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If You Build It, Will They Use It? Preferences for Antiretroviral Therapy (ART) Adherence Monitoring Among People Who Inject Drugs (PWID) in Kazakhstan

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Abstract

Adherence to antiretroviral therapy (ART) is an important predictor of long-term treatment success and is associated with optimal individual and public health outcomes. Novel technologies, such as electronic monitoring devices (EMDs) or pharmacokinetic testing, provide more objective measures of ART adherence than traditional measures of adherence (e.g., self-report) and may facilitate improved adherence through the provision of patient feedback. This study examines preferences for ART adherence monitoring among people who inject drugs (PWID) in Kazakhstan. In-depth interviews were conducted with 20 HIV-positive PWID, 18 of their intimate partners, and 7 AIDS Center healthcare providers in Almaty, Kazakhstan. Results indicated that patients varied in their preferences of which strategies would be most effective and acceptable to use in monitoring their adherence. Overall, patients were highly enthusiastic about the potential use of pharmacokinetic testing. Many participants supported the use of EMDs, though some were concerned about having their adherence tracked. Other participants thought reminders through text messaging or smart phone applications would be helpful, though several had concerns about confidentiality and others worried about technological difficulties operating a smart phone. Future

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Conflict of Interest Alissa Davis declares that she has no conflict of interest. Lyailya Sarsembayeva declares that she has no conflict of interest. Valeriy Gulyaev declares that he has no conflict of interest. Sholpan Primbetova declares that she has no conflict of interest. Assel Terlikbayeva declares that she has no conflict of interest. Gaukhar Mergenova declares that she has no conflict of interest. Robert H. Re-mien declares that he has no conflict of interest.

Ethical Approval This study received approval from institutional review boards at the New York State Psychiatric Institute, Columbia University, and the Kazakhstan School of Public Health. All procedures performed in studies involving human subjects were in accordance with the ethical standards of the institutional and/or National Research Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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studies should evaluate the feasibility and impact of providing quantitative drug levels as feedback for ART adherence using bio-markers of longer-term ART exposure, (i.e., hair sampling or dried blood spot testing).

Keywords

Antiretroviral therapy adherence; People who inject drugs; Drug monitoring; Kazakhstan

Introduction

Eastern Europe and Central Asia (EECA) is the only region globally where new HIV infections and HIV-related mortality are increasing [1]. New HIV infections in EECA increased by 57% in 2015, while numbers of incident HIV cases in all other global regions remained static or declined [1]. The rapid increase in incident HIV cases in EECA is largely driven by opioid injection. In EECA, HIV-positive people who inject drugs (PWID) have low rates of antiretroviral therapy (ART) adherence and viral suppression [2, 3]. In Kazakhstan, it is estimated 53% of HIV-positive PWID on ART are virally suppressed [4]. HIV-positive PWID in Kazakhstan face many individual, social, and structural barriers to ART adherence and are in need of strategies to facilitate improved adherence [5]. Adherence to ART is key to increasing viral suppression, decreasing transmission of HIV, and reducing HIV-related morbidity and mortality. Adherence has become a particularly important topic in Kazakhstan as the Ministry of Health has shifted to a new “test-and-treat” protocol where HIV-infected individuals are immediately placed on ART rather than waiting to meet a CD4 threshold [6]. Non-adherence to ART is a major public health issue that impedes attainment of the UNAIDS 90-90-90 goals [7]. Effectively measuring and monitoring ART non-adherence is a crucial step toward improving it, yet there is little monitoring of ART adherence in many countries globally, including Kazakhstan, particularly among marginalized populations, such as PWID.

While there is currently no gold standard method to accurately measure ART adherence, the development of new strategies to achieve this goal continues to be a focus of research [8–10]. However, research on the acceptability of these strategies among diverse populations and regions of the world has remained limited [11–14]. Assumptions that emerging ART adherence technologies will be equally accepted by all vulnerable populations in all regions of the world are myopic and fail to recognize the diversity of populations affected by the HIV epidemic and the various contexts in which they live [15]. As the development of other new technological and biological strategies for HIV prevention and intervention have shown [16], “if you build it”, it does not necessarily mean they will come. Research is urgently needed to examine the acceptability of diverse methods of ART adherence measurement as part of HIV interventions for both research and clinical care among marginalized populations in diverse contexts, particularly among individuals with poor adherence living in areas with rapidly growing HIV epidemics.

