# CORRELATIONS AND CLINICAL IMPLICATIONS OF BIOMARKER-BASED ADHERENCE MONITORING METHODS

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## 1 BACKGROUND

- Adherence to HIV prevention and treatment regimens is critical to optimizing outcomes.
- Use of biomarkers to measure drug concentrations across matrices enables objective quantification of medication adherence.
- Biomarker-based adherence testing can facilitate the provision of support services to non-adherent patients.
- A literature review was performed to synthesize the existing research on objective adherence monitoring (OAM) for HIV treatment and prevention.

## 2 METHODS

- PubMed literature searches were performed across common HIV drug component and matrix names in 2019.
- Key words included tenofovir (TFV), emtricitabine (FTC), tenofovir-diphosphate (TFV-DP), emtricitabine-triphosphate (FTC-TP), urine, plasma, dried blood spot, and hair.
- Studies were reviewed to identify correlations between biomarker timeframes and clinical implications

## 3 RESULTS

### *Correlations Between Biomarkers of Adherence*

- We identified 20 studies describing a correlation between ≥2 biomarkers of adherence (Figure 1).
- Of the 21 potential correlations from the seven biomarkers reviewed, 17 had at least one peer-reviewed, published study; two studies were in progress.

**Figure 1: Correlations Between Biomarkers of Adherence**

| Biomarkers of adherence correlations | | Short-term | | | | | Long-term | |
|---|---|---|---|---|---|---|---|---|
| | | TFV Plasma | TFV Urine | FTC Urine | FTC Plasma | FTC-TP Intracellular (RBC or PBMC) | TFV-DP Intracellular (RBC or PBMC) | Hair |
| Short-term | TFV Plasma | | | | | | | |
| | TFV Urine | 100% concordance (Koenig, *HIV Med 2017*) | | | | | | |
| | FTC Urine | *Study in progress - UrSure* | SRO ρ=0.625 (Haaland, *AIDS 2017*) | | | | | |
| | FTC Plasma | 100% concordance (Grant, *NEJM 2011*) | *Study in progress - UrSure* | •SRO ρ=0.605 (Haaland, *AIDS 2017*) •SRO ρ=0.766 (Haaland, *JAIDS 2019*) | | | | |
| | FTC-TP Intracellular (RBC or PBMC) | 91-99% concordance in RBC[1] (Castillo-Mancilla, *AAC 2016*) | SRO ρ=0.75 (Spinelli, *AIDS 2019*) | SRO ρ=0.271 in PBMC (Haaland, *JAIDS 2019*) | 91-99% concordance in RBC[1] (Castillo-Mancilla, AAC 2016) | | | |
| Long-term | TFV-DP Intracellular (RBC or PBMC) | PCC 0.43 in RBC (Castillo-Mancilla, *AIDS RHR 2015*) | SRO ρ=0.52 (Spinelli, *AIDS 2019*) | N/A | 89-98% concordance in PBMC (Grant, *NEJM 2011*) | •SRO ρ=0.860 in PBMC (Haaland, *JAIDS 2017*) •71% concordance (Koss, *Clin Infect 2018*) •% of BLQ FTC-TP decreases as TFV-DP levels increase (Frasca, *JAC* 2019) | | |
| | Hair | PCC 0.41-0.86[3] (Baxi, *JAIDS 2015*) | SRO ρ=0.39 (TFV), ρ=0.48 (FTC) (Spinelli, *AIDS 2019*) | N/A | PCC 0.42-0.61 (Velloza, *JAIDS 2019*) | •PCC 0.50 in PBMC (Baxi, *JAIDS 2015*) •90% (TFV), 81% (FTC) concordance in PBMC (Gandhi, *JAIDS 2015*) •74-77% concordance (Koss, *Clin Infect 2018*) | •PCC 0.43 in PBMC (Baxi, *JAIDS 2015*) •82% (TFV), 85% (FTC) concordance in PBMC (Gandhi, *JID 2015*) •76-80% concordance[2] (Koss, *Clin Infect 2018*) | |

