

# Pre-exposure Prophylaxis in HIV Research: A Latent Dirichlet Allocation Analysis (GAP<sub>RESEARCH</sub>)

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## Abstract

*Pre-exposure prophylaxis (PrEP) has been shown to be an effective approach to prevent human immunodeficiency virus (HIV) infections; however, implementation of the service remains challenging. This global bibliometric analysis aims to describe the current trends in HIV research prevention through PrEP to reveal the potential gaps of knowledge and to put forward recommendations for future research. A bibliometric analysis was conducted through Web of Science from 1990 to 2017. Exploratory factor analysis was also employed to find research domains emerging from the abstracts' contents. Latent Dirichlet allocation, which is a topic modeling algorithm, was utilized to perform text mining and determine relationships among text documents. A total of 4852 papers regarding HIV PrEP research were retrieved. The number of papers and their impact has significantly increased. Preventing sexual transmissions, improving access, and quality of health-care services for current users, as well as men who have sex with men, pregnant women and children, were the research domains most related to PrEP. We found a data gap in research regarding sex workers, potential side effects of PrEP, and misjudgment toward PrEP users. Despite the growth in research about HIV PrEP, there exist barriers to scaling up the implementation of PrEP worldwide and for such intervention to reach its full potential. International research collaboration efforts to investigate the potential safety concerns of PrEP and develop strategies to eliminate social misjudgment against PrEP users are warranted. Addressing these knowledge gaps might facilitate the development of effective global implementation strategies for PrEP in the future. (AIDS Rev. (ahead of print))*

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## Key words

**Scientometrics. Text mining. Human immunodeficiency virus. Pre-exposure prophylaxis.**

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## Introduction

Human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) remains an important global health burden. By 2018, there have been more than 75 million of people living with HIV and about 32 million deaths due to AIDS-related illnesses<sup>1,2</sup>. On a positive note, the global scale-up of antiretroviral therapy (ART) access has resulted in remarkable progress in HIV control. Of note, this scaling-up was supported by the findings in the landmark clinical trial HPTN 052 in which the risk of HIV infection was reduced by more than 96% in 1763 serodiscordant couples, and no HIV transmission was observed when the HIV-infected partner remained virologically suppressed by adhering to ART<sup>3,4</sup>. In 2017, 59% of all people living with HIV were receiving ART treatments, and 80% of pregnant women living with HIV had access to ART to prevent mother-to-child HIV transmissions<sup>5</sup>. The annual AIDS-related deaths have also dropped by approximately 55% since its peak of 1.9 million deaths in 2004<sup>5</sup>. Despite such success in HIV care and treatment, challenges remain in preventing new cases of HIV infections given that there is currently neither a vaccine nor cure for HIV.

One of the most effective approaches to prevent HIV infection is the pre-exposure prophylaxis (PrEP) in which uninfected individuals with a high risk of becoming infected would take a pill containing two HIV antiretroviral drugs, tenofovir (TFV), and emtricitabine, daily before potential HIV exposure. Regarding TFV, in addition to tenofovir disoproxil fumarate, which has been recognized as the cornerstone of the treatment and prophylaxis of HIV infections, a novel TFV prodrug named tenofovir alafenamide with lower nephrotoxicity and loss of bone mineral density has also been available<sup>6-8</sup>. The efficacy of daily oral TFV/emtricitabine to prevent HIV infections has been demonstrated in at-risk populations, including men who have sex with men (MSM)<sup>9-11</sup>, HIV serodiscordant heterosexual couples<sup>12</sup>, and sexually active heterosexual adults<sup>13</sup>. The centers for disease control and prevention have recommended the prioritization of PrEP for injection drug users, MSM, and serodiscordant heterosexual couples<sup>14</sup>. In the meanwhile, given the fact that effectiveness and feasibility of PrEP have been proved to a certain extent by various clinical trials, many efforts from education for prevention to compliance on using drugs to suppress HIV transmission have been made and attained certain achievements<sup>15</sup>.

