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## Acceptability of drug detection monitoring among participants in an open label PrEP study

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### Abstract

In the world of HIV pre-exposure prophylaxis (PrEP) research, there is emerging interest in providing study participants with pharmacokinetic results from drug-level testing to guide adherence counseling. The iPrEx randomized control trial was the first study to produce meaningful results of PrEP in humans. In the iPrEx open-label extension (OLE) study, blood plasma samples collected in the first 12 weeks of study participation were tested for the presence of tenofovir/emtricitabine – the drugs which comprise PrEP. Study clinicians shared results (detectable/undetectable) with participants at their 24-week visit. We evaluated the acceptability of receiving these results among a subset of iPrEx OLE participants. We conducted in-depth interviews (n=59) with participants (those with and those without drug detected) enrolled in Boston, Chicago and San Francisco to assess their experiences with receiving drug detection feedback. Incorporating drug-detection results into the clinical study visit was well received and no negative reactions were expressed. For about half of participants, receiving their drug detection lab result was useful while for others it was not important. In a few cases, no drug detected results led to increased efforts to take PrEP consistently and in most cases enhanced open discussion of missed doses. Participants reported a desire for greater specificity, particularly quantitative drug levels needed for protection. We recommend exploring strategies to increase the salience of drug-level results, including using feedback to target adherence counseling, and reducing the time between specimen collection, testing and receipt of results. Future studies should evaluate the feasibility and impact of providing more specific quantitative drug-levels using biomarkers of longer-term PrEP exposure ie, hair/dried blood spots.

## Keywords

Pre-Exposure prophylaxis; HIV; Adherence; Drug detection monitoring; Qualitative methods

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## Introduction

The U.S. Food and Drug Administration approved the use of daily oral emtricitabine/tenofovir disoproxil fumarate (Truvada®) as HIV pre-exposure prophylaxis (PrEP) in July 2012. Adherence to the daily regimen is a critical factor for PrEP efficacy and has been called the “Achilles’ heel” of PrEP (Eakle et al., 2013; Stirratt & Gordon, 2008; Ware et al., 2012). Strategies to increase adherence to PrEP will be important to maximize effectiveness. One strategy to promote adherence and/or foster discussion of non-adherence is to provide patients with objective data on recent PrEP use based on pharmacokinetic laboratory results from blood plasma or dried blood spot specimen testing.

While the use of pharmacokinetic testing results as an adherence counseling tool is novel, particularly in the context of an elective disease prevention regimen, it is a strategy that builds on techniques used to support adherence to anti-retroviral therapy (ART) among people living with HIV. For example, the use of electronic drug monitoring feedback, while not entirely objective, is a good surrogate marker for ART adherence and has been shown to improve rates of adherence (Sabin et al., 2010, Gill et al., 2010). While much progress has been made in terms of developing effective adherence interventions (i.e., text messaging, directly observed therapy, counseling), we still lack a gold standard in measuring medication adherence. Given the lack of gold standard in either the use of ART for the treatment or prevention of HIV and the need to explore the acceptability of a potentially promising new non-subjective measurement of adherence to PrEP, we designed a qualitative study to investigate the acceptability of offering drug detection feedback in the context of a PrEP study. The iPrEx randomized control trial was the first study to produce meaningful results of PrEP in humans (Grant et al., 2014). The iPrEx open label extension (OLE) study was designed to identify demographic and behavioral characteristics associated with PrEP uptake and to examine adherence and its effect on HIV incidence and sexual practices and is described in detail elsewhere (Grant et al., 2014). We briefly outline the major highlights from our assessment of drug detection feedback below.

## Methods

We conducted in-depth interviews with a subset of iPrEx OLE participants in the U.S. sites: Boston, Chicago and San Francisco; per the eligibility criteria of the iPrEx OLE study, all were male, reported having had anal intercourse with men, ages 18 years or older, English-speaking and had previously participated in a randomized trial of once daily oral PrEP. Based on prior research, we felt confident we would reach saturation on our domains of interest with 20–25 participants (Guest et al., 2006) per site. Whenever possible, we purposefully recruited participants to ensure a comprehensive understanding of those receiving a ‘drug detected’ result and those receiving a ‘no drug detected’ result.