**Intracellular biomarker acronyms:** RBC=Red Blood Cell | PBMC=peripheral blood mononuclear cell
**Statistical terms acronyms:** SRO=Spearman's Rank Order | PCC=Pearson Correlation Coefficient | aOR=Adjusted Odds Ratio
[1]When both TFV/FTC in plasma were below the limit of quantification, FTC-TP was as well in 98.9% of the samples, and when either TFV or FTC in plasma was quantifiable, FTC-TP was as well in 90.5% of the samples
[2]The concordance of TFV levels in hair and TFV-diphosphate in DBS around thresholds consistent with taking ≥4 and 7 PrEP doses/week was high (76% and 80%)
[3]The correlations between hair measures and the plasma or PBMC measures were high, but generally lower at 8 weeks (range, 0.41–0.51) than 16 weeks (range, 0.61–0.86).

### *Clinical Implications*

- Four key clinical implications were identified: predictors of drug resistance, viral load, risk of HIV infection, and non-retention/loss to follow up (LTFU) (Figure 2)
- Of the eight potential correlations between biomarker timeframes and clinical implications, seven had at least one peer-reviewed, published study.

**Figure 2: Clinical Implications of Using Biomarkers of Adherence**

| Clinical implications (correlations & predictors) | | Short-term | Long-term |
|---|---|---|---|
| ART | Drug resistance | N/A | Moderate concentration of TFV-DP plus high viremia indicates potential drug resistance (Yager, *J Int Assoc Provid AIDS Care 2019*) |
| | Viral load | 83% of patients with undetectable/low FTC-TP concentrations had elevated VL; the aOR for viral suppression when FTC-TP was quantifiable was 7.2 (4.3-12.0; P<0.0001) (Frasca, *JAC* 2019) | TFV-DP, TFV, FTC in DBS and hair predict present and future viremia in PLWH (Castillo-Mancilla, Clin Infect 2019; Morrow, *JID* 2019; Gandhi, Clin Infect 2019) |
| PrEP | Risk of HIV infection | High drug concentratios in plasma associated with reduced HIV acquisition (Grant, N Engl J Med 2010; Anderson, *SciTrans* 2012; Baeten, *NEJM* 2012; Thigpen, *N Engl J Med* 2012; Van Damme, *N Engl J Med* 2012; Hosek, *JAIDS* 2013; Choopanya, *Lancet* 2013; Grant, *Lancet Infect Dis* 2014; Marrazzo, *N Engl J Med* 2015; McCormack, *Lancet* 2016; Molina, *N Engl J Med* 2015; Molina, *Lancet HIV* 2017; Spinelli, *AIDS 2019*) | High TFV-DP concentration associated with reduced HIV acquisition (Anderson, *SciTrans 2012*; Grant, *Lancet Infect Dis* 2014; *Liu, JAMA* 2016; Lahuerta, *JAIDS* 2017) |
| Retention | Non-retention/ LTFU | Patients with undetectable/low FTC-TP concentrations at highest risk for non-retention (Spinelli, *JAIDS 2019*) | Patients with undetectable/low TFV-DP concentrations at high risk for non-retention (Spinelli, *JAIDS 2019*) |

## 4 CONCLUSIONS

- This literature review demonstrates that OAM can be a useful tool with diverse clinical implications to optimize outcomes for HIV treatment, prevention, and retention.
- These correlations between OAM biomarkers suggest that applications proven out in one matrix-metabolite combination could apply to others.
- These data indicate that OAM can have widespread clinical utility today, even as additional research is forthcoming.
- This analysis should inform research priorities and advocacy for the scale-up of existing OAM methods.

### KEY TAKEAWAY:

**OAM can be a useful tool with diverse clinical implications for HIV treatment, prevention, and retention.**

## CONTACT

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