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Acquired syphilis in the context of pre-exposure prophylaxis for HIV: a systematic review of the scientific literature

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Abstract

The aim of this study was systematically review the acquired syphilis before and during follow-up of pre-exposure prophylaxis (PrEP) for HIV. We analyzed articles that studied PrEP users with the outcome of acquired syphilis. The eligibility criteria were studies retrieved from the United States National Library of Medicine (Pubmed), Latin American and Caribbean Health Sciences Literature (Lilacs), Embase and Scopus databases, published between 2012 and 2023, in English, Spanish or Portuguese. We performed the descriptive synthesis and quality analysis of selected studies using the Newcastle Ottawa scale or Cochrane scale. We also used random-effects models to generate pooled rate estimates for syphilis before PrEP and during follow-up. A total of 4412 studies were found and 35 were selected, all in English, and almost all with high or satisfactory quality. The review found a PrEP syphilis rate of 6.0%. A summary of three studies estimated a 2.34-fold increased risk of syphilis acquisition during PrEP, with an incidence rate of 8.89 cases/100 person-years. These findings warrant caution due to study heterogeneity. Compared to HIV-positive individuals, PrEP users exhibit potentially higher syphilis rates, particularly among those aged 33-38 years, and factors such as age ≥ 35 years, MSM status, prior sexually-transmitted infections, and longer PrEP duration (every 6 months) are associated. Future research should further investigate these PrEP-related factors contributing to heightened syphilis risk.

Keywords

Syphilis. Pre-exposure prophylaxis. Systematic review. Public health.

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Introduction

Oral pre-exposure prophylaxis (PrEP) is an effective measure for preventing HIV infection, recommended for people at high risk of transmission, such as men who have sex with men (MSM) and female sex workers[1]. However, people who would benefit most from PrEP do not use condoms as often as they should, resulting in an increased risk of sexually transmitted infections (STIs)[2].

The increased use of PrEP has been associated with rising rates of sexually transmitted bacterial infections in various settings. This phenomenon has generated discussions about risk compensation, resulting from the lower use of condoms among individuals who receive PrEP[3]. This higher incidence of STIs among people who use PrEP can be justified by a real effect of behavioral disinhibition or by the apparent increase in the screening of people involved in preventive sexual care[4].

Syphilis is an STI that can be transmitted through different ways, the most common being through sexual intercourse. It manifests itself in three distinct phases – primary, secondary, and tertiary – interspersed with moments of latency, in which the disease becomes asymptomatic. In the current scenario, syphilis has regained visibility in recent years as a serious with public health problem, due to the new trend of the high rate of disease spread, especially in underdeveloped countries[5].

In a cohort of 2019 PrEP users in Brazil, there was no significant variation in the number of sexual partners during the follow-up, but there was a significant reduction in the use of condoms during sexual intercourse ($p < 0.001$). Although there was a non-significant increase in the incidence of syphilis ($p = 0.080$), there was a 50% decrease in notifications of signs and symptoms of STIs[6].

Given this scenario, and to fill the knowledge gap about the behavior of acquired syphilis in people who use PrEP, the aim of this study was systematically review the acquired syphilis before and during follow-up of PrEP and its evaluated possible associated factors.

Materials and methods

Design

This study is a systematic review, which uses primary studies as its data source and seeks to answer a clearly formulated question. This review assessed the rates of acquired syphilis in people who use PrEP. The methodological recommendations of the preferred reporting items for systematic review and meta-analysis (Prisma) were used. The review protocol was submitted to prospero under registration number CRD42022382890.

Table 1. Pi(e)cos strategy of the systematic review

Acronym	Concept	Description
P	Population	Population over 16
I (E)	Intervention or exposure	PrEP
C	Comparison	Where applicable, people who are eligible for PrEP but did not benefit from the intervention or exposure of interest
O	Outcomes	Laboratory-proven primary, secondary, latent or tertiary syphilis infection
S	Type of study	Articles that were descriptive and analytical observational studies and randomized clinical trials where the population and the outcome described above were analyzed.

