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Achievements and gaps to provide Pre-Exposure Prophylaxis (PrEP) for women across the European Region – Results from a European survey study

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Abstract

Introduction: The use of pre-exposure prophylaxis (PrEP) is a safe and effective prevention option to all people at substantial risk of HIV acquisition, irrespective of gender. However, in most European countries PrEP services focus on key populations, in particular men who have sex with men (MSM). This study aims to explore PrEP availability and implementation for women across the European region.

Methods: An online survey was sent to all members of Women Against Viruses in Europe (WAVE) from 50 countries in September 2019. It consisted of 19 questions, including both multiple choice and free text answers.

Results: In total, responses from 34 countries were included in the study (Western Europe n=12, Central Europe=12, Eastern Europe n=6). PrEP was accessible in 30 WHO European countries. More than half of them stated that PrEP was available for all groups at-risk of HIV acquisition (n=18), while in many countries PrEP was only available to men who have sex with men (MSM) and transgender persons. Two-thirds of country respondents confirmed the availability of a national guideline for PrEP (n=23), of which six countries had specific recommendations for PrEP in women. The most cited obstacles for PrEP access were lack of information about PrEP, lack of political support, and high cost for the individual. Fifteen country respondents stated that there were specific obstacles for PrEP access for women, such as guidelines prioritizing MSM, women not being seen as a target population for PrEP, and lack of knowledge about which subgroup of women would benefit most from PrEP. Seven countries had made efforts to encourage women´s access to PrEP, most of which were individually based or initiated by local NGOs.

Conclusions: PrEP is an important addition to HIV combination prevention. Women´s access to PrEP in Europe remains limited. Women are often not included in the guidelines or targeted with education or information, resulting in a general lack of information about the use of PrEP for women.

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Introduction

In 2018, nearly 50 000 women were newly diagnosed with HIV, representing 36% of the 140 000 new HIV diagnoses overall in the WHO European region. The majority of these newly HIV diagnosed women were in the Centre and East of the region, where an increase in new HIV diagnoses among both men and women was observed between 2009 and 2018. Heterosexual sex was the most commonly reported HIV acquisition mode among women in the region [1]. Over half of the newly diagnosed women were diagnosed late, highlighting that women need more attention in Europe´s prevention and testing effort to reduce infections amongst women and children and enable the goal of ending AIDS by 2030 [1,2].

Many prevention strategies available to women at risk of HIV acquisition through sex depend on the male partner, i.e. condoms, antiretroviral therapy or male circumcision [3]. Pre-exposure prophylaxis (PrEP) is the use of an antiretroviral medication taken by those who are HIV negative but who are at risk of acquiring HIV [4]. In 2015, WHO recommended that PrEP should be offered as a prevention option to all people at substantial risk of HIV acquisition, irrespective of gender [4]. These recommendations were based on a systematic review and meta-analysis of documenting the effectiveness and safety of PrEP across heterogeneous populations when taken with high adherence, with no difference in effectiveness by sex. For event-driven PrEP regimens, the evidence was less conclusive [5]. Several recent studies have been published with further information on PrEP effectiveness and safety for women, including studies of alternative PrEP agents, including long acting injectables and vaginal rings [6–9]. Current safety data also support the use of PrEP in pregnant and breastfeeding women [10,11]. Thus, PrEP offers women an efficacious, female-controlled HIV prevention choice [12].

Truvada (tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)) was authorized by the European Medicines Agency (EMA) in 2016 to be used as PrEP [13]. France was the first European country to make PrEP nationally available and reimbursed by their health care system [14]. Recent surveillance data from the European Centre for Disease prevention and Control (ECDC) show that there has been a marked increase in the number of countries in the WHO European Region implementing PrEP, either as part of national healthcare provision or through pilot or research projects [14,15]. However, these data also highlight that availability of PrEP in Europe is complex

and fragmented, and in many countries PrEP services focus on key populations, in particular men who have sex with men (MSM) and, to a lesser extent, transgender women [12,14,16].

