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A Community Guide Systematic Review: Digital HIV Pre-exposure Prophylaxis Interventions

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Abstract

Introduction: HIV preexposure prophylaxis (PrEP) is highly effective when taken as prescribed. Digital health adherence interventions have been identified as effective for improving antiretroviral therapy adherence among people with HIV, but limited evidence exists for PrEP adherence interventions among people without HIV. The purpose of this Community Guide systematic review was to present the characteristics and effectiveness of digital PrEP adherence interventions.

Methods: The author searched the CDC HIV Prevention Research Synthesis cumulative database for digital health interventions with PrEP adherence outcomes published in peer-reviewed journals from 2000-2022. Studies with comparison arms or pre-post data evaluating interventions in high-income countries were included. Two reviewers independently screened citations, extracted data, conducted risk of bias assessment, and resolved discrepancies through discussion. Summary effect estimates were calculated using median and interquartile interval.

Results: Nine studies were included and all focused on gay, bisexual, and other men who have sex with men. Eight studies were U.S.-based while the other was conducted in the Netherlands. Five were randomized control trials and four were pre-/post studies. All studies showed improved adherence in the intervention arms compared with comparison groups or pre-intervention data. One study also reported improvement in PrEP care retention.

Discussion: Digital health adherence interventions with different strategies to improve PrEP and HIV-related outcomes were identified. The small number of studies identified is a limitation. Findings from this review served as the basis for the Community Preventive Services Task Force recommendation to use these interventions to increase PrEP adherence to prevent HIV infection.

Introduction

Ending the HIV Epidemic in the U.S. (EHE) is the operational plan developed by agencies across the U.S. Department of Health and Human Services (DHHS) to pursue the goal to

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reduce new HIV infections by 75% by 2025 and 90% by 2030.[1] DHSS identified four key strategies to achieve these goals in the United States, including 1) diagnosing people with HIV as early as possible after infection, 2) treat people with HIV rapidly and effectively to reach sustained viral suppression, 3) prevent new HIV transmission through evidence-based interventions including pre-exposure prophylaxis (PrEP) and syringe services programs (SSPs), and 4) respond quickly to potential HIV outbreaks to get prevention and treatment services to people who need them. The National HIV/AIDS Strategy (2022-2025) is closely aligned with and complements the EHE.[2] The national strategy encourages collaboration between all sectors of society to prevent new HIV infections, improve health outcomes of people with HIV, and reduce HIV-related disparities and health inequities.

The U.S. Preventive Services Task Force (USPSTF) recommends clinicians offer PrEP to persons who are at high risk for HIV acquisition.[3] When taken daily as prescribed, PrEP reduces the risk of getting HIV from sex by 99% and from injection drug use by at least 74%.[4] There is a strong connection between adherence to PrEP and its effectiveness in preventing HIV acquisition; reduced adherence is associated with a decline in effectiveness.[4–6] The CDC Prevention Research Synthesis (PRS) Project has been closely following the research on PrEP use and adherence to identify Best Practices (i.e., evidence-based, evidence-informed interventions)[7]. The CDC PRS Project collaborated with the Community Guide Program (CGP; ”Community Guide”) to provide evidence for the Community Preventive Services Task Force (CPSTF) to make a recommendation. CPSTF was established by DHHS to complement the work of the USPSTF, and the recommendations by CPSTF are considered to be the gold standard for what works to protect and improve population health.[9] CGP provides administrative, scientific, and technical support for CPSTF.[8] Results from the systematic review was the basis for the CPSTF’s recommendation for digital health interventions to increase adherence to PrEP.[10]

A digital health intervention is an umbrella term that covers all technology meant to improve patient outcomes and uses text messages, mobile applications (apps), phone calls, or websites to deliver reminders, guidance, and support that may be tailored to an individual’s needs. Digital health interventions have been identified as effective for improving HIV care among people with HIV.[11] Digital interventions provide one or more of the following:

- Information about HIV, PrEP, and strategies for being in care and persistence.
- Services such as automated or interactive feedback, online forum discussions, virtual support groups, or adherence tracking intended to motivate participants.
- Regular reminders for medications, virtual check-in appointments, and clinic visits.

Digital interventions may be combined with in-person activities such as one-on-one counseling, peer-led group sessions, or patient navigation.