A number of different strategies to improve ART adherence monitoring have been developed and are currently in development. The most commonly used strategies are those that require

the least logistical burden (e.g., self-reported adherence); however, these methods frequently have problems with validity [17, 18]. Other non-technological methods used to monitor ART adherence include pill counts or pharmacy refill data, but these methods can place substantial burden on providers and patients, particularly in busy clinics [19, 20]. Many clinics rely on viral load testing to measure ART adherence [21]. However, this approach is problematic as there is not a simple relationship between adherence problems and viral breakthrough. There are variations in time to re-emergence of detectable viral load depending on (1) the stage of ART treatment (early/longer term); [22–24] (2) type of ART; [25] (3) duration of previous viral suppression; [26, 27] and (4) non-adherence patterns (sustained gaps vs intermittent brief lapses) [28, 29]. It would be advantageous to identify adherence problems prior to viral rebound and the development of resistant virus. If current viral load testing standards (in Kazakhstan, typically once every 6 months) are used as the only clinical indicators of adherence, important opportunities for adherence intervention to prevent viremia are missed. New and emerging technological and biological methods for measuring ART adherence may hold promise in providing a more objective, accurate assessment of nonadherence and identifying adherence problems at earlier stages [30–32]. These strategies include monitoring through mobile phones, electronic monitoring devices, and biological monitoring of drug levels.

Cellular technology is widely used globally and is a tool that may provide promising opportunities for improving ART adherence and clinical outcomes [33–36]. Mobile phones allow regular communication with patients remotely, thus reducing the need for costly and time-consuming travel to clinical sites. Text messaging or reminders through smart-phone apps could provide valuable reminders to patients on a daily basis to take their ART medications [37–40]. This technology could be particularly helpful for PWID, who may forget to take medications if they are under the influence of drugs. Cellular technology could also provide a medium for patients to more easily communicate with providers when facing adherence challenges, which may be especially important for stigmatized populations who hesitate to access healthcare services in traditional settings due to fear of discrimination, disclosure, or lack of money or transportation. However, cellular service provision and ownership differs widely in different global regions, and further information is needed on the acceptability and logistics of using this technology to monitor adherence in under-researched regions.

Electronic monitoring devices (EMDs) store medications and transmit records of device openings [30]. Although EMDs cannot measure whether medication has actually been ingested, they provide real-time feedback on when pill containers have been opened, thus, providing clinicians the opportunity to regularly monitor patient adherence and intervene promptly to attempt to close adherence gaps before viral rebound and subsequent drug resistance develop [37]. Such devices could be used to facilitate discussion between patients and providers about strategies to address adherence challenges [41]. Newer EMDs also allow for increased functionality through connection to smartphone apps, such as programming alarms to remind patients to take their medications. However, with their tracking functions, it is unclear how acceptable EMDs will be to PWID, who may be wary about being tracked by healthcare providers or researchers.

One newer strategy in development to promote adherence and foster discussion of non-adherence is to provide patients with objective data on recent ART ingestion based on pharmacokinetic laboratory results from hair sampling or dried blood spot (DBS) testing. Anderson and colleagues developed a novel assay that measures the intracellular anabolite of tenofovir-diphosphate (TFV-DP) in red blood cells, where its longer half-life can reflect medication ingestion adherence over weeks [42]. Combined with the measure of the parent drug tenofovir, which reflects recent ingestion, DBS testing could be a convenient clinical measure for both recent adherence and cumulative adherence over time. DBS testing also has many advantages over traditional whole blood and plasma sampling, including the low blood volume required, easier collection technique, and less intensive labor.

Measuring ART drug concentrations in hair samples is also another novel pharmacological method that can assess medication adherence over time [32]. Because the concentration of drugs in hair reflects uptake from the systemic circulation over an extended time window (weeks to months) [43], hair analysis provides an advantage over plasma monitoring in assessing average drug exposure over a longer period of time. This method of ART measurement may be particularly useful for PWID, who frequently have high levels of non-adherence and difficulty providing blood samples due to a lack of venous access. However, there may be some hesitation from patients to provide hair samples.

In order to increase viral suppression and reduce the spread of HIV transmission in Kazakhstan, research is needed to examine patient and provider acceptability of different measures of ART adherence, particularly newer measures. Understanding which ART drug monitoring methods are most acceptable to HIV-positive PWID and their healthcare providers is crucial to inform the design of future interventions and research among this population and implementation of these strategies into limited resource settings. Thus, we designed a qualitative study to investigate the acceptability of using different methods of ART adherence measurement among HIV-positive PWID in Kazakhstan.

Methods

Participants

We aimed to conduct in-depth interviews with HIV-positive PWID and their intimate partners and with their healthcare providers in Kazakhstan to understand participant attitudes and preferences for different ART monitoring methods. We aimed to recruit enough participants to achieve data saturation and anticipated needing to recruit 25 couples and 10 healthcare providers. Participants were recruited through a non-governmental organization (NGO) that works with PWID and HIV-positive individuals. This organization has an office located in the AIDS Center where individuals can go to receive additional information and support about HIV and drug use. Individuals visiting the NGO were informed about the study by trained staff members and informational flyers were available. Interested participants were referred for screening by an NGO staff member to a research assistant at the Global Health Research Center of Central Asia (GHRCCA). In order to be eligible for participation, for HIV-positive PWID, participants had to: [1] be at least 18 years of age, [2] have injected drugs in the past year, [3] have been diagnosed HIV-positive, and [4] fluently speak Russian. For partners of HIV-positive PWID, to be included in the study, they had to:

[1] be at least 18 years of age, [2] have been in a relationship with an HIV-positive PWID for at least 6 months, and [3] fluently speak Russian. For healthcare providers, participants had to: [1] be at least 18 years of age, [2] have worked at the AIDS Center as a healthcare provider for at least 6 months, and [3] fluently speak Russian. Participants were excluded if they were not willing or able to consent to or participate in study procedures.

