Since 2012, HIV pre-exposure prophylaxis (PrEP) has been available to prevent HIV transmission; yet, uptake, adherence, and persistence to PrEP have been suboptimal. This narrative review examines the latest interventions and programs to improve all 3 stages of PrEP adherence and reviews ongoing studies to promote effective PrEP use. From 2017 to 2020, a total of 20 studies analyzed different individual- and structural-level approaches to increase PrEP adherence, including behavior change interventions, technology-based interventions (e.g., short message service messages and mobile applications), and alternate delivery strategies (e.g., pharmacy-based PrEP, integration with other services, and home delivery). Most published interventions involved men who have sex with men, although 3 assessed women (2 transgender, 1 cisgender). Randomized, controlled data support 3 behavioral change interventions and 1 technology-based intervention. Alternate delivery strategies seem promising, although more robust study designs are generally needed. In addition, data on the alignment of ongoing HIV risk and PrEP persistence (i.e., prevention-effective adherence) were limited. The authors also identified 20 ongoing studies that are promoting PrEP adherence. Future work should be inclusive of all at-risk groups in the U.S., including African American and Latinx heterosexual populations and people who inject drugs. Proven and promising approaches may work well in combination and may also need to be adapted with the introduction of long-acting pre-exposure prophylaxis formulations. Collectively, this body of work indicates considerable progress toward understanding the role PrEP adherence will play in Ending the HIV Epidemic in the U.S. that will be bolstered by the outcomes of ongoing trials.

INTRODUCTION

The U.S. Food and Drug Administration approved HIV pre-exposure prophylaxis (PrEP) for once-daily use (tenofovir [TFV]—emtricitabine) in 2012 after clinical trials showed its safety and efficacy in reducing new HIV infections among at-risk individuals.1–5 These same clinical trials also indicated vastly different levels of adherence to PrEP, revealing how strongly adherence impacts its effectiveness.6 More recent demonstration projects and implementation studies have continued to show variability in the 3 phases of adherence: uptake, executed adherence (i.e., day-to-day pill taking), and persistence (i.e., duration of ongoing use). Each phase plays a critical role in the overall use of PrEP and may require distinct interventions.7 Key barriers to PrEP adherence have been identified across a sociocognitive spectrum, including the individual (e.g., lack

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of awareness of PrEP or HIV risk, forgetfulness), community (e.g., stigma), and healthcare structures (e.g., lack of health insurance coverage, limited numbers and types of PrEP providers).

In 2018, the U.S. Centers for Disease Control and Prevention (CDC) estimated that only 18% of people at risk for HIV in the U.S. were prescribed PrEP, despite PrEP use increasing >10-fold from 2012 to 2017. PrEP prescriptions to date have largely focused on men who have sex with men (MSM), although increasing PrEP use among additional at-risk populations is a key component of CDC’s strategies for HIV prevention.

In 2019, the U.S. HHS released a plan for Ending the Epidemic in the U.S. in which increased PrEP use is an essential component. Beyond uptake, efforts to support PrEP use must also target adequate levels of adherence, which vary by route of infection and population. In MSM, ≥4 doses per week has been shown to reduce the risk of HIV infection by 90%. Data are less robust in women, although modeling analyses suggest that as many as 6 doses per week may be necessary to achieve high levels of protection. The current level of executed adherence among PrEP users in the U.S. is largely unknown, and persistence on PrEP remains a challenge for many. Moreover, PrEP use should be aligned with seasons of risk—a concept known as prevention-effective adherence. Unlike antiretroviral therapies (ARTs), PrEP use may not be a lifelong need, owing to individuals’ changing risk perceptions and behaviors. Interventions are thus needed to continue increasing uptake while also promoting high levels of both executed adherence and persistence among those at ongoing high risk of HIV infection.

In this narrative review, the authors summarize the recent (2017–2020) interventions aimed at improving all aspects of PrEP adherence in the U.S. This review presents effective interventions focused at the individual and structural levels as well as recommendations for future directions for research and clinical care.

METHODS

This narrative review is based on a structured search of the literature as well as personal knowledge of the field. To identify interventions for uptake, executed adherence, and persistence of PrEP in the U.S., the authors searched PubMed and 4 HIV/AIDS conferences (i.e., the International AIDS Society Conference, the Conference on Retroviruses and Opportunistic Infections, HIV Research for Prevention, and the U.S. Conference on AIDS) from 2017 to 2020 using the following terms: pre-exposure prophylaxis, PrEP, uptake, prescription, adherence, and persistence. The authors also reviewed ClinicalTrials.gov and NIH Reporter to discover any ongoing studies that may not yet be published and cross-referenced CDC’s list of evidence-based interventions (EBIs) and included discrete interventions as well as novel approaches to PrEP prescription, delivery, and access. This review excluded opinion papers and interventions that did not specifically target adherence (e.g., those promoting PrEP conceptually or linkage to care without measuring PrEP use). In addition, although adherence monitoring can have interventional effects, studies focusing solely on monitoring methodology were excluded. Both authors reviewed the identified papers and abstracts, resolving any uncertainties about inclusion through discussion, and considered the design, participant populations, and outcomes of each study.