Several systematic reviews summarizing the current knowledge on the efficacy, safety and barriers to PrEP use among women have been published [12,17,18]. Most of these focus on the use of PrEP internationally, with limited information on the implementation and access to PrEP for women living in the European region. Women Against Viruses in Europe (WAVE) within the European AIDS Clinical Society (EACS) (http://www.eacsociety.org/wave/about-wave/wave.html) was established in 2014 to promote the health and wellbeing of women living with HIV (WLWH) and HIV prevention for women in Europe. The initiative involves health care professionals, researchers and community representatives. WAVE endeavours to promote equality of access to care, including HIV prevention for women, and contributing to the body of evidence for using such prophylaxis for women. [19,20]. Therefore, in 2019 a survey conducted within WAVE, exploring PrEP availability and implementation for women across the European region was performed with an aim to describe the current situation and encourage future opportunities.

Methods

Data collection and analysis

The survey was designed and finalised by a steering group consisting of PrEP activists and clinicians. Surveys were sent initially to all WAVE members, i.e. healthcare professionals, members of the community, advocacy groups and others. To ensure inclusion of all regions, people from countries known to have an interest in women and HIV but who were not WAVE members were approached personally by the WAVE Scientific Committee members.

An invitation email to participate in the WAVE survey on PrEP and women was sent to 1965 people from 50 countries on September 10, 2019. A reminder was sent 3 weeks later. Invitees were encouraged to collaborate with other people in their country working with PrEP and to send one response from their country. Thus, the aim was not for the survey to be answered by all invited participants, but rather those who are prescribing PrEP in the country, i.e. those thought of as being in a good position to give relevant and trustful answers because of their expertise. If more

than one response was received from the same country, the respondents were contacted and asked to provide one consensus response. The survey was an online questionnaire, taking approximately 15 minutes to complete. It consisted of 19 questions, including both multiple choice and free text answers.

Results were analysed using the European Centre for Disease Prevention (ECDC) geographical division of the WHO European region, grouping countries into three sub-regions based on geographic and broad epidemiological patterns: West, East, and Centre [21]. The quantitative results are presented descriptively, while the qualitative text from the open questions are used to elaborate and illustrate aspects of the quantitative results.

Individual consent was provided by respondents completing the survey. Ethical approval was not required as no patient data was used and no biomedical intervention was performed.

Results

Of the 1965 invitation emails sent, 30% (n=590) opened the email, and 4.4% (n=86) clicked on the link and opened the survey. In total, 38 respondents completed the survey, of which 4 responses where received from the same country. Thus, responses from the following 34 countries are included in the study; 16 from the West (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Israel, Italy, the Netherlands, Portugal, Spain, Sweden, Switzerland, the United Kingdom), 6 from the East (Belarus, Kyrgyzstan, Lithuania, Moldova, Russia, Ukraine), and 12 from the Centre (Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Hungary, Poland, Romania, Serbia, Slovenia, Turkey). Based on the number of countries completing the survey the response rate is 67% (34 out of 51 countries).

PrEP accessibility in Europe

Of the 34 countries within the WHO European Region included in the survey, 30 (88 %) reported yes to the question of whether PrEP was accessible in their country. The countries who reported that PrEP was accessible were then asked in which way people can access PrEP in their country (Figure 1). Based on these responses, access to PrEP is divided into four main categories; (i) PrEP reimbursed within the national health service, (ii) PrEP available in health care settings or by purchasing it legally online, but is not fully reimbursed, (iii) PrEP available only through clinical

trials, by purchasing it illegally online, or via the underground market, and (iiii) PrEP not available by any means.

