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EHEALTH AND HIV (J STEKLER AND D KATZ, SECTION EDITORS)

Ingestible Electronic Sensors for Monitoring Real-time Adherence to HIV Pre-exposure Prophylaxis and Antiretroviral Therapy

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Abstract

Purpose of Review This review summarizes the recent advancements and future directions of digital pill systems (DPS) — which utilize ingestible sensors to directly measure medication ingestion events in real-time — in the context of HIV prevention and treatment.

Recent Findings Two DPS are cleared by the US Food and Drug Administration. The bioequivalence and stability of digitized pre-exposure prophylaxis (PrEP) and antiretroviral therapy (ART) have been established, and pilot studies have demonstrated the feasibility and acceptability of using DPS for PrEP and ART adherence measurement. Important bioethical and implementation considerations have been identified for future clinical trials. Continued technological advancement may reduce barriers to use, and integration of DPS into behavioral interventions may facilitate adherence improvement efforts.

Summary DPS represent an innovative tool for PrEP and ART adherence measurement. Future work will optimize the technology to reduce operational barriers. DPS have significant potential for expansion across a diverse array of diseases, though key bioethical considerations must be examined prior to large-scale implementation.

Keywords Ingestible sensors · Digital pill system · Medication adherence, Electronic adherence · Pre-exposure prophylaxis · Antiretroviral therapy

Introduction

Suboptimal adherence to pharmacotherapy contributes to significant morbidity and mortality across disease states and costs the US health care system approximately $528 billion per year [1]. The initiation and persistence of HIV pre-exposure prophylaxis (PrEP) and antiretroviral therapy (ART) as HIV prevention and treatment are two pillars of the national strategy to end the HIV epidemic [2]. For both PrEP and ART regimens, maintaining consistent adherence over the long-term is important for preventing disease acquisition and transmission, as well as reducing hospitalizations and medical costs [3, 4]. While advances in PrEP and ART have created opportunities for forgiveness around missed doses (e.g., event-driven dosing and prevention-effective adherence [5]), there continues to be an important need to develop tools for accurately measuring adherence behavior.

A variety of strategies has been used to measure adherence to PrEP and ART, including indirect approaches such as self-report, pharmacy refills, and pill counts, and direct approaches like directly-observed therapy (DOT),

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video-based observed therapy (VOT), and measurement of drug concentrations in biological matrices [3, 6, 7]. Each of these tools is subject to limitations, particularly those that offer surrogate measurements of adherence (e.g., self-report, pharmacy refill data, and pill counts) or that provide direct verification of adherence but are costly to implement and difficult to scale (e.g., DOT, VOT, and pharmacologic measures) [3]. Additionally, many traditional approaches measure aggregate adherence over time, thereby missing key events that may be associated with transient lapses in adherence. Moreover, individual-level variations in adherence may represent key junctures at which to deliver adherence interventions to mitigate the development of ingrained nonadherence behaviors.

Advancements in wireless technologies have led to an increased focus on leveraging connected devices in an Internet of Things (IoT) for medication adherence measurement. Some systems measure adherence via surrogate actions that are suggestive of pill-taking behaviors. For example, medication event monitoring system (MEMS) caps indirectly measure adherence by detecting when a pill bottle cap has been opened and registering the date and time of each such event [8]. Another approach, 99DOTS, utilizes customized medication blister packaging containing a unique phone number behind each pill, which are revealed once opened; users then call the unique number to report each ingestion, and the data are electronically recorded by a computer program [9]. Other surrogate measurement tools involve the use of accelerometry and gyroscopic data from wearable electronic sensors to detect the opening of pill bottles and subsequent ingestion behavior [10], as well as piezoelectric sensors and magnets that can detect swallowing [11]. Wireless technologies have also led to advances in direct adherence measures, including smartphone-based artificial intelligence platforms that use facial recognition and computer vision to confirm medication ingestion events via smartphone cameras [12].

One commonality across many IoT systems is their focus on processes outside of the body that correlate with the act of taking a medication. By contrast, ingestible electronic sensors enable the direct detection of ingestion events from within the gastrointestinal tract. A medication is overencapsulated or coencapsulated with an ingestible sensor, which is activated within the stomach and transmits a signal indicating detection of an ingestion. Other ingestible sensor-based systems deliver a medication coupled with various sensors that can detect physiological parameters, such as pH or gasses, which mark the location of the system within the gastrointestinal tract [13, 14]. While most ingestible sensor systems remain in preclinical stages, several technologies have advanced to human trials and are currently being studied as adherence measurement tools across a variety of disease states [15, 16••].

This review will focus specifically on ingestible electronic systems that directly measure medication ingestion events via stomach-activated sensors. While several such systems exist across varying stages of development, this review will summarize recent advances in the use of digital pill systems (DPS) for adherence measurement in HIV prevention and treatment.