RESULTS

This search identified 20 published interventions designed to increase PrEP uptake, executed adherence, or persistence in the U.S. (Table 1). A total of 9 of these stated MSM as their target audience, whereas 2 specified transgender women (TGW), 1 identified cisgender women, and 1 identified at-risk men. The remaining interventions were designed for the general population. The authors identified 20 additional studies that are ongoing (Table 2). In this paper, a summary of key elements is presented, grouped by intervention category.

Individual-Level Interventions

Behavior change interventions. The search identified 9 interventions (including 5 studies in progress) focused on alleviating individual barriers to adherence, identifying each PrEP user’s specific needs and challenges. These interventions build on behavioral science models and address multiple barriers, such as mental health comorbidities (e.g., depression) and practical factors (e.g., forgetfulness).

Life-Steps for PrEP was adapted from a similar intervention shown to improve ART adherence and is included on CDC’s list of EBIs. This intervention involves cognitive behavioral therapy with additional motivational interviewing and problem-solving techniques. Nurses delivered 4 counseling sessions focused on PrEP adherence, barriers to improving adherence, and sexual behavior. Life-Steps for PrEP was assessed among MSM in the Northeast in a small RCT (N=50). Adherence was high among participants in both the intervention and control groups; yet, at 6 months, 84% of the intervention group had drug levels indicative of daily PrEP use versus 63% in the comparison group (p=0.03).

A PrEP demonstration/implementation project (Spark PrEP Awareness Research and Knowledge [SPARK]) in New York City tested a counseling intervention that framed PrEP use as part of a sexual health decision-making process among MSM and TGW (N=301) and is grounded in the Information, Motivation, and Behavioral model. The intervention includes
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Location</th>
<th>Population</th>
<th>Overview</th>
<th>Impact on adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Behavior change interventions</strong></td>
<td></td>
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<tr>
<td>Life-steps for PrEP</td>
<td>Boston, MA</td>
<td>MSM</td>
<td>CBT-based intervention with motivational interviewing and problem-solving therapy, which focuses on PrEP adherence and barriers and sexual behavior. The nurse-delivered intervention consists of 4 counseling sessions with 2 booster sessions.</td>
<td>Improved executed adherence at 6 months (84% vs 63%)</td>
</tr>
<tr>
<td>SPARK</td>
<td>New York City, NY</td>
<td>MSM and TGW</td>
<td>Counseling intervention with logistical adherence support and problem solving.</td>
<td>Improved executed adherence at 6 months (92% vs 86%)</td>
</tr>
<tr>
<td>iNSC</td>
<td>Boston, MA; Chicago, IL; Los Angeles, CA; Memphis, TN; New Orleans, LA; Philadelphia, PA</td>
<td>YMSM</td>
<td>The iNSC discussion emphasizes that the client (the person taking PrEP) is the expert of their experiences and, with the help of a counselor, can help identify strategies for improvement.</td>
<td>Modest executed adherence at 48 weeks (34% vs 28%)</td>
</tr>
<tr>
<td>PATH-PrEP</td>
<td>Los Angeles, CA</td>
<td>MSM and TGW</td>
<td>PrEP participants received iNSC at each visit. If they had adherence struggles, they were escalated to targeted iNSC and then the Life-Steps counseling package.</td>
<td>Improved executed adherence among those with adherence challenges (n=34, 12%)</td>
</tr>
<tr>
<td><strong>Technology-based interventions</strong></td>
<td></td>
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</tr>
<tr>
<td>PrEPmate</td>
<td>Chicago, IL</td>
<td>YMSM</td>
<td>Multicomponent mHealth intervention with SMS (weekly check-in messages, daily adherence reminders) and interactive online content. The platform also supports 2-way communication and peer testimonials.</td>
<td>Improved executed adherence at 36 weeks (56% vs 40%)</td>
</tr>
<tr>
<td>AEGIS/iTAB</td>
<td>Southern California</td>
<td>Cisgender women</td>
<td>2-way text messaging to support adherence.</td>
<td>Improved persistence: among those who remained in the study (n=84), 74% remained on PrEP</td>
</tr>
<tr>
<td>Viral combat</td>
<td>Jackson, MS</td>
<td>MSM</td>
<td>iPhone game developed to information and skills around PrEP adherence and HIV prevention behaviors.</td>
<td>Improved executed adherence (55% vs 25%)</td>
</tr>
<tr>
<td><strong>Pharmacy-based PrEP</strong></td>
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</tr>
<tr>
<td>P-PrEP</td>
<td>Nebraska</td>
<td>General population</td>
<td>Compared PrEP prescription across a university-based HIV clinic, community pharmacy, and 2 separate primary care facilities.</td>
<td>Not reported</td>
</tr>
<tr>
<td>Mississippi pharmacy PrEP</td>
<td>Mississippi</td>
<td>General population</td>
<td>Patients at high risk for HIV were referred to an on-site pharmacist for same-day PrEP initiation.</td>
<td>Improved uptake: 77% of patients filled their prescription within a week</td>
</tr>
<tr>
<td>Miami Veterans Affairs Health System PrEP</td>
<td>Miami, FL</td>
<td>General population</td>
<td>A hybrid approach where pharmacists provided adherence counseling and monitoring between visits.</td>
<td>Improved persistence: 41% received continuous PrEP for ≥12 months</td>
</tr>
</tbody>
</table>

