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MAPPING THE STUDY CHARACTERISTICS AND TOPICS OF HIV PRE-EXPOSURE PROPHYLAXIS RESEARCH LITERATURE: A SCOPING REVIEW

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Abstract

Since WHO released the first PrEP guidance in 2012, the PrEP research literature has rapidly increased, but PrEP uptake is still low. To identify research gaps, this scoping review describes study characteristics, identifies populations, and maps study topics in PrEP publications. We identified 561 PrEP primary studies published in English between 2006 and 2018. The most commonly used study design was cross-sectional. Almost half of studies were conducted in non-U.S. countries and focused on men who have sex with men. We mapped study topics using five categories. The most studied category was Potential PrEP user/prescriber (41.3%) followed by Considerations while on PrEP (28.2%), PrEP efficacy and safety (20.9%), Cost-effectiveness or economic evaluation (5.2%), and Methods of and experiences with PrEP clinical trials (4.2%). Although the PrEP literature has dramatically increased, some research areas (e.g., PrEP awareness in non-U.S. countries, intervention studies to promote PrEP use) and populations (e.g., Black women) are still understudied.

Keywords

pre-exposure prophylaxis; HIV; scoping review; research disparity

Approximately 1.8 million persons are infected with HIV every year globally (World Health Organization [WHO], 2017). To reduce the number of new HIV infections, the Joint United Nations Programme on HIV/AIDS (UNAIDS) has implemented 5-year HIV strategic plans; namely, Getting to Zero (2010) and On the Fast-Track to End AIDS (2015). These strategic plans focused on eliminating vertical transmission and cutting the number of sexual transmission events in half by increasing access to HIV combination prevention services (UNAIDS, 2015, 2010)

Pre-exposure prophylaxis (PrEP) plays an important role for achieving these goals. The daily oral pill, emtricitabine/tenofovir disoproxil fumarate (FTC/TDF), is known to reduce HIV

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acquisition in clinical trials and community-based studies (Grant et al., 2010; Liu et al., 2016; McCormack et al., 2016; Volk et al., 2015). In 2012, the United States (U.S.) was the first country to approve FTC/TDF for HIV prevention, and the WHO released the first PrEP clinical practice guideline (U.S. Food and Drug Administraion [FDA], 2012; WHO, 2012). Since then, many countries have followed suit; as of December 2018, 44 countries, including Brazil, Malawi, Thailand, and South Africa have approved FTC/TDF for PrEP (AIDS Vaccine Advocary Coalition, 2018).

As the effectiveness of PrEP was established, behavioral and structural factors associated with PrEP use have become important aspects to study. For example, lack of awareness and HIV-related stigma are associated with PrEP non-use in high-risk populations as well as not prescribing PrEP among health care professionals (Grace, Jollimore, MacPherson, Strang, & Tan, 2018; Smith, Mendoza, Stryker, & Rose, 2016). Behavioral factors such as medication adherence are strongly related to PrEP effectiveness; PrEP is less effective if it is not taken consistently (Centers for Disease Control and Prevention [CDC], 2018a; Grant et al., 2010). In addition, new administration methods (e.g., topical gel, injectable) and dosage schedules (e.g., on demand, four times a week) for PrEP have been developed (Grant et al., 2014; Molina et al., 2015; National Institutes of Health, 2018), prompting more research and evaluation of these new PrEP tools. With the expansion of topic areas, the PrEP research literature has grown considerably over the past decade. Meanwhile, although it has been seven years since FDA approval and the release of the initial WHO guideline, PrEP uptake is still limited, especially in marginalized sub-populations (e.g., women, persons with low socioeconomic status; Kamitani et al., 2018). Examining the scope of the PrEP research literature may illuminate potential research gaps such as understanding limited PrEP use among these marginalized groups.

Scoping review methodology is designed to assess the potential size of the literature and substantive content of available studies to identify evidence gaps in the research literature (Arksey & O'Malley, 2005; Grant & Booth, 2009). To our knowledge, no scoping review on the PrEP research literature has been published to date. The purpose of this scoping review is to map study characteristics (i.e., publication years, study designs, countries where studies were conducted, population characteristics) and study topics in publications focused on PrEP to assess the current research, explore research gaps, and frame future research directions.

METHODS

The protocol for this review was published elsewhere (Kamitani et al., 2019). We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) statement checklist as a guideline to structure this report (see Appendix Table A1; Tricco et al., 2018). Scoping review methodology is similar to that of systematic reviews; thus, we applied established systematic review techniques to locate, screen, assess, and abstract data.

SEARCH STRATEGY

A comprehensive search to identify research focusing on HIV PrEP was performed using the CDC HIV/AIDS Prevention Research Synthesis (PRS) Project database (Lyles, Crepaz, Herbst, & Kay, 2006). The PRS database had amassed over 92,000 citations (November 2018) related to HIV, AIDS, or sexual transmitted infection (STI) prevention research literature, collected by comprehensive automated and manual search strategies developed by librarians with expertise in building and conducting systematic literature searches (DeLuca et al., 2008).

Five comprehensive automated searches (risk reduction, medication adherence, linking and retention in care, PrEP, and HIV systematic reviews) for HIV prevention literature retrieve primary studies and systematic reviews. All searches are implemented annually using the following databases: MEDLINE (OVID), EMBASE (OVID), PsycINFO (OVID), CAB Global Health (OVID), CINAHL (EBSCOhost), and Sociological Abstracts (ProQuest; DeLuca et al., 2008). Each automated search was developed in MEDLINE (OVID) using indexing and keyword terms cross-referenced with Boolean logic and had no language limits. The finalized search was tailored to the other databases to adhere to each proprietary indexing system. The latest PrEP search/update (for citations published in 2016 and 2017) was downloaded in February 2018. Citations fully indexed by the databases searched were added to the PRS database. The most recent manual search (performed in July 2018) for the PRS database included a quarterly hand search of newly published studies from 52 journals (list available from the PRS website review chapter documentation), a review of publication alerts, and reference harvesting from relevant HIV behavioral prevention research literature.

For this scoping review, the librarian queried the PRS database for studies related to HIV PrEP using citations found only with PrEP-specific searches. The complete PRS search strategy, databases search, and database query are listed in Appendix Table A2.