An expert interviewer unaffiliated with the iPrEx team conducted audio-recorded, one-on-one, in-depth interviews. Interviews lasted approximately 60 minutes and were conducted in a private office. The interview guide included questions such as “When they tell you how much Truvada® you have in your blood, what was that experience like for you?” and “What could they do to improve how they talk to you about that?”

All data were transcribed verbatim and entered into *Dedoose*, an internet-based program designed to facilitate organization of qualitative data. We used an inductive content analysis approach to understand the experience of receiving drug detection results (Hsieh & Shannon, 2005). One analyst performed line by line coding and generated analytic memos for each transcript. Then, working with a second analyst, we systematically reviewed the coded excerpts related to the drug detection narratives, drafted summaries and tables which we then used to derive the themes described below. We obtained IRB-approved written informed consent from all participants.

### **Drug detection testing and sharing of results**

iPrEx OLE participants received drug detection feedback approximately 24 weeks after starting PrEP based on a blood specimen collected at the 4, 8, or 12-week visit. The drug level results were embedded into the existing procedure used to discuss all other lab results. Study clinicians, usually nurse practitioners, reminded participants of drug level testing, noted when their specimen was collected and reported whether their specimen had a ‘drug detected’ result. Detection was explained as indicative of recent PrEP dosing, and ‘no drug detected’ was explained as no PrEP protection at time of blood collection.

### **Findings**

From April to August 2012, we conducted 59 in-depth interviews. The median age was 29 years, and most were African American MSM. Participant characteristics are detailed in Table 1. Of those participants interviewed, 12 (25%) had received a ‘no drug detected’ result, which is similar to the proportion that received this result in the entire iPrEx OLE U.S. cohort (Grant et al., 2014). During our analyses, it became clear that participants described two distinct reactions to the receipt of drug detection results. We classified participants into two categories: results were not useful and experienced as a non-event, or results were useful and experienced as a memorable event.

#### **Experience as a non-event: Lab result imparts no new information**

Approximately half of our participants described receiving the drug detection result as inconsequential, or what we labeled as a ‘non-event.’ Most participants, but not all, had been told they had drug detected. Many explained that because they took their pills as directed, they expected that evidence of the drug would appear in their blood sample. The lab result “you have drug in your system” was information that they already believed to be true. Those experiencing the feedback as a non-event felt that there was no added value in receiving the lab result.

A subset of the ‘non-event’ participants intimated that the drug detection information was not intended for study participants, but was collected strictly for the purposes of research.

They did not see themselves as the consumers of this information and brushed off both the experience as well as the information. The following excerpts represent the “non-event” attitudes (Table 2 includes additional quotes):

I: Does knowing that it’s in your blood mean anything for you?

P: Not really, because in my mind, there’s a direct connection to me taking it every day and having it be in my blood... *Chicago, age 23, African-American*

I: When they take your blood, do they give you feedback about whether or not Truvada® is in your bloodstream?

P: All I’ve been told was that they can tell I’m taking it regularly.

I: ... is that information useful to you...

P: I already know. It’s got to be because I know I’m taking it every day. And hopefully, [they] get something useful out of those results. *Boston, age 46, White*

### Experience as an event: Lab result imparts useable information

The other half of participants described their experience receiving drug detection results as encouraging and affirming. Some felt protected or empowered when they learned they had drug detected. Other participants found the results useful because it helped them to establish that the pill was not a placebo or that one’s metabolism was not interfering with drug absorption.

I guess it makes me feel a little safer, to be honest, ‘cause I know that I have ... I don’t want to call it immunity, but I have the drug in me that’s supposedly preventing my body from getting those HIV antibodies. ... or preventing me from having someone pass their infection over to me. So it makes me feel good actually that it’s in my system. *Boston, age 47, White*

It’s just that it solidifies that all your efforts are being... So you know you’re taking this pill, you see it in your bloodstream. You know it’s working. You know it’s there. You know you’re not doing it just in vain. *Chicago, age 22, African-American*

### Reactions from participants with ‘no drug detected’

The research team emphasized that the ‘no drug detected’ group be handled with care so that participants did not feel penalized for having a ‘no drug detected’ result. Among the participants (n= 12) interviewed, the lab result did not appear to be experienced as a threat nor did anyone report feeling penalized by this explicit evidence of low adherence. We classified the majority (n = 10) as those experiencing this as an ‘event,’ including two participants who could not recall receiving the lab result, but expressed a theoretical interest in learning their results. Two participants did not find the information to be useful; both assumed that the information was collected for research purposes only. One participant reported that the ‘no drug detected’ result motivated him to improve his adherence. Other participants articulated that they were more likely to provide accurate information when it came time to report on missed doses, after receiving a no drug detected result. Aside from

the case described above/quoted below, participants did not explicitly describe the drug detection feedback as a motivator to take PrEP.