Guiding question

The guiding question used to answer the objective of the study was formulated using the Pi(e)cos strategy: population, intervention or exposure, comparison, outcome, and type of study. The guiding question used was Do PrEP users have a higher risk of acquiring syphilis and what are the possible described and associated factors? The description of the Pi(e)cos strategy is shown in table 1.

Criteria for selecting studies

The inclusion criteria were articles published after 2012 (the start of PrEP use worldwide); articles that were descriptive observational studies, analytical studies, and randomized clinical trials, which met the

following criteria: the population studied was PrEP users whose outcome was acquired syphilis infection during PrEP follow-up and that were published in Portuguese, English, or Spanish.

Studies meeting the following criteria were excluded: case series, case studies, studies carried out *in vitro*, studies carried out in animals and conference abstracts, letters to the editor, results and award reports; studies with methodological limitations that prevent the incidence of syphilis during PrEP use or that did not include the abstract or full text. Articles indexed repeatedly in two or more databases were only considered once. In addition, articles that analyzed the same cohort of subjects and throughout the same period were also considered only once, and the most complete in terms of data was selected.

Search strategy and data extraction

The initial search was carried out in July 2021 and updated in May 2023. The data source comprised the scientific production indexed in the following databases: United States National Library of Medicine (PubMed), available at: https://pubmed.ncbi.nlm.nih.gov/; Latin American and Caribbean Health Sciences Literature (Lilacs), available at: https://lilacs.bvsalud.org/en/Embase and Scopus, available at: https://www.embase.com/landing?status=grey and https://www.scopus.com/standard/marketing.uri#basic, respectively.

The basic search strategy used to obtain the articles was: "pre Exposure Prophylaxis" OR "Pre Exposure Prophylaxis (PrEP)" OR "Pre-Exposure Prophylaxis" OR "Pre-Exposure Prophylaxi (PrEP)" OR "Pre-Exposure Prophylaxis (PrEP)" OR "Prophylaxi, Pre-Exposure" OR "Prophylaxi, Pre-Exposure (PrEP)" OR "Prophylaxis, Pre-Exposure" OR "Prophylaxis, Pre-Exposure (PrEP)" AND "Bejel" OR "Bejels" OR "Infection, Treponemal" OR "Infections, Treponemal" OR "Treponemal Infection" OR "Latent Stage Syphilis" OR "Syphilis, Latent Stage" OR "Syphilis" AND NOT "Syphilis, Congenital."

Study selection

The studies were initially selected by evaluating the titles and abstracts, using the Rayyan® tool (https://www.rayyan.ai/), carried out independently by two researchers, and any possible discrepancies were resolved by a third researcher, according to a previously defined protocol. The articles considered eligible had their texts assessed in full. During the full-text reading, they were again submitted to the same eligibility criteria, adding the criterion of having at least the incidence coefficient of acquired syphilis during the period of PrEP use. After the final selection, data extraction began.

Data extraction and presentation

The data extracted from the included studies was related to the characteristics of the publication (author, year of publication, journal), the study design (type of study, research site, period of collected data, study population, number of followed people, age, PrEP modality (daily or on demand), follow-up interval, diagnostic tests) and its findings related to syphilis (incidence and recurrence of acquired syphilis during follow-up), syphilis data before PrEP, possible associated factors/subgroups.

Meta-synthesis and presentation in the form of tables presented in the supplementary material are based on frequency to facilitate data interpretation.

Quality of evidence

The quality of the evidence of the included experimental and observational studies was assessed using the Cochrane Collaboration scale and the Newcastle Ottawa scale (NOS), respectively. For the NOS, studies that received 7 stars or more were considered to be of high quality; between 5 and 6 stars were considered to be of satisfactory quality; and those with 4 stars or less were considered to be of low quality[7].