Digital Pill Systems (DPS)

Digital pill systems (DPS) comprise a small radiofrequency or electronic sensor integrated into a standard gelatin capsule, which overencapsulates a medication (e.g., PrEP or ART) to form a digital pill [17–19]. Gelatin capsules can be resized using commercially available capsules. Following ingestion, in DPS that utilize a radiofrequency sensor, the sensor inside the digital pill is activated by chloride ions in gastric fluid, emitting a radiofrequency signal off the body, which is then acquired and recorded by a wearable device (reader). Advancements in the design of the reader, as well as in signal boosting, have allowed the reader to take multiple forms, including a wrist-borne device, and a device worn around the neck on a lanyard during use. In DPS that utilize an electronic sensor, activation of the sensor in the stomach produces a specific electrochemical signal, which is acquired by a cutaneous wearable patch. In both types of DPS, the reader (or the patch) transmits ingestion data via low energy Bluetooth (BLE) to a smartphone interface and online platform, allowing both patients and clinical stakeholders to view on-demand adherence information (Fig. 1).

Regulatory Status of DPS

As of this review, two companies have developed and commercialized DPS and have obtained clearance by the US Food and Drug Administration (FDA) for use in humans. Similar to xenobiotics, which require rigorous safety data prior to FDA approval, medical devices must demonstrate that they are similar enough to previous devices reviewed by the FDA (predicate devices), or produce safety data for expected risks based on the device classification. After meeting these guidelines, DPS have then obtained FDA clearance for marketing. Prior to clearance, the use of a novel DPS can still occur in human trials, but the safety determinations of such devices are typically made by individual institutional review boards. In 2013, the FDA designated DPS as Class II medical devices, providing a regulatory pathway to obtain clearance for these systems by commercial companies [20].

The first FDA-cleared DPS was the Proteus Digital Health Feedback System (DHFS; Proteus Digital Health, Redwood City, CA), which received clearance through

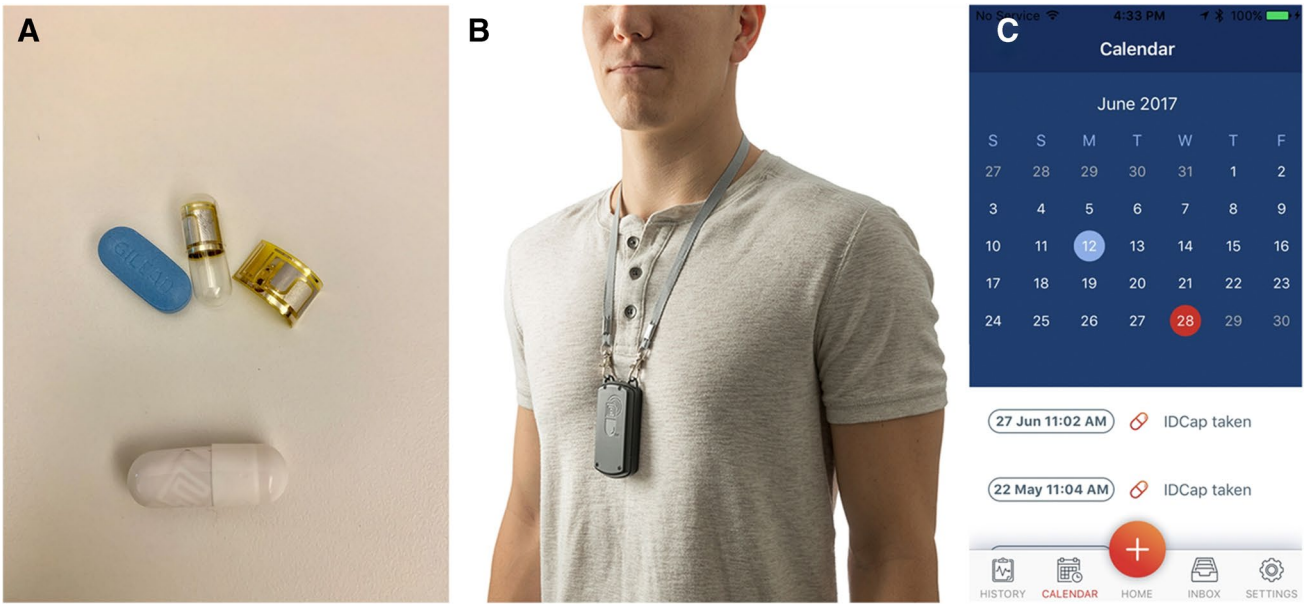

Fig. 1 Components of a digital pill system (DPS). The digital pill system (DPS) comprises an ingestible electronic radiofrequency emitter integrated into a gelatin capsule, which overencapsulates a medication to form a digital pill (**A**). The radiofrequency emitter is activated upon ingestion, and transmits a signal to a wearable reader device (**B**). The reader captures, stores, and sends the ingestion data to a patient-facing smartphone application (**C**). Images courtesy of etectRx, Inc. (Gainesville, FL)

an FDA de novo 510(k) in 2014 [21]. The Proteus system utilizes a cutaneous receiver patch, worn on the abdomen, to acquire ingestion data from activated ingestible sensors following ingestion. The Proteus ingestible sensor can be coencapsulated or integrated into the medication itself during manufacturing process. Importantly, the combination of the Proteus DHFS with aripiprazole then gained FDA approval in 2017 as a drug-device combination product to measure adherence to aripiprazole [22]. Notably, Proteus Digital Health filed for bankruptcy in June 2020 [23], and its assets were acquired by Otsuka America Pharmaceutical Inc. in August 2020 [24].The second FDA-cleared DPS, the etectRx ID-Cap system (etectRx, Inc., Gainesville, FL), was approved as an adherence measurement tool in 2019 through a similar FDA pathway [25] and uses an off-body wearable reader device to detect ingestions via an overencapsulated radiofrequency sensor.

