# Preliminary feasibility of a wrist-worn receiver to measure medication adherence via an ingestible radiofrequency sensor


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***Abstract*— Adherence to medications is a complex task that requires complex biobehavioral support. To better provide tools to assist with medication adherence, digital pills provide an option to directly measure medication taking behaviors. These systems comprise a gelatin capsule with radiofrequency emitter, a wearable Reader that collects the radio signal and a smartphone app that collects ingestion data displays it for patients and clinicians. These systems are feasible in measuring adherence in the real-world, even in stigmatized diseases like HIV treatment adherence. While the current iteration of the digital pill system utilizes a wearable Reader worn like a necklace, preliminary feedback demonstrated that a miniaturized system that was worn on the wrist could be more functional in the real-world. This paper therefore describes the development and preliminary field testing of a wrist-borne wearable Reader to facilitate acquisition of oral HIV pre-exposure prophylaxis (PrEP) adherence data among individual prescribed PrEP.**



***Keywords—ingestible sensor, radiofrequency, medication adherence***


## I. Introduction

Medication adherence is an expensive and vexing problem worldwide.[1] In the United States (US), nearly 50% of individuals prescribed chronic medications experience nonadherence, leading to $528 billion in excess healthcare expenditures attributable to managing exacerbations of chronic disease.[2] Challenges to achieving adherence are structural (e.g., lack of access to medication, cost), behavioral (e.g., lack of knowledge of a medication regimen), psychological (e.g., motivation, mood, substance use) and medical (e.g., experience of adverse drug events).[3] Each of these factors can substantially impact individual efforts to consistently take a daily medication.

Adherence is especially important in the context of HIV prevention. In 2010, the iPrEx study, a multinational phase III randomized controlled trial, demonstrated that oral emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) taken once daily as HIV pre-exposure prophylaxis (PrEP) experienced a 44% decreased incidence of HIV infection.[4] Among individuals with high adherence, HIV protection exceeded 90%.[5] Since this trial, numerous demonstration studies have confirmed the high efficacy of PrEP for HIV prevention. PrEP rollout, initiation, and persistence among individuals who could benefit most from PrEP use remains a high priority for the World Health Organization (WHO) and the US Ending the HIV Epidemic (EHE) initiative. Despite these efforts, adherence to PrEP – especially among individuals with substance use disorder, for whom adherence challenges can be particularly acute – continues to be suboptimal. Some investigations have found that, among individuals who use stimulant drugs, a missed PrEP dose was predictive of next-day nonadherence, which suggests that suboptimal adherence can lead to frank nonadherence, and, ultimately, a lapse in protection against HIV.[6] Therefore, there is an urgent need to develop biobehavioral strategies that can accurately measure and response to PrEP nonadherence.

In response to this need, multiple strategies, both indirect and direct, have been developed to measure adherence. Indirect methods infer medication ingestions, and include techniques

such as self-report, patient diaries, pharmacy refills, and technological systems, like smart pill bottles that measure the opening of a pill bottle cap as a surrogate measure of ingestion events.[7] These strategies are limited in that they do not confirm medication ingestion, can be manipulated by users, and be fraught with bias. Direct methods confirm ingestion of medication using directly observed, video observed therapy, or measurement of drug concentrations in biological matrices.

Ingestible sensor systems are another direct measure, which are a novel strategy that has been demonstrated to be feasible, accurate, and acceptable to measure PrEP adherence among men who have sex with men (MSM) who use substances.[8] These systems, known as digital pill systems (DPS), are comprised of an ingestible radiofrequency (RF) emitter (ID-Tag) integrated into a standard gelatin capsule, which overencapsulates the desired medication (Figure 1, eTectRx).[9] Once ingested, gastric hydrogen ions activate the RF emitter, which broadcasts a signal up to three feet off the body, which is acquired by a wearable receiver – the Reader. The legacy Reader is a lanyard-based device (1 x 2 x 3 inches) that is wirelessly charged. The Reader acts as a store and forward system, simultaneously logging the time of each ingestion and forwarding this ingestion data via low energy Bluetooth to a smartphone, which displays adherence data on an app to both users as well as clinicians.