All research procedures were approved by Institutional Review Boards at the New York State Psychiatric Institute, Columbia University, and the Kazakhstan School of Public Health.

Procedures

Interviews were conducted in a private room in a field office of the GHRCCA or in a private room at the Almaty AIDS Center. A trained research assistant explained all study procedures and obtained written informed consent from the participants. Interviews were conducted in Russian by a trained research assistant at GHRCCA, who has been conducting research among PWID and people living with HIV (PLWH) in Kazakhstan for many years. Interviews lasted approximately 45 to 90 min. All interviews were digitally recorded and transcribed verbatim into Russian. No personally identifiable information was contained in the transcripts. Interview questions followed a guide with core questions and prompts that covered specific topics related to [1] participants' history with ART adherence/providers' perception of patients' ART adherence, [2] barriers and facilitators to ART adherence, [3] attitudes toward different ART adherence measures, [4] acceptability and willingness to use different ART adherence measures, and [5] emergent themes. Participants were reimbursed $15 for travel and time spent.

Data Analysis

We used thematic analysis to analyze transcripts [44]. Data were analyzed using NVIVO (version 11, Doncaster, Australia). First, three members of the research team (the primary investigator and two trained research assistants) developed a set of preliminary descriptive codes based on an initial review of the transcripts and pre-identified domains. Then, each trained qualitative analyst coded the same two interview transcripts in Russian using these codes to ensure reliability. Any discrepancies in coding were discussed between the three analysts and resolved by consensus. Once reliability was established and the codebook finalized, all transcripts were divided between the three analysts for coding. Excerpts were selected to illustrate the main findings and expand upon the selected themes.

Results

Participant Characteristics

In-depth interviews were conducted with 20 HIV-positive PWID, 18 of their intimate partners (11 HIV-positive and 7 HIV-negative), and 7 AIDS Center healthcare providers (total N = 45) in Almaty, Kazakhstan between September and December 2017. Sociodemographic characteristics are presented in Table 1. The average age of both index cases and partners was 42 years old (Range 30–52). The majority of index cases and partners had some form of employment, with 20% (n = 4) of index cases and 27.8% (n = 5) of

partners unemployed. The majority of index cases and partners had a high school diploma or higher. Only one (5.0%) index case had less than a high school degree. The mean year index cases were diagnosed with HIV was 2008 (SD 4.1; Range 2001–2016), and the mean year partners were diagnosed with HIV was 2009 (SD 5.2; Range 2002–2017).

Detailed sociodemographic data were not collected for medical providers. Four nurses and three doctors at the AIDS Center were interviewed. All providers were female, which is reflective of the predominately female staff at the Almaty AIDS Center.

Pill Counts

Most HIV-positive individuals and most healthcare providers strongly disliked the use of pill counts to monitor ART adherence. Providers said that they already perform pill counting in the clinic, but cited a number of problems with this approach. They said that pill counting added extra time into their busy schedules and that many patients do not remember to bring back their pills or will lie about their adherence.

> We have this approach for medication adherence monitoring. For example, when a patient comes, we say, ‘Bring your remaining medications’. He brings them and we count how many pills are left. But we don’t always use this approach every visit… Patients can dump their pills at home. I had a patient who dumped most of their pills at home, then brought me the rest and said ‘I have five days left.”… Patients sometimes lie, unfortunately. I always say, ‘You don’t lie to me, you lie to yourself.’—female infectious disease doctor at the AIDS Center.

Many HIV-positive individuals stated that pill counts seemed paternalistic, and they did not think that it provided an accurate measure of adherence, nor would it help them better adhere to their ART regimens. Several participants stated that patients would lie and not remember to bring their pills back, but say they had taken them all or only bring back some of the pills.

> No, I don’t think [pill counting] is effective… A person can lie, right? Maybe he didn’t take his medicine, threw it out, but there [at the AIDS center] they’ll check his pills and think that everything is normal. He lies to himself.—42 year old HIV-positive male who injects drugs.

Other participants cited additional time needed to count pills during clinic visits and hygiene issues as reasons why they did not want to use pill counts.