IDENTIFYING RELEVANT STUDIES

Inclusion criteria for this scoping review were primary studies that were (1) focused on PrEP to prevent HIV, (2) conducted with human subjects, and (3) published in English. We excluded systematic reviews and literature reviews, commentaries, guidelines, protocols, letters to editors, gray literature (e.g., newsletters), and conference abstracts. We also excluded laboratory (e.g., in vitro) or pre-clinical studies (e.g., animal studies). Other excluded studies were research studies estimating drug efficacy and/or drug resistance for people with HIV (PWH) and studies focused on PrEP to prevent diseases other than HIV (e.g., other STI). We also excluded studies not published in the English language since this scoping review required trained coders to abstract data from full reports.

A three-step approach was used to identify eligible studies. First, one reviewer screened the citations by title and abstract to identify PrEP primary studies that met the study inclusion criteria. Citations that were excluded by the first reviewer were verified by a second reviewer. Second, two reviewers independently reviewed the full text of the included citations to confirm the eligibility of the studies for the review. Disagreements were resolved through discussion. If the two reviewers failed to reach agreement, a third reviewer resolved

the discrepancy. All forms were pilot tested and revised as necessary. All identified citations were exported to the systematic review software DistillerSR (Evidence Partners, Ottawa, Canada) for data management, citation screening, and data abstraction.

DATA ABSTRACTION

For eligible citations, two reviewers independently abstracted data on study design, country where the study was conducted, and population characteristics by using a standard data abstraction form. Study population characteristics were determined using the primary study's participant eligibility criteria. Based on the purpose of each study as reported by the authors, we assigned codes indicating study topics that were developed through our preliminary study (see details described below). When the pair of reviewers failed to reach agreement, a third reviewer resolved the discrepancy.

CATEGORIZATION

We mapped study topics by using 19 codes that were further collapsed into five categories. These codes and categories were identified through our preliminary study, and the process of developing codes, categories, and definitions has been described elsewhere (Kamitani et al., 2019). The following briefly describes each of the categories. Categories are not mutually exclusive, meaning that one study can be assigned with multiple categories.

Category 1: Potential PrEP User/Prescriber.—We assigned this category to studies discussing behaviors of or issues for potential PrEP takers or PrEP health care professionals. This category included four codes: Access/Routine health care visit, Acceptability/Willingness, Knowledge/Awareness, and PrEP candidacy/HIV risk.

Category 2: Considerations While on PrEP.—We assigned this category to studies reporting experiences of and problems related to staying on PrEP encountered by PrEP users as well as experiences of and problems related to prescribing PrEP encountered by health care professionals. This category included nine codes: Adherence, Retention and Re-engagement in Care, Adverse event, Risk compensation, Risk perception, Conception, PrEP user issues and characteristics/PrEP uptake, PrEP prescription/PrEP clinic, and Routine HIV testing/health screening.

Category 3: PrEP Efficacy and Safety.—We assigned this category to studies focusing on biomedical aspects of PrEP and medication efficacy. This category includes two codes: Effectiveness/Safety/Drug resistance and Estimate impact and effectiveness/drug resistance.

Category 4: Methods of and Experiences With PrEP Clinical Trials.—We assigned this category to studies focusing on processes or experiences of clinical trials. This category included two codes: Trial methods and Trial experiences.

Category 5: Cost-Effectiveness or Economic Evaluation.—We assigned this category to all types of cost studies. This category included two codes: Cost-effectiveness and Economic evaluation.

DATA ANALYSIS

Publication year, study design (e.g., cross-sectional, randomized controlled trials, cohort), country where the study was conducted, and population characteristics (e.g., sexual orientation, gender, risk behavior, age, race/ethnicity) were analyzed using descriptive statistics (e.g., frequencies, percentages). Study topics were summarized with the codes and categories by using descriptive statistics. We did not synthesize the findings from the included studies since our goal was to provide a scope or broad perspective of the research literature (Arksey & O'Malley, 2005). We also did not assess the study quality since it is generally considered to be optional for scoping reviews (Rumrill, Fitzgerald, & Merchant, 2010).

RESULTS

Out of 1,496 citations, we excluded 849 studies by screening titles and abstracts, and another 86 studies by reviewing full reports (Figure 1). Excluded studies included those that did not cover PrEP (n = 451), were non-primary studies (e.g., commentaries) (n = 341), were laboratory/pre-clinical studies (n = 73), were not published in English (n = 58), and were systematic reviews (n = 12). The remaining 561 citations were included in this review.

The earliest studies we identified were published in 2006 (n = 2, 0.4%). The number of PrEP studies steadily increased until 2011; from 2 (0.4%) in 2007 to 11 (2.0%) in 2011 (Figure 2). Since 2012, with the FDA approval of PrEP and the introduction of the WHO guideline, the number of studies has been increasing rapidly; from 29 (5.2%) in 2012 to 205 (36.5%) in 2017. We also found two studies (0.4%) published in 2018 with our most recent manual search.

The most commonly used study design was cross-sectional (n = 137, 24.4%) followed by experimental (n = 118, 21.0%), qualitative (n = 97, 17.3%), modeling (n = 90, 16.0%), cohort (n = 80, 14.3%), and 27 (4.8%) used mixed methods (qualitative and quantitative; Figure 3a). Six studies (1.1%) were case studies and another six studies (1.1%) were case-control studies.

Slightly more studies have been conducted in non-U.S. countries including low and middle-income countries (LMIC; n = 262, 46.7%) than in the U.S. (n = 230, 41.0%). Forty-three studies (7.7%) were conducted in both the U.S. and non-U.S. countries while 26 studies (4.6%) did not specify countries (Figure 3b).

Among these included studies, the most frequently studied population was men who have sex with men (MSM; n = 266, 47.4%, including a study of racial minority gay pride event attendees; Figure 3c). Fifty-two studies (7.5%) included heterosexuals, 22 (3.9%) were focused on men who have sex with men and women (MSM/W), and one (0.2%) was focused on lesbians. We found nine studies (1.6%) that were focused on men in general (i.e., no sexual orientation specified), 88 (15.7%) on women, 59 (10.5%) on transwomen, and nine (1.6%) on unspecified transgender persons.

