

REVIEW ARTICLE

PrEP for women in Europe: a systematic literature review

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Abstract

Background: Prevention of HIV transmission is fundamental to ending the HIV epidemic. Pre-exposure prophylaxis (PrEP) with oral tenofovir-emtricitabine (TDF-FTC) is an established HIV-prevention method; however, most PrEP services in Europe have been targeted at men who have sex with men (MSM). A survey in 2021 by Women Against Viruses in Europe (WAVE) showed considerable variation in PrEP access and guidance for women throughout Europe. WAVE therefore commissioned this systematic review to provide insight into PrEP provision and barriers to uptake for women in Europe.

Methods: PubMed, Embase, and Scopus were searched for studies (January 2013–May 2021) that reported on actual (e.g., efficacy and safety) or hypothetical (e.g., awareness, barriers, PrEP impact models) use of oral PrEP involving women (including cis, transgender, pregnant, migrant, and breastfeeding women). Search terms included HIV, pre-exposure prophylaxis (specifically TDF-FTC), and women. Studies performed outside of the World Health Organization European region were excluded.

Results: The search identified 4716 unique citations, and 45 peer-reviewed articles (44 studies) were included. The majority of these studies (34/44 [77%]) included recipients or potential recipients of PrEP, representing 4699 women (243 transgender women). However, few studies were women focused (4/34 [12%]) or took place outside of Western Europe (3/34 [9%]). Across the three clinical studies that reported women-specific outcomes (60 transgender women, 13 pregnant, and 19 cis women), no breakthrough infections were recorded during the use of PrEP. Lack of awareness of PrEP, low self-estimation of HIV acquisition risk, concerns about stigma, lack of protection against other sexually transmitted infections, and PrEP interaction with hormones (for transgender women) were identified as barriers to use. The remaining studies examined healthcare professionals' perceptions of PrEP (9/44 [20%]), asked for public opinion (2/44 [5%]), or modelled the potential of PrEP for HIV prevention (1/44 [2%]).

Conclusions: This review revealed a notable lack of literature on PrEP for cis and transgender women in Europe. This is synonymous with a lack of PrEP provision for women in this region. Barriers to PrEP uptake are complex and rooted in institutional and societal stigma, which must be addressed at policy level. HIV prevention with PrEP is not ‘one size fits all’ and requires a nuanced gender-responsive approach. Further research into the use of PrEP in cis, pregnant, breastfeeding, and transgender women is essential if we are to stop HIV transmission by 2030.

KEYWORDS

cis women, Europe, HIV, PrEP, Pre-exposure prophylaxis, transgender women

INTRODUCTION

Prevention of HIV transmission is fundamental to ending the HIV epidemic. The Joint United Nations Programme on HIV/AIDS 90:90:90 targets and Fast-Track initiative [1], now the Global AIDS Targets 2025, aim to end AIDS as a public health threat by 2030. Ways to achieve this include the use of pre-exposure prophylaxis (PrEP) with oral tenofovir-emtricitabine (TDF-FTC) and other prevention methods such as condoms, focusing on key at-risk populations, male circumcision, and targeted communication. In 2015, the World Health Organization (WHO) recommended PrEP as a safe and effective prevention option in all people at risk of HIV acquisition, irrespective of gender [2]. TDF-FTC was licensed for PrEP use in 2012 in the United States and in 2016 in Europe. In total, 53% of the global population living with HIV are women, and – in 2018 – nearly 50 000 women were newly diagnosed with HIV, representing 36% of the total 140 000 new HIV diagnoses in the WHO European region [3]. To date, most PrEP services in Europe have been targeted at men who have sex with men (MSM), with very few women-centred initiatives. The number of new diagnoses in women suggests this approach should be reviewed.

One of the three main UN targets for 2025 for 95% of people at risk of HIV infection is the use of appropriate, prioritized, person-centred, and effective combination prevention options, which includes the use of PrEP in addition to condoms, high coverage of key populations with a focus on young women, conditional cash transfer programmes; whereby safer sexual health practices, regular HIV testing and attending education are financially incentivized, voluntary medical male circumcision, focused communication, and use of digital media. The effectiveness of PrEP depends on reaching at-risk populations, uptake, and adherence. Understanding the perspectives of women with regards to PrEP is essential for successful implementation of PrEP programmes.