Methods

Community Guide methods were used to conduct this systematic review.[12–14] In brief, the methods include the steps of 1) forming multidisciplinary chapter development teams, 2)

developing a conceptual approach to organizing, grouping, selecting and evaluating the interventions; 3) selecting interventions to be evaluated; 4) searching for and retrieving evidence; 5) assessing the quality of and summarizing the body of evidence of effectiveness; 6) translating the body of evidence of effectiveness into recommendations; 7) considering information on evidence other than effectiveness; and 8) identifying and summarizing research gaps. PRS librarians conducted a digital health and PrEP search query in the CDC PRS Project database, a cumulative HIV database created using search results from ongoing targeted comprehensive literature searches that include a PrEP focused literature search.[15] The PrEP search is run in the databases (platforms) MEDLINE (OVID), EMBASE (OVID), PsycINFO (OVID, and CINAHL (EBSCOhost), supplemented by additional hand searches (e.g., journals, reference list checks). A PRS trained coder screens each citation by title and abstract to identify articles published in English that report PrEP-related behavioral (e.g., behaviors or behavioral intentions related to PrEP uptake) or biologic (e.g., any aspect of the use or effects of a PrEP medication for HIV prevention) outcomes and assigns a "PrEP" code to the article. Next, a pair of the PRS trained coders independently screen the full text of these PrEP articles to identify those reporting PrEP adherence outcomes (i.e., any subset or grouping based on PrEP adherence) and assign the code "PrEP adherence".[16,17] The coders meet to discuss and reconcile coding discrepancies. If coders could not reach consensus, a third PRS team member was consulted. Articles with keywords "PrEP" and "PrEP adherence" were identified from the PRS Project database and were eligible for inclusion in the systematic review. Eligible articles published 2000 – 2022 were identified in June 2021 with an update in May 2023 by using the same search query. A detailed search strategy is available from the Community Guide website.[10]

Primary studies (e.g., research studies that included data gathered and analyzed by the authors) published in a peer-reviewed journal were included if they 1) evaluated digital health interventions to improve PrEP adherence, 2) reported PrEP adherence, 3) had comparison arms or pre-post data 4) were conducted in a country with a high-income economy[18], and 5) were written in English. Commentaries, reviews, and non-peer-reviewed publications were not eligible for this review.

Three team members who were authors for this review and had extensive systematic review experience were trained to code studies specific for this review. They independently screened potential publications for inclusion and abstracted information from included studies. Coding pairs assessed included studies on their quality of execution using an established set of criteria.[12–14] The tool addressed threats to internal and external validity and included six domains with nine possible limitations for each study.[12–14] These domains are: description of the intervention and population (0-1 limitation); description of the sampling process (0-1); validity and reliability of the intervention exposure and measurement (0-2); description and use of appropriate analytic methods (0-1); interpretations of results including attrition (i.e., whether more than 20% of study participants was lost to follow-up), confounding and potential bias (0-3); and other (0-1). Studies were classified as having good (0–1 limitations), fair (2–4), or limited (>4) quality of execution. Studies with limited quality of execution were excluded from the analyses.[12,13] Discrepancies between coder pairs were reconciled via discussion and, if needed, a senior

coder was consulted. All screening and data abstract forms were pilot tested and revised as necessary.

The primary outcome of interest was daily PrEP adherence while HIV incidence and HIV-related morbidity (i.e., the state of being symptomatic or unhealthy for a disease or condition) and mortality (i.e., the number of deaths caused by the health event under investigation) were secondary outcomes.[19] PrEP adherence was assessed using "excellent adherence", defined as taking seven doses of PrEP per week, "good adherence", defined as taking four or more doses of PrEP per week, or "poor adherence", defined as less than four doses per week.[20] For summary measures, medians and interquartile intervals (IQI) were calculated. Studies that performed stratified analysis based on different intervention or demographic characteristics were narratively summarized.

