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Commentary

What Can Urine Tell Us About Medication Adherence?

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Several large, placebo controlled trials evaluated the efficacy of daily tenofovir (TFV) disoproxil fumarate (TDF) and emtricitabine (FTC) for HIV preexposure prophylaxis (PrEP), leading to FDA approval in 2012. However, in some PrEP trials adherence was astonishingly low, greatly complicating the interpretation of trial results [1]. Retrospective analyses showed that an objective measure of adherence (i.e. TFV concentrations in biological matrices) correlated much stronger with PrEP efficacy and trial outcomes, as compared with subjective adherence measures including self-report and pill-counts [2]. As time went on, drug concentrations became widely accepted as a surrogate marker for adherence and PrEP efficacy in demonstration projects [3].

In contrast, HIV viral load serves as a surrogate of adherence and efficacy for antiretroviral therapy (ART) in those with HIV infection. Yet, an objective measure of ART adherence, such as drug concentrations, could inform clinical care beyond HIV viral load. For example, an undetectable drug concentration paired with a high HIV viral load, would suggest non-adherence and could steer clinical care to address non-adherence rather than test for drug resistance.

Unfortunately, current drug assays for TFV are expensive, require specialized personnel and equipment, and have long turn-around times. In this issue of EClinicalMedicine, Gandhi et al. report on the development of an immunoassay that measures TFV in urine [4]. The immunoassay is currently at the laboratory-based testing stage. However, the expectation is that this new immunoassay eventually will transfer to a low-cost, point of care, cartridge platform, called a lateral flow immunoassay. These types of point of care cartridge tests are common in medical practice and available over the counter to the public [5]. Examples include HIV and infectious disease diagnostics, opioid or recreational drug screening tests, and pregnancy tests. Point of care lateral flow immunoassays typically provides a positive or negative result.

To test their laboratory-based immunoassay, Gandhi et al. used urine samples from a clinical study in human volunteers who either received ($n = 10$ contributing 102 samples) or did not receive ($n = 115$) TDF/FTC. In those not receiving TDF/FTC, 115/115 samples were negative for TFV, yielding 100% (95% CI 97%–100%) specificity. In those receiving TDF/FTC, 70 urine samples had quantifiable TFV by liquid chromatography tandem mass spectrometry, the gold-standard measurement. Sixty-seven/70 of these were also positive for TFV with the new immunoassay, yielding 96% (88%–99%) sensitivity. These promising results support further development. This will require additional testing including cross-reactivity with other key medications/metabolites such as other antiretrovirals, antivirals, and over the counter drugs (the author's study used healthy volunteers not receiving other medications). Finally, additional validation steps will be needed when the technology is transferred to the point of care test cartridge.

Once available, how might a new point of care immunoassay for TFV in urine be used clinically? Several considerations are relevant here. First, sample collections for adherence are by convenience and untimed, so concentrations represent an unknown/random time post-dose. In this setting, adherence interpretation depends on the half-life of the drug moiety. As the authors discuss, TFV in urine mirrors TFV in plasma [6]. These are short half-life moieties (e.g. 15 h), which is relevant because these moieties do not accumulate appreciably with repeated dosing. This means that TFV concentrations following a single dose almost mirror those at steady-state, following repeated doses.

If the patient stopped dosing, or took a single dose several days ago, TFV in urine (and plasma) will enter a washout elimination phase, where sensitive assays could detect the most recent dose as long ago as 2 to 7 days [7]. Taken together, this means that the absence of TFV in urine (or plasma) indicates no dose was recently ingested in the preceding several days. However, the presence of drug is less informative, in that it only indicates recent dosing, but cannot inform if any additional doses were ingested before the most recent dose.

This interpretation is in contrast to long half-life TFV moieties, which include TFV in hair [8] and intracellular tenofovir-diphosphate in dried blood spots [9]. These moieties have half-lives of 2–3 weeks, and they accumulate with repeated dosing such that concentrations represent gradients of cumulative adherence over the preceding weeks. Interpreting adherence for long half-life drug concentrations is analogous to interpreting hemoglobin A1C measurements that inform cumulative glucose exposures.

In conclusion, Gandhi et al. have made significant strides toward a point of care urine TFV assay. A negative TFV in urine would unambiguously indicate no dosing in the preceding 2 to 7 days, depending on cut-off concentration that is validated for the test. Such a finding could prompt a non-accusatory conversation about adherence, at the point of care. How providers message this information to patients will be important. A few studies have evaluated drug concentration-adherence feedback, but more research is needed in this area [10]. Ultimately, a point of care assay such as this would be a significant advance for assessing adherence to PrEP and ART.

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