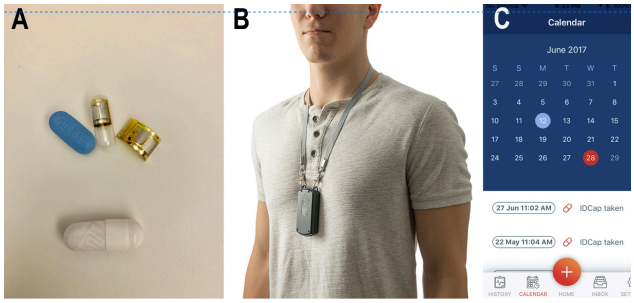


Figure 1. The ID-Cap system, comprised of a digital pill (A), lanyard-based Reader (B), and corresponding smartphone app (C). Images courtesy of etectRx.

We have previously demonstrated the feasibility of using a DPS to measure real-time PrEP adherence. In these investigations, we found that MSM, while accepting of the ID-Cap System overall, have reported that miniaturization of the Reader into a wearable wristband may improve acceptability. In particular, past participants reported that the legacy Reader's size and use of contactless charging were impediments to operation (e.g., incorrect placement of the Reader on the charging pad, or Reader slipping off, leading to a lack of battery life). In this paper, we describe the miniaturization and preliminary feasibility, accuracy, and acceptability testing of a novel wrist-worn Reader, grounded in user-centered design, that captures adherence data from a digital pill.

## II. Materials and Methods

We conducted an open-label, observational study to measure the feasibility, usability, and acceptability of a wrist-worn Reader to collect real-time adherence data from a digital pill.

### A. *Wrist-worn Reader*

The wrist-worn Reader is a miniaturized version of the legacy FDA-cleared ID-Cap System Pendant Reader, worn on a lanyard around the neck, and was designed to enhance the usability of the ID-Cap system.[10] The smaller size was developed for users to wear discreetly and comfortably around the wrist. A charging clip was designed to operate on a standard USB connection to charge the Reader's lithium-ion battery pack. The same materials of construction as the legacy Reader were utilized for the injection molded, skin-contacting Lustran 348 housing. A damage and scratch resistant coversheet (Corning Gorilla Glass 3) was selected as a display cover for the OLED display unit, which was integrated to communicate pill detection notifications and basic Reader status indicators to the user. A single-button user interface was integrated to provide users with control of functions, such as screen waking and cycling, and powering the Reader on or off (Figure 2).

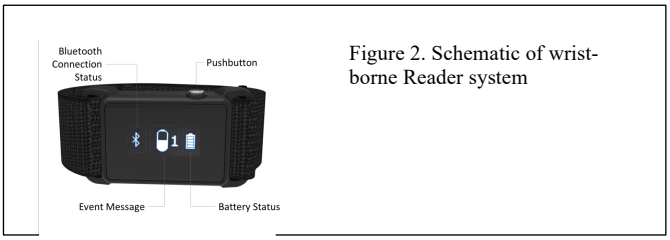


Figure 2. Schematic of wrist-borne Reader system

A custom printed circuit board (PCB) was designed to accommodate key electronic components including etectRx's proprietary eBurst™ RF Receiver ASIC, processor (Texas Instruments), Bluetooth IC, and antennas. An accelerometer was integrated for advanced power management and Reader state monitoring. PCBs were assembled by a contract manufacturer and integrated into the Reader housing by etectRx.

The finished Reader measured 1.84 x 1.10 x 0.48 inches – an 84% volume reduction from the lanyard-based legacy Reader. Each Reader was affixed to an adjustable elastic "sport loop" strap (Halco, Inc). Screen bitmaps were designed and programmed into the Reader to display time of day, battery life, Bluetooth connectivity, charging, and Reader error status, and pill detection confirmations.