(continued on next page)
Table 1. Overview of PrEP Adherence Interventions Studied From 2017 to 2020 in the U.S (continued)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Location</th>
<th>Population</th>
<th>Overview</th>
<th>Impact on adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Project slip</td>
<td>Southern California</td>
<td>At-risk men</td>
<td>Developed and piloted a screening instrument to provide a consultation and referral or PrEP prescription at a primary care clinic.</td>
<td>Significant increase of PrEP referrals compared with that in the previous 12 months</td>
</tr>
<tr>
<td>PrEP@Home (NCT03569813)</td>
<td>San Francisco, CA; St. Louis, MO; Boston, MA</td>
<td>MSM</td>
<td>PrEP@Home incorporates all aspects of PrEP follow-up care, including STI testing, in a home-based delivery system.</td>
<td>Not yet demonstrated; study will be completed in May 2022</td>
</tr>
<tr>
<td>PrEP in the local health department</td>
<td>Atlanta, GA</td>
<td>General population</td>
<td>Open-access free PrEP at the county health department.</td>
<td>Modest executed adherence (57% self-reported not missing a dose in the previous month); low persistence (32% engaged in quarterly follow-up or seen in last 6 months)</td>
</tr>
<tr>
<td>THRIVE</td>
<td>Alabama, Maryland, Louisiana, New York, Pennsylvania, Virginia, Washington DC</td>
<td>MSM</td>
<td>7 state health departments developed peer navigation models with both professional and peer navigators.</td>
<td>Not yet demonstrated</td>
</tr>
<tr>
<td>Epi-PrEP</td>
<td>Boston, MA; Pittsburgh, PA</td>
<td>MSM</td>
<td>Analyzed episodic use of PrEP on short-term, fixed intervals, such as vacation.</td>
<td>Executed adherence at 3 months (93% had TFV levels consistent with daily use)</td>
</tr>
<tr>
<td>Direct-to-individual delivery</td>
<td>Nurx, Plushcare</td>
<td>Online pharmacy</td>
<td>Online pharmacies that prescribe PrEP by telemedicine and mailed testing visits.</td>
<td>Not yet demonstrated</td>
</tr>
<tr>
<td>Cost support</td>
<td>Ready, set, PrEP</td>
<td>Federal program</td>
<td>Federal program to provide free PrEP for patients who have tested negative for HIV, have a valid PrEP prescription, and lack insurance coverage for outpatient prescription drugs.</td>
<td>Not yet demonstrated</td>
</tr>
<tr>
<td>Gilead patient support programs</td>
<td>Corporate program</td>
<td>General population</td>
<td>Corporate program to provide copayment support for eligible patients.</td>
<td>Not yet demonstrated</td>
</tr>
</tbody>
</table>

AEGiS/ITAB, Adherence Enhancement Guided by Individualized Texting and Drug Levels/Individualized Texting for Adherence Building; CBT, cognitive behavioral therapy; Epi-PrEP, episodic PrEP; INSC, integrated next step counseling; MSM, men who have sex with men; P-PrEP, pharmacy PrEP; PATH, PrEP and Testing/linkage to care for HIV Prevention; PrEP, pre-exposure prophylaxis; PrEP-OI, PrEP Optimization Intervention; SMS, short message service; SPARK, Sparking PrEP Awareness Research and Knowledge; SPARK, Sparking PrEP Awareness Research and Knowledge; STI, sexually transmitted infection; TFV, tenofovir; TGW, transgender women; THRIVE, Targeted Highly-Effective Interventions to Reverse the HIV Epidemic; YMSM, young men who have sex with men.
Table 2. Overview of Ongoing Studies Assessing PrEP Adherence Interventions in the U.S.