> First, it’s not effective. Second, it’s not hygienic. When he [healthcare worker] counts my pills, will he wear gloves every time he counts or what?—38 year old HIV-positive male who injects drugs.

Both HIV-positive and HIV-negative partners also thought that pill counts would be an ineffective way of monitoring adherence and that it would only encourage patients to lie about their adherence.

> I think that 50% of people who don’t take their medication will not bring their pills to be counted. Why admit that they don’t take their pills? It will be very difficult to get someone who doesn’t take their pills to bring them with them to be counted. The person will just think, ‘Why do I need this? I’m not going to bring any pills,

I'll just say I took them all.'—45 year old HIV-negative male partner who does not inject drugs.

Other partners talked about the difficulty using pill counts in seroconcordant partnerships where both partners were taking the same medication. One participant stated that it is common for seroconcordant partners to share pills, making it difficult to gauge individual adherence levels by counting pills.

> Look at me and my husband, for example. We both take Truvada [as part of an ART regimen]. Sometimes I may be too lazy to go to my bag and get my medication, so I take my husband's. Or we go somewhere and he didn't bring his medication, so he takes mine. That's where there would be difficulties. Because you would see discrepancies in these medications. I know many couples who [take medications] like this. 'Today we'll take my medicine. My medicine is finished we'll take yours.' We take the same medication. Both of our medicine is in the cabinet, so I say to my husband, 'We have this much Truvada left. Your bottle has this much, my bottle has this much, it's time to get more.' So we combine them.—40 year old HIV-positive female partner who injects drugs.

Although most participants were against using pill counts, a few thought that pill counts would be helpful, because they themselves don't track their adherence.

> It would be interesting to see for yourself how many you missed. There are 30 pills in a bottle. I don't count how many pills are left. I just take them and when I run out of pills, I get a refill and take those.—51 year old HIV-positive male who injects drugs.

Text Messaging

Overall, providers thought daily text messaging could be helpful for some participants and appreciated automated texts that would not add to their busy schedules. Many felt that text messaging could streamline their workload and reduce the amount of time spent calling patients for follow-up appointments.

> It would be good if we could send messages electronically to all patients. Something like, 'You have an appointment tomorrow or day after tomorrow.' Because when the nurse has to call all the patients by phone and remind them to come in, it takes a lot of time.—female infectious disease doctor at the AIDS Center.

Some HIV-positive participants were enthusiastic about the use of text messaging to monitor ART adherence. Some participants found adherence to daily doses of ART medications challenging due to variations in daily schedules. Several thought that daily text messaging would help remind them to take their medications in diverse settings.

> If you work and you have a busy job, I think text messaging would be very effective, very good [at helping you remember to take ART medications]… Even if you are at home, it's also good, because you can forget, watch TV or sleep, but the text reminds you.—42 year old HIV-positive female who injects drugs.

Others liked the idea of using text messaging to monitor ART adherence because it made them feel like someone cared about them. Particularly for participants who reported feeling socially isolated or ostracized because of their HIV diagnosis, they thought text messaging would be a way to feel more connected and would evoke a sense that healthcare providers were investing time and effort in their treatment and showing that they cared about them.

> Answering text messages [to monitor ART adherence] would be easy and simple. And it would be nice to feel that someone cares about me.—42 year old HIV-positive male who injects drugs.

Other participants did not want to use text messaging. Several were worried about privacy concerns and disclosing their HIV status to family, friends, and co-workers. The ease with which others could access or read messages on a person's phone was seen as a significant limitation of using text messaging to monitor and encourage ART adherence.

> I don't like it…Women here are snoopy. They can get on your phone and read [your text messages]. Mothers and boyfriends are the same way. And then scandals will start [if they read your texts about HIV treatment].—44 year old HIV-positive female who injects drugs.

There were others who were worried about logistical concerns around responding to text messaging for adherence monitoring. These concerns included using up too much money on their phone plans or not having enough money to respond to texts, not having their phone with them, losing their phone, having their phone battery die, or not having time to respond to texts and continuing to receive constant reminders.

> In theory, yes, [text messaging] would be convenient. But to be honest, I had four different phones over the summer. I lost a phone, then a phone broke, etc. What then? But in principle, yes, [text messaging could be effective].—43 year old HIV-positive male who injects drugs.

In addition, within couples, individuals' views on the acceptability of using text messaging to monitor adherence frequently differed. For example, one HIV-positive woman said:

> I don't know where I will be when I get this text message. I don't want someone near me to see that text. We have a lot of curious people. 'What is that? Who's that from?' No.—47 year old HIV-positive female who injects drugs.

However, her HIV-positive male partner was very enthusiastic about using text messaging to monitor ART adherence. He said:

> I think text messaging is the best [method of monitoring ART adherence], because I'm more familiar with a mobile phone, and it is always near me. With text messaging, it's already clear what to do and what not to do. And on the phone there's also a count. The phone counts how many "Ok" texts you send, so it's possible to go back and check [your adherence].—50 year old HIV-positive male partner who injects drugs.