A phantom test setup was designed to conduct testing of the Reader in a simulated body environment to gauge the relative performance of the Reader in lanyard- versus wrist-borne positions prior to conducting the full bench verification test panel. A tank was constructed and filled with saline solution to simulate a human torso and arm. The Reader was placed in various positions on the phantom and ID-Tags were suspended in the solution to initiate RF signal transmission. ID-Tags (N=20) were detected by both the legacy and wrist-worn Reader in the simulated body positions and passed initial screening tests. The Reader was designed to meet or exceed current legacy Reader design specifications for connectivity, and pill detection performance. Reader performance was evaluated using the same series of tests designed for the legacy Reader.

We enrolled individuals without HIV ⩾18 years old who had been prescribed oral PrEP. At the enrollment visit, consenting participants were trained on the ID-Cap System using a standardized onboarding program, and completed a baseline quantitative assessment. Participants then ingested digital PrEP pills and operated the ID-Cap System with the wrist reader daily for 30 days.

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At the 30-day study visit, participants returned to the study site and completed a brief usability assessment using the System Usability Scale [SUS], a validated usability questionnaire where mean score >70 suggests a usable system.[11] We collected and conducted a pill count of all unused digital pills from the 30-day study period. We also conducted a timeline follow-back discussion, involving a review of all nonadherent days (i.e., 24-hour period in which no ingestion was registered on the ID-Cap System) to better understand user factors and operational challenges that contributed to nonadherence.

### *B. Data analysis*

Descriptive statistics were calculated to describe sample demographics for this preliminary analysis. Pill counts from the 30-day study visit (30 minus number of pills left over / 30 days) were used as a comparator for adherence measured by the DPS. The overall PrEP adherence rate was calculated for each participant using both DPS and pill count data. We also measured the mean adherence rate and 95% confidence interval (CI) for digital pill ingestions for the sample. Finally, we calculated a correlation coefficient to understand the relationship between DPS detected ingestions and pill counts. Items of the SUS were summed and a mean and 95% confidence interval was calculated.

## III. RESULTS

We aim to enroll 15 participants on PrEP in total. Five enrolled participants are included in this preliminary analysis (mean age=50.4, SD=11.7). All were cisgender male, 40% (n=2) were White, and 40% (n=2) were Hispanic or Latino (Table 1).

| Demographics | *n* (%) |
|---|---|
| Age | |
| Mean (SD) | 50.4 (11.7) |
| Gender | |
| Cisgender male | 5 (100) |
| Race | |
| White | 2 (40) |
| Multiracial | 3 (60) |
| Ethnicity | |
| Hispanic/Latino | 2 (40) |
| Not Hispanic/Latino | 3 (60) |

Table 1. Demographics of the study sample.

Participants successfully recorded a total of 141 ingestion events over the combined study period of 152 days (Table 2). Of these 141 ingestions, 134 (95.0%) were recorded through successful operation of the Reader, and 7 (5.0%) were manually recorded by participants in the smartphone app due to perceived malfunction of the Reader. There was a total of 11 days on which no ingestions were detected by the system or entered manually, which were interpreted as nonadherent days.

The mean adherence rate based on DPS-detected ingestions was 92.7% (95% CI: 81, 105), which was consistent with the mean adherence rate as measured via pill counts. There was also a strong positive correlation (r=0.96, p=0.0097) between DPS derived adherence measures and pill counts. Engagement and operation of the system remained consistent with no significant change in ingestion frequency between week one and week three. Overall, participants rated the wrist-borne ID Cap system 77 (95%CI: 68.11, 85.88) on the SUS indicating they perceived the system as usable.

| Participant | DPS Directly Detected | DPS-Manual Entry | DPS-Total Detected | Missed doses/ Pill counting | Adherence rate |
|---|---|---|---|---|---|
| A | 20 | 3 | 23 | 6 | 76.7% |
| B | 29 | 1 | 30 | 0 | 100% |
| C | 29 | 0 | 29 | 0 | 93.5% |
| D | 28 | 2 | 30 | 0 | 100% |
| E | 28 | 1 | 29 | 1 | 93.5% |

Table 2. Description of individual participant operation of the DPS.