<table>
<thead>
<tr>
<th>Intervention name</th>
<th>Location</th>
<th>Population</th>
<th>Overview</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Behavior change interventions</strong></td>
<td></td>
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</tr>
<tr>
<td>Life-steps for PrEP for youth (NCT03805451)</td>
<td>Chicago, IL; Atlanta, GA; Boston, MA</td>
<td>YMSM</td>
<td>Adapted intervention for ages 16–24 years</td>
</tr>
<tr>
<td>PrEPare for work (NCT03086057)</td>
<td>Providence, RI</td>
<td>MSW</td>
<td>Intervention participants will receive the peer-led strengths-based case management for PrEP initiation and a counseling intervention to address individual barriers to PrEP use</td>
</tr>
<tr>
<td>PrEP n’Sine (NCT03208674)</td>
<td>Providence, RI</td>
<td>TGW</td>
<td>Phase 1: peer-led SBCM for PrEP linkage and initiation. Phase 2: daily 2-way text messaging reminders with intensive counseling sessions for those with poor adherence. Intervention arm receives SBCM to navigate the PrEP care system</td>
</tr>
<tr>
<td>RAMP (NCT03256435)</td>
<td>Jackson, MS</td>
<td>Black YMSM</td>
<td></td>
</tr>
<tr>
<td>MI-NAV (NCT03281343)</td>
<td>Northeast, U.S.</td>
<td>Incarcerated women</td>
<td>2-phase study—Phase 1: promote PrEP uptake through motivational interviewing; Phase 2: link at-risk women to PrEP care on release</td>
</tr>
<tr>
<td><strong>Technology-based interventions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOT Mobile app (NCT04633200)</td>
<td>Cambridge, MA</td>
<td>YMSM</td>
<td>Daily PrEP reminders and supportive messages to support adherence</td>
</tr>
<tr>
<td>DOT diary mobile app (NCT03716385)</td>
<td>Atlanta, GA; San Francisco, CA</td>
<td>YMSM</td>
<td>Integrates artificial intelligence with the smartphone camera to confirm that the individual prescribed PrEP is taking it</td>
</tr>
<tr>
<td>PrEP iT! (NCT04509076)</td>
<td>San Diego, CA</td>
<td>YMSM</td>
<td>Multicomponent intervention that includes text message PrEP and appointment reminders, gamification components, virtual peer support, among others</td>
</tr>
<tr>
<td>P3 (prepared, protected, empowered) (NCT03320512)</td>
<td>Atlanta, GA; Boston, MA; Bronx, NY; Chicago, IL; Houston, TX; Philadelphia, PA; Tampa, FL; Chapel Hill, NC; Charlotte, NC</td>
<td>YMSM and YTGW</td>
<td>Compared the standard of care with access to the P3 application and P3+, which gave access to the application and adherence counseling. The application includes social networking and gamification components</td>
</tr>
<tr>
<td>LYNX (NCT03177512)</td>
<td>Tampa, FL; Chicago, IL</td>
<td>YMSM</td>
<td>An interactive mobile app with a personalized risk score, linkage to PrEP care, and online PrEP navigation</td>
</tr>
<tr>
<td>MyChoices (NCT03179319)</td>
<td>Boston, MA; Bronx, NY</td>
<td>YMSM</td>
<td>Access to the MyChoices mobile app, which includes PrEP and STI resources, links to testing and PrEP services, and HIV testing reminders</td>
</tr>
<tr>
<td>PrEP-3D</td>
<td>San Francisco, CA</td>
<td>MSM</td>
<td>Pharmacy-led PrEP program with a mobile app that includes a sexual and adherence diary to track PrEP protection and includes reminders as well as a bidirectional messaging system</td>
</tr>
<tr>
<td>Unified approach to address PrEP cascade for BMSM (NCT03666247)</td>
<td>Not listed</td>
<td>Black MSM</td>
<td>Text messaging intervention designed to address PrEP stigma and perceived costs and benefits of taking PrEP</td>
</tr>
<tr>
<td>HealthMindr (NCT03666247)</td>
<td>Atlanta, GA; New York, NY; Detroit, MI</td>
<td>MSM</td>
<td>Smartphone messaging platform to improve self-reported sexual health behaviors and beliefs</td>
</tr>
<tr>
<td>Telehealth PrEP counseling (NCT03897725)</td>
<td>Alabama</td>
<td>AGYW</td>
<td>The adolescent visit schedule is supplemented with SMS sent every 4 weeks and 2 telehealth visits between clinic visits</td>
</tr>
</tbody>
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(continued on next page)
Table 2. Overview of Ongoing Studies Assessing PrEP Adherence Interventions in the U.S. (continued)

<table>
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<th>Intervention name</th>
<th>Location</th>
<th>Population</th>
<th>Overview</th>
</tr>
</thead>
<tbody>
<tr>
<td>PrEP Communication</td>
<td>Not listed</td>
<td>Women who inject drugs</td>
<td>Perceptual mapping will guide the development of counseling and mHealth strategies to increase PrEP uptake and adherence at a needle exchange</td>
</tr>
<tr>
<td>ePrEP (NCT03729570)</td>
<td>Georgia, Mississippi, North Carolina, Alabama</td>
<td>YMSM in rural areas</td>
<td>Mobile phone app for secure messaging and video-based telemedicine for PrEP consultations and mail-delivered PrEP and self-collected specimen kits</td>
</tr>
<tr>
<td>Project caboodle!</td>
<td>U.S.</td>
<td>MSM</td>
<td>Self-collection of biological specimens for PrEP adherence monitoring</td>
</tr>
</tbody>
</table>

Other delivery strategies

<table>
<thead>
<tr>
<th>Intervention name</th>
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<th>Population</th>
<th>Overview</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planning4PrEP (NCT04097834)</td>
<td>Atlanta, GA</td>
<td>Women</td>
<td>PrEP integration in family planning clinics</td>
</tr>
<tr>
<td>PrEP-OI</td>
<td>San Francisco, CA</td>
<td>General population</td>
<td>Web-based panel management tool and centralized PrEP coordination</td>
</tr>
</tbody>
</table>