Daily Diaries

Some participants thought that daily diaries would be helpful for some people, but not for others. One woman talked about how she would not like to use daily diaries (on either paper or a smartphone), but that daily diaries were helpful for her husband.

> My husband did this earlier. He had a notebook, and on the calendar he marked a plus sign if he took his medicine that day, and a minus if he didn't take his medicine. For him, it was effective. He started out [using a daily diary]. But for others, I don't know. Some have calendars to remind them, others have mothers, grandmothers, or even pill boxes. In my opinion, all methods that are simpler will always be more effective and always help, especially in the beginning when a person is not yet used to taking pills.—44 year old HIV-positive female who injects drugs.

Her husband also discussed how a simple handwritten daily diary was helpful in improving his ART adherence.

> The more medications you have, the more complicated it becomes. I had to write down and check of which medications I took daily to keep track of them. I wrote down how many pills were in each bottle and the date when they should inish. It can happen that a person forgets whether they took their medication that day, especially if they have a lot of pills to take. It even happened to me. A person can take their medicine and then forget, in an hour for example, whether they took it. Maybe he was busy, quickly took his medications, then rushed on and then doesn't remember later whether he took his pills. If you don't keep track, it's difficult to remember when you took the pills and how many you are supposed to have left. Therefore, [daily diaries] are convenient.—48 year old HIV-positive male partner who injects drugs.

A number of participants were open to using daily diaries through a smartphone application; however, others expressed reservations about tracking ART adherence daily through a smartphone app. Some thought it would take too much time to record their adherence every day.

> Why do I need to mark this [on my smartphone]? You need to take your pills, then mark it on your phone. I don't know, that's a lot of time. It's faster to open my bottle, take my pills, then continue about my business.—40 year old HIV-positive female who injects drugs.

Others said they were already used to taking their medications, and therefore, did not want to spend extra time doing something they did not need.

> I don't know. I'm already so used to taking pills. I get up in the morning and take pills at 9 am. Before I go to bed, I take my pills at 9 pm. It's already automatic for me. I don't need a daily diary or something. Maybe I would even take my pills, but then be too lazy to write it down.—47 year old HIV-positive female who injects drugs.

Providers thought daily diaries on smart phones could be helpful for some patients, but due to the low income of many patients, many thought that not all patients would have access to smartphones. This concern was also echoed by some HIV-positive PWID. Several expressed that a daily diary would be helpful, but thought it should not be on paper, not a smartphone.

> I will say that not everyone has smartphones. Many have ordinary phones. But if you were to hang a calendar on the wall so that it's in front of the eyes in a prominent place, then that could be helpful. It can be small, cute, with an insert for the pen, hanging in the kitchen in sight all the time to remind you to take your pills. —43 year old HIV-positive male who injects drugs.

Other participants talked about their lack of familiarity with technology and the difficulty of using smartphones. Several participants expressed not feeling comfortable with newer technology and thought these types of methods of monitoring ART adherence would be too burdensome and ineffective in helping them better adhere to their ART regimens.

> It wouldn't be comfortable for me honestly. My daughter says I have "Shrek" fingers. I try to avoid using smartphones altogether. Sometimes I use a smartphone, but usually I use a regular phone for communication. I don't use gadgets to get on the Internet. If I need the Internet, then it's better to sit at a computer and get on… This method would not suit me.—38 year old HIV-positive male who injects drugs.

As with text messaging, some participants were worried about confidentiality and inadvertently disclosing their HIV status with the use of paper or smartphone versions of daily diaries.

> For example, I will forget to complete this diary. And then, on the other hand, if my son sees it, he'll say, 'What is that calendar for?' There may be unnecessary questions. Therefore, I wouldn't want to use this, it could compromise something. —50 year old HIV-positive female who injects drugs.

Electronic Monitoring Devices

Participants were asked their opinions on electronic monitoring devices (EMDs). Most participants were in support of EMDs and thought they would be helpful in improving ART adherence. Some thought it would be helpful to be accountable to someone else and have someone monitoring their adherence.

> On the contrary, it will be a motivator to take medication because there will be a record if you took it. You aren't responsible if it's just yourself, and you think "Oh, I'm not going to take them". But if you know they are observing you, that will be an incentive.—32 year old HIV-positive female who injects drugs.

Several participants and their partners remarked that EMDs would be improved and more helpful if they also had beepers or alarms to remind participants to take their medications.

> It would be better if the device had a beeper. I think technology is not standing in one place. It's evolving. I think it's already time to develop such a device for convenience.—39 year old HIV-positive male who injects drugs.

Other participants were not opposed to using EMDs to monitor adherence, but did not think such devices would be helpful for them personally. These participants tended to have already been taking ART for many years and had a routine established.