A survey of 34 countries in Europe conducted by Women against Viruses in Europe (WAVE), a subcommittee of the European AIDS Clinical Society, demonstrated that women's access to PrEP in Europe remains limited [4]. Only six countries reported having specific recommendations for PrEP in women (Austria, France, Germany, Ireland, Ukraine, and the UK); 15 countries (47%) reported specific obstacles to PrEP access for women (Austria, Croatia, Denmark, France, Germany, Greece, Israel, the Netherlands, Poland, Portugal, Spain, Sweden, Turkey, Ukraine, and the UK), where women were neither included in PrEP guidelines nor targeted in clinical studies as they were generally not seen to be at risk for HIV acquisition.

We found one systematic review focusing on pregnant and post-partum women that included a total of 1042 PrEP-exposed pregnancies, but the studies included women living in Kenya, Uganda, Zimbabwe, and South Africa [5].

We did not find any reviews focusing on cis women in Europe. Other reviews published focussed on MSM [6–8] or on PrEP use in regions other than Europe [9].

Although data from these PrEP studies in women can be extrapolated, there also needs to be an understanding of how to provide HIV prevention to the hugely diverse population of at-risk women and transgender women in Europe, which is the focus of WAVE.

We conducted a systematic review of the literature to follow on from the survey conducted by WAVE to inform on the experience of provision, barriers and access to, and use of PrEP for women in Europe and to identify gaps in research.

METHOD

Search strategy and selection criteria

In this systematic literature review, we searched PubMed, EMBASE, and SCOPUS using the date ranges 1 January

2013 to 18 May 2021. We used the following search terms across all databases: (pre-exposure prophylaxis or preexposure prophylaxis or antiretroviral prophylaxis or preexposure chemoprophylaxis or chemoprevention or PrEP) AND (HIV OR AIDS) AND (women OR females). We considered studies of PrEP with oral TDF-FTC antiretroviral in cis and transgender women living in the WHO European region for prevention of HIV acquisition that reported on uptake of PrEP, outcomes including HIV acquisition, and any adverse events.

We included studies in the review if they met the following criteria: (1) included PrEP willingness and awareness, barriers to and facilitators of PrEP use, and uptake and outcomes pertaining to cis and transgender women; (2) presented primary data (qualitative or quantitative); and (3) were published as a peer-reviewed journal article. We excluded studies that did not include any women. Studies outside of the WHO European region were excluded during the title-abstract screening phase. Conference abstracts were not considered.

Data extraction and management

Titles and abstracts identified by the search strategy were independently screened for relevance by two reviewers (Naomi Fitzgerald and KF) in duplicate. Potentially eligible studies were selected and the full text of each article was read by the two independent reviewers. Discrepancies were resolved through discussion. The full text of papers meeting the inclusion criteria were obtained and reviewed, and key data were extracted using standardized forms. Extracted data included citation information, population studied, country, sample size, whether or not the study was focused on women, number of cis women included (including numbers specifically of transgender, breastfeeding, or pregnant women, and other), and key findings pertaining to uptake frequency of PrEP in women living in Europe, HIV acquisition during use of PrEP, knowledge and perceptions of PrEP among women in Europe, and attitudes and perceptions of healthcare workers with regards to PrEP.

Findings were categorized according to the following population groups (not mutually exclusive): (1) cis women, (2) transgender women, (3) pregnant and/or breastfeeding women, and (4) healthcare providers.

Findings from studies specific to women or transgender women or that included more than 10 women were classified according to the following five themes to evaluate PrEP uptake and factors that may impact uptake and use:

1. PrEP willingness and awareness
2. Barriers to and facilitators of PrEP use

3. PrEP uptake and outcomes
4. PrEP impact studies
5. Healthcare providers' knowledge and attitudes

Description of data

A summary table of geographical location by country and area of Europe, type of PrEP use (actual vs. hypothetical), and number of women included in the studies was created. Studies evaluating recipients or potential recipients of PrEP were further categorized according to the number of women included.

The main findings for each population group were summarized descriptively under each theme.

Although risk-of-bias assessments, meta-analysis, and other quantitative analyses were specified in the original protocol, they were not possible because of the very limited number of clinical follow-up studies specifically focused on PrEP in women in Europe.

Registration

The protocol for the systematic review was pre-registered in PROSPERO (ID number: CRD42021269414).