The PATH-PrEP (PrEP and Testing/linkage to care for HIV Prevention-PrEP) study involved MSM and TGW aged >18 years in Los Angeles and combined the behavior change interventions in iNSC and Life-Steps to address undetectable TFV levels in plasma (<10 ng/mL). All participants who received PrEP (n=283) had an iNSC discussion during all study visits. Participants received a targeted iNSC discussion, specifically around adherence support and problem solving for improved pill-taking behavior, at the first instance of an undetectable TFV level (n=34, 12%). If they had an additional undetectable TFV level (n=4), the intervention was escalated to the 6-session Life-Steps for PrEP intervention. Among participants who achieved undetectable TFV levels, 50% had sustained improvements in TFV levels, and 13% had ≥1 detectable TFV level. Only 1 of the 4 participants who received the Life-Steps for PrEP intervention remained in the study after the intervention, and no improvement in TFV level was seen.
Work in progress. Several studies are ongoing that involve MSM, male sex workers, and TGW. Life-Steps for PrEP is currently being refined for YMSM to ensure that the materials are adapted for the specific needs of that audience in the Chicago, Atlanta, and Boston metropolitan areas. The PrEPare for Work study engages male sex workers in Rhode Island and is a 2-component intervention, which includes a strengths-based case management intervention for PrEP initiation led by peers. Participants then receive a counseling intervention to address individual barriers around optimal PrEP use (as measured in hair samples). The PrEP N’Shine intervention engages TGW in Providence, RI in peer-led strengths-based case management for PrEP uptake and utilizes 2-way short message service (SMS) reminders to improve PrEP adherence. If adherence is poor, participants receive 4 intensive counseling sessions. In another study in Jackson, MS, strengths-based case management is being used in the RAMP (Retention in PrEP Care for African American MSM in Mississippi) intervention to help Black YMSM navigate the PrEP care system.

In addition, the Motivational Interviewing-Navigation (MI-NAV) study is a 2-phase study focused on women that is ongoing in a Northeastern integrated jail/prison facility (>80% of these women are sentenced to <6 months). The first phase of the study takes place during incarceration, in which PrEP initiation after release is promoted among at-risk individuals using motivational interviewing techniques. The second phase focuses on linking at-risk women to PrEP care once they are released.

The interventions mentioned earlier indicate that individual counseling can improve PrEP adherence. Notably, the data from the 2 trials had relatively high adherence even in the control group. The ongoing work to adapt these interventions for youth and other populations with more adherence challenges will be important for improving the PrEP roll out more broadly.

Technology-based interventions. Numerous mobile health (mHealth)-based interventions have been studied for supporting ART adherence in numerous populations and contexts with mixed results. For PrEP adherence, the authors identified 3 completed interventions and 11 ongoing studies that incorporate 1- and 2-way text messaging, mobile phone apps, or a mobile phone–compatible website.

PrEPmate is a multicomponent mHealth intervention tailored to YMSM in Chicago and builds on the earlier work completed in the iText study, which involved 2-way SMS support in the Iniciativa Profilaxis PrExposiciones OLE (open-label extension) study (2011−2012). Both PrEPmate and iText are included on CDC’s list of EBIs. PrEPmate includes SMS reminders in the first 2 weeks after PrEP initiation and weekly check-in messages as well as a password-protected website with access to peer PrEP testimonials, an online discussion forum, and a messenger feature with 2-way communication. In an RCT (N=121), PrEPmate users were more likely to attend study visits (OR=2.62, 95% CI=1.24, 5.54) and significantly more likely to have TFV-DP levels ≥4 doses per week (OR=2.05, 95% CI=1.06, 3.94) than participants in the control group. At Week 4, 90% of participants in the intervention had protective levels of TFV-DP versus 77% in the standard of care group; yet, at Week 36, protective levels decreased to 56% and 40%, respectively. Overall, acceptability was high, with 92% of participants stating that they would recommend the intervention to others and 88% reporting that PrEPmate was somewhat or very helpful.

Similarly, among cisgender women, the Adherence Enhancement Guided by Individualized Texting and Drug Levels (AEGIS) study utilized the Individualized Texting for Adherence Behavior (iTAB) intervention on the basis of a rapid turnaround of TFV-DP concentrations in DBSS, iNSC for regular brief check-ins on PrEP at care visits, and targeted iNSC sessions for low TFV-DP levels (<1,050 fmol/punch). This demonstration project took place at 5 sites across southern California for 48 weeks. Among the 61.8% (n=84) of participants who were retained for the duration of the study, 74% (n=62) remained on PrEP. Of 120 participants with drug concentrations measured, 67 (56%) had >1 protective concentration (defined by the study as ≥1,050 fmol/punch, suggesting ≥6 doses per week), and 22 participants (18%) had consistently protective levels at all attended study visits. Across all visits, participants with protective TFV-DP levels had typically responded positively to the daily iTAB prompts, compared with those with TFV-DP levels <1,050 fmol/punch. iTAB was added to the CDC’s EBI list in early 2021.

In addition, the iPhone game Viral Combat was developed to provide adherence support and HIV prevention behaviors for MSM in Jackson, MS. This intervention increased PrEP adherence among a small sample (N=82). DBS were collected for 27 participants; 15 (55%) of the intervention participants had >700 fmol/punch, compared with 7 (25%) in the control group, on the basis of preliminary data from an ongoing RCT.

Work in progress. A total of 8 SMS/mobile app intervention studies are ongoing among MSM, many involving YMSM. The DOT Mobile app is being developed for YMSM in Cambridge, MA on the basis of principles of behavioral economics, positive psychology, and social cognitive theory. It includes daily PrEP intake reminders, supportive messages, calendars for pharmacy...
refills and clinic appointments, and adherence graphs. A similarly named but distinct intervention, the DOT Diary Mobile app, integrates artificial intelligence technology with a smartphone camera to confirm that the intended individual is taking PrEP at the anticipated time.48 The app, targeted to YMSM in Atlanta and San Francisco, contains a sexual diary, which synchronizes with the pill-taking data, to provide an estimated level of protection achieved from their PrEP use (i.e., low, medium, high). It also provides specific messaging around the number of additional doses needed to maximize HIV prevention.