P: One time she did tell me, she said it wasn't that much in there. She said it wasn't really any traces ...She was saying it could be a different amount of reasons. I don't know.... like I said when I first started it was a little bit harder for me to remember. So I thought it was pretty much me. It coulda been just me missing days. Not taking it consecutive. Missing every now and again. I don't know. So I just felt like... I guess really after hearing that, that made me really wanna make sure that I take it every day. 'Cause I feel like why take it at all if it's not effective? *Chicago, age 21, African-American*

I: When you come to the clinic and they take your blood, do they tell you about how much Truvada® you have in your blood?

P: At first they did. You know, they was like, you know are you taking the pill every day? You have to be honest with them you know. Say if you missed a day and then, because they have to, you know they have to know everything like, when I told them I missed a few days recently they was like, okay cool. But when I came back they told me that the time that you told me matches up with what they [*found from drug detection results*], so you know everything matches up, so actually when you miss any days you have to be honest with them. *Chicago, age 22, African-American*

### **Making drug detection information meaningful**

We asked men about how to improve the delivery of the drug detection results. While a few felt the binary detected/not-detected result was “good enough,” others wanted quantifiable information, including information on the level of drug needed for optimal protection against HIV.

I don't think the science is to that point yet, but if I had the level in my blood that they've determined is the threshold necessary to get maximum protection, that would be useful. *San Francisco, age 57, White*

### **Discussion**

Providing feedback on drug detection was acceptable to the participants in our study. In general, drug detection results were well or neutrally received. The neutral reaction may be explained by the limited nature and neutral delivery of the information. First, the usefulness of the information was limited as only the presence or absence of drug detection was shared with participants. Some participants clearly expressed a desire for greater specificity in results, particularly quantitative drug levels needed for maximal protection. Second, the team intentionally adopted a neutral delivery approach based on prior research with iPrEx participants which suggested that some believed that non-adherence could result in negative consequences, including being terminated from the study (Vargas et al., 2010). In providing drug detection results, the study clinicians were encouraged to make the provision of drug detection results a regular part of care. The experience may have been more meaningful if

the results had been delivered in the context of the counseling session, which included a discussion about pill taking - a strategy being tested in two PrEP demonstration projects in California (Burack, 2013; Wohl & Landovitz, 2013).

Limitations of this study included providing drug detection results to participants at only one point in time and several months after the visit when blood was collected. We tested plasma samples which reflect a shorter period of use than other biological specimens such as dried blood spots. While we purposively recruited participants with drug or no drug detected, less than 1/5<sup>th</sup> of the participants interviewed had no drug detected and were predominantly from one site (Chicago). The reason for the poor representation of the 'no drug detected' cases in Boston and San Francisco was primarily due to exceedingly high overall drug detection rates within these cohorts. Despite this limitation regarding our sample, we are encouraged by the findings that some participants wanted the information in both the drug and no drug detected categories.