Other than MSM, HIV-serodiscordant couples (n = 71, 12.7%) were also frequently reported as a HIV risk behavior characteristic followed by persons who inject drugs (PWID)/ substance users (n = 31, 5.5%), sex workers (n = 21, 3.7%), clinic patients (e.g., STI clinic, family planning; n = 7, 1.2%), and persons living in high-risk neighborhoods or with low socioeconomic status, including Medicaid recipients (n = 5, 0.9%). We also found two studies (0.4%) on persons using sex-seeking social media, two studies (0.4%) on truck drivers, one study (0.2%) each on sex workers' clients, victims of intimate partner violence, and persons sharing HIV pills.

Forty-one studies (7.3%) were on young adults (≤ 40 years of age or defined by the author as young adult), while 17 studies (3.0%) were on youth (< 18 years of age or defined by the author as youth). One study (0.2%) focused on older adults. In terms of race and ethnicity, 28 studies (5.0%) focused on blacks or African Americans followed by six studies (1.1%) on Hispanics/Latino(a)s, two (0.4%) on whites, three (0.5%) on persons of color (e.g., nonwhite race, Kenyan), and one (0.2%) on migrants. Persons who were diagnosed with HIV while on PrEP were the focus of 13 studies (2.3%) while three studies (0.5%) included PWH whose partners were on PrEP.

Forty-six studies (8.2%) were on health care professionals (e.g., medical doctors, nurses). Eleven studies (2.0%) examined other type of providers including care coordinators, public health stakeholders, and policymakers. Forty-seven studies (8.4%) did not specify target population.

As for study topics, the most frequently assigned category was Category 1, PrEP user/ prescriber (n = 272, 48.5%) followed by Category 2, Considerations while on PrEP (n = 186, 33.2%); Category 3, PrEP efficacy and safety (n = 138, 24.6%); Category 5, Cost of economic evaluation (n = 34, 6.1%), and Category 4, Methods of and experiences with PrEP clinical trials (n = 28, 5.0%).

CATEGORY 1: POTENTIAL PREP USER/PRESCRIBER

The majority of these studies were assigned the code Acceptability/Willingness (n = 219, 80.5%). These studies typically reported data such as the proportion of MSM who would take PrEP if it was available, or factors associated with acceptability and willingness (e.g., insurance, stigma, risk perception) for starting PrEP. Other studies that were assigned this code assessed health care professionals' willingness to prescribe PrEP. Ninety-seven studies (35.7%) were assigned the code Knowledge/Awareness. These studies typically reported on data such as proportions of study participants aware of PrEP and their perceptions of PrEP safety. Thirty studies (11.0%) discussed eligibility for PrEP (PrEP candidacy/HIV risk). These studies explored HIV risk behaviors of study participants to assess who met the PrEP indications described in the CDC clinical practice guideline (CDC, 2018b). Seven studies (2.6%) were assigned the code Access PrEP/Routine health care visit and discussed structural issues that prevent access to PrEP or medical visits such as lack of transportation or lack of medical providers to start a PrEP clinic.

Very few studies (n = 7, 2.6%) in this category were published before 2010, but the number of studies increased rapidly after 2011, from 4 (1.5%) in 2011 to 84 (30.9%) in 2017. The

most common study design was cross-sectional (n = 117, 43.0%) followed by qualitative (*n* = 64, 23.5%), and cohort study (*n* = 34, 12.5%) (Figure 3a). More than half of these studies (*n* = 143, 52.6%) were conducted in the U.S. only (Figure 3b). MSM (*n* = 88, 32.4%) was the most studied population followed by health care professionals/PrEP prescribers (*n* = 22, 8.1%), blacks or African Americans (*n* = 20, 7.4%), and young adults (*n* = 19, 7.0%) (Table 1).

CATEGORY 2: CONSIDERATIONS WHILE ON PREP

The most commonly assigned code was Adherence (*n* = 87, 46.8%), followed by the code PrEP user issues and characteristics/PrEP uptake (*n* = 59, 31.7%). The studies assigned this latter code addressed topics such as disclosure of PrEP use to their partners, insurance coverage, and PrEP sharing. The code Risk compensation was assigned to 35 studies (18.8%) that covered topics of engagement in condomless sex while on PrEP or STI incidence. The code PrEP prescription/PrEP clinic was assigned to 13 studies (7.0%) focusing on health care professionals or clinics. Eleven studies (5.9%) were coded as Conception (e.g., getting pregnant while on PrEP). Six studies (3.2%) discussed Routine HIV testing/health screening (e.g., type of testing and sensitivity of HIV testing for correctly identifying those who could benefit from PrEP), five studies (2.7%) were coded with *Adverse event* and four studies (2.2%) were each coded as Risk perception (e.g., perception of how likely one will get infected with HIV while on PrEP) and Retention and Re-engagement in Care.

Few studies (*n* = 6, 3.2%) in this category were published before 2012, then the number increased rapidly, from 4 (2.2%) in 2012 to 75 (40.3%) in 2017. Cross-sectional and experimental were the most common study designs (*n* = 45, 24.2%) followed by cohort (*n* = 40, 21.5%) and qualitative studies (*n* = 29, 15.6% (Figure 3a). More studies in this category were conducted in the U.S. only (*n* = 87, 46.8%) than in non-U.S. countries only (*n* = 77, 41.4%) (Figure 3b). MSM (*n* = 86, 46.2%) was the most studied population followed by HIV-serodiscordant couples (*n* = 36, 19.4%), women (*n* = 32, 17.2%), and transwomen (*n* = 24, 12.9%) (Table 1).

CATEGORY 3: PREP EFFICACY AND SAFETY

In addition to studies on the effectiveness, safety or drug resistance of PrEP medication, studies on viral mutation or the effect of PrEP on contraception were also included in this category. Most of these studies (*n* = 105, 76.1%) assessed Effectiveness/Safety/Drug resistance by clinical trials while 33 other studies (23.9%) estimated them by using modeling methods (assigned the code Estimate the impact and effectiveness/drug resistance).