RESULTS

Description of included studies

Our search identified 4716 citations, providing 2371 unique records after duplicates were removed. After screening, 113 articles were selected for full-text review, of which 68 were excluded. The main reasons for exclusion were lack of original data (e.g., reviews, commentaries, $n = 19$) and no clear inclusion of women in the study ($n = 18$).

Finally, 44 original studies represented in 45 peer-reviewed articles were included. See Figure 1 [10–42] [43–53].

In total, 34 of the 44 (77.3%) studies included women recipients or potential recipients of PrEP, representing 4699 women, including 243 transgender women. Less than half of these studies (16/44 [36.4%]) were women focused or included more than 10 women. These women-focused studies were categorized into the study themes as follows: PrEP willingness and awareness ($n = 6$) [14, 25, 32, 43, 48, 51], barriers and facilitators ($n = 5$; three of these also examined 'willingness and awareness') [24, 32, 48, 50, 51], PrEP uptake and clinical outcomes ($n = 5$) [18, 31, 44, 45, 47], and PrEP impact studies ($n = 3$) [26, 42, 54]. Almost all

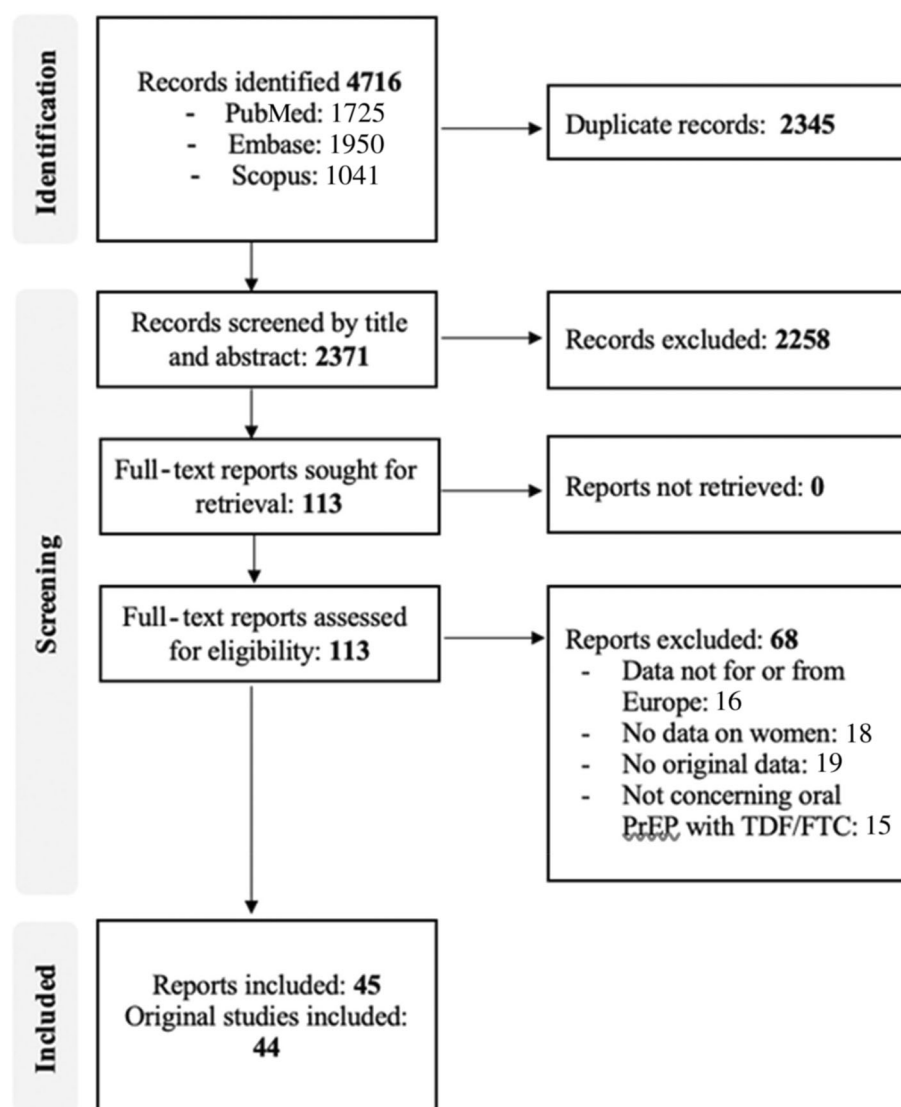


FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart detailing study inclusion. PrEP, pre-exposure prophylaxis; TDF-FTC, tenofovir-emtricitabine

studies of recipients or potential recipients of PrEP took place in Western Europe (32/34 [94.1%]). See Table 1.