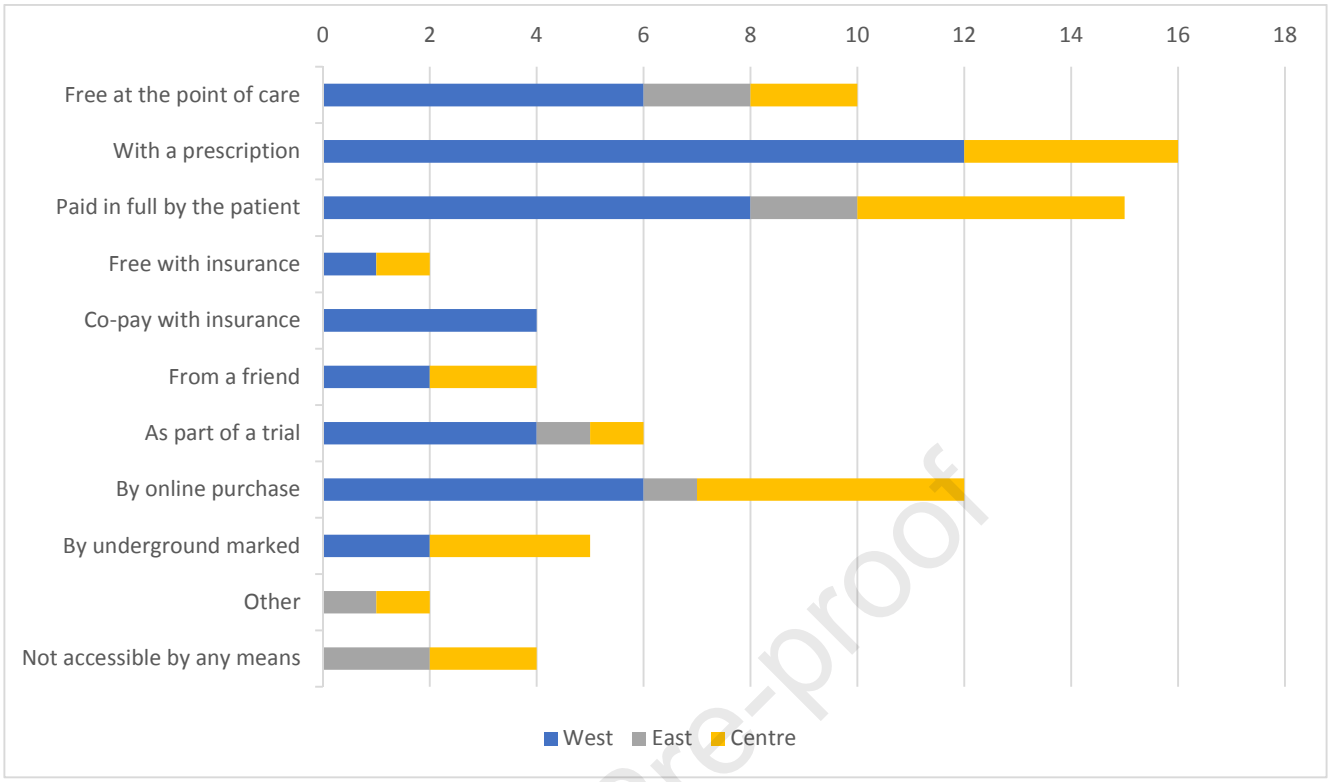
(i) Eight countries (24 %) reported that PrEP was available for free at the point of care, either by the public sector or through insurance (Bosnia and Herzegovina (only Sarajevo), Croatia, Denmark, France, the Netherlands, Moldova, Portugal, and Ukraine). Five of these countries commented that reimbursed PrEP was available with a medical prescription provided by an HIV specialist, after candidates were screened for HIV and sexual transmitted infections (STIs) and counselled on minimising risk-taking behaviour.

(ii) Seventeen countries (50 %) reported that PrEP was available in health care settings or by purchasing it legally online, but it was not fully reimbursed (Austria, Belgium, Czech Republic, Finland, Germany, Hungary, Ireland, Israel, Italy, Lithuania, Poland, Russia, Serbia, Slovenia, Sweden, Switzerland, and the United Kingdom). In Scotland, Wales and in Northern Ireland PrEP was free at point of care but in England it was still officially only available via a clinical trial. The cost of PrEP in all mentioned countries varied considerably depending on how much was subsidised by social service or insurance. For example, the cost for PrEP in Germany was €10 per prescription, while it was almost €200 in Russia.

(iii) Five countries (15 %) reported that PrEP was only available through clinical trials, by purchasing it illegally online, via the underground market, or by procuring it from someone living with HIV but non-adherent to their medication (Bulgaria, Cyprus, Greece, Romania, and Spain). The respondent from Spain commented that some individuals got PrEP for free by asking for PEP.

(iiii) Four countries (12 %) reported that PrEP was not accessible by any means (Albania, Belarus, Kyrgyzstan, and Turkey).

Figure 1: Main ways of accessing PrEP in the included 34 European countries reporting



Importing PrEP

Eleven country respondents answered yes to the question of whether importing PrEP via post was legal in their country (32 % of the participating countries; Denmark, Finland, Hungary, Kyrgyzstan, Lithuania, Poland, Russia, Switzerland, Turkey, Ukraine, and United Kingdom), but only within the European Union and only for personal use. A prescription was also needed in Turkey and Lithuania. Thirteen (38%) countries reported that it was illegal to import PrEP via post (Albania, Austria, Belarus, Bosnia and Herzegovina, Czech Republic, France, Ireland, Israel, Italy, the Netherlands, Portugal, Serbia, and Slovenia), but the respondents from Israel and Slovenia commented that this was not enforced. Ten (29%) countries responded that they did not know whether importing PrEP via post was legal or illegal (Belgium, Bulgaria, Croatia, Cyprus, Germany, Greece, Moldova, Romania, Spain, and Sweden).

