Rare Incidence of Proximal Tubulopathy in Tenofovir-based PrEP

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BACKGROUND

- Tenofovir disoproxil fumarate (TDF) pre-exposure prophylaxis (PrEP) is associated with small non-progressive decline in estimated glomerular filtration rate (eGFR) without severe glomerular dysfunction.
- Limited data are available on whether TDF causes proximal tubular dysfunction among HIV-uninfected men and women with high adherence to TDF-based PrEP or whether proximal tubular dysfunction predicts subsequent clinically relevant decline in GFR.

STUDY POPULATION AND DESIGN

Population: Data were from the Partners PrEP Study, a randomized, placebo-controlled trial of daily oral TDF and emtricitabine (FTC)-TDF PrEP among 4747 African HIV-uninfected men and women who had a baseline creatinine clearance >60 mL/min.

Approach for the current analysis: We conducted two complementary analyses:

1. Cohort analysis: A randomized comparison of HIV-infected men and women assigned to FTC-TDF versus placebo to determine whether TDF causes proximal tubular injury.
- Eligible persons were randomized at least 24 months prior to termination of the placebo arm and had concurrently obtained urine and serum samples at the 24-month visit or last on-treatment visit.

2. A nested-case-control analysis: Included participants on TDF or FTC-TDF to investigate whether proximal tubular dysfunction predicts subsequent clinically relevant decline in eGFR (≥25%) and whether participants on FTC-TDF who experienced ≥25% eGFR decline and controls were randomly selected participants with similar drug exposure and duration without the ≥25% eGFR decline, frequency-matched 1:4.

OUTCOME MEASURES AND STATISTICAL ANALYSIS

- Cohort analysis: The primary outcome was proximal tubulopathy, pre-defined as ≥22 of the 22 markers of proximal tubular dysfunction (Table 1) compared between persons randomized to FTC-TDF versus participants randomized to placebo. Additional analysis considered individual markers of tubular injury.
- Case-control analysis: The predictor of interest was proximal tubular dysfunction (as defined in Table 1) compared between participants on FTC-TDF and without ≥25% eGFR decline
- Differences in proportions were tested using exact or asymptotic methods where appropriate adjusted for age, sex, body mass index, and indicator for elevated systolic blood pressure.

RESULTS

Table 2. Participants characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FTC-TDF (n=572)</th>
<th>Placebo (n=733)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>65%</td>
<td>63%</td>
<td>0.30</td>
</tr>
<tr>
<td>Age-years</td>
<td>37 ± 9</td>
<td>37 ± 9</td>
<td>0.90</td>
</tr>
<tr>
<td>Creatinine clearance/mL/minute</td>
<td>107 ± 24</td>
<td>107 ± 25</td>
<td>0.79</td>
</tr>
<tr>
<td>BMI</td>
<td>22.3 ± 3.3</td>
<td>22.3 ± 3.7</td>
<td>0.30</td>
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</tbody>
</table>
| Nested-case control analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FTC-TDF (n=206)</th>
<th>Placebo (n=206)</th>
<th>Odds ratio (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>40%</td>
<td>68%</td>
<td>&lt;0.01</td>
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<tr>
<td>Age-years</td>
<td>38 (19-58)</td>
<td>34 (18-58)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance/mL/minute</td>
<td>100 (80-162)</td>
<td>111 (80-172)</td>
<td>0.02</td>
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</tr>
</tbody>
</table>

Table 3. Frequency of markers of proximal tubular dysfunction among FTC-TDF to placebo

<table>
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<tr>
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<th>Placebo (n=733)</th>
<th>Odds ratio (95%CI)</th>
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</thead>
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<tr>
<td>Proximal tubulopathy — ≥22 markers of tubular dysfunction</td>
<td></td>
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</tbody>
</table>

Table 4. Nested-case-control analysis of relationship between eGFR decline ≥25% and proximal tubulopathy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FTC-TDF (n=206)</th>
<th>Placebo (n=206)</th>
<th>Adjusted odds ratio† (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal tubulopathy — ≥22 markers of tubular dysfunction</td>
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CONCLUSION

- In this large placebo-controlled, proximal tubulopathy was rare and was not significantly associated with any adverse event.
- These findings suggest that monitoring of kidney function with routine urine markers of proximal tubular dysfunction will not be an efficient approach to predict the rare events of tubulo-renal injury associated with FTC-TDF and using PrEP.
- These data support the safety of PrEP and indicate that creatinine clearance is sufficient for safety monitoring of kidney function in healthy persons using TDF-based PrEP.

Table 1. Definition of proximal tubulopathy

| Tubular proteinuria | Urinary protein excretion of proteinuria ≥0.1 and urine albumin:protein ratio ≥0.4 |
| Eulycemic glycosuria | Positive urine glucose and serum glucose <126 mg/dL |
| Phosphaturia | Fractional urinary excretion of phosphorus <16% or TimP/creatinine <0.81 mmol/L |
| Uromelenuria | Fractional urinary excretion of uric acid ≥15% |

†TimP/creatinine, maximum rate of tubular phosphate reabsorption in the proximter tubule filtration rate.