Clinical Infectious Diseases

EDITORIAL COMMENTARY

Adherence to Antiretroviral Therapy and Pre-exposure Prophylaxis: TARGETing the Ideal Measure

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(See the Major Article by Drain et al on pages 2143–51.)

Keywords. adherence; pre-exposure prophylaxis; antiretroviral therapy; urine; tenofovir.

While the current medications available for antiretroviral therapy (ART) and pre-exposure prophylaxis (PrEP) are potent, effective, and safe, they remain dependent on durable adherence to achieve therapeutic success [1–3]. However, an accurate, reproducible, generalizable, and readily available method to quantify adherence that can be used as a gold standard in clinical practice and research settings remains elusive. Different subjective (eg, self-report) and objective (eg, pharmacologic) adherence measures have been developed, validated, and applied in research studies and clinical practice in recent years, each with unique advantages and limitations [4]. Some are easily implementable and cheap, but tend to overestimate adherence, while others are objective and quantitative, but are expensive and not widely accessible. Thus, the quest for novel methods that can overcome some of these barriers continues.

Pharmacological measures of adherence are based on the quantification of drug concentrations in various body fluids and matrices, including plasma, saliva, urine, cells, hair, and dried blood spots [5]. These measures provide objective evidence of drug intake, and many of them have been associated with clinical outcomes in both ART [6–8] and PrEP [9, 10]. However, their main limitations have been misinterpretation, distinguishing adherence from biological variability [5], and the lack of real-time availability in the "front lines" of clinical care. Thus, in order to maximize their impact and outreach, these measures should evolve into user-friendly, implementable methods at the point of care that can be easily interpretable by both patients and clinical providers.

In the current issue of *Clinical Infectious Diseases*, Drain and colleagues [11] provide a step towards achieving this goal by presenting the results of the tenofovir adherence to rapidly guide and evaluate PrEP and human immunodeficiency virus (HIV) therapy (TARGET) study, which aimed to assess the pharmacokinetics of tenofovir (TFV) in urine in 28 Thai healthy adults randomized to 3 different adherence patterns of oral tenofovir disoproxil fumarate (TDF)/emtricitabine [11, 12]. In TARGET, participants took either daily dosing (Group 1: perfect adherence), 4 doses per week (Group 2: moderate adherence), or 2 doses per week (Group 3: low adherence) for a period of 6 weeks, during which drug intake was confirmed via directly observed therapy, followed by a 4-week washout period. Paired trough plasma and urine samples were obtained at various time points during the study period and washout, in addition to several other matrices, including oral fluid, whole blood, peripheral blood mononuclear cells, and red blood cells. Urine and plasma TFV concentrations were quantified using a validated liquid chromatography-tandem mass spectrometry assay and the primary comparisons reported were the correlation between urine and plasma drug concentrations and the time to undetectability in both matrices after drug discontinuation. The study population was young (median age 33 years) and almost equally balanced between men and women.

Among the findings from the TARGET study, several are of particular significance. First, the authors demonstrated a strong correlation between plasma and urine TFV concentrations across all the adherence groups, both at steady state and during washout (rho = 0.78; $P < .0001$), consistent with observations from a recent study in persons living with HIV [13]. This is important, because it demonstrates that urine and plasma exhibit similar pharmacokinetics. Second, predose drug concentrations of TFV in urine at steady state were different across the 3 adherence groups, although significant overlap was identified, including between the low adherence arm and the other 2 arms (moderate and perfect adherence). This is expected, as the predose samples represented 24 hours (daily dosing), 72 hours (4 doses/

Received 2 July 2019; editorial decision 9 July 2019; accepted 12 July 2019; published online July 17, 2019.

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Clinical Infectious Diseases® 2020;70(10):2152–4

DOI: 10.1093/cid/ciz651

week), and 120 hours (2 doses/week) of washout for a short half-life (ie, 15–20 hours) moiety. Third, although marginally different in plasma, no differences in the TFV urine concentrations during the washout period (at 2 and 4 days after drug discontinuation) or in the time to undetectability were identified among the 3 adherence groups. Of note, TFV was undetectable in the urine in most participants 14 days after drug discontinuation (except in 1 participant in the moderate and 1 in the high adherence groups), and could not be detected by 3 weeks after the last dose in any group. This indicates that an undetectable TFV concentration in the urine represents a long period off the drug, which is clinically valuable information.

To best interpret the results from TARGET, we must first understand its strengths and potential limitations. The 2 major strengths of this study lie within the rigorous study design, using directly observed therapy dosing and the focus on urinary concentrations of TFV. For a pharmacological measure of adherence to be useful and applicable in the general population, any established drug concentration:adherence relationship must be derived from data obtained through a well-controlled study such as TARGET (and similar studies) [14–16]. This minimizes the potential bias introduced by behavior (ie, adherence) that contributes to variability of the drug concentrations. In addition, the focus on urine will complement previous studies that have established adherence benchmarks for recent and cumulative adherence measures, such as TFV in plasma [16], hair [15], peripheral blood mononuclear cells [15], and TFV diphosphate in dried blood spots [14]. Given some of the potential limitations in the collection and processing of these matrices, TFV in urine offers a minimally invasive and readily available adherence measure that can be collected and processed without any specialized training in any clinical or research setting. These advantages could be further enhanced by the researchers' ongoing development of a urine TFV immunoassay [17, 18], which has leveraged data from TARGET and can inform future studies and clinical practice to monitor adherence to ART and PrEP. Such a strategy could be used to objectively assess drug detection/adherence during a clinical visit in real time and at the point of care, triggering informed discussions between providers and patients at the time when they are most effective.

The main cautionary points from the TARGET study were the considerable overlap in TFV urine concentrations (biological variability), leading to the inability of the drug concentrations to discriminate between adherence groups during the washout period. Additionally, the short half-life and lack of accumulation of TFV in plasma and urine indicate that steady-state concentrations achieved after repeated dosing are similar to those achieved after a single dose. Therefore, as Drain and colleagues [11] recognize in their manuscript, this adherence measure can be influenced by recent dosing not reflective of a true adherence pattern (the so-called white coat adherence [19]), leading to the misclassification of someone as being highly adherent when she/he may have been nonadherent preceding that white coat dosing. Consequently, a detectable TFV concentration in urine would be indicative of recent dosing. The duration of time where the drug is detectable in the urine would inform the timeframe for the most recent dose, which—based on the TARGET results—would be between 7 to 10 days in most participants (and up to 14 days in a few participants). Certainly, a TFV concentration in the urine below the limit of quantification is useful information, as it would be indicative of no dosing event within that same time frame.

In conclusion, Drain and colleagues [11] present novel data on the potential utility of urinary TFV concentrations as a pharmacologic measure of recent adherence to TDF/ emtricitabine. Based on the TARGET results, TFV would be most helpful to determine the absence of recent dosing within the preceding week, and could be included in the armamentarium of available tools to identify patients with significant adherence gaps, in particular once it becomes available as a point-of-care test. Future studies evaluating the utility of this method will be indispensable to understand its clinical application in PrEP and ART.

Notes

Financial support. J. R. C.-M. has received funding from National Institutes of Health/ National Institute of Allergy and Infectious Diseases (grant number 1R01AI145453-01 A1).

Potential conflicts of interest. Both authors have submitted the ICMJE form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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