One concern behind the increasing use of PrEP in preventing HIV infections is the risk of contracting

other sexually transmitted infections (STIs). Indeed, higher STI incidence among PrEP users has been observed in multiple research<sup>16,17</sup>. The results from a meta-analysis by Kojima et al. showed that MSMs using PrEP were significantly more likely to acquire *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Treponema pallidum* (syphilis) infections (25.3, 11.2, and 44.6 times, respectively) compared to those who were not using PrEP<sup>18</sup>. To address this issue, initiatives in PrEP prescribing practice, such as prescribing PrEP together with doxycycline as prophylactic treatment of syphilis and chlamydia, have yet to be evaluated in terms of efficacy, drug resistance, and gut microbiota modification<sup>19</sup>. Furthermore, PrEP failure in which HIV infections occur during the PrEP continuum of care has been documented in multiple studies. The failures may be attributed to the lack of or limited access to PrEP, lack of awareness and poor adherence among PrEP users, insufficient knowledge about PrEP among healthcare providers, low sensitivity of HIV diagnosis tests to detect early HIV infections, and, to a lesser extent, and HIV drug resistance<sup>20</sup>.

In recent years, the issues around the use of PrEP amongst individuals who are at high risk of HIV infection have attracted more attention. In 2017, a study by Silapaswan et al. summarized findings from the previous research which assessed prescribers' behavior in terms of PrEP provision and offered recommendations on how to optimize the implementation of PrEP in primary healthcare settings<sup>21</sup>. Koechlin et al. also reviewed the values and preferences of populations who may benefit from PrEP, including women, adolescent girls, homosexual men, sex workers, serodiscordant couples, transgender individuals, and people injecting drugs. The study also assessed the values and preferences of health-care providers who can prescribe PrEP<sup>22</sup>. Furthermore, a process for examining the evidence regarding existing PrEP studies in terms of design and characteristics was described in a protocol for scoping review by Kamitani et al.<sup>23</sup>. Nevertheless, to the best of our knowledge, there is currently no study apply bibliometric analysis to quantitatively as well as qualitatively examine the available literature of PrEP in HIV prevention.

Considering both the advantages and emerging barriers of the use of PrEP as an approach to prevent HIV infections, this global bibliometric analysis aims to describe the current global trends in HIV research prevention through PrEP, thereby revealing the potential gaps of knowledge and putting forward implications for future research in this area. Findings from this study may provide valuable insights into future design of HIV

prevention health policies and programs across diverse health-care settings and populations.

## Methods

### Search strategy

Data about HIV/AIDS bibliography were obtained from the Web of Science (WoS) database. The search query consists of HIV and AIDS. Research articles and research reviews were selected for analysis, whereas other types of publications, for example, books, conference reports, or data papers, were excluded from the study. Only items published in English on or before the end of 2017 were chosen. This decision was made because our search was conducted in the third quarter of 2018, and the data we collected for last year might not reflect fully the trend of this year. Non-English items were excluded due to their being a minority in WoS database.

### Data extraction

Data download from the WoS, include general information of the studies (journal name, title, authors' names and affiliations, author-generated keywords, number of citations, and abstracts). We also downloaded reports automatically generated by WoS for more information on the rankings. The data were converted to XLSM form (Microsoft Excel) for data checking error. The downloaded data were then filtered to exclude those which were: (1) not research articles and reviews, (2) not about HIV/AIDS, and (3) not in English. Due to the large number of records, four researchers were employed in two independent teams to filter the data. Finally, from the data set retrieved, we selected all papers containing the keywords of "PrEP" or "Pre-exposure Prophylaxis."

### Data analysis

To calculate the total citations of a country based on the authors' affiliations, we performed descriptive statistical analysis on Stata. Two network graphs, one illustrating the inter-country collaboration and one for authors' keywords cooccurrence were generated by VOSviewer (version 1.6.8, Center for Science and Technology, Leiden University, the Netherlands). Each node in the network was assigned to one cluster. The number of clusters was proportional to a resolution parameter and each cluster was indicated in a distinct color<sup>24</sup>. For analyzing the content of the abstracts, research domains emerging from the content of the abstracts were

identified exploratory factor analysis to identify. We also utilized latent Dirichlet allocation (LDA), which is a common topic modeling algorithm for text mining to determine the relationships of text documents. LDA has been recognized as an effective technique to classify papers into similar topics. In LDA, each term is regarded as a random vector with the probability of drawing the words/texts associated with that vector and the papers with relatively similar probability are classified into one group<sup>24-29</sup>. Thus, by applying LDA, we would be able to recognize the interdisciplinary structure of research development of PrEP in the field of HIV as well as obtain an in-depth view of the trends of PrEP in HIV research and annotate the documents' topic discover hidden themes<sup>30</sup>. In addition, we used coincidence analysis to build a dendrogram which shows the similarity among the sets of research areas. The analytical techniques used for each data type are shown in Table S1.