Drug Bioequivalence and Stability of DPS Components

Several investigations have evaluated the bioequivalence and stability of medications used with DPS to ensure that gelatin capsules and radiofrequency emitters do not interfere with drug release [26, 27, 28••, 29]. Based on US FDA guidance [30, 31] around bioequivalence, two single-dose, randomized crossover trials in healthy volunteers have measured the area under the curve (AUC) and maximum concentration (C_{max}) of coencapsulated or overencapsulated PrEP formulations to evaluate bioequivalence with standard, unencapsulated PrEP. The first trial used the Proteus DHFS and randomized participants to coencapsulated or standard FTC/TDF ($n = 24$, mean age 28, 46% male) [26]. A non-compartmental analysis for AUC and C_{max} demonstrated the bioequivalence of both the TDF and FTC components in coencapsulated FTC/TDF compared to standard FTC/TDF [26]. A second study, involving the etectRx ID-Cap system, examined the bioequivalence of the tenofovir component of overencapsulated emtricitabine/tenofovir/rilpivirine, compared to standard tablets, in a similar single-dose, randomized crossover trial ($n = 10$, mean age 27, 20% male) [27]. Analysis of AUC and C_{max} demonstrated the bioequivalence of the overencapsulated tenofovir component of tenofovir/rilpivirine/emtricitabine, as compared to the standard, unencapsulated formulation [27].

An additional trial evaluated eight formulations of ART when coencapsulated with the Proteus DHFS sensor (i.e., FTC/TDF, FTC/tenofovir alafenamide [TAF]; efavirenz [EFV]/FTC/TDF; abacavir [ABC]/lamivudine [3TC]; dolutegravir [DTG]/ABC/3TC; FTC/rilpivirine [RPV]/TAF; elvitegravir [EVG]/cobicistat [COBI]/FTC/TAF; and bictegravir [BIC]/FTC/TAF) [28••]. Participants were people with HIV (PWH) on a stable ART regimen for at least 3 months, with undetectable viral loads ($n = 48$, mean age 50, 92% male). AUC and C_{max} values were not statistically significantly different from package insert or literature values for all formulations except the C_{max} of FTC/TDF, BIC,

and RPV. In a follow-up crossover trial of FTC/TDF and BIC/FTC/TAF, geometric mean ratios of AUC and C_{max} values were calculated. In this trial ($n = 12$, mean age 51, 100% male), coencapsulated FTC/TDF did not meet bioequivalence criteria (90% *CI* of each ratio being 80–125%), but bioequivalence was established for BIC, FTC, and TAF in the BIC/FTC/TAF formulation [28••].

Finally, a single study has investigated the stability of the ingestible sensor component of a DPS in pharmacy storage conditions [29]. Following a pilot demonstration trial — involving the etectRx ID-Cap system for PrEP adherence measurement [16••] — undispensed, overencapsulated FTC/TDF pills were stored in a temperature-controlled environment for 400 days, disassembled, and inspected for signs of damage. Ninety undispensed digital pills were recovered from the trial, from which 17 pills were randomly selected for stability testing and activated in simulated gastric fluid. A passing evaluation was defined as (1) activation of the radiofrequency emitter within 30 min of immersion, (2) broadcasting of the radiofrequency signal for 10 min, and (3) reader acquisition of the signal. No physical damage was recorded, and all 17 digital pills passed the stability test (activation time: mean 3.3 min, SD = 1.5; active broadcasting time: mean 47.7 min, SD = 1.8) [29].

Taken together, these investigations have demonstrated the bioequivalence of multiple PrEP and ART formulations when used with a DPS [26, 27, 28••], as well as the stability of ingestible sensor components following long-term storage over 12 months [29].

PrEP Studies Involving DPS

Several investigations to date have assessed the feasibility and acceptability of DPS for PrEP adherence measurement among prospective and actual users of the technology (Table 1). These studies have primarily been conducted among cisgender men who have sex with men (MSM) and have sought to understand attitudes toward DPS use, willingness to engage with the technology (among prospective users), real-world experiences with operating a DPS (among actual users), potential barriers to implementation, and suggested improvements for optimizing the technology [16••, 18, 19, 32••, 33]. Two additional studies, currently ongoing, are investigating the feasibility and acceptability of using a DPS for measurement of PrEP adherence [34, 35].