National guidelines

Almost two-thirds of country respondents confirmed the existence of a national guideline for PrEP (n=23 (68%); Austria, Bosnia and Herzegovina, Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Israel, Italy, Moldova, the Netherlands, Poland, Portugal, Russia, Spain, Sweden, Switzerland, Turkey, Ukraine, and the United Kingdom). Twenty of those countries

reported having prescription guidelines (i.e. guidelines relating to the drug prescription itself). Austria, Bosnia and Herzegovina, and Belgium reported having provision guidelines (i.e. guidelines relating to the social/ political part of PrEP role out and attitude towards offering PrEP). Eleven countries reported that they did not currently have national guidelines (Albania, Belarus, Bulgaria, Croatia, Cyprus, Greece, Kyrgyzstan, Lithuania, Romania, Serbia, and Slovenia), four of which however had guidelines in development but not yet approved by the relevant authority (Belarus, Greece, Lithuania, and Romania). The guidelines in Croatia were approved as of September 2018. Slovenia did not have national guidelines but did use the EACS guidelines.

Six countries reported having specific recommendation for PrEP in women (Austria, France, Germany, Ireland, Ukraine, and the United Kingdom). The comments from France and Austria, state that these recommendations were related only to women highly exposed to HIV such as sex workers or women with multiple partners. Among the countries with no specific guidelines for women (n=20), the comments from Finland, Moldova, Spain and Sweden highlighted that their guidelines were not gender specific but targeted to individuals at most risk of HIV acquisition. The country respondent from Spain highlighted in the comments that there where specific recommendations on the use of PrEP in pregnant women. Eight country representatives respondents reported that they did not know whether there were any national guidelines with specific recommendations for PrEP in women.

Populations prioritized and eligible for PrEP

Of the 30 countries with access to PrEP, 18 (60 %) reported that PrEP was accessible for all groups at-risk of HIV acquisition irrespective of gender or sexuality (Austria, Bosnia and Herzegovina, Belgium, Czech Republic, Finland, France, Germany, Hungary, Ireland, Italy, Moldova, Poland, Portugal, Russia, Slovenia, Switzerland, Ukraine, and United Kingdom). However, the comments show that provision of PrEP in many countries were guided by specific criteria i.e. access only for individuals with a high risk or PrEP only being available at major hospitals and/or only after an assessment by an infectious disease/HIV specialist. Among the countries where PrEP was not available to all groups (n=12), the comments were that PrEP was only accessible for groups deemed at-risk groups, specifically MSM and transgender individuals.

Number of people accessing PrEP via any means

The respondents were asked to provide an estimate on the number of people accessing PrEP by any means and also, how those numbers where obtained. Overall, the total estimated number of people accessing PrEP via any means varied across the European Region, from <10 in Moldova and Lithuania to over 30,000 in France. The number of people accessing PrEP in the East and Centre of the Region is relatively low, and limited official data exists. One exception is Poland, where it is estimated that approximately 1500-2000 people are accessing PrEP. Numbers were obtained through inquiry or surveys at the clinical departments responsible for PrEP treatment.

Formal clinical follow-up

Of the 30 countries where PrEP was accessible 25 (83 %) reported that there was a formal clinical follow-up advice for PrEP users. Four countries reported that there was no formal clinical follow-up. In Cyprus and Greece PrEP is only accessible through clinical trials or by purchasing it illegally online, while the respondents from Lithuania and Serbia did not know if there is any formal follow-up for PrEP users.

The most common model of care for PrEP users was a follow-up every three months (n=18 (72%)), with each visit including an adherence review, drug side-effects review and testing for HIV, hepatitis and sexually transmitted infections (STIs). It was less common to include a pregnancy test, general health promotion advice, and drug and alcohol services, if needed (Table 1).