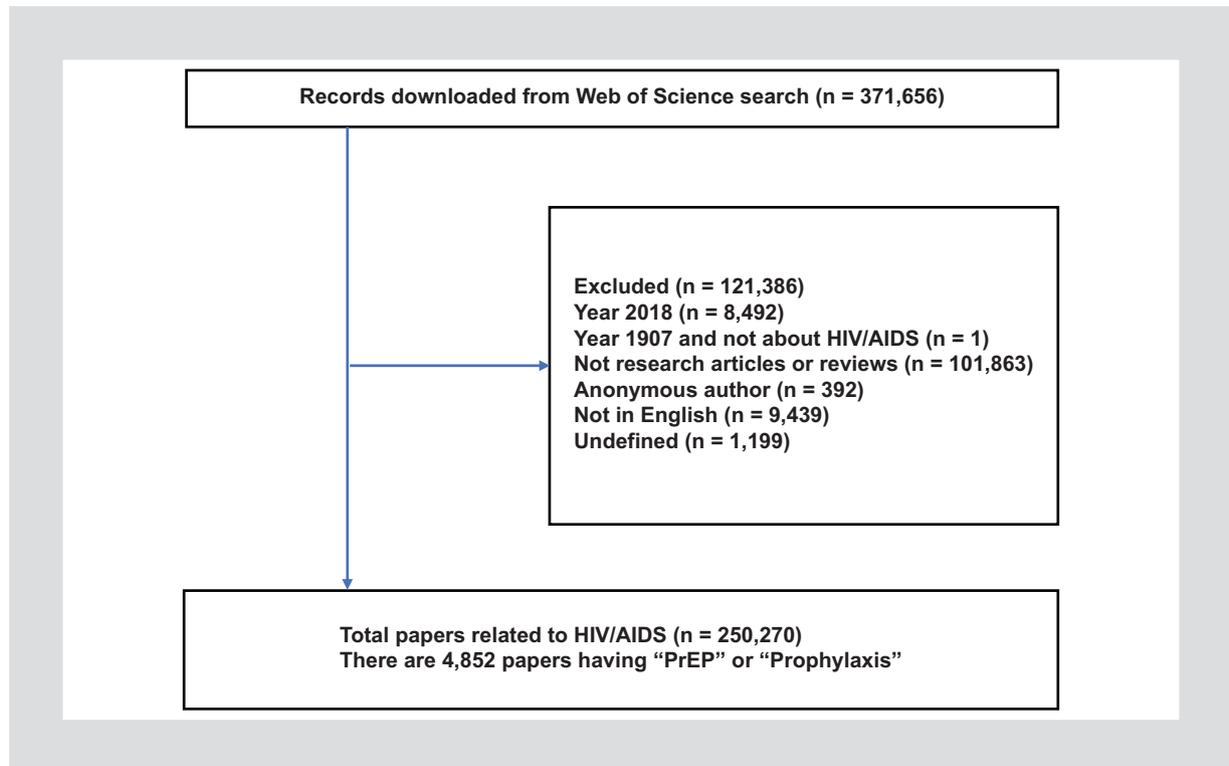
## Results

Fig. 1 describes the paper selection process that identified 4852 papers related to HIV "PrEP" or "Pre-exposure Prophylaxis."

The number of studies concerning PrEP/prophylaxis within HIV/AIDS research during 1990-2017 has been increasing. Particularly, the research productivity in the past 10 years accounted for more than 60% of the 4852 papers. Rates of citations and usages have also been growing rapidly. The total usage (downloads) in the past 6 months of the publications of the past 1-2 years was twice as high as those published in the past 3-4 years (Table S2).

Table 1 examined the study setting (country where the study was conducted) mentioned in the abstracts of publications. There have been 2307 times where the bibliography included country settings. Of those papers, the U.S. was mentioned in 25.9%, and the five of the top ten countries reported as study settings were African nations.