## IV. DISCUSSION

Real-time objective measures of medication adherence, such as the DPS, also provide opportunities to understand barriers to adherence which, if addressed as they occur, can potentially be mitigated prior to the onset of frank nonadherence. In HIV prevention research, understanding the contextual basis of PrEP nonadherence and patterns of PrEP use can empower clinicals to better support participants in achieving adherence. Measuring and responding to PrEP nonadherence events also may advance progress toward ending the HIV epidemic by advancing a highly efficacious medication regimen. This preliminary analysis demonstrates that the next-generation ID-Cap System with a wrist-borne Reader that collects ingestion data from the stomach, accurately measures medication ingestion events. Our work also creates a new opportunity to leverage a wrist-borne reader as a location to develop or adapt future behavioral interventions linked to nonadherence.

Our previous research demonstrated that the ID-Cap System can be operated in the real-world to measure PrEP adherence among MSM who use substances. Despite engagement with and correct operation of the system, MSM in these studies identified the legacy, lanyard-based Reader as a barrier to daily use.[8,12,13] Participants reported that size and the design of the Reader, as well as the contactless charging pad, were impediments to daily use. Based on this feedback, we successfully miniaturized the microchip and RF receiver into a module with an integrated display that is placed on a wristband, similar to a fitness tracker, or integrated onto the band of a smartwatch.[12] Our benchtop and real-world testing demonstrated that the wrist-worn Reader can reliably collect ingestion data from inside the stomach. This suggests that signal boosting with improved efficiency of energy harvesting from the ingestible RF sensor may eventually permit an extension of the off-body signal capture distance.

This preliminary analysis also demonstrates that, in the future, we may have the capability to deploy multiple form factors of Readers that would cater to a variety of user preferences and lifestyles. While we found that the wrist-borne Reader was acceptable by our early cohort of users, others may prefer the lanyard-based version that is currently offered. Tailoring the design of the Reader to individuals' preferences may help to improve overall acceptance of the technology and decrease barriers to daily use of the ID-Cap System.

A wrist-borne Reader represents a unique opportunity to explore the use of wrist-based systems as a site for adherence interventions. With increasing uptake of smartwatches, along with improved technologies that permit cellular communications from the wrist, it may be possible in the future to adapt smartphone-based behavioral interventions that utilize cognitive behavioral therapy, which have been associated with improved adherence behavior, onto the wrist. This would advance the saliency and immediacy of cybernetic feedback from systems that measure real-time adherence, as ingestion reminders and adherence skills support can be delivered directly to the wrist in the moment nonadherence occurs. While some of these rudimentary systems exist on today's smartwatches, future innovation surrounding empirically based behavioral adherence interventions is needed. This paper provides the technical impetus to advance intervention development in the setting of a feasible, accurate Reader that can record digital pill ingestions.

This study has several limitations. First, the small sample size of this preliminary proof-of-concept analysis does not permit us to draw conclusions about the generalizability of accuracy, recording fidelity or feasibility. Instead, we define formative findings that motivate continued research in this space. Second, this research focused on PrEP adherence within the broader context of a significant public health emergency linked to ending the HIV epidemic. Individuals with other disease conditions may have different experiences operating the ID-Cap System. Third, our study was conducted at a single site with significant expertise in HIV treatment and prevention. Experiences deploying and using the ID-Cap System in other healthcare settings may vary.

Overall, this study reports formative findings on the feasibility, accuracy and acceptance of a wrist-borne Reader that collects PrEP adherence data from an ingestible RF sensor. Future analyses from this work will focus on assessing acceptability data and understanding design features that impact real-world use, as well as the development of interfaces that facilitate intervention delivery based on the novel wrist-borne Reader. We anticipate that these developments will help to optimize adherence measurement tools and novel treatments designed to support medication adherence specifically and patient care generally.

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