Table 1: Clinical follow-up among countries reporting PrEP accessibility

	All countries	West	East	Centre
	n=30	n=16	n=4	n=10
Formal follow-up of PrEP users, n (%)				
Yes	25 (83)	15 (94)	3 (75)	7 (70)
No	3 (10)	1 (6)	0	2 (20)
Unknown	2 (7)	0	1 (25)	1 (10)

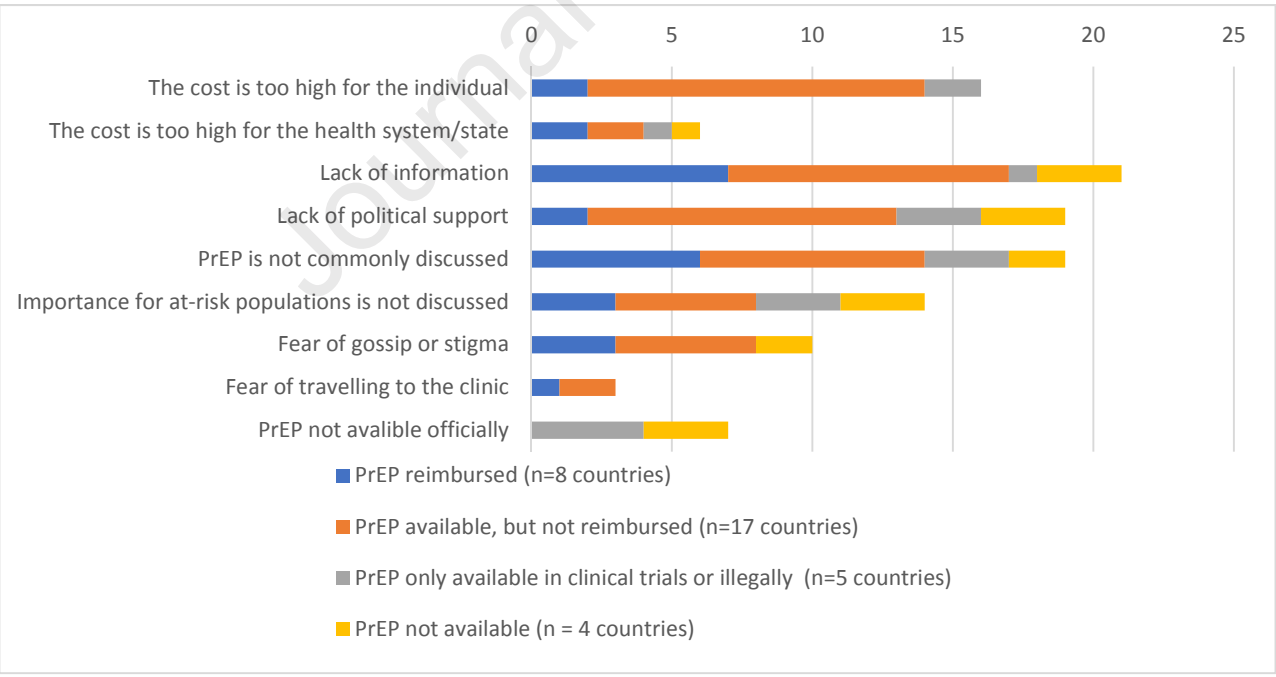
Content of clinical follow-up in countries reporting formal clinical follow-up	An adherence review	A side effects review	An HIV test	An HCV Test	Tests for bacterial STIs	A Serum creatinine/eGFR/urinalysis for kidneys	A pregnancy test, for women not using reliable contraception	A pregnancy test, for women using reliable contraception	Health promotion advice
Center region									
Bosnia and Herzegovinia									
Croatia									
Czech Republic									
Hungary									
Poland									
Romania									
Slovenia									
Eastern region									
Moldova									
Russia									
Ukraine									
Western region									
Austria									
Belgium									
Denmark									
Finland									
France									
Germany									
Ireland									
Isreal									
Italy									
The Netherlands									
Portugal									
Spain									
Sweden									
Switzerland									
United Kingdom									