Fig. S1 presents the global network for collaboration in HIV PrEP research among countries having at least ten coauthorships with other countries. Authors from the United States appeared to have the most expansive collaboration network in PrEP research with the largest number of studies and the broadest international partnerships. Meanwhile, European nations (England, Italy, France, Netherlands, etc.), countries in Africa (South Africa, Uganda, Zimbabwe, etc.), and Asian countries (Thailand, India, Japan, etc.) preferred regional collaborations.



**Figure 1.** Selection of papers.

In Fig. S2 and Table S3, we analyzed the keywords and abstracts' content to better understand the objectives of studies and to establish current research landscapes. In Fig. S2, we presented keywords that cooccurred most frequently. There were four main clusters emerging from 268 keywords with cooccurrence of at least 120 times. Some major clusters include: cluster 1 (red) refers to the management, coverage, implementation strategy, and knowledge of PrEP among large populations of people being at risk of HIV infection, such as MSM. Cluster 2 (green) describes the widely used test in detection for HIV infection (CD4 cell count) and prophylaxis for comorbidities of HIV/AIDS, namely, malaria, such opportunistic infections as pneumocystis pneumonia. Cluster 3 (blue) focuses on the delivery of PrEP drugs to pregnant women and children. Cluster 4 (yellow) mentions concerns about PrEP medications.

Top emerging research domains determined from the content analysis of the abstracts are listed in Table S3. PrEP/prophylaxis-related studies within HIV/AIDS research have focused mostly on sexual transmission and the most at-risk population (MSM), available services (vaccine, trial, service uptakes and barriers, cost effectiveness), and transmission to children.

Fig. S3 presents the research landscapes identified based on the cooccurrence of research domains, including (1) treatment-related aspects (green), (2) sex-

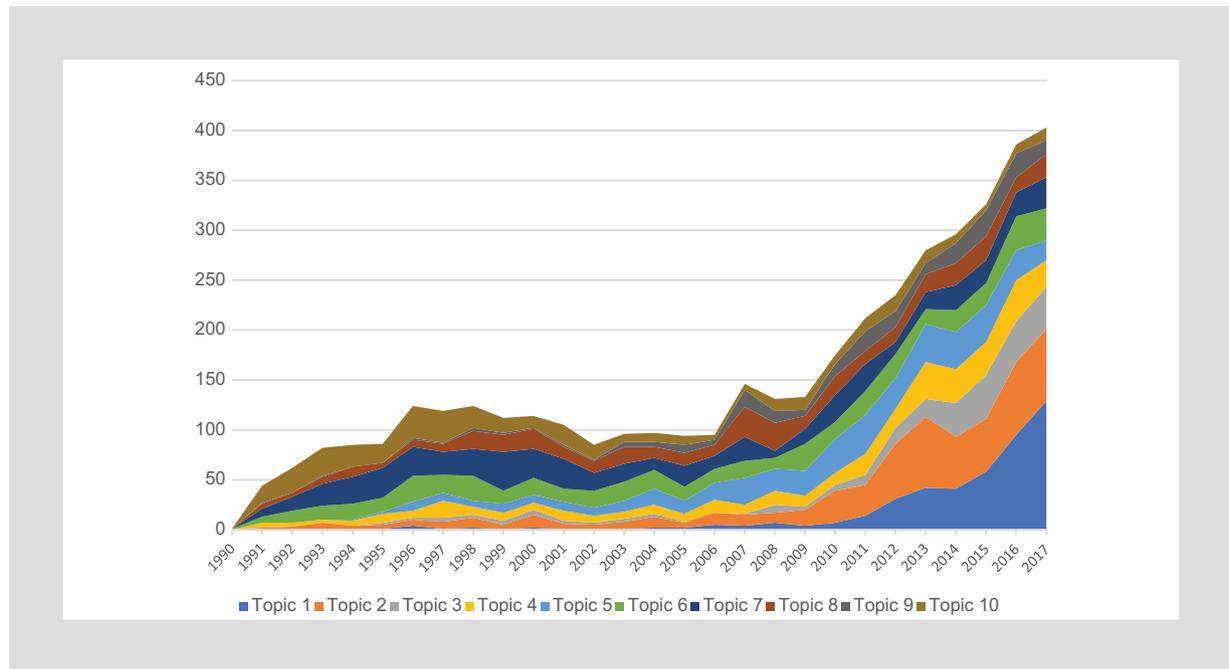
ual transmission and its at-risk population (red), and (3) PrEP among women and children (yellow).