Results

This review found 1,260 citations (1,259 citations in the PRS database and 1 citation through the PubMed hand search) with the initial search and 27 from the updated search. Overall, the authors screened 23 full texts. Of these, 14 studies did not meet the study criteria. Thus, this review included nine[21–29] studies evaluating eight unique interventions (Figure 1). These nine intervention studies are:

- DOT[29], a culturally- and youth-tailored app that sent pill reminders and educational texts,
- Enhanced AMPrEP [21] a mobile app plus visualized feedback,
- enPrEP[22] that sent automated weekly text message reminders with an online support group,
- iTAB[23] that sent daily and customized text messages via a mobile app,
- iTEXT[24] that sent weekly bidirectional text or email messages via a mobile app,
- mSMART that evaluated an app with a camera-based medication event-monitoring tool
  - among gay, bisexual, and other men who have sex with men (collectively referred to as MSM) in general,[25] and
  - among African American MSM,[28]
- PrEPmate[26] that provided daily at customized time text messages and youth-tailored interactive online support groups, and
- ViralCombat[27], a gaming adherence intervention.

Details about the included studies are available on the Community Guide website.[30]

Five[21–23,26,27] studies were individual randomized controlled trials (iRCTs) and four[24,25,28,29] used pre-post only design. Studies evaluating enhanced AMPrEP[21], iTAB[23], PrEPmate[26], and mSMART among African American MSM[28] had good quality of execution; the remaining studies[22,24,25,27,29] had fair quality of execution. The commonly

assigned limitations were unclear sampling process[24–26,28,29], use of self-reported data or outcome measures without validation[22,24,29], and high attrition[21,22,27].

Most of included studies are U.S.-based (n=8)[22–29], but Enhanced AMPrEP[21] is from the Netherlands. Sample sizes were 10 to 398, and all the U.S. studies were implemented in urban areas and covered all four regions as defined by the U.S. Census Bureau, with iTAB[23] in the West, PrEPmate[26] in the Midwest, mSMART[25,28] and ViralCombat[27] in the South, DOT[29] and enPrEP[22] in the Northeast, and iTEXT[24] in both Midwest and West regions.

The included studies provided various digital health services and communicated with participants using different methods at varied frequencies. The digital health services included medication reminders for daily PrEP use (n=7)[21–23,25,26,28,29], information and education (n=5)[22,23,26,27,29], adherence tracking (n=4)[21,25,28,29], support groups (n=2)[22,26], and counseling (n=1).[23] These services were delivered through a digital app only (n=3)[21,25,28], an app plus text messaging (n=2)[27,29], text messaging only (n=1)[23], or text messaging plus email, phone, or internet (n=3)[22,24,26]. Study participants received digital communications at least daily (n=5)[23,25,26,28,29], weekly (n=3)[22,24,27], or monthly (n=1).[21] These communications could be unidirectional where pre-set messages were sent to the participants (n=3),[21–23] bidirectional with automated messages where participants' questions were answered by pre-set messages (n=5),[24–26,28,29] or bidirectional with personalized messages where participants' questions were answered by live support (n=2).[24,26]

In addition to the digital health services, enPrEP[22] provided an in-person support group. ViralCombat[27] provided smartphones to study participants while other interventions required participants to have a smartphone and data plan. None of the studies provided information about the languages used for communications, though PrEPmate[26] and ViralCombat[27] recruited only English speaking participants while iTAB[23] included both English- and Spanish-speakers.

All studies used standard forms saved in a central cloud location to collect data, obtain lab work, and provide information or instructions to participants. The median for intervention duration was nine months, with five studies[24,25,27–29] lasting six months or less and four studies[21–23,26] lasting longer than six months.

In terms of demographic characteristics of participants in included studies, six studies[23,25–29] reported the mean age of participants; the median was 25 years. Two studies reported median ages of 39[21] and 49[24] years, and the remaining study[22] did not report age.

Most participants were male (median of 99%). Five studies[24,25,27–29] only recruited male participants. Four recruited transgender women and they accounted for a median of 3% of participants.[21–23,26] All studies focused on MSM.

All studies conducted in the United States (n=8[22–29]) reported racial or ethnic distributions. Participants were White (median of 60%, n=6[23–26,28,29]), Black or African American (median of 23%, n=8[22–29]), Hispanic or Latino (median 11%, n=7[22–27,29]), or Asian American (median of 5%, n=5[23,25,26,28,29]). Study participants were demographically similar to the U.S. general population. EnPrEP[22] and one of mSMART[28] studies recruited

only Black or African American participants and showed the intervention to be effective in increasing PrEP adherence. No study analyzed whether intervention effectiveness varied based on race or ethnicity.