Assessment of heterogeneity and data synthesis

When data were available, we summarized the proportion of syphilis at baseline, the pooled risk relative before and after PrEP, and the incidence of infection during PrEP follow-up, performing meta-analysis of studies using random effects models. At this stage, we previously excluded clinical trials and low-quality observational studies. We also defined the weight assigned to each study as being the inverse of its variance, in addition to the effect estimation being calculated using the double arcsine transformation of the Freeman–Tukey type.

To evaluate the heterogeneity between studies, we calculated I-squared statistic (I^2), with 75-100% value indicating considerable heterogeneity. In these cases, we also conducted subgroup analyses to explore possible reasons for heterogeneity, stratifying by regions

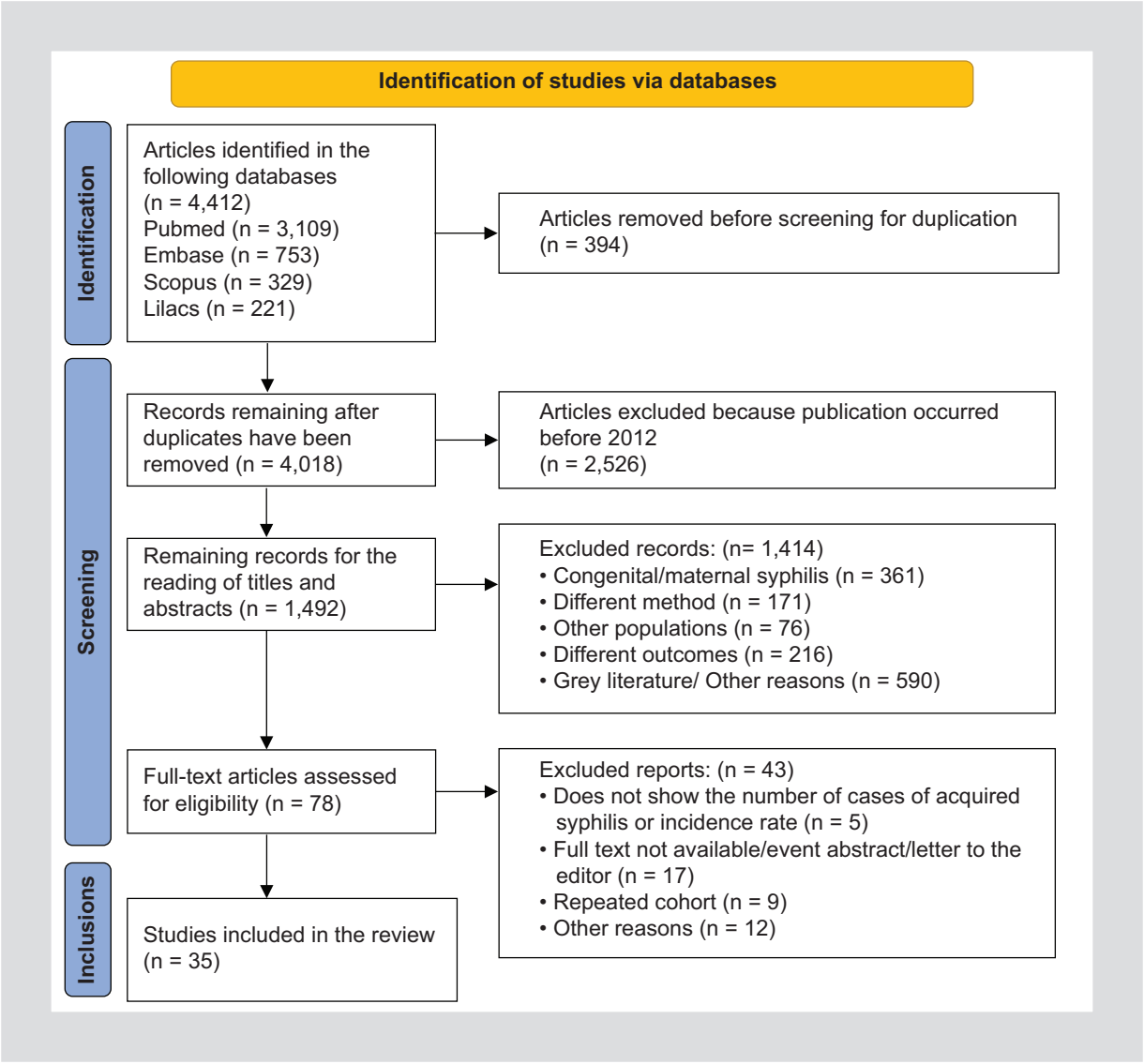

Figure 1. *Prisma flow diagram of the study identification process.*

of the sustainable development goals (SDGs) and by population of study (any PrEP users versus MSM or trasngender women that have sex with men) using the same statistical methods.