The PrEP iT! study involves a website optimized for mobile use, with several components to increase PrEP adherence among YMSM in San Diego, CA.49 It includes text message reminders for pill taking and clinic appointments, an ask the expert feature, feedback on PrEP adherence, and sexual health information specifically tailored to YMSM. Adherence is being assessed with self-report and TFV-DP in DBS.

The P3 (Prepared, Protected, and EmPowered) study targets their app to YMSM and TGW across sites in Atlanta, Boston, the Bronx, Chicago, Houston, Philadelphia, Tampa, Chapel Hill, and Charlotte, comparing the standard of care, the P3 application, and P3+ (i.e., the P3 application plus adherence counseling).70 P3 involves social networking and gamification components, including a personalized profile, daily discussion prompts and quizzes, a multimedia library with PrEP-related information and other sexual health material, and a choose your own adventure narrative, to help navigate health problem solving.50

The LYNX study also aims to increase PrEP uptake (assessed by self-report) and accurate risk perception among YMSM in Chicago and Tampa.51 A mobile app provides participants with Sex Pro (a personalized HIV risk score), access to HIV/sexually transmitted infection (STI) testing information, reminders, and home-based testing options as well as PrEP videos and a diary to track sexual encounters. This type of intervention is a good example of efforts to promote prevention-effective adherence through accurate risk perception.

The MyChoices study includes a mobile app to provide YMSM in Boston and the Bronx with HIV and STI testing and services, HIV testing reminders, and PrEP and STI resources, with the goal of increasing HIV/STI testing and PrEP uptake (per self-report).52 The PrEP-3D study, based in San Francisco, has a similar mobile app but also provides PrEP through pharmacies to adult MSM.53 Another study targeting adult Black MSM is developing a text message intervention to address PrEP stigma and perceived costs and benefits around PrEP use.54 The HealthMindr app provides targeted sexual risk messages to sexually active MSM, some of whom are on PrEP.55 Two technology-based interventions in development involve women. A telehealth intervention in Alabama aims to facilitate PrEP implementation for adolescent girls and young women (aged 15–21 years) in a primary care setting.56 The intervention supplements the adolescent girls and young women’s follow-up schedule with SMS sent every 4 weeks after the in-person visits and 2 telehealth visits using an app between in-person visits to allow for more frequent monitoring (including DBSs for emtricitabine/TFV concentrations) and adherence counseling. Another study among adult women who inject drugs uses perceptual mapping to develop communication messages, including text messages, to improve PrEP uptake and adherence among participants at a needle exchange clinic.57

On the basis of these ongoing projects, the trend seems to be multicomponent mHealth interventions that take advantage of smartphone proliferation throughout the U.S. These apps may serve as an immediate resource when an individual has adherence challenges or during a less critical time when they are just looking for information on PrEP or other sexual health questions. However, evidence on their impact will be critical given the mixed findings for ART adherence.64–67

**Structural-Level Interventions**

**Pharmacy pre-exposure prophylaxis.** A total of 4 studies have looked at the provision of PrEP in local pharmacies with the goal of removing some of the structural barriers around accessing PrEP within the healthcare system. Moreover, stigma may be lower because PrEP is often available only through infectious disease or HIV-specific clinics.71

The One-Step PrEP clinic service in Seattle demonstrated high PrEP uptake when it was provided in a pharmacy setting (97% [695 of 714] initiated with 74% on the same day).28 Of the prescriptions filled in the study pharmacy, 90% of patients had a mean proportion of days covered >80%, and 98% had a $0 patient out-of-pocket cost per month, including uninsured individuals. At the end of data collection, 372 patients remained active in the service, with 41 (11%) returning after a brief interruption in PrEP use. Of those who discontinued the service, the mean duration on PrEP was 241 days. The main reasons for discontinuing included linking to a primary care physician for PrEP services (n=114, 34%), decreased risk perception (n=40, 12%), and relocation (n=34, 11%). Importantly, this model was financially sustainable because the Washington State legislature recognized pharmacists as providers, allowing them to bill insurance plans, which was passed independently of the One-Step PrEP service.
A similar law in Nebraska authorized collaborative practice agreements, granting pharmacists the rights to manage certain patient care services. The P-PrEP program in that state looked at PrEP prescriptions comparatively across a university-based HIV clinic, a community pharmacy, or 2 separate primary care facilities (N=60). A total of 92% of participants chose to receive PrEP at the university-based HIV clinic (n=28, 47%) or community pharmacy (n=27, 45%), and the pharmacists felt comfortable prescribing and managing PrEP. In a similar pilot study in Mississippi, patients at high risk for HIV were referred to an on-site pharmacist for same-day PrEP initiation with a clinical appointment scheduled within 6 weeks for laboratory work (N=69). This study found that 77% of PrEP patients filled their prescription within a week.