Few studies (*n* = 17, 12.3%) in this category were published before 2013. From 2013 (*n* = 15, 10.9%) to 2016 (*n* = 33, 23.9%), the number rapidly increased, but then declined (*n* = 27, 19.6% in 2017; *n* = 1, 0.7% in 2018). Experimental (*n* = 57, 41.3%) was the most common study design followed by modeling (*n* = 54, 39.1%), and cohort study (*n* = 17, 12.3%) (Figure 3a). The majority were non-U.S. studies only (*n* = 77, 55.8%) (Figure 3b). The most studied population was MSM (*n* = 50, 36.2%) followed by women (*n* = 24, 17.4%),

heterosexuals (*n* = 23, 16.7%), HIV-serodiscordant couples (*n* = 23, 16.7%), and transwomen (*n* = 19, 13.8%) (Table 1).

CATEGORY 4: METHODS OF AND EXPERIENCES WITH PREP CLINICAL TRIALS

While 15 studies (53.6%) were assigned the code Trial's method/characteristics (e.g., describing intervention processes and participants' characteristics of clinical trials), 14 studies (50.0%) were assigned the code Trial's experience, and covered topics such as male partner's influence and roles on women's HIV prevention trial participation, facilitators and barriers to participating in a PrEP trial.

There was only one (3.6%) publication for this category until 2012, and then the number gradually increased after 2014, from 2 (7.1%) in 2014 to 12 (42.9%) in 2017. Qualitative studies were the most common study designs (*n* = 16, 57.1%) followed by experimental (*n* = 7, 25.0%) and cross-sectional (*n* = 3, 10.7%) (Figure 3a). The majority of these studies were conducted in non-U.S. countries (*n* = 15, 53.6%) (Figure 3b). MSM (*n* = 12, 42.9%) was the most studied population followed by women (*n* = 7, 25.0) and transwomen (*n* = 6, 21.4) (Table 1).

CATEGORY 5: COST-EFFECTIVENESS OR ECONOMIC EVALUATION

Most studies (*n* = 30, 88.2%) in this category were assigned the code *Cost-effectiveness*, and the other four studies (11.8%) were assigned the code Economic evaluation (e.g., estimate maximum benefits of ART and PrEP programs, cost of PrEP care).

Only a few studies have been published in this category and the number of publications has been increasing slowly, from 1 (2.9%) in 2008 to 7 (20.6%) in 2017. Most of the studies used modeling methods (*n* = 33, 97.1%) (Figure 3a) and discussed cost issues in non-U.S. countries (*n* = 25, 73.5%) (Figure 3b). The most studied population in this category was also MSM (*n* = 13, 38.2%), followed by heterosexuals, HIV-serodiscordant couples, and substance users (*n* = 5, 14.7% each) (Table 1).

DISCUSSION

This scoping review identified 561 PrEP primary studies published between 2006 and 2018. The number of studies has dramatically increased on some topics including potential PrEP user/prescriber (*n* = 1 in 2006 to *n* = 84 in 2017) and Considerations while on PrEP (*n* = 1 in 2006 to *n* = 75 in 2017), especially after FDA approval and release of the WHO clinical guidelines in 2012. On the contrary, the number of PrEP efficacy studies has declined since 2016.

Overall, the most common study topics were assessment of Acceptability/Willingness, Effectiveness/Safety/Drug resistance, Knowledge and Awareness of PrEP, and PrEP Adherence. The commonality of these topics may reflect the gradual adoption of a new efficacious biological intervention by consumers. After the effectiveness of PrEP was established, the focus of studies shifted to assess PrEP seeking behavior and the promotion of integrating PrEP into public preventative health care. These studies also assessed persons at high risk for HIV for awareness of and willingness to take PrEP. Once persons start taking

PrEP, adherence becomes important since PrEP effectiveness is strongly related to adherence (Grant et al., 2010). This issue may be reflected in the high number of studies on PrEP adherence (e.g., assessing the barriers and facilitators for PrEP compliance) in our review.

In contrast, this scoping review found that the topics of Risk Perception, Retention and Re-engagement in Care, and Economic evaluation of PrEP were the least common. HIV/STI risk perceptions are important to examine because they may play a role in PrEP uptake and adherence, risk compensation, and overall sexual health (Storholm, Volk, Marcus, Silverberg, & Satre, 2017). Assessment of and intervening with risk perceptions may be helpful in providing holistic PrEP care that also includes adherence counseling, consistent condom use, and STI testing and treatment. Our findings also indicated that retention in medical care for persons on PrEP has been understudied. In order to maintain high adherence and receive routine HIV/STI testing and other health check-ups while on PrEP, persons need to be retained in medical care (CDC, 2014). Finally, PrEP is not cheap. It costs approximately $1,300 per month for medication, routine health care visits, and lab work in the U.S. (Farrow, Killelea, & Treston, 2016). Financial barriers may prevent people from seeking or continuing to take PrEP, especially in resource-poor settings (Yi et al., 2017). Better understanding of how the high cost of PrEP and lack of health insurance may be factors in accessing and adhering to PrEP may be useful.

MSM was by far the most common target population overall and for each category of study topic. This finding may reflect the PrEP recommendation for MSM issued by WHO in 2012. The recommendation was later expanded to all populations at substantial risk of HIV (WHO, 2018). In the meantime, CDC has recommended PrEP to high-risk MSM, heterosexual men and women, and PWID (CDC, 2014). Compared to MSM, the number of studies on high-risk heterosexual men and women and PWID was significantly smaller, pointing to a need for future studies to also include these vulnerable populations. In addition, other populations, such as persons with intellectual disabilities (who are at twice the risk for sexual assault compared to persons without disabilities) should be considered for future studies (Davis, 2011).