For each presented finding, we estimated the pooled rate or incidence, confident interval (CI) - 95%, I^2, and p-value (≤ 0.10).

Ethical aspects

The study was not submitted to the research ethics committee, as it was based on data from scientific studies published in electronic databases in the public domain, using only secondary data that had already been published.

Results

Results of the study selection process for the systematic review

The process of searching for articles that answered the research question identified 4412 documents, most of which were found in the PubMed database. After screening by the researchers, 35 articles were selected for extraction (Fig. 1).

Characteristics of the publications included

The characterization of the publications can be found in Supplementary Table 2. All the publications

Table 2. Incidence of acquired syphilis in PrEP users

Study (participants; country)	Before PrEP n (/100 py)*	After PrEP (/100 py)	IRR†	95% CI§
Beymer et al., 2018[11] (275; USA)	11 (11.94)‡	29 (17.65)	2.97	1.23-7.18
Nguyen et al., 2018[12] (109; Canada)	9 (8.26)	16 (14.68)	1.74‡	0.64-3.40
Azarnoosh et al., 2021[31] (46; Denmark)	1 (4.30)	5 (21.70)	5.00	0.58-42.80

*Per 100 person-year.
†IRR: Incidence rate ratio.
‡aIRR: Adjusted incidence rate ratio.
§95% confidence interval.
PrEP: Pre-exposure prophylaxis.

were published in English, from 2014 to 2022, with the highest number of publications in 2022 (10 studies), observing a growing increase over time of studies published on the subject. In addition, the majority of publications (69.4%) were in journals geared towards STIs.

Based on the NOS for observational studies, 21 studies had good quality (references) and 11 studies had moderate quality (references). The two clinical trials showed a low risk of bias.

Characteristics of the studies

To contextualize the selected studies, their main characteristics were extracted (Supplementary data - Chart 2). Regarding the study design, almost all were cohort studies, with only two clinical trials. It should be noted that most of the cohort studies were extracted from the ones evaluating the efficacy of PrEP, called "PrEPX"[8], "Be-Prep-ared" and "Amprep"[9], "NZPrEP"[10], among others. In addition, the most common country of study was the United States, with more studies carried out in developed countries (Australia, Canada, France, Belgium, Germany) than in developing ones.

The target populations were mostly any individual who met the national criteria for PrEP use. Some studies, however, further delimited their scope, such as PrEP users who were MSM[11-16], or men at birth and black individuals[4]. Only three studies had comparator groups other than PrEP users, namely post-exposure prophylaxis (PEP) users[12], people living with HIV (PLHIV)[17], and a non-PrEP group[13]. The study by Iniesta et al.[18] compared PrEP users from different health services (community center, HIV referral hospital, STI referral hospital, and STI outpatient service) and Van Dijck et al.[19] compared mouthwash intervention groups (mouthwash - placebo - Group I and placebo/mouthwash - Group II).

Data were collected through visits, consultations (in person or through telemedicine), or by accessing health databases. The PrEP modality (daily dose or on-demand) was reported by 25 studies that comprise the review, most of them using daily doses. The predominant follow-up interval was quarterly or 6-monthly. In addition, the outcome of syphilis during follow-up was measured by laboratory testing, following national protocols, using serological tests (rapid plasma reagin, venereal disease research laboratory, TTPA, treponema pallidum hemagglutination assay), although 17 studies did not provide information on the method used. In the meantime, the number of people followed in the studies ranged from 46 to 22,730 (median = 429; interquartile range = 150-1,343), with the most common age range being between 30 and 40 years (Supplement Table 3).