Table 2 presents the scientific research topics related to PrEP constructed by LDA, and Fig. 2 illustrates their growth in the number of publications. After using LDA to classify the 4852 papers into ten topics with the highest number of publications in the past 5 years, we scrutinized the studies included in each group and manually assigned the name of the topics. As the effectiveness of PrEP has been proved to a certain extent<sup>9-13</sup>, researchers pay increasing attention to the economic aspect of PrEP implementation in recent years (Topic 1). Despite receiving a negligible amount of attention at the beginning, there has been a robust increase in the interest of cost-effectiveness of PrEP in the past 5 years (Fig. 2). The implementation of PrEP among vulnerable populations (Topic 3, Topic 4, and Topic 9), clinical research interests (Topic 2, Topic 5, Topic 7, Topic 8, and Topic 10), and multidisciplinary concerns (Topic 6) has also been highly considered.

We constructed the dendrogram of research areas based on the classification of WoS (Fig. S4). The horizontal axis (Haberman distance) shows the dissimilarity between the research fields. Each joining (fusion) of two clusters is represented on the diagram by the splitting of a vertical line into two vertical lines. The vertical position of the split, shown by a short bar,

**Table 1. Number of papers by countries as study settings**

Country settings	Frequency (%)	Country settings	Frequency (%)
United States	580 (25.9)	Cambodia	11 (0.5)
South Africa	192 (8.6)	Congo	11 (0.5)
Uganda	151 (6.8)	Congo	11 (0.5)
Kenya	119 (5.3)	Switzerland	11 (0.5)
Malawi	80 (3.6)	Ukraine	11 (0.5)
India	71 (3.2)	Germany	10 (0.4)
Brazil	67 (3.0)	Georgia	9 (0.4)
United Kingdom	53 (2.4)	Israel	9 (0.4)
Thailand	52 (2.3)	Swaziland	9 (0.4)
Zambia	48 (2.1)	Benin	8 (0.4)
Tanzania	40 (1.8)	Ghana	8 (0.4)
Australia	37 (1.7)	Mexico	8 (0.4)
Zimbabwe	37 (1.7)	Rwanda	8 (0.4)
Ethiopia	35 (1.6)	Senegal	8 (0.4)
Niger	35 (1.6)	Japan	7 (0.3)
Nigeria	35 (1.6)	Austria	6 (0.3)
Botswana	32 (1.4)	Iran	6 (0.3)
Canada	32 (1.4)	Jersey	6 (0.3)
China	30 (1.3)	Lesotho	6 (0.3)
Italy	28 (1.3)	Taiwan	6 (0.3)
Cameroon	27 (1.2)	Hong Kong	5 (0.2)
Ireland	27 (1.2)	Indonesia	5 (0.2)
France	22 (1.0)	Malaysia	5 (0.2)
Mozambique	21 (0.9)	Mali	5 (0.2)
Spain	20 (0.9)	Argentina	4 (0.2)
Burkina Faso	19 (0.8)	Belgium	4 (0.2)
Haiti	15 (0.7)	Jamaica	4 (0.2)
Netherlands	15 (0.7)	Poland	4 (0.2)
Peru	15 (0.7)	Burundi	3 (0.1)
Viet Nam	12 (0.5)	Dominica	3 (0.1)



**Figure 2.** Changes in the number of publications of ten topics in Table 2.

gives the distance (dissimilarity) between the two research areas<sup>31</sup>. The dendrogram reveals that infectious diseases, immunology, health-care services, and policies are among the research areas most strongly related to PrEP.