All studies reported at least one measure of socioeconomic status. A median 81% of participants were employed full time or part-time (n=6[21,22,25,26,28,29]); the remaining three studies[23,24,27] did not report employment status. In two studies, the majority of participants had an annual income less than $20K (59%[26], 66%[22]). Three studies[21,23,25] reported a median of 22% of participants who had an annual income less than $24-25K. Four studies[24,27–29] did not report income. Eight studies[22–29] reported a median of 89% of participants who completed some college or more. Most participants were insured (78%[26] and 100%[21], n=2), covered by Medicaid or Medicare (64%[22] and 90%[27], n=2), or paid for healthcare through private insurance or self-pay (19%, n=1[22]). One study[27] reported that just under 50% of participants were receiving PrEP payment assistance. Five studies[23–25,28,29] did not report insurance status.

Four studies assessed participants' drug use history using questionnaires such as the Drug Abuse Screening Test[31] and reported no or low (63%[23] and 100%[25]) or excessive substance use (median of 37%, n=3[21–23]). In two studies, the majority of participants reported they engaged in "any" recreational substance use (64%[26] and 72%[23], n=2). Of four studies that reported alcohol use, study participants reported low alcohol use (100%, n=1[25]) or excessive alcohol use (median of 29%, n=3[21,22,26]). Additionally, three studies reported on mental health issues and showed a median of 13% of study participants reporting mild depression, depression, or anxiety symptoms (n=3).[21,22,25]

In terms of changes in PrEP adherence, all studies showed participants receiving interventions had greater improvement on adherence (e.g., self-reported, dried blood spot) and higher adherence compared with comparisons (e.g., standard of care, no intervention, in-person adherence counseling) (Table 1). Most studies reported "good adherence" only[21,25,26] or "excellent adherence".[23,25,27] When evaluated against comparisons, a higher proportion of intervention participants achieved good adherence (median of 13.0 percentage points higher; Interquartile Interval (IQI): 6.4-25.3 percentage points; n=6[21,23,25–28]) or excellent adherence (median of 16.8 percentage points higher; IQI: 12.7-26.7 percentage points; n=4[23,25,27,29]). ITEXT[24] provided weekly bidirectional personalized texts or email reminders for pill taking and reported that the post-intervention group missed statistically significant fewer PrEP doses when compared to the pre-intervention group (Relative Risk 0.50; 95% Confidence Interval [CI] 0.29-0.84).

The intervention group in Enhanced AMPrEP[21] received visualized feedback in the app while the comparison group only received text messages. More participants in the intervention group achieved excellent adherence (Odds Ratio [OR] 2.0, 95% CI 1.1-3.8; p = 0.026) but the number of participants with "poor adherence" didn't change (OR 1.5, 95% CI 0.61-3.8; p = 0.36). The authors also found poor adherence was associated with symptoms of depression or anxiety (OR 3.2, 95% CI 1.1-9.5) and low concern of acquiring HIV (OR 4.3, 95% CI 1.6-12).

iTAB[23], PrEPmate[26], and ViralCombat[27] intervened throughout the follow-up periods and examined intervention effects over time. While all three studies found effects diminishing over time (duration of 3 to 12 months), iTAB[23] and ViralCombat[27] reported higher adherence in the intervention groups when compared with the control groups over time.

There is no evidence/report from the included studies that intervention effectiveness differed by interventions or participants' characteristics including age, socioeconomic status, or drug use history.

In terms of HIV incidence and HIV-related morbidity and mortatlity, iTAB[23] and PrEPmate[26] studies reported HIV incidence. PrEPmate[26] reported no HIV seroconversions in either the intervention or comparison groups. iTAB[23] reported two HIV seroconversions in the intervention group among patients who discontinued PrEP. None of included studies reported HIV-related morbidity or mortality outcomes.

Other intervention benefits include that PrEPmate[26] found that a significantly larger proportion of PrEP care visits were completed by participants in the intervention group compared with those in the comparison group (OR 2.62, 95% CI 1.24-5.54; p=0.01).

DOT[29], enPrEP[22], and PrEPmate[26] identified a reduction in sexual risk behaviors as an additional benefit of these interventions. Studies reported decreases in the mean number of anal sex partners and the proportion of study participants who reported condomless anal sex. The studies also found lower proportions of participants with a diagnosed sexually transmitted infection (STI) at follow-up. Reductions were similar for both intervention and control groups.