Syphilis acquired before PrEP

The presence of acquired syphilis before prophylaxis was assessed mainly through the results of serological tests or during follow-up before the period (Supplement Table 3) although it was not possible to identify a pattern regarding the identification of syphilis before PrEP. In addition, 10 studies did not provide data on the presence of syphilis before follow-up.

The proportion of syphilis before follow-up ranged from 0.2 to 41.1%, with the most common range being 1-13% of syphilis in the baseline cohorts. It was possible to summarize the proportion of syphilis before PrEP from

Table 3. Rate of acquired syphilis during follow-up of PrEP users and non-users

Study (participants; country)	PrEP n (/100 py)*	Non-PrEP n (/100 py)	aIRR†	95%CI‡
Nguyen et al., 2018[12§] (304; Canada)	16 (14.68)	3 (3.49)	3.03	0.85-10.76
Montaño et al,. 2019[13¶] (1.095; USA)	NI†† (6.90)	NI (2.30)	2.90	1.50-5.60
Lemmet et al., 2022[17**] (10.265; France)	12.20%	12.50%	-	-

*Per 100 person-year.
†Adjusted incidence rate ratio.
‡Confidence interval.
§People using post-exposure prophylaxis (PEP).
¶People living with HIV (PLHIV).
**MSM eligible for PrEP.
††Not Informed.
PrEP: Pre-exposure prophylaxis.

14 studies (pooled rate [95% CI]: 6.0 [3.0-9.0]), but the studies were considerably heterogeneous (I^2 = 99%, p ≤ 0.10). Subgroup analysis was conducted by SDGs and target population (Supplement Table 4), in which neither could explain the possible heterogeneity of the studies.

The rate of 41.1% was possibly found by the eligibility criteria of the study by Van Dijck et al.[19], which consisted of PrEP users diagnosed with an STI in the past 2 years.

Three studies compared the incidence of syphilis before and after PrEP (Table 2), among which Beymer et al.[11] identified an increased risk of infection after the prophylaxis. The pooled relative risk of theses studies was 2.34 (95% CI = 1.42-3.87, I^2 = 0, p = 0.59.

Syphilis acquired during PrEP

Syphilis during PrEP was verified through the proportions and incidence rates extracted from the studies.

We summarized the incidence of syphilis/100 person years during PreP follow-up as well, resulting a pooled incidence of 8 studies (pooled incidence [95% CI]: 8.89 [6.45-13.32] cases/100 person years), with considerating heterogeneity (I^2 = 92%, p ≤ 0.10). Subgroup analysis was conducted by SDGs also (Supplement Table 5), with lower heterogeneity in studies that occurred in Australia (I^2 = 69%) when compared to studies carried out in Europe or North America (I^2 = 94%). When it was realized subgroup analysis by target population, we identified lower heterogeneity also in studies realized just with MSM or transgender women who have sex with men (pooled incidence [95% CI]: 12.06 [8.40-15.71] cases/100 person years; I^2 = 69%; p = 0.02).

Syphilis follow-up was also carried out through comparison with similar groups (Table 3), such as interviewed people who had an indication for PEP[12], PLHIV[13], and MSM with eligibility criteria for PrEP but who did not use it[17]. In this comparison, an increased risk was identified when compared to people with HIV. In the other unexposed groups, there was no evidence of additional risk in the context of PrEP. Due to the distinct nature of the comparator groups, it was not feasible summarizing this difference rate.

Table 4. Syphilis rate in PrEP users by follow-up period

Study (participants; country)	Syphilis detection rate per month of follow-up%
Barbosa et al., 2022[6] (219; Brazil)	Month 4 = 14.00 Month 7 = 15.60 Month 10 = 21.40
Volk et al., 2015[20] (657; USA)	Month 6 = 3.30 Month 12 = 5.50
Schumacher et al., 2020[21] (290; USA)	Month 6 = 9.90 Month 12 = 8.70
Freeborn, Portillo, Boyer and Santos, 2020[22] (81; USA)	Month 1 = 11 Month 4 = 1 Month 7 = 15 Month 13 = 1
Laurent et al., 202123 (598; Africa)	Month 1 = 0.20 Month 6 = 1

PrEP: Pre-exposure prophylaxis.

