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Associations Between Urine Tenofovir Levels, Pharmacy Measures, and Self-Report for HIV Pre-Exposure Prophylaxis Adherence Monitoring

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Background

- PrEP efficacy is dependent on adherence
- Objective adherence monitoring tools are needed in real-world clinics to help identify potential adherence problems
- Dried blood spot (DBS) testing is the research gold standard
 - Clinical settings often lack access to DBS
- Other strategies include: patient self-report (subjective) and medication possession ratio (MPR) (an objective proxy)
 - $MPR = \# \text{ pills dispensed by pharmacy} / \text{days between refills}$
- Urine tenofovir (TFV) testing is gaining evidence as a non-invasive, inexpensive method for monitoring adherence, that can be collected at the same time as other urine studies
- Self-report and MPR have not been established against urine, but have been compared with DBS and plasma



Background: Urine Assay

| Urine TFV (ng/mL) | Adherence Level | Date Last Dose | Implication |
|-------------------|------------------|-----------------|---|
| >1000 | Recent adherence | Within 48 hours | HIV protection |
| 10-1000 | Low adherence | 2-7 days ago | Sub-optimal HIV protection, at risk of resistance |
| <10 | Non-adherence | >7 days ago | No HIV protection, low risk of resistance |

STUDY OBJECTIVES:

1. Evaluate the association of 3-Month MPR with urine TFV testing
2. Evaluate the association of 7-day self-report with urine TFV testing



Methods

- Washington University St. Louis PrEP Clinic, May-Aug 2016
- Urine & blood samples collected at routine clinic visits
- Eligibility: ≥ 18 years, on PrEP for ≥ 1 month, ≥ 1 urine TFV test
- Adherence definitions by method
 - Urine TFV levels > 1000 ng/mL (dosing in the past 48 hours)
 - 3-Month MPR: 0.60 which is equivalent to 4 pills/week
 - Patient 7-day self-report (4 or 7 pills taken in last 7 days)
- Gold standard = urine TFV test
- Calculated sensitivity, specificity, PPV, and NPV of MPR and self report relative to urine TFV testing



Results

- 84 participants; 92 urine samples
- 84 participants
 - Median time on PrEP (IQR): 11 months (7-14)
 - Median age (IQR): 27 (24-33)
- 92 urine samples
 - 89% had urine TFV >1000 ng/mL
 - 94% (85/90) had 3-Month MPR \geq 0.60
 - 89% had 7-day self-report \geq 4 pills/week
 - 66% had 7-day self-report \geq 7 pills/week



| Participant Characteristics | N = 84 | % |
|------------------------------------|---------------|----------|
| Age (Years) | | |
| 18-24 | 28 | 33.3 |
| 25-34 | 38 | 45.2 |
| ≥ 35 | 18 | 21.4 |
| Gender | | |
| Male | 77 | 91.7 |
| Female | 6 | 7.1 |
| Other | 1 | 1.2 |
| Race | | |
| White | 43 | 51.2 |
| African American | 28 | 33.3 |
| Latino | 5 | 6.0 |
| Other/Mixed Race | 8 | 9.5 |
| Men who have sex with men | 76 | 90.5 |
| Education | | |
| Less than college | 28 | 33.3 |
| College graduate | 56 | 66.7 |



Concordance of MPR and Self-report with urine TFV levels at 7 pills/week adherence

| | Urine TFV <10 ng/mL N (%) | Urine TFV 10 -1000 ng/mL N (%) | Urine TFV >1000 ng/mL N (%) | Total N (%) |
|-------------------------|---------------------------------|--------------------------------------|-----------------------------------|-------------|
| MPR <1.0 | 5 (83) | 3 (75) | 49 (61) | 57 (63) |
| MPR ≥1.0 | 1 (17) | 1 (25) | 31 (38) | 33 (37) |
| Total | 6 | 4 | 80 | 90 |
| Self-report <7 pills | 5 (83) | 3 (75) | 23 (28) | 31 (34) |
| Self-report 7 pills | 1 (17) | 1 (25) | 59 (72) | 61 (66) |
| Total | 6 | 4 | 82 | 92 |

*No significant difference found among age or race



Concordance of MPR and Self-report with urine TFV levels at **4 pills/week** adherence among **MSM**

| | Urine TFV <10 ng/mL N (%) | Urine TFV 10- 1000 ng/mL N (%) | Urine TFV >1000 ng/mL N (%) | Total N (%) |
|-------------------------|---------------------------------|--------------------------------------|-----------------------------------|-------------|
| MPR <0.60 | 2 (40) | 2 (100) | 1 (1) | 5 (6) |
| MPR ≥0.60 | 3 (60) | 0 (0) | 74 (99) | 77 (94) |
| Total | 5 | 2 | 75 | 82 |
| Self-report <4 pills | 4 (80) | 2 (100) | 3 (4) | 9 (11) |
| Self-report ≥4 pills | 1 (20) | 0 (0) | 74 (96) | 75 (89) |
| Total | 5 | 2 | 77 | 84 |



| MPR | Pill/wk equivalent | Specificity (95% CI) | NPV (95% CI) | Sensitivity (95% CI) | PPV (95% CI) |
|-------------|---------------------------|-----------------------------|---------------------|-----------------------------|---------------------|
| 1.00 | 7 | 80 (55-100) | 14 (5-23) | 39 (28-49) | 94 (86-100) |
| 0.90 | 6-7 | 80 (55-100) | 28 (11-44) | 74 (64-83) | 97 (92-100) |
| 0.80 | 5-6 | 80 (55-100) | 42 (20-64) | 86 (79-94) | 97 (93-100) |
| 0.70 | 4-5 | 50 (19-81) | 50 (19-81) | 94 (88-99) | 94 (88-99) |
| 0.60 | 4-5 | 40 (10-70) | 80 (45-100) | 99 (96-100) | 93 (93-87) |
| 0.50 | 3-4 | 40 (10-70) | 100 | 100 | 93 (88-98) |

* Urine TFV adherence definition is > 1000 ng/mL

* Specificity: Probability that MPR below cut off when urine TFV < 1000 ng/mL

* Sensitivity: Probability that MPR above cutoff when urine TFV > 1000 ng/mL

* Negative predictive value (NPV): Probability that the urine TFV < 1000 ng/mL when MPR is below cutoff

* Positive predictive value (PPV): Probability that the urine TFV > 1000 ng/mL when MPR is above cutoff

**** A cutoff at 0.80 MPR or equivalent to on average 5-6 pills/week had the highest specificity and sensitivity for predicting adherence when compared to urine TFV (clinical relevance)**



Limitations

- There were a low number of non-adherent patients in this study, which limits generalizability
- This patient population had few women
- Adherence methods measure different time periods (i.e. recent dosing for urine TFV vs. 3-Month MPR)
- The study includes repeat samples from the same patients
- MPR is a proxy of patient adherence



Conclusions

- There is a growing need to accurately and easily monitor PrEP adherence in clinical settings
- Urine TFV objectively screens for PrEP non-adherence
- MPR and self-report mapped out well onto urine TFV (used as a gold standard) with high sensitivity, specificity, PPV, and NPV
- Urine > 1000 ng/mL is highly concordant with MPR and self report suggestive of protective PrEP dosing (>4 /wk)
- Urine < 10 ng/mL allows you to detect more nonadherence than MPR and self-report alone
- These measures can be used to enhance PrEP care



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