Although the majority of studies did not assess acceptability of the intervention, in the few studies[25,29] that did, digital interventions to improve adherence to daily-use HIV PrEP were highly acceptable. Of the services offered, study participants were most likely to use daily pill reminders and weekly check-ins.[22,24–27]

Discussion

This systematic review found that digital PrEP adherence interventions improved both daily-use pill taking and retention in PrEP care, thereby improving health for population groups which are at risk for HIV infection. Findings from this review served as the basis for the CPSTF's recommendation to use these interventions to increase PrEP adherence to prevent HIV infection.[10]

Based on the CDC's PrEP clinical practice guideline, clinical visits every three months are recommended for daily PrEP users to receive HIV testing, medication adherence counseling, behavioral risk reduction support, side effect assessment, STI symptom assessment, and renal function and bacterial STI testing.[32] This review found that some of these strategies including counseling and behavioral risk reduction support can be provided by digital interventions between clinical visits.

Digital health may enhance care access for persons no matter where they live[33] but it has technology and equipment requirements. Eight of the nine included studies only recruited participants who had smartphones and adequate data plans. In 2021, 85% of U.S. adults used a smartphone[34], 77% had high-speed broadband service at home[35], and 93% used the Internet[35], suggesting digital interventions could be widely implemented. Inequalities of smartphone ownership have diminished by race or ethnicity, but still exists for Americans with lower incomes[36], older adults, and people living in rural areas.[37] In addition, even those who do own a smartphone may have pay-as-you-go type plans and face financial barriers to pay the cost of data and text messaging. It is important to consider participants' income, age, and geographic location when implementing these interventions.

Most participants in the included studies were insured, but such coverage may not represent the general population in the U.S. Most insurance plans and state Medicaid programs cover the cost of PrEP.[38] Other programs provide PrEP for free or at a reduced cost, such as Ready, Set, PrEP[39] that provides medication at no cost to those who qualify, co-pay assistance programs[40] that lower costs of PrEP medications, and state PrEP assistance programs[41] that cover the costs for medication, clinical visits, and lab testing. Despite these programs, people who earn incomes that are too high for marketplace subsides or earn incomes below the federal poverty level in states that do not have expanded Medicaid may not be on PrEP due to the costs of PrEP medications and other costs including clinical visits and lab tests. Finally, the potential privacy risks, and need to ensure confidentiality and privacy are important to consider for digital health interventions. One of the included studies reported confidentiality concerns around receiving HIV-related text messages.[22] The study used innocuous language such as "time to take vitamin pills" or "time to take mints" to replace HIV-specific language to help protect confidentiality.[22] Digital health intervention materials also need to be compliant with Health Insurance Portability and Accountability Act (HIPAA) to protect privacy.[42]

Limitations

This review has several limitations. All studies focused on MSM; thus, the findings may not be applicable for other groups with risk factors for HIV infection such as people who share needles or equipment or people who exchange sex for money. This review also has a limited number of included studies and only included digital health interventions conducted in high-income countries, limiting its findings' applicability to mid- and low-income countries. In response to the COVID-19 pandemic, use of digital health has been expanded, and more studies may be available in the next few years. Further reviews with more studies would help fill in the evidence gaps and increase understanding about the generalizability of the findings.

Conclusions

Based on the findings, CPSTF recommends digital health interventions to increase adherence to HIV PrEP based on sufficient evidence of effectiveness.[20] These interventions improve both daily-use pill taking and retention in PrEP care, thereby potentially improving health for population groups not infected with HIV but at high risk for HIV infection.