The evolution of syphilis rates during the PrEP follow-up period was estimated by Volk et al.[20], Schumacher et al.[21], Freeborn et al.[22], Laurent et al.[23], and Barbosa et al.[6] (Table 4). There was no evidence of an increase or decrease in rates over the course of follow-up, although there was heterogeneity in the testing interval (quarterly or 6-monthly). As for the studies with peri-

odic rates, the study by Barbosa et al.[6] and Freeborn et al.[22], both with quarterly evaluation, showed higher point estimates of detection rates than the other studies with 6-monthly serological follow-up.

A comparison of new cases of acquired syphilis was also carried out by Iniesta et al.[18] between health services where PrEP users were followed. The same study found that, at baseline, people eligible for PrEP had lower rates of syphilis in community centers than other specialized HIV or STI services. However, over the course of follow-up, this difference was not significant.

Regarding syphilis reinfection, the study by Lemmet et al.[17] showed that 17.1% of followed PrEP users had reinfection, with a greater chance of this occurring in older people (adjusted odds ratio [aOR] 1.31; 95% CI 1.04-1.67) and in MSM (aOR 2.71; 95% CI 1.89-3.96).

Regarding the characterization of people diagnosed with syphilis while taking PrEP, the average age was 33 years and 33.9% had a history of syphilis infection[16]. In the study by Lemmet et al.[17], people with syphilis had the disease detected at a median age of 38.5 years, but there was no difference from other PrEP users without a diagnosis of syphilis. In general, risk behaviors were comprehensively assessed in PrEP users or people diagnosed with STIs in general, and it was not possible to specify behaviors in people diagnosed with acquired syphilis.

Finally, three studies provided evidence on the possible factors associated with acquired syphilis in the context of PrEP, such as age, gender, sexual orientation, history of STIs, and length of time taking the medication. The age groups identified as those being at risk were 35-47 years[17] and 50-59 years[24]. While being female was considered a protective factor[17], being MSM had a 6.60 chance (95% CI 5.10-8.66) of having syphilis over the course of the follow-up when compared to other groups. Furthermore, according to Schmidt et al.[24], having a previous history of STIs in the 6 months before PrEP or an unknown history may confer a 3.32 (95% CI 2.66-4.14) and 1.75 (95% CI 1.29-2.39) chance of having acquired syphilis infection, respectively. In addition, prolonged PrEP use was also identified as a factor associated with syphilis infection (adjusted incidence rate ratio 1.08, $p < 0\text{-}0001$)[8].

Discussion

Although syphilis is an old disease, the "phenomenon" of PrEP has brought the need to study this relationship, with several publications revealing, among other outcomes, syphilis during prophylaxis. In all, 35 publications were found, published from 2012 to 2022, which provided relevant information on this context. The findings of this review showed that before starting PrEP, the pooled syphilis rates were 6.0%. The estimated summary of three studies indicated that PrEP users may have a 2.34-fold increased risk of acquiring syphilis during PrEP use. In turn, the pooled incidence of acquired syphilis during PrEP use was 8.89 cases/100 person-years. These values, however, should be viewed with caution due to the high heterogeneity of the studies. During the use of PrEP, the rates can vary between the followed groups, with a higher risk in older individuals, MSM, those with a history of STIs in the 6 months before PrEP and with a longer duration of use of prophylaxis (every 6 months); being a woman, however, was shown to be a protective factor. Compared to similar groups, people taking PrEP have a higher risk of syphilis infection than PLHIV and, over time, there was no heterogeneity in the rates. Primary care services may have a lower prevalence of active syphilis on admission to PrEP; however, the incidence of people using the medication over the course of the follow-up does not vary between community centers and specialized services. In turn, reinfection with syphilis can be observed in MSM and older individuals.