The remaining studies did not include recipients or potential recipients of PrEP: six studies looked at healthcare professionals' opinions and behaviours for prescribing PrEP to women (6/44 [13.6%]) [46, 52, 53, 55, 56, 57], public opinion with regards to PrEP (2/44 [4.5%]) [49, 58], and a hypothetical PrEP impact model (1/44 [2.3%]) [17] (Hahn).

PrEP willingness and awareness

Cis women

Six studies, including 1009 women, examined awareness of and willingness to use PrEP [14, 25, 32, 43, 48, 50].

Generally, PrEP awareness was low, but once information on PrEP was provided, most participants across these studies viewed PrEP as a potential prevention option they would use.

Among 678 women from 11 European countries, almost half (46.8% [$n = 317$]) knew of PrEP prior to the survey conducted by Delebre et al. in 2016, but only 122 women (18.0%) stated that they 'probably' or 'definitely' would be interested in using PrEP [14]. Seven variables were associated with greater interest in using PrEP: younger age (18–29 years), 'bad' self-perceived financial status, being a migrant, not being in a relationship (single or dating), history of sexual abuse, 'high' self-perceived risk of acquiring HIV, and high objective risk (HOR) for HIV status. HOR status was identified using the following criteria based on European AIDS Clinical Society and

TABLE 1 Studies including recipients or potential recipients of PrEP

Study characteristics		Studies (n)	Women (n)	
			All	TGW ^e
Location	Eastern European region	2	75	0
	• Czech Republic	1	1	0
	• Russia	1	74	0
	Western European region	31	1082	243
	• UK ^a	13	542	151
	• France	8	515	69
	• Spain	3	10	9
	• Germany	2	13	10
	• Italy	2	2858	0
	• Belgium	1	4	0
	• Ireland	1	2	2
	• the Netherlands	1	2	2
	Pan-Europe	1	678	0
	Type of PrEP use investigated			
	• actual use ^b	19	263	179
	• hypothetical use ^c	13	3605	59
	• mixed	2	831	5
	Inclusion of women			
	• ≤10 women included	18	67	37
	• >10 women included	12	3785	69
	• Women focused	4	847	137
	• PrEP willingness and awareness ^d	6	1009	58
	• Barriers to and facilitators of PrEP ^d	5	265	53
	• PrEP uptake and outcomes	5	217	148
	• PrEP impact	3	3245	0
Total		34	4699	243

Abbreviations: PrEP, pre-exposure prophylaxis; TGW, transgender women.

^aWhole of UK (two studies), Wales (two studies), England (four studies), Scotland (four studies), England and Scotland (four studies).

^bIncluding PrEP uptake or clinical follow-up studies.

^cIncluding knowledge, attitudes, and practice surveys or potential PrEP impact studies.

^dThree studies looked at both 'barriers and facilitators' and 'willingness and awareness'.

^eAt least (many studies did not mention whether women included TGW).

Centers for Disease Control and Prevention guidance for assessing risk: (i) two or more occasional male sex partners in the previous 6 months and inconsistent condom use during vaginal or anal sex in the previous 6 months, (ii) two or more diagnoses of sexually transmitted infections (STIs) in the previous 12 months, (iii) drug injection in a sexual context in the previous 12 months, or (iv) seropositive main sex partner with a detectable or unknown viral load [14]. A small proportion 4.0% ($n = 27$) evaluated their risk of becoming infected with HIV as 'rather high' or 'high'; however, 85 women (12.5%) were considered at HOR for HIV according to the

defined criteria. Among women identified as at HOR, 40.0% ($n = 34$) were interested in PrEP. It is worth noting that this study was conducted when PrEP was only available in France. Another limitation was that most women included had higher degrees and had accessed the survey through non-governmental organization website promotion; therefore, the population is perhaps not representative of more marginalized groups.