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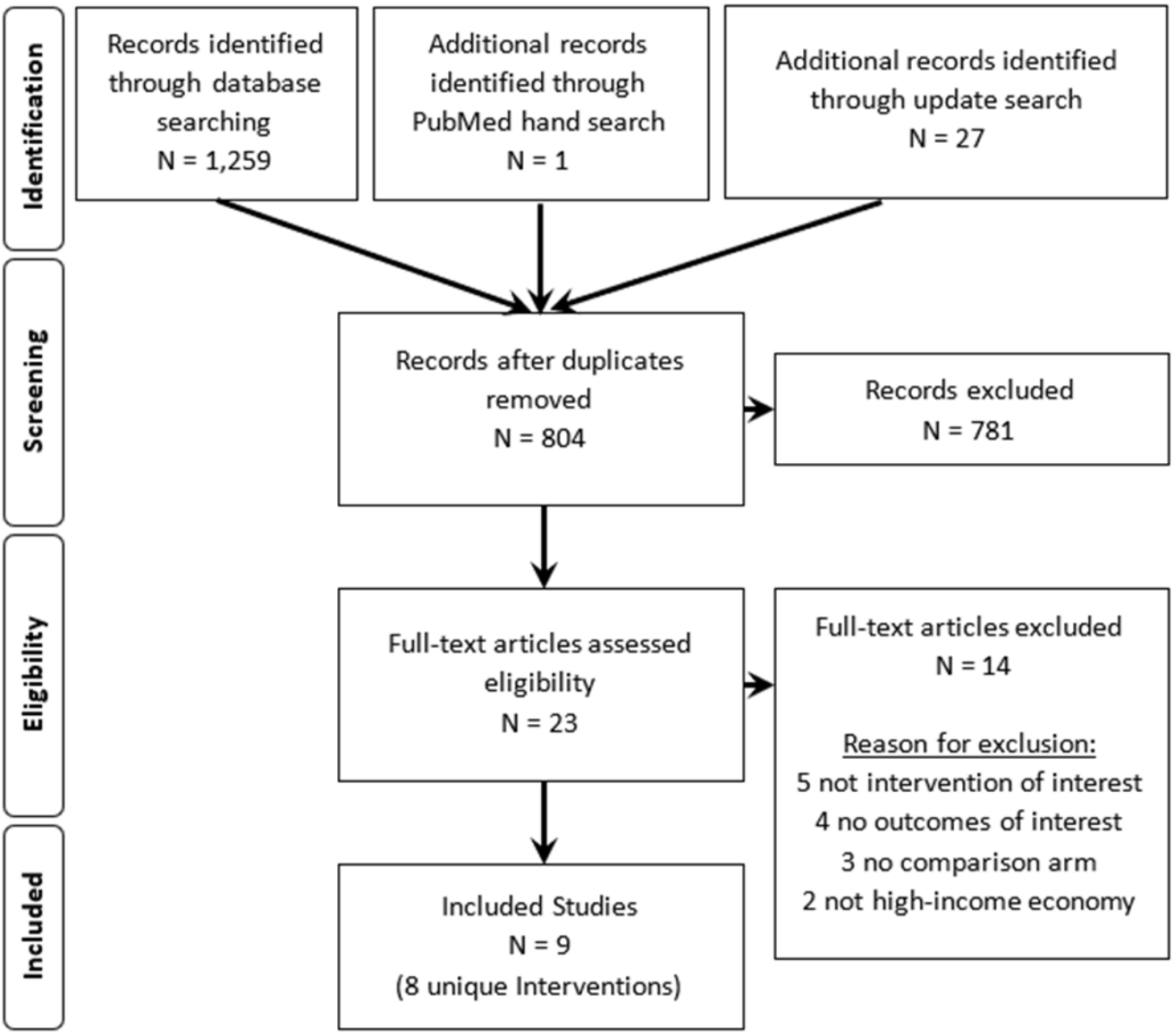

Figure 1:
PRISMA flowchart

Table 1.

Effectiveness of Digital Health Interventions to Increase PrEP Adherence

Outcome Measure	Number of Studies	Effect Sizes
Good adherence[a]	6	Absolute difference: Median: 13.0 pct pts (IQI[d]: 6.4 - 25.3 pct pts[e])
		Relative difference: Median: 19.3% (IQI[d]: 9.0 - 40.0%)
Excellent adherence[b]	4	Absolute difference: Median: 16.8 pct pts (IQI[d]: 12.7 - 26.7 pct pts[e])
		Relative difference: Median: 75.5% (IQI[d]: 12.7 - 26.7%)
Retention[c]	1	OR[f]: 2.62 (95% CI 1.24 - 5.54; **p=0.01**)

Note: Boldface indicates statistical significance (p<0.05)

[a]Good adherence: consistent with four or more doses of PrEP per week

[b]Excellent adherence: consistent with 7 doses of PrEP per week

[c]Retention: proportion of participants making all clinical visits

[d]IQI: interquartile interval

[e]Pct pts: percentage points

[f]OR: odds ratio