The rates of syphilis extracted from the selected studies were significantly high. The World Health Organization estimates that, in the general population, 7.5 million people between the ages of 15 and 49 acquired syphilis in 2020. However, the MSM and gay populations are disproportionately affected, with an estimated prevalence of acquired syphilis of 7.5% in gay men and MSM and 0.5% in men in the general community[25]. This notably vulnerable population needs to be considered by countries in their responses to the elimination of syphilis, converging with the goals set out in the 2030 Agenda for sustainable development[26].

People who take PrEP, mostly MSM, may have an increased frequency of sexual intercourse without using condoms; therefore, they should be tested for syphilis every 3 months, due to the high risk of infection. With regard to syphilis prevention, although doxycycline has been shown to be effective in some studies, it has not been possible to predict the long-term risk of resistance of STI bacteria to tetracyclines. Therefore, prevention combined with PrEP is still the best measure to prevent syphilis and other STIs[27].

In one of the evaluated studies, individuals receiving PrEP in community centers had lower rates than those in specialized HIV/STI services, although this disparity did not remain significant throughout the follow-up.

It should be noted, however, that trends in acquired syphilis rates can be greatly affected by the quality of primary care, such as coverage of the territory, availability of rapid tests, distribution of condoms, availability, and application of penicillin in primary care[28].

Although few studies have compared syphilis rates with other groups not using prophylaxis, one study found a significant higher rate of syphilis in PrEP users compared to PLHIV, and no difference when compared to similar MSM or PEP users. In a study of MSM and transgender women, a higher proportion of syphilis was found in PLHIV (29.1% vs. 5.3%, for HIV-positive and negative individuals, respectively, p = 0.002)[29]. The eligibility criteria for PrEP may therefore reveal important aspects that should be better analyzed in the context of STI and HIV transmission, such as the number of sexual partners, condom use, and recreational drug use.

In the studies, being a man who has sex with men (MSM) was identified as a sexual orientation with greater vulnerability to syphilis during PrEP use. MSM, even when considered low risk for HIV, can show syphilis rates similar to high-risk groups, reaching 12.5 cases/100 person-years for STIs; however, unlike our findings in the context of PrEP, the syphilis rate was associated with younger age[30].

There are limitations to this study. Firstly, findings from the gray literature were not included because it was not possible to extract relevant information or there were not enough data to assess the quality of the research, and the representativeness of the included studies may have been reduced. Second, the method for measuring syphilis rates varied among studies, particularly in the assessment of syphilis prior to PrEP initiation. Thus, the pooled estimates should be viewed with caution, and better studies should be carried out aimed at assessing the factor of prophylaxis in the incidence of syphilis even with the considered limitations, this study provides important information and incorporates knowledge about acquired syphilis in the context of PrEP, highlighting the need to explore the subject with a view to more assertive STI prevention protocols.

Conclusion

This review allows us to conclude that the rates of acquired syphilis in the PrEP-using population can be quite high, with variations throughout follow-up, mostly in MSM, in the 33-38 age groups. Nevertheless, given the challenge of establishing a comparative analysis between syphilis incidence before and after PrEP, further studies are warranted to explore this topic and assess the prophylaxis's impact on the infection's magnitude. The significant presence of syphilis recurrence in the follow-up may reveal the need for a syphilis prevention approach in specific subgroups of PrEP users, aiming to reducing syphilis rates in this population.

Moreover, there are factors within the context of PrEP, such as age, sexual orientation, history of STIs, and time of prophylaxis use, which may pose an additional risk of acquired syphilis; although numerous studies have reported the rate of syphilis during PrEP, it is appropriate that other variables, such as socioeconomic and behavioral variables, should be better explored in future studies. In this sense, it is recommended to direct the offer of PrEP to primary care as a strategy to reach the most vulnerable populations.

Supplementary data

Supplementary data are available at DOI: 10.24875/AIDSRev.24000006. 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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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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