The Miami Veterans Affairs Health System implemented a hybrid approach for pharmacy-supported PrEP care. A total of 79 individuals initiated PrEP, and pharmacists provided adherence counseling and monitoring between clinic visits, either in person or by telephone; the pharmacists were able to order laboratories and consultations as needed. Overall, 32 patients (41%) received continuous PrEP for ≥12 months. Other delivery approaches. Other approaches have attempted to avoid disparities in PrEP access and provider-level barriers by leveraging sites of ongoing care delivery. For example, PrEP screening in a primary care system in Southern California resulted in a significant increase in PrEP referrals, compared with that in the previous year. Other programs, such as the San Francisco Magnet Clinic, leverage the opportunity to provide PrEP to those already seeking STI treatment and other sexual health services. Notably, most participants remaining in care in the U.S. PrEP Demonstration Project (2012–2015), which provided PrEP in 2 STI clinics and 1 community health center, achieved adherence consistent with ≥4 doses per week at 48 weeks according to TFV-DP levels in DBS. However, prevention-effective adherence is unclear because data on ongoing risk were not available for the 47% (263/557) of enrolled participants who did not persist on PrEP.

Local health departments (HDs) can provide other venues for PrEP delivery, particularly in collaboration with community-based organizations, which is consistent with their mandate to increase awareness of PrEP and HIV prevention strategies. As an example, the Fulton County Health Department in Atlanta began an open-access free PrEP program in 2015 to capitalize on the HD’s knowledge of high-risk populations. Overall, 216 (92%) patients received a prescription for PrEP, and executed adherence was reasonably high, with 57% (138 of 159) reporting not having missed a dose in the previous month at their last follow-up visit. However, persistence in PrEP care was low, with only 32% (n=69) engaged in quarterly follow-up visits or seen in the last 6 months.

Others have engaged peer navigators and laypersons who are often matched with individuals of similar race, sexual orientation, or age to provide assistance with linkage to PrEP as well as with uptake, adherence, and persistence. The THRIVE (Targeted Highly-Effective Interventions to Reverse the HIV Epidemic) demonstration project, involving 7 state HDs (Alabama, Maryland, Louisiana, New York, Pennsylvania, Virginia, and the District of Columbia), found that navigation models that combined professional and peer navigators with protocols designed by clinics/community-based organizations were >3 times as likely to link eligible MSM of color to PrEP as navigation models that combined peer navigators with protocols designed by HDs (89% vs 22%). However, data specific to adherence have not been reported by this study.

Additional research is looking at the role of providers themselves as a barrier to PrEP uptake, including the use of inclusivity and integration to overcome stigma as well as management of the logistics of prescribing. The PrEP Optimization Intervention (PrEP-OI), which involves a web-based panel management tool and centralized PrEP coordination, was found to be feasible and acceptable in a San Francisco clinic.

A unique intervention, Epi-PrEP, involves the episodic use of PrEP on short-term, fixed intervals, such as vacation, when condom-less sex and drug use may be prevalent. A feasibility study among MSM in Boston and Pittsburgh found that 93% (44 of 47 with plasma measurements) had TFV levels consistent with daily use in the previous week. This study shows a clear alignment of PrEP use with HIV risk.

Direct-to-individual delivery. Direct-to-individual delivery strategies have also been developed to reduce structural barriers to PrEP and improve adherence. For instance, the PrEP@Home intervention incorporates PrEP follow-up care as well as STI testing into a home-based delivery system. Participants collected samples themselves (DBSs, blood in a microtube, rectal swab, and urine in a cup) and mailed them in a prelabeled box for testing. This intervention was found to be feasible and acceptable, with all but 4 participants (n=54) able to collect adequate samples for analysis. PrEP@Home reduced the number of annual in-person visits for PrEP from 4 to 1. A larger RCT is currently ongoing in Georgia, Massachusetts, Mississippi, and Missouri to assess executed adherence and persistence.

Similarly, online pharmacies with phone physician consultation such as Nurx or PlushCare shift all the
PrEP delivery systems online through telemedicine visits and mailed testing kits, similar to PrEP@Home. Both pharmacies accept insurance plans, and patients can receive help in navigating payment assistance programs. However, this approach has not been studied to assess its impact on PrEP uptake, executed adherence, or persistence.

**Cost support.** Programs to reduce cost barriers may have significant implications for PrEP use independently or in combination with other approaches. Ready, Set, PrEP is a federal program established in 2019 to reduce the financial barriers around PrEP use by providing PrEP medication at no cost to some patients. Eligible patients must have tested HIV negative, must have a valid PrEP prescription, and must lack insurance coverage for outpatient prescription drugs. In early 2021, Ready, Set, PrEP added a mail-order feature, which allows participants to have PrEP delivered to their home or healthcare facility, which may be especially beneficial for patients initiating PrEP in rural or difficult-to-access settings. Data on program implementation (both free PrEP and mail delivery) have not yet been published. In addition, Gilead Sciences, the manufacturer of Truvada, has several medication access programs that help people to understand their coverage and identify financial support options. These programs may help to increase access to PrEP, but similar to online pharmacies, studies are required to assess their impacts on adherence.

**Work in progress.** Other interventions are being studied to integrate PrEP care into existing healthcare facilities, including Planning4PrEP, which evaluates PrEP implementation in 3 family planning clinics across Atlanta; the objective is to offer PrEP to an at-risk population while they are already interacting with the health-care system for sexual and reproductive health services. The 3 different family planning clinics will assess uptake, adherence, and persistence over a 6-month period. The PrEP-OI mentioned earlier is currently being evaluated for impact on PrEP prescriptions in a stepped-wedge trial.