## Discussion

Besides a comprehensive review of current research trends regarding HIV PrEP, this bibliometric study introduced a comprehensive approach to examine the extent of collaboration networks in HIV PrEP from a large body of existing research literature. Research interest focusing on the use of PrEP in HIV prevention has indeed increased globally. We found that research on PrEP mainly focused on preventing sexual transmissions, improving the access and quality of health-care services for current users and vulnerable populations, including MSM, pregnant women, and children (Figs. S2 and S3). Moreover, we also observed the potential shift in global efforts from demonstrating scientific basis of PrEP effectiveness to addressing the socioeconomic issues around PrEP usage and implementation (Table 2). However, based on the research topics that have emerged from currently available literature, we found a data gap in research regarding sex workers, potential side effects of PrEP, concerns about stigma, and misjudgment toward PrEP users. Our findings support an enhanced effort to increase

both research focusing on the safety of PrEP and educational programs addressing potential misjudgment against PrEP and its users.

With regard to the countries that participated in PrEP research, we found a large number of empirical studies on PrEP took place in Africa, particularly South Africa, Uganda, and Kenya (Table 1). This concentration of research interest might be due to the observation that African countries have been significantly impacted by HIV epidemics<sup>1</sup>, while the United States is currently the leading nation in terms of accessibility to PrEP with about 225,000 people accessing these services<sup>32</sup>. On the other hand, despite having a significant contribution to the literature regarding HIV PrEP and a broad collaboration network by the Europa (Fig. S1), a relatively small number of 22,000 people who are currently receiving PrEP has been recorded in European countries. In other words, while the total population of Europe is approximately double that of the United States, the number of European residents with access to PrEP is only under one-tenth compared to the United States<sup>32</sup>.

Research topics about HIV PrEP appeared to focus on children and pregnant women at high risk of HIV infections in addition to prevention effect against HIV sexual transmission among the MSM population (Figs. S2 and S3). In particular, there are studies suggesting the potential protective effect of PrEP during breastfeeding for infants, especially newborns, who are

**Table 2. Ten most developed research topics related to pre-exposure prophylaxis classified by latent Dirichlet allocation**

Rank by the highest volume in the past 5 years	Research topics	n (%)
Topic 1	Cost-effectiveness of implementation of PrEP	456 (10.7)
Topic 2	Comorbidities among oral PrEP users	579 (13.6)
Topic 3	Implementation of PrEP among adolescents	255 (6.0)
Topic 4	Identification of populations having the demand for PrEP implementation	385 (9.1)
Topic 5	PrEP and residual risk from sexual activities	457 (10.8)
Topic 6	Barriers and facilitators of PrEP	503 (11.8)
Topic 7	Clinical and biological impacts of PrEP	592 (13.9)
Topic 8	Impact of adherence on PrEP effectiveness	397 (9.3)
Topic 9	Infant PrEP through breastfeeding	215 (5.1)
Topic 10	Drug resistance during PrEP	409 (9.6)

PrEP: pre-exposure prophylaxis.

at substantial risk of HIV infection. Moreover, it has been suggested that infant PrEP as well as implementation of PrEP in women during pregnancy has a potential to be part of a comprehensive strategy for the prevention of HIV mother-to-child transmission<sup>33-36</sup>. Nevertheless, based on the results, we found a lack of research on the utility of PrEP among serodiscordant couples who wish for natural pregnancies. There have been studies that demonstrated promising safe reproductive possibilities among serodiscordant couples, as long as complete suppression of viremia with HAART is achieved in the HIV-positive partner<sup>37-39</sup>. Although the ethical issue of natural conception among serodiscordant couples has remained controversial due to the residual risk of vertical as well as sexual HIV transmission, along with HAART, PrEP has shown its effectiveness in protecting uninfected partners against seroconversion to a certain extent<sup>38,40,41</sup>. With thorough consideration of contextual aspects, such as stigmatization, social norms, and cultural factors, PrEP has the potential to provide the couples with the opportunity of having safer pregnancy<sup>40</sup>. Further achievements regarding the use of PrEP against HIV acquisition have also been obtained among the lesbian, gay, bisexual, and transgender populations, as illustrated by the reduction of approximately 90% of incident HIV infections due to the use of PrEP<sup>10,42</sup>. Interestingly, sex workers were absent from the top research domains (Table S3), despite the observation that this population has been facing a substantial risk of HIV

