 1165 individuals with at least one eGFR measurement within 365 days before and after the switch were included (**Figure 2**)

Figure 2. Study Participant Disposition



eGFR, estimated glomerular filtration rate; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; PrEP, pre-exposure prophylaxis.

Renal Function

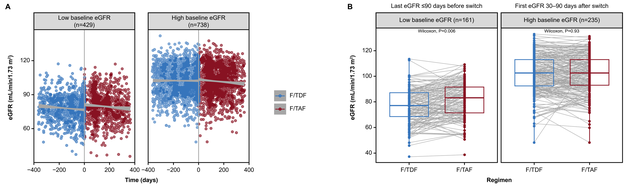
- In the overall population of eligible individuals (N=1165), annualized eGFR decreased while individuals were receiving F/TDF but not F/TAF, with an estimated mean difference in slope of +3.98 on F/TAF compared with F/TDF (**Table 1**)
  - Annualized change in eGFR and differences in slope stratified by baseline eGFR are shown in **Table 1** and **Figure 3A**
- The overall expected increase in eGFR immediately after switching to F/TAF was 2.21 mL/min/1.73 m^2 (95% CI: 1.40; 3.03) (**Table 1**)
  - After stratification, significant increases in eGFR (immediately after the switch) were observed in the low baseline eGFR group but not in the high baseline eGFR group (**Table 1, Figure 3B**)

Table 1. Estimated Change in Annualized eGFR after Switching from F/TDF to F/TAF for PrEP

Model	n	Annualized change in eGFR (95% CI)		Difference in annualized slopes before and after switch (F/TAF–F/TDF)† (95% CI)	Expected change at switch‡ (95% CI)
		F/TDF	F/TAF		
Overall					
Eligible individuals	1165	−3.22 (−4.39; −2.05)*	0.76 (−0.97; 2.49)	3.98 (1.35; 6.61)*	2.21 (1.40; 3.03)*
Stratified by baseline eGFR categories					
Low baseline eGFR (<90 mL/min/1.73 m^2)	429	−3.65 (−5.50; −1.81)*	0.87 (−1.82; 3.55)	4.52 (0.40; 8.64)*	4.50 (3.23; 5.76)*
High baseline eGFR (≥90 mL/min/1.73 m^2)	736	−2.25 (−3.70; −0.79)*	−0.04 (−2.25; 2.16)	2.21 (−1.10; 5.51)	0.74 (−0.29; 1.77)

eGFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation. Annualized eGFR change calculated as coefficients for time (F/TDF) and time after switch (F/TAF) multiplied by 365.
*P<0.05 for a comparison of F/TDF vs F/TAF. †Determined using a Z-test. ‡Expected change in eGFR after switching from F/TDF to F/TAF was estimated using an interrupted time series model with random slopes and intercepts for each individual, calculated as: eGFR ~ time + switch + time after switch + (time | individual).
CI, confidence interval; eGFR, estimated glomerular filtration rate; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; PrEP, pre-exposure prophylaxis.

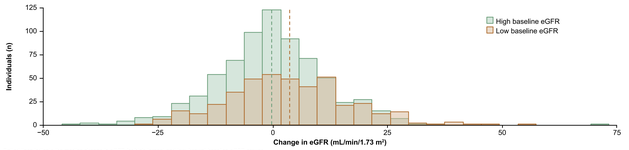
Figure 3A. eGFR Values 1 Year Prior to and after Switching from F/TDF (Blue) to F/TAF (Red) and B. Change from Last eGFR before Switch to First eGFR after Switch, in Individuals With Low and High Baseline eGFR*



Scatterplots with trendlines plotted separately for each regimen type. eGFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation.
*Low and high baseline eGFR were defined as <90 mL/min/1.73 m^2 and ≥90 mL/min/1.73 m^2, respectively. eGFR, estimated glomerular filtration rate; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate.

- In the low baseline eGFR group, the distribution of the change in eGFR after switching was shifted toward larger increases compared to the high baseline eGFR group (**Figure 4**)

Figure 4. Distribution of Change in eGFR before and after Switch in People With High and Low Baseline eGFR*

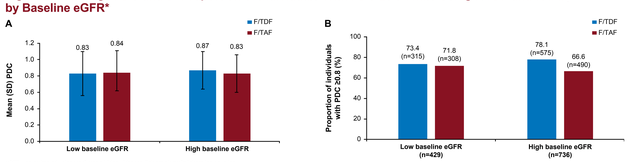


Dotted lines indicate the median change in eGFR for high (green) and low (brown) baseline eGFR groups.
*Low and high baseline eGFR were defined as <90 mL/min/1.73 m^2 and ≥90 mL/min/1.73 m^2, respectively.
eGFR, estimated glomerular filtration rate.

Adherence to PrEP

- Adherence was similar while individuals were using F/TDF and F/TAF, as measured by mean PDC and as a proportion of those with PDC ≥0.8, suggesting that observed effects of eGFR are reasonably attributable to regimen (**Figure 5**)

Figure 5A. Average PDC and B. Proportion of Individuals With PDC ≥0.8 While Using F/TDF and F/TAF, by Baseline eGFR*



eGFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation.
*Low and high baseline eGFR were defined as <90 mL/min/1.73 m^2 and ≥90 mL/min/1.73 m^2, respectively.
eGFR, estimated glomerular filtration rate; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; PDC, proportion of days covered; SD, standard deviation.

Limitations

- Renal function assessment relied on availability of laboratory test results in datasets, and individuals may not have been consistently tested on a fixed schedule
- Data collection based on medical and pharmacy claims data may lead to the omission of clinically relevant data in real-world settings
  - Claims-based research may not capture clinically relevant factors affecting renal function (e.g., lifestyle, behavior, over-the-counter medication use, comorbidities)
- Reasons for switching were not collected in the records
- The impact of switching on non-renal outcomes (e.g., weight, lipids, and blood pressure) was not investigated in the study

References:
1. CDC. HIV Nexus: Clinical Guidance for PrEP. Available at: https://www.cdc.gov/hivnexus/hcp/prep/index.html. (accessed October 2024). **2.** Petruccelli, K.C.S.,et al. *AIDS Res Ther*. 2022;19:12. **3.** Ogbuagu O, et al. *Lancet HIV*. 2021;8(7):e397–e407. **4.** Mayer KH, et al. *Lancet*. 2020;396(10246):239–254.

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Conflicts of Interest:
Xiwen Huang, Seojin Park, Li Tao, and **Joshua Gruber** are employees and shareholders of Gilead Sciences, Inc. **Kaori L. Ito** was an employee of Gilead Sciences, Inc. at the time of the analysis.
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