The majority of PrEP efficacy, trial methods, and cost studies were conducted in non-U.S. settings while studies that assessed knowledge, awareness, and adherence were conducted mainly in the U.S. It should be noted that currently the majority of PrEP users live in the U.S. (UNAIDS, 2016). To meet the UNAIDS target to provide PrEP to three million people at substantial risk for HIV infection by 2020, more studies to help increase PrEP access in non-US countries are essential (UNAIDS, 2016). Although this review did not specifically examine the characteristics of non-U.S. studies (e.g., high-income countries vs. LMIC), more studies to help increase PrEP access in especially LMIC are important. Such studies may include development and testing of interventions to promote PrEP use and access. These interventions can increase knowledge and awareness and minimize associated factors (e.g., stigma, cost) that negatively influence acceptability and willingness to use PrEP. It is also important to more fully understand health care professionals' PrEP prescription behaviors (Krakower & Mayer, 2016). Our review found that only 8% ($n = 22$) of the studies coded as Potential PrEP user/prescriber specifically focused on health care professionals. More studies are needed to understand the barriers and facilitators for health care

professionals to prescribe or support PrEP, especially in LMIC help to reach the UNAIDS target. As noted earlier, the majority of behavioral studies we reviewed used cross-sectional designs. This suggests the need for studies with more rigorous designs (e.g., experimental, preferably randomized controlled trials) to potentially increase the number of interventions that effectively enhance acceptability and willingness to use or prescribe PrEP.

LIMITATIONS

One limitation of our scoping review is including only published research. Excluding gray literature and unpublished reports may miss studies with negative or null findings. We also excluded studies that were published in non-English languages. Although we conducted a comprehensive search, our search strategy could fail to find studies that did not use our PrEP-related search terms (e.g., Pre-Exposure Prophylaxis, chemoprevention). For instance, the FHI TDF (Family Health International TDF) study, known as the first PrEP clinical trials, was not included because it did not use the term PrEP (Peterson et al., 2007). In addition, due to a lag in adding and indexing articles in various online databases, our review could fail to locate the most recent publications and research on PrEP. Another limitation is that we used the eligibility criteria of the included primary studies to determine study participants' characteristics and the study's stated purposes or objectives for assigning codes for study topics. Consequently, our review did not consider other information (e.g., research sites and reported sample characteristics) reported elsewhere in the full text.

CONCLUSION

This scoping review found several research gaps in the HIV PrEP literature. While the volume of research has dramatically increased in the past decade, certain populations and topics were still understudied. The gaps we found in the literature suggest that it is important for future research to examine the role of health care professionals and increase the number of interventions that promote access to PrEP. Efforts to understand more about PrEP remain a high priority for providing PrEP to three million people at substantial risk of infection to achieve the goals of the On the Fast-Track to End AIDS and Getting to Zero HIV strategic plans implemented by UNAIDS (UNAIDS, 2010, 2015, 2016).

Appendix

TABLE A1.

Preferred Reporting Items for Systematic Reviews and Meta-analyses Extension for Scoping Reviews (PRISMA-ScR) Checklist

Section	Item	PRISMA-ScR Checklist Item	Reported on Page no.
Title			
Title	**1**	Identify the report as a scoping review.	505
Abstract			
Structured summary	**2**	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	505

Section	Item	PRISMA-ScR Checklist Item	Reported on Page no.
Introduction			
Rationale	**3**	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	506
Objectives	**4**	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	506
Methods			
Protocol and registration	**5**	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	506
Eligibility criteria	**6**	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	507
Information sources	**7**	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	506–507
Search	**8**	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	506–507
Selection of sources of evidence	**9**	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	507
Data charting process	**10**	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	507
Data items	**11**	List and define all variables for which data were sought and any assumptions and simplifications made.	508–509
Critical appraisal of individual sources of evidence	**12**	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	N/A
Synthesis of results	**13**	Describe the methods of handling and summarizing the data that were charted.	509
Results			
Selection of sources of evidence	**14**	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	508–509
Characteristics of sources of evidence	**15**	For each source of evidence, present characteristics for which data were charted and provide the citations.	510 – 511
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	N/A
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	509–514
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	510–514
Discussion			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	515–516
Limitations	20	Discuss the limitations of the scoping review process.	516
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	516

Section	Item	PRISMA-ScR Checklist Item	Reported on Page no.
Funding			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	N/A

Appendix

TABLE A2.

Search Strategy and Methods

I. **Search Strategy**	
MEDLINE (OVID) PrEP Search	
Symbol Key	
/ = MeSH term	
ti = title	
ab = abstract	
$ = truncation	
HIV or AIDS or STI MeSH and Keywords	
1	HIV infections/
2	AIDS/
3	Sexually transmitted diseases/
4	HIV seropositivity/
5	HIV seronegativity/
6	AIDS serodiagnosis/
7	Hepatitis C/
8	HIV.ti,ab
9	(AIDS not hearing).ti,ab
10	Hepatitis C.ti,ab
11	HCV.ti,ab
12	Sexually transmitted disease$.ti,ab
13	Sexually transmitted infection$.ti,ab
14	(STD or STDs or STI or STIs).ti,ab
15	or/1–14
Pre exposure Prophylaxis MeSH and Keywords	
16	Pre-exposure prophylaxis/
17	Chemoprevention/
18	Pre exposure prophylaxis.ti,ab
19	Preexposure prophylaxis.ti,ab
20	PrEP.ti,ab
21	(Chemoprophylaxis or Chemo prophylaxis or chemoprevention).ti,ab
22	or/16–21

23	15 and 22

II. Databases Searched (Platform)

1	MEDLINE (OVID)
2	EMBASE (OVID)
3	PsycINFO (OVID)
4	CINAHL (EBSCOhost)

Notes:

- Search update is implemented annually for the previous two years to cover publication lag.
- The manual search for citations includes a hand search of journals with a high yield of subject specific citations, contacts in the field and reference list checks.
- More information on the search methods for the Prevention Research Synthesis (PRS) database can be found here http://www.cdc.gov/hiv/dhap/prb/prs/

III. Query of the PRS Database

Last performed: April 2018

Criteria:

1	PrEP review searches only
2	Published years: 2000–present
3	Citations coded with the following information:
	<Specify HIV/AIDS/STD/HBV/HCV prevention focus> = ([PrEP/PEP] OR [PrEP]
4	Languages: English only

Please contact the corresponding author for the searches of EMBASE (OVID), PsycINFO (OVID), and CINAHL (EBSCOhost).