> It's not that I don't like it, it's just that I don't think it will be helpful…I already have an alarm on my phone so that exactly at 10:30 in the evening I take my pills. I don't forget, and I don't take them earlier or later.—43 year old HIV-positive female who injects drugs.

Some participants did not want others monitoring their adherence and viewed EMDs as an invasion of their privacy. A number of participants remarked that they did not want someone tracking them. Other participants were opposed to using EMDs as they felt such devices would violate their confidentiality and disclose their HIV status.

> For example, not everyone knows that B20 [on medical ID card] means that a person has HIV or AIDS, but some know, therefore, I try not to show my medical card to anyone so that they don't find out my HIV status. [If you use this device], suddenly someone's relatives or acquaintances could know that person's status. Why does he need that?—34 year old HIV-positive female who injects drugs.

Several participants recognized that EMDs were not a foolproof method of calculating adherence and that some people could cheat. They recognized that some individuals could open a MEMS Cap or a Wisepill device, but not take the pills, thus, recording an inaccurate result.

> In my opinion, they still don't control adherence. A person who is normal could open the device and take the pills. Or a person could open the device and not take the pills but make it look like they took them.—48 year old HIV-positive male who injects drugs.

The majority of partners, both HIV-positive and HIV-negative partners, thought that EMDs would be helpful in improving ART adherence for their partners (and themselves if they were HIV-positive). Similar to comments from other participants, however, HIV-negative partners in particular remarked about the inability of EMDs to detect whether a patient had actually taken the medication or whether they had simply opened the device. One partner stated,

> On the one hand, I think [EMDs] could be an effective way of improving ART adherence for those who are interested. On the other hand, there is no guarantee that a person won't just open the device, take out the pills, throw them away, and then close the device. (Laughs.) That could also happen.—52 year old HIV-negative female partner who does not inject drugs.

Overall, providers thought EMDs would be an effective method for monitoring ART adherence and encouraging improved adherence. Several commented that it would be helpful to have real-time monitoring of patient adherence to be able to identify adherence problems earlier. Some providers stated that it would be useful to implement such technology on a wide scale.

> Excellent. I think [EMDs] would be convenient for our patients, not only for research projects, but to distribute it on a wide-scale. That would be even better. Especially at the beginning of treatment when the patient is getting used to taking medications, a device like this would be excellent.—female infectious disease doctor at the AIDS Center.

Some providers recognized potential problems with EMDs. A few commented that EMDs may place too much of a time burden on providers if they had to upload adherence information into their computers. Others were worried that EMDs might violate confidentiality if they were used to monitor ART adherence.

> If the patient's family knows their status, they can just put [the Wisepill device] anywhere, but if the family doesn't know the patient's status, where will they hide this device? Where will they put it?—female nurse from the AIDS Center.

In terms of preferences for type of EMD, several participants and partners thought that MEMS Cap was a better method for measuring ART adherence than Wisepill due to the fact that it is less obtrusive and portable.

> I like this device [MEMS Cap], because you can carry it with you. It's not too big to it in your pocket. You can put your tablets there.—39 year old HIV-positive male who injects drugs.

However, some participants and partners preferred Wisepill over MEMS Cap due to the fact that Wisepill automatically transmits a signal and does not need to be brought to healthcare providers or research staff to upload data.

Providers liked both MEMS Cap and Wisepill, though some had a slight preference for Wisepill because it immediately transmits when the device is opened, thus, reducing provider burden in uploading and saving adherence patterns.

> Both devices [Wisepill and MEMS Cap] are good. To me it seems there isn't a big difference. The only thing is this option [Wisepill], where the information is transmitted immediately, is a bit easier for the nurses. They don't have to count or do anything themselves. Everything is done automatically.—female infectious disease doctor at the AIDS Center.

Biological Testing

Both PWID and providers were enthusiastic about using biological measures of adherence. They felt that biological measures would provide a more objective measure of adherence and that, unlike other measures, patients would be unable to "cheat".

Providers felt that biological testing would provide an objective way of measuring adherence and could facilitate discussions about adherence between providers and patients.

> I think it would be convenient. We would no longer need to try and determine whether the patients took their pills or not. We could just say to them, 'Look, here's your results.' Now, the only thing we can say to them is, 'Your CD4 count was this,

> your viral load began to decline, but now your viral load went up, which means you skipped your medicine, you're not taking it.'—female nurse at the AIDS Center.

PWID thought it would be useful and motivating to have the objective feedback that biological testing could provide. A few participants made the comparison to monitoring of other chronic conditions, such as diabetes.

> For example, it's convenient when a person can test their sugar levels. A device shows what blood sugar levels a person has. It would be nice if there was such a device for HIV. Do a finger prick and see if your blood levels have fallen or risen. —39 year old HIV-positive male who injects drugs.