infection worldwide<sup>43</sup>. Furthermore, sexual contact is the major and most common route of HIV transmission, and sex workers, especially females, are usually exposed to unprotected sexual activities, including condom-less and/or anal sex, which can put them at 13-time higher risk of HIV infection compared to the general population<sup>43,44</sup>. Therefore, PrEP-relevant research for this population deserves more attention and requires further empirical studies. On the other hand, for PrEP to be implemented at a population level, it is necessary to take the economic aspects of PrEP into account. Without health insurance, the out-of-pocket cost for PrEP can be as high as \$13,000 and the cost of PrEP is an important concern, even for high-income countries<sup>45,46</sup>. According to a survey of 31 European countries conducted by the European Centre for Disease Prevention and Control, 21 countries considered the cost of PrEP regimens and the cost of service delivery to be highly important limiting factors against its implementation<sup>45,47</sup>. Conceivably, with the rising interest in the cost-effectiveness of PrEP (Table 2 and Fig. 2), researchers and policymakers may address the issue and overcome potential barriers caused by the high cost of PrEP.

Our study also identified other research gaps in the literature of PrEP for HIV. First, although medical aspects of PrEP have been extensively examined, it appeared that safety concerns regarding the use of PrEP have not received adequate consideration. This finding was evident from its relatively low position in top research

domains (#22) and absence from the topics of most interest of Table 2. In addition to the inadvertent increase of other STIs among PrEP users, such a lack of research regarding PrEP safety might pose challenges in the future for long-term PrEP users. For example, in the initial stage, subclinical decreases of bone mineral density, lower renal and liver functions, and disturbances of the gastrointestinal tract, including abdominal pain, nausea and vomit, and diarrhea have been reported among PrEP users<sup>48-53</sup>. Long-term daily intake of PrEP medications might, therefore, result in bone thinning, kidney damage, and liver function problems<sup>54</sup>. Another concern about the safety of PrEP implementation is the potential of developing HIV drug resistance<sup>53,54</sup>, which urgently needs to be addressed as the aim of PrEP is to prevent HIV infection. Second, research focusing on strategies to reduce stigma and discrimination associated with using PrEP remains limited. Stigmatization is likely to occur among PrEP users, as the drugs used in PrEP can be the same medications for individuals already living with HIV. People using PrEP, therefore, might be perceived erroneously to be HIV-positive and hence stigmatized<sup>55-57</sup>. This issue is important because the target populations of PrEP are people facing a substantial risk of HIV acquisition, namely, MSMs and female sex workers, who have already experienced high level of social stigma and discrimination, especially in developing countries. Along with the misjudgment when taking PrEP, these individuals tend to have higher rates of anxiety and depressive disorders, which could negatively affect their medication adherence<sup>58-60</sup>.

Based on the research gaps identified from this study, some implications can be drawn. Further research on the potential safety issues of PrEP usage is warranted. This knowledge might help motivate future studies of novel medication regimens that can minimize the side effects of PrEP, especially for long-term PrEP users. In addition, more studies on the integration of combined strategies for HIV prevention might be necessary to effectively implement PrEP and to prevent potential increase in HIV resistance, including having enhanced patients' education toward safe sex and increased condom use, training on proper PrEP prescription for health-care providers, improving HIV diagnosis tests, and developing more robust drug combination. Furthermore, continued efforts should be made to lessen the misjudgment and stigmatization toward PrEP users. For example, studies on the effectiveness of media campaigns regarding PrEP usage to educate the public about PrEP may inform future designs of more effective strategies to reduce PrEP-relat-

ed stigma and discrimination, and hence increasing PrEP adherence and effectiveness, in socioeconomically disadvantaged settings.

This study has several limitations. As only publications in English were included for the analysis, the selection is biased toward searches belonging to English-speaking countries. In addition, this study focused on research articles and review papers rather than all types of publications, which could have an influence on the thoroughness of the inferences.

## Conclusions

By conducting a bibliometric analysis under a scientometric approach, we revealed the global research patterns and current interests in multiple areas of HIV PrEP research. We also identified several research gaps for future studies in the areas of PrEP implications. Despite a large amount of research in recent years on PrEP, there are still barriers, such as the lack of research on the potential long-term safety of PrEP usage and on strategies to eliminate social misjudgment against PrEP users. A greater understanding of these issues across health-care settings could provide important insights into scaling up PrEP implementation worldwide and for PrEP to reach its full potential.

## Supplementary data

Supplementary data are available at AIDS Reviews online (<http://www.aidsreviews.com/index.php>). These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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