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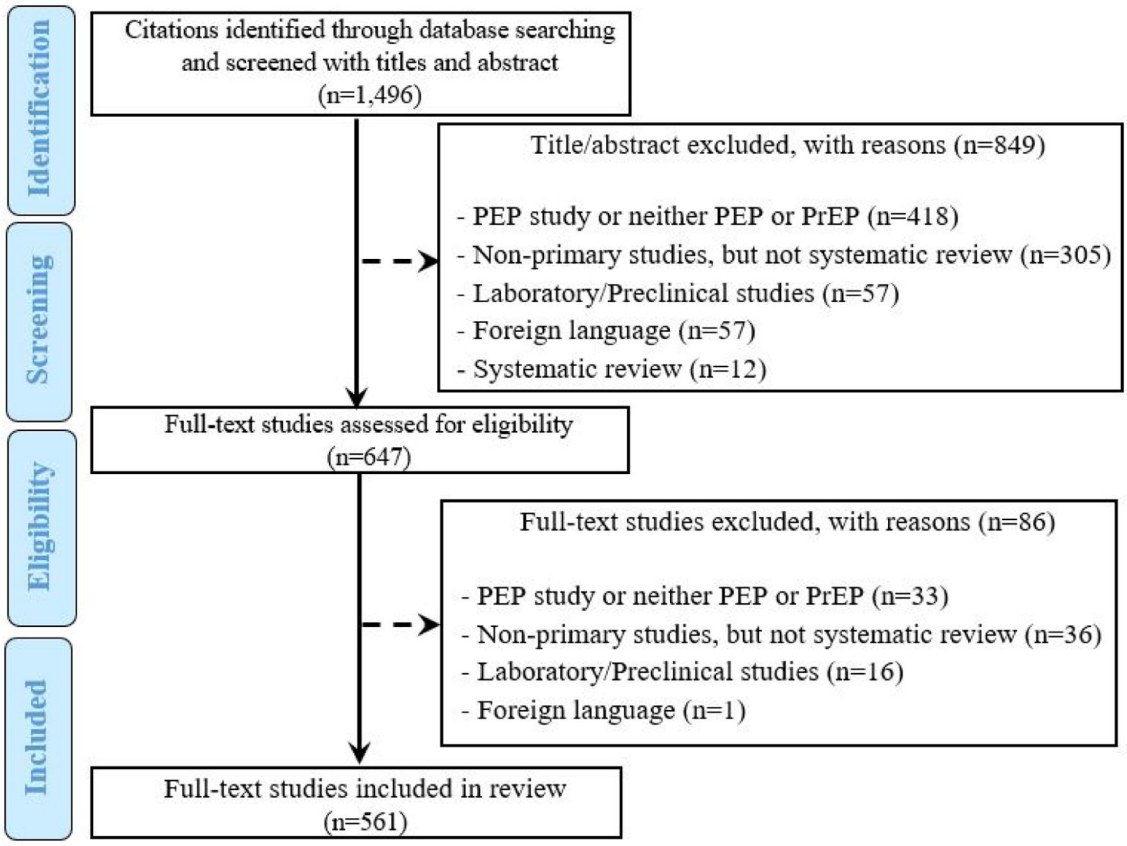

FIGURE 1.
PRISMA flowchart for screening.

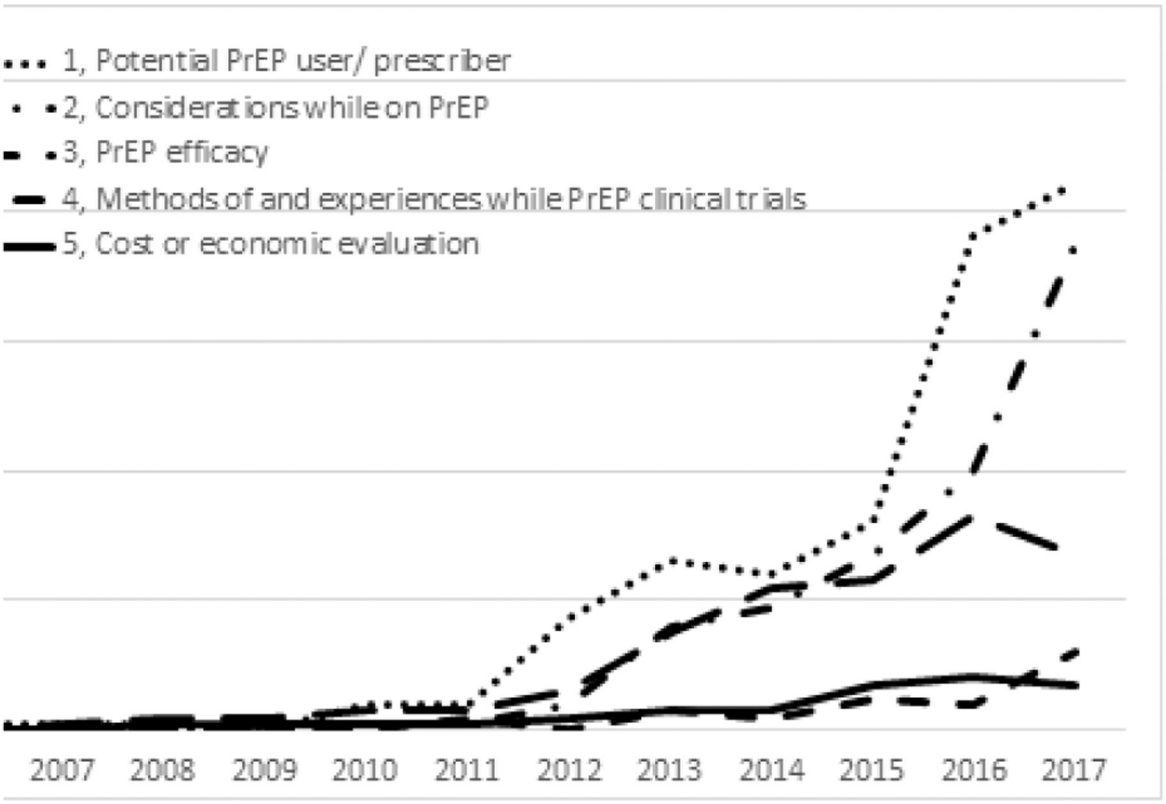

FIGURE 2.
Number of studies by category of study topic and published year (2006–2017) ($N = 561$).