PWID and their partners stated that they would be willing to undergo biological testing for ART adherence on a regular basis, every one to 3 months. A number of PWID commented about the ease and comfort of conducting dried blood spot (DBS) testing to measure ART blood levels.

> [I like that] blood is not taken from your veins, but from your finger. When they take blood from your veins, it's very unpleasant.—51 year old HIV-positive male who injects drugs.

A few participants who disliked needles and giving blood stated that they would prefer to give a hair sample instead of a blood spot sample from a fingerprick.

> [Giving a hair sample] would of course be more comfortable. Don't need to pierce your skin, don't need to give blood. Just a quick snip of hair.—44 year old HIV-positive female who injects drugs.

Other participants did not like the idea of giving hair samples, either because they did not have enough hair or because they did not want to ruin their hair styles. Statements like the one below were common.

> No, I don't like this [giving hair samples]. It would be better to give blood. [Giving hair samples] would ruin my haircut.—50 year old HIV-positive female who injects drugs.

Others perceived the results of hair sampling to be less accurate than the results obtained from DBS sampling. One partner stated,

> DBS is easier to give. And I would believe the results from blood more than hair. I know that medical experts have worked on the hair tests, I know that. But stereotypes exist, and I would trust the results from blood more.—40 year old HIV-positive female partner who injects drugs.

Although some participants recognized advantages to hair sampling, such as the ability to analyze adherence over a longer period, much like the ability to analyze ingestion of illegal drugs over a long period through hair sampling, the majority of participants preferred DBS sampling to hair sampling. Many cited a number of limitations to hair sampling, including that many individuals lacked a sufficient amount of hair to provide an adequate sample size, that frequent hair sampling would ruin participants' hair styles, that it's more difficult to

obtain a proper sample, and the perception that hair sampling results were not as accurate as the results from DBS testing.

Overall, providers also preferred DBS testing to hair sampling. Although they thought both would be useful in providing objective feedback to participants, they thought that DBS testing would be logistically easier.

> I think dried blood spot testing would be better. As I said, what if there is a patient without hair, then what will we do? Or a patient with three hairs and he says, 'No, I'm not giving you my hair.' I think dried blood spot testing would be more suitable. Still, this part also needs to be thought through. You don't want to place a huge financial burden on patients.—female infectious disease doctor at the AIDS Center.

Discussion

We examined preferences for measurement of ART adherence among HIV-positive PWID, their partners, and healthcare providers using qualitative interviews. Our results indicate that both patients and providers were enthusiastic about using different EMDs or biological testing as a way of monitoring adherence levels. Previous studies have found text messaging and mobile applications to be acceptable and feasible among different populations of HIV-infected individuals, including those in the US [45], in sub-Saharan Africa [46], methamphetamine users [36], and HIV-positive drug users and non-drug users in China [47]. As in other studies, this study found many participants expressed enthusiasm over using text messaging or mobile applications to track their adherence. However, among this study population, there was particular concern expressed over privacy issues in relation to text messaging and mobile apps and around lack of technical abilities and the frequency at which phones are lost. While there seemed to be an overall acceptability of using text messaging or mobile apps in ART adherence interventions among this population of PWID, there were some logistical concerns raised that could threaten feasibility. Researchers planning to conduct ART adherence intervention research among PWID may need to provide backup phones or incentives to help encourage participants to avoid losing their phones. Additionally, some PWID, particularly older PWID who are not as familiar with mobile phones, may need to be given additional technical training before the start of an intervention. In addition, several participants expressed concern about inadvertent disclosure of HIV-status and loss of privacy. As these findings and the findings of other studies show, careful consideration is necessary when developing text messages in order to avoid revealing personal or sensitive information to others who may gain access to participants' phones. Effective strategies used by other researchers, such as showing PWID the text messages that will be used in studies and assuring them that they do not contain HIV or drug-related information, can help alleviate participant concerns.

EMDs have been shown to improve adherence in a number of studies [11, 12, 14, 38]. However, there are a number of concerns around the use of EMDs, including privacy concerns about real-time monitoring and logistical concerns in implementing monitoring technology in real-world settings. Although Sabin et al. [47] found high acceptability of

EMDs among ART patients in China and few concerns about being monitored, several participants in this sample were concerned about being ‘watched’ or ‘tracked’ by EMDs. A number of participants were concerned that EMDs would violate their confidentiality or disclose their HIV-status to others. The increased concern about being tracked or monitored through EMDs among this population may be due to their engagement in an illegal and stigmatized behavior (i.e., injection drug use) and the cultural context in which they live (i.e., a post-Soviet country where government tracking has historically been high and often resulted in negative outcomes). However, other researchers have shown that these participant concerns can be overcome and that it is possible to use EMDs effectively among stigmatized populations engaging in illegal activity or living in countries where government distrust is high [14, 41].