Prospective Users of DPS for PrEP

In one investigation, qualitative interviews were conducted among cisgender, HIV-negative MSM currently on PrEP or eligible for PrEP, who reported non-alcohol substance use ($n = 30$) [18]. Interviews explored perceptions of DPS technology, design features, safety considerations, and perceived uses of DPS for adherence measurement. Participants found the DPS (etectRx ID-Cap system) to be acceptable, innovative, and valuable for increasing accountability around PrEP adherence. Access to real-time, individualized adherence data was identified as a facilitator to engaging with the technology. The majority of participants reported a willingness to use a DPS for PrEP adherence measurement in the research context, particularly if such studies were likely to benefit the MSM community. Participants described the design of the wearable reader as a barrier to use, due to its size and the perceived hassle of charging and transportation. With respect to safety, some participants worried about potential adverse side effects of ingesting digital pills (i.e., radiofrequency emitter component) and noted that providing additional safety information during the initial technology training would help to assuage concerns before use; notably, this study was conducted prior to FDA 510 k clearance of the etectRx ID-Cap system in 2019 [36]. New PrEP users and individuals who use substances and/or engage in casual sexual encounters, as well as frequent travelers and those with unstable living situations, were identified as optimal users of DPS with PrEP [18].

A separate qualitative analysis as part of the same investigation [18] focused on prospective users' preferences around data privacy and data sharing in the DPS context [32••]. Participants ($n = 30$) reported some privacy-related concerns surrounding adherence data recorded by the DPS. They stressed the need for data security features that would ensure the protection of adherence data. These individuals were still willing to engage with a DPS, not only for gaining insight into their own PrEP adherence, but also for the purposes of sharing PrEP adherence data with select individuals. In particular, participants were interested in sharing data with clinical care teams to increase both their own accountability for maintaining adherence, as well as their providers' capacity to monitor their adherence between appointments. Participants were also open to sharing adherence data with long-term relationship partners, which was seen as potentially helpful for improving trust and transparency, including within the context of serodiscordant partnerships. Attitudes about sharing data with casual sexual partners were mixed; while some reported that this could make such encounters more transactional, others noted that using a DPS would better enable individuals to approach casual sexual interactions with confidence and protect themselves against HIV and could also increase the sense of connection and comfort between new partners. Participants did not raise any privacy or confidentiality concerns with respect to the reader itself [32••].

In another study, qualitative focus group discussions were conducted to inform the development of a cognitive behavioral therapy–based adherence intervention (LifeSteps) [37,

Table 1 Studies involving DPS for PrEP adherence measurement

Authors	Study design	Population	DPS studied and intervention architecture	Key findings
Prospective users of DPS for PrEP				
Chai et al., 2021 [18]	Qualitative interviews	$N=30$ adult, cisgender, HIV- MSM, on or eligible for PrEP, non-alcohol substance use in past 6 months	etectRx ID-Cap System with off-body wearable reader; no interventions	•DPS viewed as acceptable and useful for increasing accountability for PrEP adherence •Majority willing to use DPS in PrEP research •reader design seen as primary barrier to DPS use •Some concerns about potential adverse effects from ingestion of digital pill •DPS most useful for new PrEP users, substance users, and those who engage in casual sex
Goodman et al., 2022 [32••]	Qualitative interviews (sub-analysis from above study [18])	$N=30$ adult, cisgender, HIV- MSM, on or eligible for PrEP, non-alcohol substance use in past 6 months	etectRx ID-Cap System with off-body wearable reader; no interventions	•Some DPS-related privacy concerns •Emphasized need for robust data security measures to protect personal data •Largely willing to share DPS data with primary care providers and long-term relationship partners •Mixed attitudes toward sharing DPS data with casual sexual partners
Chai et al., 2022 [19]	Qualitative focus group discussions	$N=20$ adult, cisgender, HIV- MSM, on or eligible for PrEP, stimulant use in past 6 months	etectRx ID-Cap System with off-body wearable reader; development of intervention respondent to ID-Cap System data	•Corrective feedback and contingent reinforcement messages viewed as acceptable adherence interventions linked to DPS •LifeSteps booster messages useful for contextualizing nonadherence events •Substance use-related messages perceived as less acceptable and a barrier to DPS use
Actual users of DPS for PrEP				
Chai et al., 2022 [16••]	90-day, open-label pilot demonstration trial, including qualitative exit interviews	$N=15$ adult, cisgender, HIV- MSM, on FTC/TDF as PrEP, non-alcohol substance use in past 6 months	etectRx ID-Cap System with off-body wearable reader; no linked interventions	•DPS viewed as a feasible, acceptable, accurate tool for PrEP adherence measurement •DPS engagement consistent over 90-day period •Overall acceptance of DPS, but reader identified as main barrier to use of technology •Ingestion events recorded by DPS 98% of the time, when operated properly •DPS-detected PrEP adherence correlated with pill counts and dried blood spots

Table 1 (continued)

