Urine Tenofovir Concentrations Correlate with Plasma Tenofovir and Distinguish High, Moderate and Low PrEP Adherence:
A Randomized Directly-observed Pharmacokinetic Trial

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Background & Objective

• Efficacy of daily PrEP and ART highly dependent on sufficient adherence to maintain protective or therapeutic drug concentrations

• Existing tools to monitor PrEP and ART adherence (self-report, pill counts) have limitations

• In a directly observed therapy (DOT) study, we assessed correlation between urine and plasma TFV concentrations and the impact of adherence patterns on TFV concentrations
Methods

• TARGET (Tenofovir Adherence to Rapidly Guide and Evaluate PrEP and HIV Therapy) was an open-label, three arm randomized controlled trial in Chiang Mai, Thailand

• Enrolled adults ages 18-49 years, if HIV and Hep B negative, and with normal renal function

• 3 study arms for TDF/FTC (300/200 mg) dosing given DOT:
  • Perfect adherence - TDF/FTC 7 days/week
  • Moderate adherence - TDF/FTC 4 days/week
  • Low adherence – TDF/FTC 2 days/week
Methods

Three study phases with sampling

- Lead-in TDF/FTC dosing for 6-week period
- Intensive 24-hour pharmacokinetic period
- Drug washout for a 4-week period
Methods – Analyses

All tenofovir drug testing performed by liquid chromatography tandem mass spectrometry (LC-MS/MS):

- **Urine** – validated over range of 50 – 50,000 ng/mL
- **Plasma** – validated over range of 3 – 2,500 ng/mL

Statistical Analyses:

- Spearman’s correlation coefficient (r)
- One-way repeated measures analysis of variance (ANOVA)
- Cox proportional hazard models
Results – Consort

- Assessed for eligibility (n=32)
  - Excluded (n=1)
    - HBs Ag positive (n=1)
  - Randomized (n=31)
    - Assigned to low adherence (n=10)
      - Did not complete study requirements (n=1)
        - Completed follow-up (n=9)
          - Eligible for analysis (n=9)
    - Assigned to moderate adherence (n=10)
      - Completed follow-up (n=10)
        - Eligible for analysis (n=10)
    - Assigned to perfect adherence (n=11)
      - Withdrew (n=1)
      - Did not complete study requirements (n=1)
        - Completed follow-up (n=9)
          - Eligible for analysis (n=9)
## Results – Participant Characteristics

<table>
<thead>
<tr>
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<th>Adherence Arm</th>
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<tbody>
<tr>
<td></td>
<td>Low (N=9)</td>
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<tr>
<td><strong>Median (interquartile range)</strong></td>
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<tr>
<td><strong>Sociodemographic and Clinical</strong></td>
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<tr>
<td>Male – N (%)</td>
<td>3 (33)</td>
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<tr>
<td>Age (years)</td>
<td>38 (27-40)</td>
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<tr>
<td>Body Mass Index (kg/m²)</td>
<td>23.1 (20.2-28.4)</td>
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<td><strong>Laboratory Measures</strong></td>
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<td>White blood cells (cells/mm³)</td>
<td>6,700 (5200-7700)</td>
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<tr>
<td>Hemoglobin (g/dL)</td>
<td>13.3 (13.3-15.0)</td>
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<tr>
<td>eGFR (Cockcroft-Gault equation)</td>
<td>108 (102-115)</td>
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Results – Correlation of TFV between Urine and Plasma
Results – TFV levels at Steady State

Plasma

Urine

Tenofovir concentration (ng/mL)

Low  Mod  Perfect

Low  Mod  Perfect

p<0.0001  p=0.0002
Results – Washout of TFV for Plasma (solid) and Urine (dashed)
Results – Washout of TFV in Urine by Adherence Arm

![Graph showing washout of TFV in urine by adherence arm. The x-axis represents days after ingestion of the last dose, ranging from 2 to 14. The y-axis represents median drug concentration (ng/mL), ranging from 100 to 10,000. Three lines represent different levels of adherence: perfect, moderate, and low. Each line shows a decrease in drug concentration over time.](image-url)
Conclusions

- Urine TFV concentrations correlated with plasma TFV during steady-state and washout period in adults receiving TDF/FTC

- Spot urine and plasma TFV concentrations were significantly different among the 3 adherence arms at steady-state

- Urine TFV concentrations did not differ between the 3 adherence arms during the washout period, suggesting that POC TFV urine testing could provide useful information about timing of recent dosing
Conclusions

• Results suggest plasma and spot urine TFV samples suitable for objectively evaluating recent adherence to PrEP and TDF-based ART

• This data will inform the interpretation of recently-developed point-of-care immunoassays

• Data contributed to development of new tenofovir LFA now launched and ready for further testing in treatment and PrEP
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