The ePrEP intervention combines a mobile phone app to facilitate secure messaging and video-based telemedicine for PrEP consultations, with alternate delivery strategies by mailing participants PrEP and self-collected specimen kits. This study is targeted to YMSM in rural areas of Georgia, Mississippi, North Carolina, and Alabama with known barriers to transportation, health care, and privacy.

Project Caboodle! is a pilot program assessing the feasibility and acceptability of collecting biological specimens by mail to eliminate some of the clinic visits associated with taking PrEP. This study involves a nationwide sample recruited online. Test results are delivered by trained counselors by telemedicine. Although this approach still requires an initial visit with a prescriber, the quarterly laboratories can be completed remotely.

These various approaches to structural interventions show the potential to overcome numerous barriers to access by offering convenience, reduced stigma, increased support, and reduced cost. The data are encouraging, although randomized trials with adherence and persistence as specific outcomes are needed for most approaches.

**DISCUSSION**

This review identified 20 interventions designed to support PrEP adherence in the U.S., including uptake, executed adherence, and persistence. Individual-level interventions focus on behavior change, in some cases, with the support from technology. Structural barriers include delivery of PrEP through pharmacies and integration with other service delivery as well as mail and online services, although many of these approaches are not yet fully evaluated. Importantly, legislation was necessary to enable some of this work. Complementary programs such as task shifting and engagement of federally qualified health centers could provide further benefit and warrant formal study. Programs to help lower the cost of PrEP for uninsured individuals may also reduce structural barriers and could be combined with the other developed interventions. A total of 20 additional interventions are in development, many leveraging mHealth, which hold promise for better PrEP adherence in the future.

Although exciting to see this body of research, the quality of evidence for PrEP adherence interventions to date is generally low. Only 4 completed studies involved RCT designs. The remainder presented observational data, leaving considerable room for evidence generation in further studies. Moreover, only 9 completed studies utilized objective adherence measures (e.g., TFV levels in DBSs or plasma). Although more complex to implement than self-report, objective measures are needed to avoid the social desirability and recall bias commonly associated with self-reports. However, the ongoing studies should help provide more robust evidence because 15 involve RCTs and 12 include objective measures.

In addition, only a few studies presented ongoing assessments of HIV risk. Although it is reasonable to assume some degree of risk among those starting PrEP (and several studies specifically enrolled high-risk individuals), many may simply be curious about PrEP, and their circumstances may change over time. This
information is critical when assessing the effectiveness of a given intervention. Ongoing inclusion of this concept of prevention-effective adherence, particularly when examining persistence, should be included in future work. This concept is increasingly prevalent in studies of PrEP use in diverse settings.

Most of the identified interventions focused on MSM or TGW, which mirrors the HIV epidemic in the U.S. However, other populations are also at risk, principally Black women as well as people who inject drugs; further work should focus on these populations. In addition, the majority of interventions are being studied in large metropolitan areas, and the unique needs of rural settings should be considered.81,87

Importantly, as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus changes many aspects of the healthcare landscape, delivery strategies direct to individual’s homes may be effective options to retain individuals in PrEP care, without as many clinic-based visits. Furthermore, behavioral change interventions could potentially be conducted by telehealth, improving adherence between visits without overly burdening the individual on PrEP with facility-based visits. The trend of multicomponent interventions through smartphone apps may make it possible to address several potential barriers at once and reflects an important avenue for future studies. However, it is important to note that telehealth may introduce a new set of barriers to overcome, including access to technology and the Internet. Understanding the mechanisms of effect and relative efficacy of each component will be important for achieving optimal impact on the multitude of factors influencing PrEP adherence in diverse settings.

Limitations
This review has important limitations. First, it focused on individual- and structural-level interventions to support PrEP adherence and did not address larger systemic factors, such as racism, homophobia, transphobia, medical mistrust, and poverty, which impede access to care and comfort with receiving services.88,89 Interventions to overcome these barriers are critical for all aspects of the PrEP cascade, including adherence, and much work is needed in these areas not only for HIV prevention but also for well-being and social justice more broadly. Second, the review is limited to the U.S. Numerous PrEP interventions are being developed globally and may have potential applications in the U.S.

Looking to the future, PrEP is moving beyond daily pill taking because other formulations (e.g., long-acting injectable PrEP and vaginal rings)90 have proven effective and will soon come to market. However, interventions will still be necessary to support delivery and follow-up on missed dosing, even if it is required less frequently. The addition of new formulations will importantly bring choice, which has been shown to improve uptake and adherence in other prevention fields, such as contraceptives, which warrants inclusion in future research.51

CONCLUSIONS
The interventions reviewed in this paper collectively show promise for achieving the higher levels of uptake and effective use of PrEP that will be needed to end the HIV epidemic. Rigorous trial designs in expanded populations are needed to maximize the understanding of effectiveness and impact, including alignment of adherence and risk of HIV exposure. Further research is needed to understand the comparative advantage of different approaches as well as the optimal means for implementation in clinical practice.

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REFERENCES