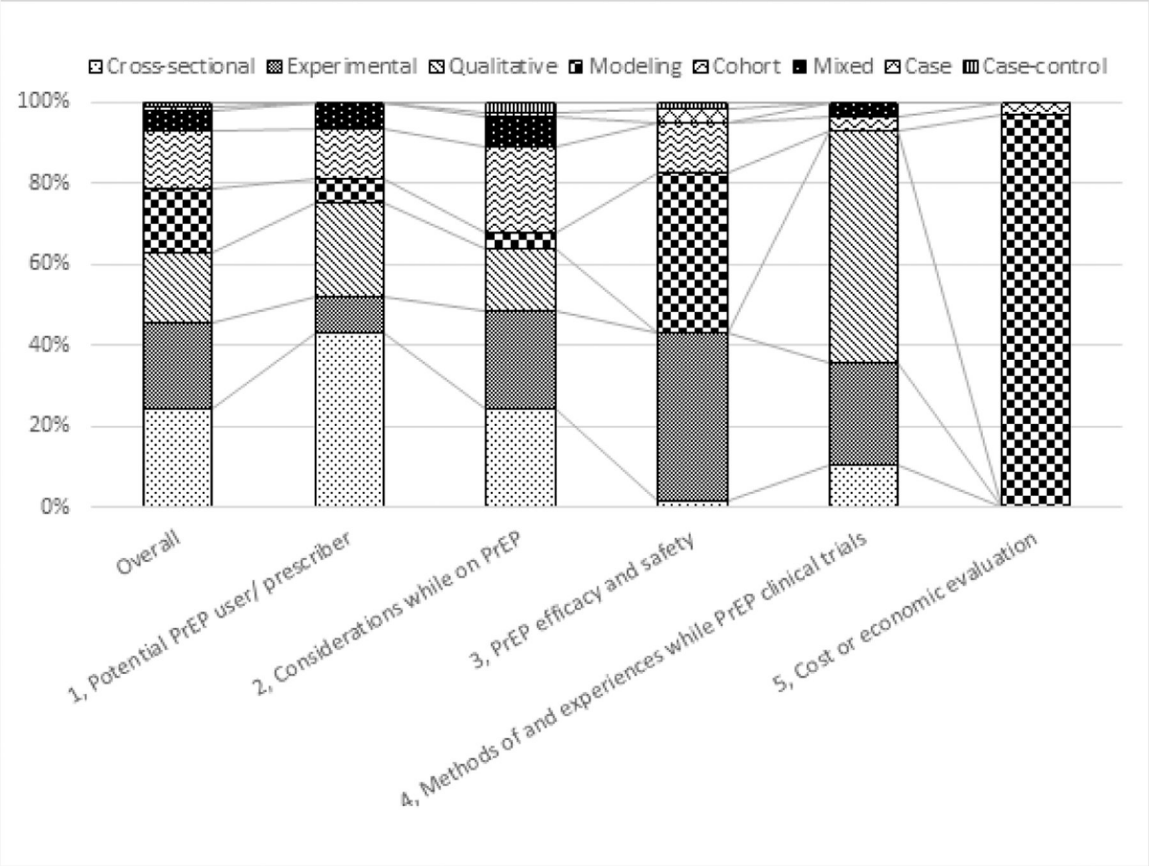

FIGURE 3A.
Type of study design by category of study topic.

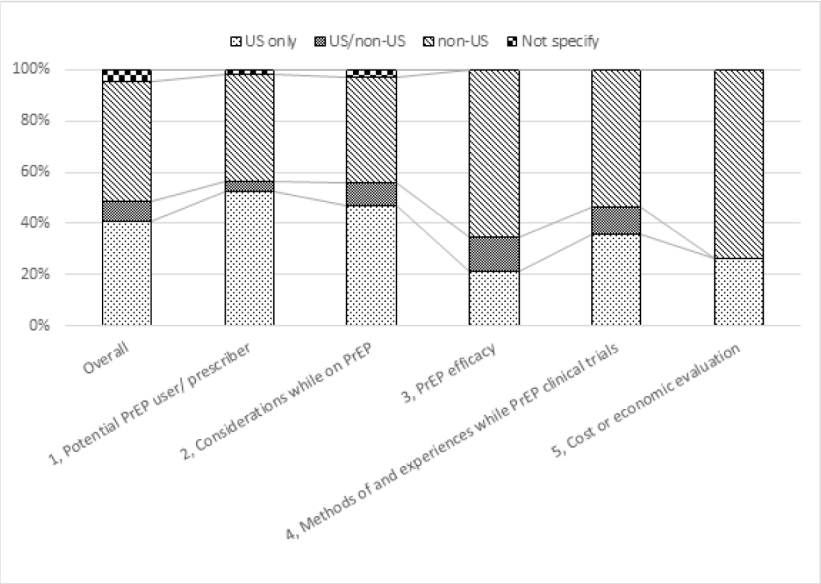

FIGURE 3B.
Country of study by category of study topic.