Conversely, in a study of Black African and Black Caribbean women in the UK conducted in 2018, few respondents knew about PrEP; however, after receiving information about PrEP, participants described it as a

necessary intervention and one that could be useful for 'women they knew' [32].

In Russia, a sub-sample of participants in a study looking at serodiscordant partnerships and opportunities for PrEP among partners of women and men living with HIV in St. Petersburg ($n = 56$), only 25% were aware of PrEP for the prevention of sexual transmission of HIV [25]. Couples-based interventions were suggested as one way to increase PrEP awareness and uptake.

Pregnant and breastfeeding women

No studies examined willingness to use and awareness of PrEP in pregnant or breastfeeding women.

Transgender women

Awareness of PrEP was also low among transgender women. Wolton et al. [33] found that 83.9% of 130 transgender people surveyed in a sex-on-premises venue in central London (including 55 transgender women) had not heard of PrEP and 86.2% did not know where to access it.

Barriers to and facilitators of PrEP use

Five studies, including 265 participants, examined barriers to facilitators of PrEP use [24, 32, 48, 50, 51].

Cis women

Stigma was the most commonly cited barrier to PrEP use in cis women. Low self-perception of HIV risk was identified across four studies. This was a particular problem among Black, Asian, and minority ethnic (BAME) women [14, 32]. Another barrier was concern that PrEP only prevents HIV and not pregnancy or other STIs. Efficacy of PrEP was a fourth barrier, particularly because PrEP is not 100% effective and depends on adherence. Other barriers included concern about both short-term and long-term side effects of PrEP medication, lack of appropriate PrEP messaging outside of that to MSM, and concerns about partner intimacy. Nakasone et al. reported that many women in their study regarded safer sex practices as those that built trust and intimacy. Women saw joint HIV testing as a way to strengthen a relationship and ensure fidelity and viewed PrEP as something that may obstruct conversations about risk [32].

Pregnant and breastfeeding women

No studies examined barriers to and facilitators of PrEP use in pregnant or breastfeeding women.

Transgender women

Wolton et al. surveyed 53 transgender women in London at a sex-on-premises venue between 2016 and 2017 and reported three main barriers to PrEP uptake: concern about drug interactions with hormones, reliability, and prohibitive cost [33].

Facilitators of PrEP use identified across all studies were community engagement, inclusion of women in designing PrEP services, and messaging specific to BAME and transgender women. Promoting PrEP as an empowering tool for women to negotiate safe sex was identified as a facilitator for PrEP use in one study, and Nakasone et al. [32] identified that making PrEP available through general practice was another potential facilitator in BAME women.

PrEP uptake and outcomes

Three clinical cohort studies reported on PrEP outcomes that were specific to women or transgender women and included 92 women and 60 transgender women who were taking PrEP. There were no breakthrough HIV infections during follow-up across all studies.

Cis women

Whetham et al. [32] looked at PrEP uptake and outcomes in 32 serodiscordant couples aiming to conceive between January 2008 and October 2012 in Brighton and Birmingham, UK. Of note, this was before U = U (undetectable = untransmissible), and their male partners with HIV were all receiving suppressive HIV treatment. In total, 13 couples used PrEP, and 11 pregnancies in 10 couples resulted in seven live births, one ongoing pregnancy, and four miscarriages. None of the women taking PrEP discontinued PrEP because of side effects.

Two studies looked at informal PrEP use.* A cross-sectional survey looking at PrEP use in people accessing AIDS organization services in France (2014) found that some women were using PrEP informally but that being

*Informal PrEP use: obtaining PrEP medication that is not prescribed, for example ordering online, purchasing PrEP abroad, using medication for post-exposure prophylaxis as PrEP, or any other source.

a woman was not associated with informal PrEP use (vs. formal PrEP use), whereas being MSM was [44]. Rosenthal et al. [27] found that women rarely reported sharing antiretrovirals (ARVs) for HIV treatment for PrEP (1.7%) but that some women (17%) were using ARVs for PrEP and that informal PrEP use was ‘potentially’ underreported by women. The authors did not describe where women were accessing ARVs [27].

Transgender women

Only one of 88 transgender women was accessing PrEP according to the UK lesbian, gay, bisexual, and transgender sex and lifestyle survey conducted between April and June 2018 [18]. This was before PrEP was available on the government funded NHS (National Health Service). However, the PrEP IMPACT [61] study, which aimed to recruit 26 000 people at risk of HIV, was underway by 2017 in the UK. This suggests that the message was not reaching at-risk transgender women. This study also showed that transgender people were less likely to have attended a sexual health clinic recently.