Based on these findings, we recommend increasing the salience of providing drug-level results in specific ways. First, we strongly recommend reducing the time between testing and receipt of results. In the iPrEx OLE study, participants received drug detection results at the 24-week visit, sometimes as much as 20 weeks after blood was drawn for the test. Ideally, results would be available at or before the next PrEP visit after drug levels were tested; this will require a laboratory capable of providing a quick turnaround for drug level testing and reporting results. Second, providing drug detection feedback separately and within the context of adherence counseling could facilitate adherence discussions. Introducing targeted counseling, such as offering counseling sessions only to those with a 'no drug detected' result has the potential to lead to an open discussion about one's pill-taking practices. This strategy builds on the adherence research done to date using patient-level data to create opportunities for open-ended discussion about ART adherence (Sabin et al., 2010). We are curious about the similarities and differences in providing adherence support in the context of a voluntary biomedical HIV prevention regimen vs. a course of treatment for HIV disease. Assessing the benefits associated with providing targeted counseling based on biomarker data is an important next step in PrEP adherence research. Finally, because participants in this study were eager for information beyond a yes/no for drug detection, future studies should evaluate the provision of quantitative drug levels to PrEP users. Recent pharmacologic studies have established a clear relationship between dose and drug levels in dried blood spot specimens (Anderson et al., 2012) and hair (Liu et al., 2014). Hair and dried blood spots (Castillo-Mancilla et al., 2013; Liu et al., 2014) are two promising biomarkers of longer-term PrEP exposure that are relatively easy to collect and process. For drug level feedback to be adopted on a broader scale, specimen collection and processing for drug level testing will need to be inexpensive and streamlined. We recommend evaluating the feasibility of providing these quantitative drug levels in upcoming PrEP studies and implementation programs and assessing the impact of sharing these results on future drug detection and self-report accuracy.

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**Table 1**

## Participant Characteristics

Characteristic	Total (n=59)	San Francisco (n=10)	Boston (n=21)	Chicago (n=28)
Median age (range)	29 (21–65)	48 (25–65)	49 (26–61)	22 (21–25)
Race				
White	24	8	16	0
African-American	26	2	4	20
Latino	8	0	1	7
Asian/Pacific-Islander	1	0	0	1
Drug detection				
Yes	47	10	20	17
No	12	0	1	11

Table 2

## Examples of Drug Detection Result Responses

Drug Detection Result is a Non-Event	Drug Detection Result is an Event
<p>I assume that if I have been taking the drug it's in my system. I assume the staff are monitoring these things... I wouldn't be unhappy if they told me, but I don't think that they need to tell me. <i>San Francisco, age 56, White</i></p> <p>I: When they tell you yes we've, we see Truvada is in your blood. What's, how does that, how does that make you feel?</p> <p>P: I don't... It doesn't make me feel anything. I know it's... I know it's in me. It's just for their, for their records. <i>Boston, age 53, African American.</i></p> <p>I: The... when you come in here to the clinic they take your blood. Do they tell you if you have Truvada in your blood?</p> <p>P: Yeah.</p> <p>I: They do? What's that like for you?</p> <p>P: I don't know. I feel like I always joke about it but I never sit actually and think about it. Because I don't... like I don't think about it too much because I don't understand... or like have a response to it because I don't really understand it on like a, you know, biology level.</p> <p>I: what would you like to know? Like what would be ideal information for you?</p> <p>P: I guess like how... like the last time they were like, "Oh, you know, it's 47% in your blood" or something like that. And I'm just like, "Well, like, what does that mean? Like how is it in my blood? Like what's it, you know, doing to protect my body?" Like, you know. More specifics about.</p>	<p>So I totally knew from the start of the study that they were going to be checking to see if it's in your system. And I think that's good because there's some people who could be saying that they're on the drug but they're really not. So, I'm kind of glad that they're actually looking to see if the people are taking it and it's in their system. <i>Boston, age 31, White</i></p> <p>I: Did knowing that they were going to tell you about the Truvada in your system, did that motivate you to be a part of this study at all?</p> <p>P: It definitely, I mean it gave me insight to the fact that you couldn't lie about how much you were taking it. <i>Chicago, age 25, African-American</i></p> <p>I: Do they tell you if you have Truvada in your blood or not?</p> <p>P: Yeah. I mean, I've always figured it's a pretty constant level cause I take it pretty regularly... I like knowing that it's in me and that it's always at pretty much a conscious level. 'Cause I do go to somewhat, I mean I wouldn't say great pains, but I make a conscious effort to make sure that that's the case. So I like to see that that's actually what's happening. <i>Boston, age 32, white</i></p> <p>I: Do you wanna know that information?</p> <p>P: I sure do.</p> <p>I: Tell me why.</p> <p>P: I mean, I... I don't know. I wanna see how much is actually... on the inside, really. And... I don't... I just want to know. I just want to be informed how much is in my blood. Basically. Because I feel like I've been on it for a while... I just want to know for sure. <i>Chicago, age 23, African American</i></p>