Authors	Study design	Population	DPS studied and intervention architecture	Key findings
Chai et al., 2021 [33]	Development of DPS training program (part of above pilot trial [16••])	$N=15$ adult, cisgender, HIV- MSM, on FTC/TDF as PrEP, non-alcohol substance use in past 6 months	etectRx ID-Cap System with off-body wearable reader; structured text-message based teaching program	•Participants responded to 91% of check-in messages during remote follow-up portion of training program •Of 7 technical issues, 3 resolved via text/email, 3 via phone, and 1 via in-person evaluation •Both in-person and remote follow-up portions of training program seen as valuable •DPS technology refresher sessions and additional written training materials requested
Browne et al. [34]	12-week, prospective, single-arm, open-label intervention study (ongoing; NCT03693040)	Target $N=100$ adult, non-pregnant, HIV-, on or eligible for FTC/TDF as PrEP	Proteus DHFS with on-body reader	Results pending study completion
Chai et al. [35]	6-month pilot randomized controlled trial (ongoing; NCT03512418)	Target $N=60$ adult, cisgender, HIV- MSM, on or eligible for FTC/TDF as PrEP, moderate to severe substance use disorder	etectRx ID-Cap System with off-body wearable reader; adherence intervention based on digital pill data	Results pending study completion

PrEP, pre-exposure prophylaxis; *DPS*, digital pill system; *MSM*, men who have sex with men; *FTC/TDF*, emtricitabine/tenofovir disoproxil fumarate; *Proteus DHFS*, digital health feedback system

38], to be used in tandem with a DPS (etectRx ID-Cap system) in order to measure and improve PrEP adherence based on real-time data [19]. Participants — adult, cisgender, HIV-negative MSM, on or eligible for PrEP, who reported stimulant use in the past 6 months — provided feedback on four messaging components of the proposed intervention ($n=20$). Contingent reinforcement (CR) messages — confirming the successful detection of ingestions — were acceptable, and a neutral tone was preferred to a positive one. Corrective feedback (CF) messages — soliciting the reason for missed ingestions — were viewed as helpful for promoting a sense of responsibility for PrEP adherence, particularly if worded concisely and delivered in a more negative tone. LifeSteps booster messages — displaying a personalized solution to the applicable barrier to one's PrEP adherence (per their response to CF messages) — were perceived as useful for contextualizing nonadherence events. Finally, substance use–related messages — sent following nonadherence events due to substance use — were less acceptable. Participants reported that such messages could be intrusive and stigmatizing and noted that issues related to substance use would be better addressed via phone or in-person with their care teams [19].

Actual Users of DPS for PrEP

One single-arm, open-label, and pilot demonstration trial has evaluated the feasibility, acceptability, and accuracy of a DPS for measuring PrEP adherence among individuals using a DPS in the real world [16••]. Participants ($n=15$) — adult, cisgender, HIV-negative MSM, taking oral FTC/TDF as PrEP, with self-reported non-alcohol substance use in the past 6 months — used a DPS (etectRx ID-Cap system) and ingested PrEP digital pills for 90 days. They completed quantitative assessments, monthly pill counts of unused digital pills, timeline followback discussions to contextualize DPS-detected nonadherence events, dried blood spots (DBS) to quantify tenofovir diphosphate (TFV-DP), and a qualitative user experience exit interview. Findings indicated that the DPS was a feasible and acceptable means of measuring PrEP adherence; DPS engagement remained consistent over the study period, and participants reported overall acceptance of the technology, though the wearable reader was identified as the main barrier to use. The DPS accurately recorded PrEP ingestion events 98% of the time, when operated properly, and there was a strong positive correlation between DPS-detected adherence and pill counts ($r=0.91$; 95% *CI*: 0.75 to 0.97; $p<0.001$), as well as between DPS-detected adherence and TFV-DP in DBS samples at two timepoints ($r=0.85$, 95% *CI*: 0.57 to 0.95; $p=0.0002$ at month 1; $r=0.75$, 95% *CI*: 0.17 to 0.94; $p=0.0197$ at month 3) [16••].

As part of the same pilot demonstration trial [16••], a training program was developed to standardize the instruction and onboarding process for DPS users [33]. The program included both in-person and remote follow-up components [39–41]. During the in-person training, participants ($n=15$) were introduced to the DPS (Fig. 1), instructed on operation the technology, and assisted with setup of the smartphone application. Participants then ingested their first PrEP digital pill under direct observation by study staff. Remote follow-up consisted of three check-in text messages (on days 1, 4, and 6 post-enrollment) prompting participants to report technical issues and request support. All issues were resolved via a systematic process, whereby troubleshooting was first attempted via text message and/or email, followed by phone-based assistance. If still unresolved, issues were addressed in person. Overall, participants responded to 91% of check-in text messages and reported a total of seven technical issues (17%), of which three were resolved via text message and/or email, three via real-time phone support, and one via an in-person evaluation. Participants reported that both components of the training program were valuable, and suggested additional technology refresher sessions at follow-up visits and the provision of improved written training materials at enrollment [33].