A retrospective cohort analysis looking at transgender women receiving PrEP between February 2016 and January 2019 in Bichat, France, found that a high retention in care rate was reported among the 49 transgender women in their cohort (72%), with only two people (4.1%) stopping because of side effects, both of which were gastrointestinal. In total, 32.60% were receiving gender-affirming hormones; 87.7% were sex workers [31].

PrEP impact studies

Three studies used original data on women in Europe and then employed analysis techniques to estimate the actual (if already implemented) or hypothetical (for consideration of implementation) impact that PrEP would have in prevention of HIV [26, 42, 54]. Grimshaw et al. [19] used data on all new HIV diagnoses in Scotland between 2015 and 2018, comparing the characteristics of those diagnosed before and after implementation of PrEP. The PrEP delivery model included free provision of medication and associated monitoring of individuals meeting one or more risk-based eligibility criteria. This included individuals – irrespective of gender – at an equivalent high risk of HIV acquisition, as agreed with another specialist clinician, which may have been prohibitive.

They found that, after implementation of PrEP in Scotland, the relative proportion of women newly diagnosed with HIV increased by approximately 10%. Individuals with a ‘potentially preventable’ infection were less likely to be of

Black-African ethnicity. They concluded that the sexual health clinic-based national PrEP delivery model ‘appeared to best suit men who have sex with men and white indigenous individuals but had limited reach into other key vulnerable groups.’ It is not clear why more women were diagnosed with HIV in the PrEP era. One possibility could be increased HIV testing but also that women are not considered at risk of HIV and in need of PrEP.

Lions et al. (2019) also looked at the characteristics of people newly diagnosed with HIV across 15 testing centres in France before and after PrEP implementation. Data were collected during 2016. PrEP was available in France from 2015 [54]. They reported that, of the 121 and 11 women with new HIV acquisition in the pre-PrEP and PrEP eras, 110 (91%) and 6 (55%) were eligible for PrEP, respectively. In contrast to Grimshaw et al. [19], they found that women were more likely to be diagnosed with HIV in the pre-PrEP era than in the PrEP era. One explanation for this finding is that, in the pre-prep era, women were more likely to present late. Indeed, the study stated that women were more likely to be older and from Western Africa. A significant proportion of women infected with HIV may have already been diagnosed before the PrEP era, which could explain the lower numbers seen subsequently, in addition to changes in migration patterns.

One study in Italy looked at resistance mutations in PrEP-naïve and -experienced individuals through a public database; findings were not reported specifically for the 2857 women whose data were included [42].

Pregnant and breastfeeding women

No PrEP impact studies looked at PrEP in pregnant or breastfeeding women.

Transgender women

No PrEP impact studies looked at transgender women specifically.

Knowledge, Attitudes, and Perspectives of Healthcare Professionals

Nine studies examined the knowledge, attitudes, and perspectives of a range of healthcare professionals towards PrEP. Surveys of countries in Western Europe predominated. Three surveyed HIV/infectious diseases experts, four studied a mix of experts and general physicians, one studied students, and one surveyed general practitioners or equivalent across Europe.

Cis women

Two studies asked specifically about women as PrEP users. Kowalska et al. [40] surveyed HIV healthcare providers in 2017 from the Central and Eastern Europe network group and found that most respondents would provide PrEP to MSM with high-risk behaviours (88.2%) and to serodiscordant couples when the partner with HIV had detectable HIV RNA (59.2%). One-third of the respondents would provide it to heterosexual people (including women) with high-risk behaviours (30.3%), and one in five would provide it to injecting drug users (21%). Commercial sex workers and migrants were additionally identified as 'other' groups to whom respondents would provide PrEP. The survey also revealed that a lack of acceptance from clinicians (25.68% of respondents), government stigma (17.57%), and societal stigma (13.51%) were obstacles to PrEP provision [52].

Across three studies looking at PrEP acceptability and prescribing practices, it emerged that MSM were considered the 'most eligible' candidates for PrEP. A survey of general/family practitioners in rural Germany between April and July 2018 found that women were identified as at risk but in 'only a worldwide context'. Some family practitioners did not support the idea of PrEP, and others had concerns about stigma [55]. In a survey of infectious diseases physicians across Turkey in March–April 2019, 90.5% of participants thought MSM were the most suitable group for PrEP. Knowledge of PrEP was low, and there was no national guideline. Physicians had concerns about effectiveness, increased STIs, and cost [53].