Additionally, there are a number of logistical challenges to implementing EMD. Other studies have found a number of deployment challenges, including the need to keep cellular phones and EMD charged, gaps in network coverage, low education and literacy levels, obtrusiveness of the device, and cost [15, 30]. Providers in this study were concerned that some EMD devices (e.g., MEMS Cap) would place too much of a time burden on healthcare providers if providers had to upload adherence information through a cable connection to a computer every time the patient visited. In addition, patients worried that they would forget to take the device to every clinic visit to upload their adherence data. Both providers and patients preferred EMD devices that could automatically transmit signals. Participants worried that EMD devices could potentially disclose their HIV-status, and stressed the importance of having devices that were not obtrusive and looked like a normal pill bottle. Providers and participants were also concerned about cost and worried about the ability to replace the devices if they were lost, stolen, or damaged. As suggested by others [15], additional development of technology to improve battery life of EMDs or their design may address some of the logistical challenges around implementation of EMDs. Indeed, technological advances by some EMD companies have already erased the need for patients to bring the device with them to visits (thereby also reducing provider burden) and enabled the device to automatically transmit signals. An additional suggestion to reduce costs and increase scalability of EMDs include limiting implementation of these devices among select populations or among patients that are most in need, such as those who have not achieved viral suppression or are experiencing viral rebound [15]. An increased use and production of EMD devices may also serve to drive costs down. Additionally, if non-research funds were to become available for EMDs (such as through federal funding, insurance, or international aid), the uptake of these devices could more easily expand to clinical settings outside of research studies.

Pharmacologic studies have established a clear relationship between dose and drug levels in dried blood spot specimens [48] and hair [32]. Hair and dried blood spots are two promising biomarkers of longer term ART adherence that are relatively easy to collect. EMDs show promise to detect adherence lapses in real-time and could drive biological testing. However, in order for EMDs and drug-level feedback to be cost-effective, these strategies would need to be adopted on a broader scale to bring costs down, and procedures would need to be streamlined [30]. Neither of these strategies are currently used in Kazakh-stan due to high costs and lack of availability, but could potentially be used in the future if costs were

sufficiently decreased. The effort required to widely implement such strategies may prove beneficial to many individuals. Studies indicate that providing adherence feedback to patients can improve their adherence to treatment [41, 49]. A majority of patients in our study said that having EMDs or biological measures of ART medication levels would be useful in helping them adhere to their medications and know if they were sufficiently adherent. Participants expressed a desire for quantifying drug levels as reassurance that they had sufficient medication in their bodies to be effective. Further studies are needed to assess whether using biological testing and/or EMDs results in a long-term increase in adherence.

This study is limited in that it only asked participants about their preferences for ART adherence measurement, rather than having participants test each of these strategies and provide their feedback. In addition, the study was conducted among a small sample of HIV-positive PWID, their intimate partner, and healthcare providers in one city in Kazakhstan, so our ability to generalize beyond the study population is limited. However, the results are informative for the development of future studies and intervention programs. Given the enthusiasm that participants exhibited toward ART adherence measures, particularly EMDs and biological testing, we recommend including some of these measures in future studies among PWID.

Current suboptimal adherence to ART threatens the benefits of scaling up HIV treatment and prevents the achievement of the UNAIDS 90-90-90 goals. Therefore, it is crucial that additional focus is placed on ART adherence in the HIV response. Providing adherence feedback to patients on a regular basis could facilitate discussion about adherence challenges and improve adherence. Incorporating such a strategy into future work would build on other adherence research that used patient-level data to create opportunities for discussion about ART adherence [41]. Future research needs to evaluate the feasibility of providing quantitative drug levels in upcoming ART adherence studies and implementation programs and to assess the impact of sharing these results on short- and long-term adherence.

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Table 1

Demographic characteristics of HIV-positive PWID and their intimate partners in Almaty, Kazakhstan, 2017

Variable	HIV-positive PWID (index cases) (n = 20)	Partners of HIV-positive PWID (n = 18)
Age *(mean, SD, range)*	42 (6.5, 30–52)	42 (7.1, 30–52)
Year diagnosed with HIV *(mean, SD, range)*	2008 (4.1, 2001–2016)	2009 (5.2, 2002–2017)
Gender (*n* %)		
Female	9 (45.0%)	9 (50%)
Male	11 (55.0%)	9 (50%)
Employment status (*n*, %)		
Full-time	8 (40.0%)	9 (50%)
Part-time	2 (10.0%)	1 (5.6%)
Seasonal/periodic	6 (30.0%)	3 (16.7%)
Unemployed	4 (20.0%)	5 (27.8%)
Education level (*n*, %)		
Less than high school diploma	1 (5.0%)	0 (0.0%)
High school diploma	13 (65.0%)	10 (55.6%)
Some college	3 (15.0%)	7 (38.9%)
College degree	3 (15.0%)	1 (5.6%)