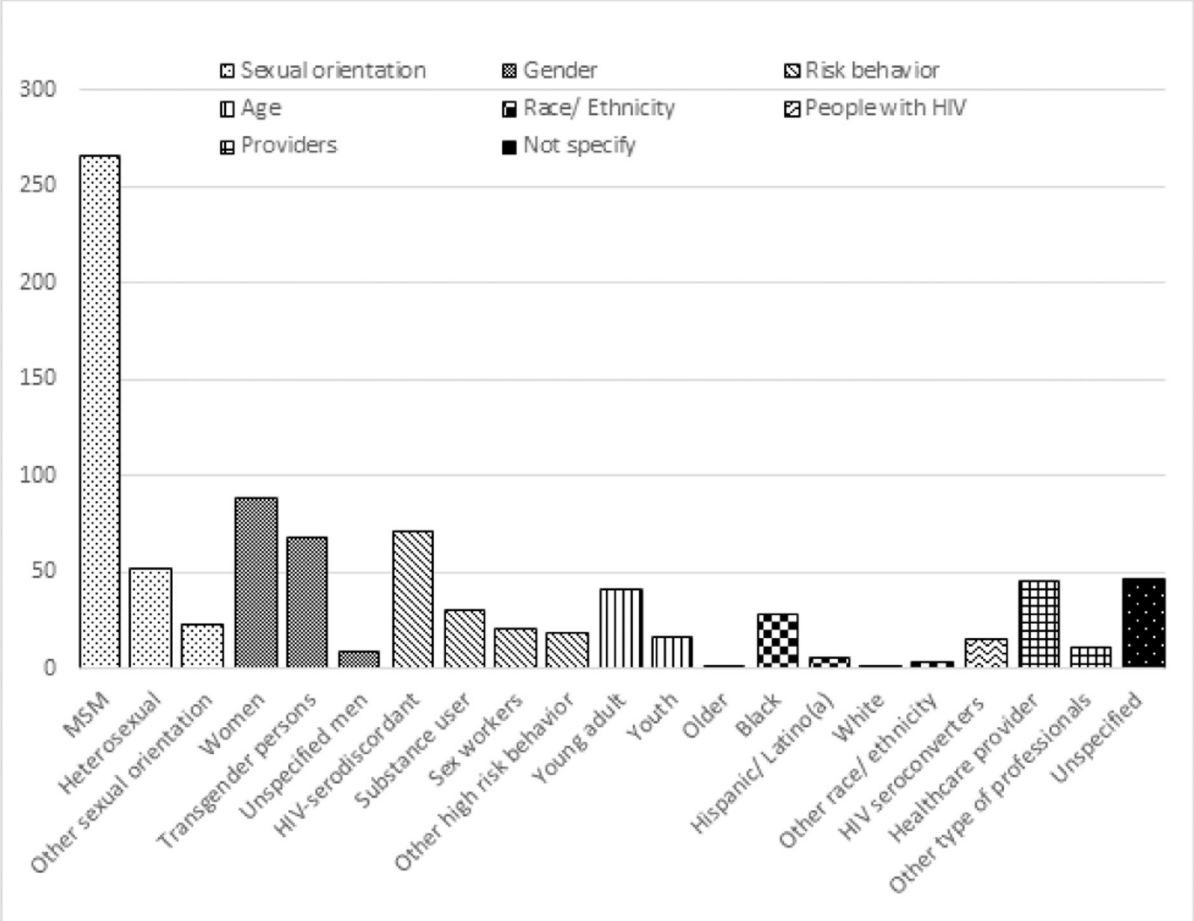

FIGURE 3C.
Overall study participant characteristics.

TABLE 1.

Characteristics of Study Participants by Category of Study Topic ($N = 561$)

	1, Potential PrEP/user prescriber	2, Considerations while on PrEP	3, PrEP efficacy and safety	4, Methods of and experiences while PrEP clinical trial	5, Cost-effectiveness or economic evaluation
	(*n* = 272)	(*n* = 186)	(*n* = 138)	(*n* = 28)	(*n* = 34)
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Sexual orientation					
Men who have sex with men	88 (32.4)	86 (46.2)	50 (36.2)	12 (42.9)	13 (38.2)
Men who have sex with men and women	12 (4.4)	4 (2.2)	1 (0.7)	1 (3.6)	—
Heterosexual	3 (1.1)	20 (10.8)	23 (16.7)	2 (7.1)	5 (14.7)
Lesbian	—	—	—	1 (3.6)	—
Gender					
Women	13 (4.8)	32 (17.2)	24 (17.4)	7 (25.0)	3 (8.8)
Transwomen	12 (4.4)	24 (12.9)	19 (13.8)	6 (21.4)	1 (2.9)
Unspecified transgender persons	6 (2.2)	1 (0.5)	—	2 (7.1)	—
Unspecified men	2 (0.7)	1 (0.5)	1 (0.7)	1 (3.6)	—
Risk behavior					
Substance user	11 (4.0)	7 (3.8)	6 (4.3)	1 (3.6)	5 (14.7)
HIV-serodiscordant couples	8 (2.9)	36 (19.4)	23 (16.7)	3 (10.7)	5 (14.7)
Sex workers	5 (1.8)	—	4 (2.9)	—	1 (2.9)
Clinic patients	4 (1.5)	5 (2.7)	—	—	—
Sex workers	5 (1.8)	—	4 (2.9)	—	1 (2.9)
Low socioeconomic status	2 (0.7)	—	—	—	—
Person living in high-risk neighborhoods	1 (0.4)	—	—	—	—
HIV-concordant couples	—	2 (1.1)	—	—	—
Medicaid recipients	—	1 (0.5)	—	—	—
Persons prescribed PrEP for >3 months	—	1 (0.5)	—	—	—
Grindr users	—	1(0.5)	—	—	—
Clients of sex workers	—	—	1 (0.7)	—	—
Sharing pills	—	—	1 (0.7)	—	—
Resource-constrained country	—	—	1 (0.7)	—	—
Age					
Young adults	19 (7.0)	10 (5.4)	4 (2.9)	3 (10.7)	—
Youth	6 (2.2)	3 (1.6)	4 (2.9)	3 (10.7)	1 (2.9)
Older adults	1 (0.4)	—	—	—	—
Race/Ethnicity					
African American/Black	20 (7.4)	5 (2.7)	1 (0.7)	1 (3.6)	—
Hispanic	7 (2.6)	—	—	1 (3.6)	—
Caucasian/White	3 (1.1)	—	—	—	—

	1, Potential PrEP/user prescriber	2, Considerations while on PrEP	3, PrEP efficacy and safety	4, Methods of and experiences while PrEP clinical trial	5, Cost-effectiveness or economic evaluation
	(*n* = 272)	(*n* = 186)	(*n* = 138)	(*n* = 28)	(*n* = 34)
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Nonwhite	1 (0.4)	1 (0.5)	—	—	—
Migrants	—	—	1 (0.7)	—	—
Kenyan	—	—	—	1 (3.6)	—
Provider					
Health care providers/ART prescribers	22 (8.1)	13 (7.0)	—	1 (3.6)	—
Persons working at community-based organizations	2 (0.7)	—	—	—	—
Policymakers	1 (0.4)	—		—	—
Virologists	—	—	1 (0.7)	—	—
Others					
Persons who seroconverted	1 (0.4)	4 (2.2)	6 (4.3)	1 (3.6)	—
Persons with HIV	1 (0.4)	1 (0.5)	1 (0.7)		—
No specified target population	4 (1.5)	11 (5.9)	27 (19.6)	4 (14.3)	7 (20.6)