Obstacles to PrEP access for women, as identified by WAVE members (healthcare professionals, members of the community, advocacy groups across Europe) surveyed in April 2019, were guidelines prioritizing MSM, a lack of recognition of women as a target population for PrEP, and a lack of knowledge about which subgroup of women would benefit from PrEP. Only five countries had efforts to encourage women's access to PrEP, most of which were individually based or initiated by local non-government organizations [4].

Pregnant and breastfeeding women

No studies in this review included healthcare workers' knowledge, attitudes, and perceptions of PrEP for pregnant or breastfeeding women.

Transgender women

None of the studies asked about transgender women specifically, and we did not find any comments about this group in the studies included.

DISCUSSION

PrEP was found to be safe and effective in the qualitative studies included in this review, including during conception. Indeed, there is an established evidence base to support PrEP efficacy and safety in all genders, which raises the question of why women at risk are not accessing it more extensively in Europe. The findings from qualitative studies included in this review help to provide some insight.

This review identified a lack of awareness of PrEP in cis and transgender women and among healthcare workers. Women were more likely to consider PrEP after being given PrEP information [32]. (Nakasone) Among healthcare workers, there was a sense that PrEP is not for women or only those perceived to be at especially high risk, such as sex workers. It was also apparent that women underestimate their HIV risk. Healthcare providers also underestimate women's risk of HIV, creating a divide. Healthcare workers need specific guidelines on PrEP for women and education on more accurate HIV risk assessment. Algorithms to identify women at risk in clinical practice may help, but women equally need the knowledge to comprehend their HIV risk and feel able to access PrEP. Peer education and support could be useful here to help at-risk communities understand the risk of HIV. There is a need for healthcare professionals, policy makers, and commissioners to recognize and understand at-risk populations in order to design and implement successful PrEP programmes, and engaging at-risk communities in strategic planning is essential.

A major barrier to women accessing PrEP identified by this review was stigma. This was described at the individual (self-stigmatization), community, and institutional level in healthcare services and government. Racism within healthcare was also highlighted as a problem. This is of particular concern since BAME populations are disproportionately affected by HIV. It emerged that BAME women may find attending sexual and reproductive health services in itself stigmatizing, raising the question of where best to situate HIV prevention for women within healthcare services. Women may worry that PrEP pills will be found and family and friends may assume they have HIV or are sexually promiscuous. We found it interesting that two studies reported that women were accessing PrEP informally, and that informal PrEP usage may be underreported by women, suggesting that getting PrEP on their own terms without fear of stigma is enabling. The barriers identified here are not dissimilar to HIV testing, where stigma, fear of isolation from community, and fear of racism from healthcare workers are well described [55]. Overcoming these barriers requires diverse community engagement and BAME leadership in

planning services. Support services that mitigate the impact of stigma need funding. Both peer and religious leader education could be a powerful way to engage community members and allay concerns about stigma. Certainly, there is an urgent need to support women to access HIV prevention without stigmatization or discrimination on any level.

Another barrier to PrEP usage identified in this review is a lack of PrEP messaging orientated toward cis and transgender women. In the UK, widespread PrEP messaging has targeted MSM, whose HIV risk is widely acknowledged and understood by both healthcare professionals and the (white) MSM community in the UK, who strongly advocated for PrEP to be made available free of charge. Indeed, surveys of healthcare workers across Europe indicated that respondents thought MSM should be the most targeted group. However, women at risk of HIV are more likely to be from a minoritized community, to underestimate their risk of HIV, and feel stigmatized. Such MSM-orientated information may even negatively impact on at-risk women and transgender women as the messaging implicitly states *it's not for me* and gay stigma may also play a part. Framing PrEP in a way that speaks to women is important, for example, the Sophia Forum in the UK has developed a webpage specifically for women, stating 'It involves HIV negative women taking a daily pill to protect them from HIV – much like women taking the contraceptive pill to protect them from pregnancy' [56]. Non-governmental and support organizations are vital in advocating for at-risk groups, but there is a need for stronger support and funding from governments across Europe for HIV prevention programmes aimed at women.