Finally, two ongoing studies are currently utilizing DPS to measure PrEP adherence [34, 35]. One is a 12-week, prospective, single-arm, and open-label intervention study (target $n=100$), enrolling adult, non-pregnant, and HIV-negative individuals who are on or eligible for oral FTC/TDF as PrEP to use the Proteus DHFS. Outcomes include PrEP adherence as measured by the DPS, system accuracy, and overall feasibility and acceptability of the DPS [34]. The other is a 6-month pilot randomized controlled trial (target $n=60$) testing the feasibility and acceptability of a personalized, smartphone-based intervention — which responds to real-time PrEP ingestion patterns detected by the etectRx ID-Cap system — as well as the potential for an effect of the intervention on adherence behavior. Participants are adult, cisgender, and HIV-negative MSM who are on or eligible for PrEP and have moderate to severe substance use disorder [35].

ART Studies Involving DPS

To date, two studies have utilized DPS in the HIV treatment context, the primary goal of which has been to assess the feasibility, acceptability, and barriers associated with using a DPS to address ART adherence among PWH (Table 2) [42••, 43]. In addition, one ongoing investigation is evaluating and assessing the use of a DPS for ART adherence measurement among hospitalized PWH [44], and a second investigation is evaluating the relationship

Table 2 Studies involving DPS for ART adherence measurement

Authors	Study design	Population	DPS studied and intervention architecture	Key findings
Daar et al., 2019 [42••]	16-week, open-label pilot study	$N = 15$ adult PWH, in HIV care, on ART with suboptimal adherence	Proteus DHFS with on-body reader; text message intervention based on detected nonadherence	•Most reported that patch was comfortable; one had skin reaction and stopped wearing patch early •Majority were comfortable receiving reminder text messages, but perceived helpfulness of varied •Most found the DPS to be helpful overall, but reported satisfaction with the system was mixed
Kamal et al., 2020 [43]	Qualitative interviews (part of above pilot study [42••])	$N = 15$ adult PWH, in HIV care, on ART with suboptimal adherence $N = 6$ HCPs providing HIV care in clinic where pilot study [42••] conducted	Proteus DHFS with on-body reader; no intervention	•Some PWH had a positive experience using DPS, reporting that system helped improve their ART adherence, and that they would recommend it •Other PWH found DPS to be inconvenient to use, and identified cutaneous patch as barrier to DPS operation •PWH reported mixed attitudes toward coencapsulated pills and text message reminders after nonadherence •HCPs would recommend DPS to patients with ART nonadherence for short-term use (e.g., up to 6 months) •HCPs viewed text message reminders and awareness of provider monitoring as most important components •HCPs identified discomfort and stigma from patch, and lack of internet, as potential barriers to DPS use
Browne et al. [44]	16-week, prospective, single-arm, open-label intervention study (ongoing; NCT04418037)	Target $N = 30$ adult PWH, non-pregnant, on or eligible for ART, hospitalized at study site	Proteus DHFS with on-body reader; no intervention	Results pending study completion
Castillo-Mancilla et al. [45]	16-week observational cohort study (ongoing; NCT04065347)	Target $N = 180$ adult PWH, non-pregnant, on or initiating TAF	etectRx ID-Cap System with off-body wearable reader; no intervention	Results pending study completion

ART, antiretroviral therapy; *PWH*, people with HIV; DPS, digital pill system; *HCP*, health care provider; *Proteus DHFS*, digital health feedback system; TAF, tenofovir alafenamide

between DPS-detected ART adherence and ART drug concentrations in the blood [45].

A 16-week, open-label pilot study assessed the functionality and acceptability of a DPS for ART adherence measurement among PWH ($n=15$) [42••]. Participants — adult PWH in HIV care, currently on ART, with suboptimal adherence (defined as < 90% self-reported adherence over the past 28 days, or clinician-reported suboptimal adherence over the past 6 months based on missed appointments or increases in viral load) — used the Proteus DHFS with ART for 16 weeks and received personalized reminder text messages 1 h after each missed dose; messages were resent as pre-dose reminders to those with prior nonadherence. Quantitative assessments at weeks 4, 8, 12, and 16 evaluated experiences using the DPS and potential adverse events. Most participants (at least 75% at each assessment) reported that the patch was comfortable; one had a significant skin reaction and stopped wearing the patch early. The majority (at least 75% at each assessment) were comfortable receiving text messages after nonadherence, but the perceived utility of these messages varied, with 71.4% at week 4, 50% at week 8, 55.6% at week 12, and 33.3% at week 16 agreeing the messages were helpful. Overall, most participants (at least 67% at each assessment) found the system to be useful, but satisfaction was mixed, with 57.1% at week 4, 83.3% at week 8, 55.6% at week 12, and 66.6% at week 16 reported being satisfied with the DPS [42••].