This review emphasizes that cis women have distinct HIV-prevention needs, requiring not only prevention of HIV but also pregnancy and other STIs. PrEP models have predominantly targeted MSM. The number of women diagnosed with HIV increased in the post-PrEP era in Scotland, which reflects that women have been left behind in the provision of PrEP [26]. Safe sex may have different definitions for women than for men and vary according to cultural background. PrEP can be promoted as an empowering tool for women to negotiate safer sex but only if this fits with a woman's personal definition of what safer sex means. Trust and intimacy and 'HIV testing together' can define safe sex for women from particular cultural backgrounds, which needs to be considered [32]. Women are subject to gender bias, and caregiver responsibilities may make it difficult to access PrEP but also to adhere to daily PrEP. Women face additional challenges compared with men who take TDF-FTC PrEP, as only daily dosing is recommended in women to achieve optimal benefits for HIV prevention. PrEP models need to address this, and long-acting injectable cabotegravir as

PrEP shows great potential for women [57]. Situating HIV risk assessment and PrEP provision within gynaecology, obstetrics, migrant health, and family practice may also help broaden access and normalize HIV prevention, just as HIV testing has become routine in many settings.

Despite prevention of HIV for pregnant and breastfeeding cis women being a global health priority, with the risk of acquiring HIV more than doubling during and after pregnancy, we found only one study related to PrEP and pregnancy. Although the cohort in the study by Whetham et al. [32] in women wanting to conceive was relatively small and motivated, the results showed a willingness to take PrEP despite the potential risk. This was also prior to any significant safety data being available [47]. Pregnant and breastfeeding women are often not included in trials because of concerns about safety and additional ethical considerations; however, without data, women are being put at risk because of the lack of evidence and knowledge of altered pharmacokinetics. Pregnant and breastfeeding women must be included in future PrEP studies.

Very few transgender women included in these studies were using PrEP despite the vulnerability of this group to HIV acquisition. Transgender women are also marginalized, subject to stigma, and suffer from health inequity. This review shows that they also have unique HIV prevention requirements and concerns about using PrEP. Drug interactions with gender-affirming hormone treatment were highlighted as a barrier to uptake, as was cost. The British HIV association guidelines state that there are no known interactions between PrEP and gender-affirming hormones, and concerns about cost should now be alleviated by government provision and insurance coverage [59]. Education of healthcare professionals on trans health is essential, and campaigns targeted at transgender women are needed. The Terrence Higgins Trust (UK) webpage entitled 'Using PrEP and PEP as a trans feminine person' is a good example, and a number of specialist trans and non-binary sexual health clinics have been established in the UK [60]. Peer education and support for transgender women is equally important, as is the involvement of transgender women in designing HIV-prevention services. Transgender women have also been underrepresented in PrEP research and must be included in future studies.

Our review has a number of limitations, which should be considered in light of our findings. Our search included studies up until 2021, so it is likely that further relevant studies have been published since. We did not include conference abstract databases in our search. It is also worth noting that some of the included studies were conducted before the more widespread implementation of PrEP.

We encourage future researchers to consider the gaps identified through this review as opportunities for future research into PrEP for cis, pregnant, breastfeeding, and transgender women in Europe at risk of HIV infection.

CONCLUSION

This review revealed a notable lack of literature on PrEP for cis and transgender women in Europe. This is synonymous with a lack of PrEP provision for women in this region, representing a serious health inequality that is leaving cis and transgender women vulnerable to preventable HIV infection. Our findings show that women have been left behind in terms of PrEP awareness campaigns, PrEP messaging, and PrEP delivery models and that barriers to PrEP uptake are complex and rooted in institutional and societal stigma, which must be addressed at policy level. HIV prevention with PrEP is not 'one size fits all' and requires a nuanced gender-responsive approach. Further research of PrEP in cis, pregnant, breastfeeding, and transgender women is essential if we are to stop HIV transmission by 2030.

AUTHOR CONTRIBUTION

Naomi Fitzgerald: Conceptualization, methodology, investigation, writing (original draft and review and editing). Holly Coltart, Lourdes Dominguez, and Kate Flanagan: Investigation. Yvonne Gillette: Supervision.

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CONFLICT OF INTEREST

None of the authors declared any conflict of interests.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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