As part of the same pilot study [42••], qualitative interviews were conducted with PWH ($n=15$), as well as with HIV health care providers (HCPs) at the study site ($n=6$), to explore experiences with and attitudes toward using DPS for ART adherence monitoring [43]. Some PWH reported that they would recommend the DPS to others, noting that the system had helped to improve their ART adherence skills. Others described the DPS as inconvenient, with many identifying the cutaneous patch as a barrier to operation. Attitudes toward other DPS components were also mixed; some participants were comfortable ingesting the coencapsulated pills, while others felt they should be smaller. Text messages following ART nonadherence were useful to some participants for staying on track, but anxiety-provoking for others. HCPs reported a willingness to recommend the DPS for short-term use (e.g., up to 6 months) for patients with demonstrated ART nonadherence and considered text message reminders to be the most important component of the system. HCPs also noted that patients' knowledge of remote monitoring by their providers could facilitate and motivate continued adherence. On the other hand, HCPs also identified a number of potential barriers to DPS operation, including physical discomfort from wearing the cutaneous patch, stigma associated with wearing the patch in front of others, and lack of access to a stable internet connection to obtain data from the system [43].

Currently, several ongoing investigations are utilizing DPS to measure ART adherence in PWH [44, 45]. One — a 16-week, prospective, single-arm, and open-label intervention study (target $n=30$) — is evaluating the feasibility of using a DPS (etectRx ID-Cap system) to improve ART adherence among adult, non-pregnant PWH, on or eligible for ART, who have been hospitalized at the study site. After 16 weeks of DPS use with ART, the percentage of participants with < 90% DPS-detected adherence, the percentage who required support to maintain > 90% adherence, and participant satisfaction with the system [44] will be assessed. In addition, an ongoing, 16-week observational cohort study (target $n=180$) is assessing the relationship between ART adherence detected by a DPS (Proteus DHFS) and antiviral drug concentrations among adult PWH who are currently on or initiating tenofovir alafenamide (TAF). The primary outcome will be the quantification of TFV-DP in dried blood spots at weeks 12 and 16 [45].

Ethical Considerations Surrounding DPS Use

Given the novelty and nature of DPS technology, a number of bioethical issues have been raised — and, thus far, explored mostly theoretically — which may be applicable for both patients and providers beyond the HIV prevention and treatment context [46••, 47–50]. Patient-specific considerations fall primarily within the domains of individual autonomy, informed consent, and data privacy and confidentiality. Such explorations have highlighted the possibility of a perceived loss of autonomy and privacy among patients using DPS for adherence monitoring (e.g., the perception that the technology could enable location tracking or other, unwanted collection of personal data), as well as key issues around establishing and preserving voluntary informed consent (e.g., limited patient comprehension of user agreements, and the implications of software updates that may be required for continued use of the technology) [46••, 49, 50]. The management and ownership of DPS-detected adherence data is another paramount concern, wherein decisions surrounding data access and confidentiality will need to be negotiated and formalized (e.g., specifying the entities and individuals with whom personal data will be shared, which types of data will be deidentified versus identifiable, to what extent patients have the right to withdraw their data from review and aggregation) [46••, 48–50].

DPS use may also lead to a "preventive misconception" among patients — that is, an overestimation of the degree to which they are protected (e.g., from HIV infection) by way of their involvement in research or use of the technology [51]. For example, a patient who is aware that the DPS can measure ingestions in real-time may incorrectly assume that their adherence behavior is being continuously monitored

— and, consequently, may expect that any adherence lapses will be promptly addressed by their care team (when, in fact, adherence data may only be queried periodically at clinical visits). In the HIV context, a false sense of security around the protection afforded by DPS technology — and an associated mismatch in expectations between patients and providers regarding its use — may inadvertently impact patients' engagement in risk behaviors and increase their chances of HIV acquisition (in the event of PrEP nonadherence), or of complications related to HIV management (in the event of ART nonadherence) [50].

A number of provider-centered bioethical issues around using DPS for adherence monitoring have also been raised, primarily in theoretical discussions, including the potentially broad implications for the patient-provider relationship [46••, 49, 50]. For example, while the goal of DPS is to enable real-time adherence measurement — and, in the context of nonadherence, to identify opportunities for intervention to avoid adverse health outcomes — providers may need to navigate the possibility that patients' trust may be eroded by use of a DPS (e.g., if providers rely solely on objective DPS data to the exclusion of their patients' word, or in instances where patients want to retain the right to withhold information from providers but are unable to do so). The implications of DPS use may extend beyond patient-provider trust; indeed, concerns have been raised around the potential for DPS to reduce in-person clinical interactions altogether — either because patient-provider relationships are viewed as increasingly distant and mediated via technology [49], or because patients may skip appointments under the assumption that providers will reach out to them directly if a change in adherence worthy of intervention is detected [50].

Questions surrounding providers' monitoring responsibilities in the DPS context also introduce ethical issues related to liability [46••, 49, 50]. For example, in a scenario where an adverse drug event has occurred and a medical malpractice lawsuit is filed, data indicating whether or not a provider was adequately supervising a patient's adherence via a DPS — and responding according to the applicable standard of care — may become increasingly important. Conversely, if DPS-detected adherence data does not appear continuous, it could be argued that a patient neglected to use a medication as prescribed, raising questions around accountability for adverse outcomes. These issues represent new legal and ethical territory with potential consequences for both patient and provider liability, which will need to be carefully considered and managed across health care systems prior to large-scale clinical DPS implementation. Moreover, if data demonstrating the degree of provider monitoring via a DPS is to be collected and used for legal purposes, such uses of DPS data may necessitate the conduct of informed consent procedures with providers (in addition to patients) prior to DPS initiation [46••, 50].

Finally, broader ethical issues raised by the use of DPS technology also exist at the societal level. Insurance companies may seek to access both patient adherence data and provider monitoring data from DPS in order to justify the cost of covering a digitized medication versus a standard one, introducing new questions surrounding the disclosure requirements for DPS-linked data on behalf of both patients and providers [46••, 50]. Equitable access to the technology will also require close examination — particularly if use of digitized medication is shown to benefit patients more than standard versions — given that DPS use depends on smartphone ownership, which varies by socioeconomic status. According to the Pew Research Center, 96% of adults in the US with an income over $75,000 reported owning a smartphone in 2021, compared to 76% of those with an income below $30,000 [52]. It is therefore incumbent upon DPS manufacturers, health insurance companies, and clinical providers to generate solutions (e.g., subsidies, DPS loaner programs, or versions of DPS technology that are compatible with less expensive smartphones) that avoid exacerbating existing health disparities across the digital divide [46••, 50].

Overall, most of the issues discussed above have been explored only theoretically, with both patient and provider perspectives surrounding the application of bioethics principles to the use of DPS for PrEP and ART adherence measurement still understudied. Only one paper to date has reported qualitative data on prospective DPS users' preferences for sharing adherence data, and privacy concerns in the context of DPS technology more broadly [32••]. Additional study is vital across these domains and should incorporate in-depth explorations of the ethical implications of DPS use on patient autonomy, informed consent, personal privacy, patient-provider relationships, monitoring expectations, liability risk, and equitable access.

Future Applications of DPS and Research Gaps

While the field of ingestible sensors to measure medication adherence in HIV prevention and treatment is still nascent, DPS technology holds significant promise for detecting and responding to adherence behavior in real time. Prior research has demonstrated the feasibility of deploying these systems for both PrEP and ART adherence measurement [16••, 42••, 43] and has explored and established the correlation of DPS-recorded ingestions with other, more traditional measures of adherence [16••]. Previously reported barriers to DPS operation — in particular, technological and design barriers related to use of the reader (e.g., the size and hassle of a lanyard-based device, or discomfort with a cutaneous patch) — may decrease with future technological advancements, including

the continued miniaturization and integration of these systems into other commonly used devices, such as smartphones or smartwatches. Efforts to increase both the range and power of ingestible sensors may eventually eliminate the need for a discrete reader device altogether, as ingestion data could be directly acquired by a smartphone through other connected systems in the home.

There are a number of potential avenues for long-term utilization of DPS across the spheres of HIV prevention and treatment. From a research perspective, future studies should concentrate on incorporating DPS technology into existing behavioral interventions designed to boost adherence to both PrEP and ART. DPS-detected adherence data could help to inform the specific timing and context of such interventions — as well as evaluations of their efficacy in clinical trials. This would uniquely position DPS as a powerful tool not only for the direct, real-time measurement of HIV prevention and treatment adherence, but also as a means of contextualizing and more meaningfully responding to episodes of nonadherence. From a clinical perspective, DPS technology may be particularly applicable for use in certain patient populations; for example, among patients initiating PrEP or ART and learning adherence skills for the first time, DPS may aid providers in measuring their adherence. Moreover, DPS may be especially useful for patients experiencing periodic lapses in adherence, and/or those in periods of increased risk where more intensive tools for adherence measurement and intervention may be desirable by both patients and providers.

Additionally, as DPS effectiveness and implementation research continues to advance, it will become increasingly important to explore the cost effectiveness of DPS technology — a current gap in the available literature. Both cost-related analyses and assessments of payors' willingness to invest in ingestible sensors to bolster adherence and thereby decrease expensive outcomes (e.g., HIV acquisition among PrEP users or worsening HIV-associated comorbidities in PWH) will be critical. Such studies might include exploring the cost of DPS deployment in populations with documented suboptimal adherence (e.g., individuals with substance use disorders), as well as at specific points on the continuum of HIV treatment and prevention during which adherence may be most challenging (e.g., medication initiation for PrEP users or in the context of increasing viral load among PWH). Taken together, these research questions may illuminate key drivers of the ultimate costs and cost effectiveness of DPS use and integration into the clinical armament of adherence tools.

Conclusion

In this review, we have summarized the recent advances in the use of ingestible electronic sensors for measuring real-time adherence to both PrEP and ART. While research in this area is still in its early stages, several investigations have demonstrated the feasibility and acceptability of DPS technology across samples of PrEP and ART users in real-world settings. These studies have established the bioequivalence of multiple PrEP and ART formulations, and the long-term stability of ingestible sensors in storage when overencapsulated with ART and PrEP. Prior investigations have explored perceptions of the technology and potential uses of DPS adherence data by patients and clinical providers, which has informed the development and delivery of personalized, DPS-based interventions — currently being tested — to improve adherence. Future work should continue to expand the body of literature around the optimization and application of DPS technology for adherence measurement across the continuum of HIV treatment and prevention research.

Declarations

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Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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