Green = included in follow-up. Red = not included in follow-up

Obstacles to PrEP use

Lack of information about PrEP was the most reported obstacle in the West and East, while PrEP not being commonly discussed as a prevention method was the main obstacle in the Centre of the Region (data not shown). Of the eight countries with reimbursed PrEP, seven countries (Croatia, Denmark, France, the Netherlands, Moldova, Portugal, and Ukraine) stated that lack of information about PrEP was the main barrier for PrEP use. The high cost for the individual (n=12 (71 %)), lack of political support (n=11 (65 %)), and lack of information about PrEP (n=10 (59%)) were the main obstacles in the 17 countries, where PrEP was accessible, but not reimbursed. In the five countries where PrEP was not officially legally accessible, the main obstacles were lack of political support (n=3 (60 %)), PrEP not being commonly discussed (n=3 (60 %) and PrEP not being officially available (n=4 (80 %)). The most commonly cited obstacles for use of PrEP in the four countries where PrEP was not available were lack of information about PrEP (n=3 (75 %)), lack of political support (n=3 (75 %)), and high cost for the individual (n=2 (50 %)) (See Figure 2).

Figure 2: Obstacles to PrEP use in the 34 countries reporting



Fifteen countries (47%) answered yes to the question of whether there were specific obstacles to PrEP access for women in their country (Austria, Croatia, Denmark, France, Germany, Greece, Israel, the Netherlands, Poland, Portugal, Spain, Sweden, Turkey, Ukraine, and the United Kingdom). Comments include that women are not included in PrEP guidelines nor targeted in clinical studies as they were generally not seen to be at risk for HIV acquisition.

Efforts to encourage women´s access to PrEP

Seven countries reported that there were organized efforts to encourage women´s access to PrEP in their country (Belarus, Moldova, Poland, Russia, Switzerland, Turkey, and United Kingdom). The comments show that most of these efforts were organised by community-based organisations and NGOs, targeting sex workers, women who were injecting drugs and/or transgender women. For example, in the United Kingdom, the Sophia Forum has developed a website with information on PrEP for women (http://womenandprep.org.uk/), while in Moldova, a consortium of NGOs have advocated to pilot community PrEP for all at-risk groups, including sex workers, women injecting drugs and transgender women (https://prepster.info/prep4women/). In Belarus and Poland, there was an effort to increase awareness and knowledge in outpatient clinics and among gynaecologists.

Discussion

This survey study was conducted among EACS and WAVE members and explored PrEP availability and implementation for women across the European region with the aim of identifying the next steps to make PrEP a successful prevention tool not only for men, but also for women. The results show that knowledge about PrEP, availability and cost varies considerably across the WHO European Region, and overall women´s access to PrEP in WHO Europe remains limited. Women are in many countries are not seen as a group at risk of HIV acquisition, and therefore not included in the guidelines. They are not either targeted with education or information, which results in a general lack of information about the use of PrEP for women. As highlighted in this study, implementation of PrEP and models of care have in many countries focused on MSM, and recent data from the ECDC estimates that less than 10% of PrEP users in Europe are women (including transgender women) or heterosexual men [15].

Provision of PrEP for women is most likely limited by multiple factors, including challenges in identifying women with an increased HIV risk [22]. Overall, there is a lack of knowledge about which sub-group of women would benefit the most from PrEP. The EACS guidelines state that "*PrEP may be considered in HIV-negative heterosexual women and men who are inconsistent in their use of condoms and have multiple sexual partners where some of whom are likely to have HIV infection and not being on treatment*" [23]. Having a history of partner violence, being recently diagnosed with a STI, and living in a high prevalence area, have also been cited in the literature as characteristics associated with PrEP eligibility among women [22,24]. Perceptions of HIV risk have been reported to be highly gendered and one challenge may be that many women do not consider themselves at risk of HIV acquisition [25,26] particularly if they consider themselves to be in a monogamous relationship. A holistic discourse about HIV risk and risk perception that includes partner, structural and community influences may thus be particularly important for women´s uptake of PrEP [25]. Access to PrEP should be based on the actual risk of HIV acquisition, not on the risk group *per se*, so that individuals, irrespective of gender, who, in the opinion of their physician, have a high risk of HIV acquisition should be eligible for PrEP.

Results from several studies suggest that women, when provided with information on the effectiveness of PrEP, are generally keen to take it [22,25,27,28]. However, one challenge to PrEP provision for women is that the awareness of PrEP is generally low among women [29]. In a recent study among 109 African-American women attending a family planning clinic, 80% reported that they were unaware of PrEP being available and 70% reported that they would probably or definitely like to use PrEP [27]. Similar results were reported in a study by Raiman et al. [30], where two-thirds of HIV-negative cis-women presenting for HIV/STD testing and meeting US criteria for PrEP use were unaware of PrEP.

A barrier mentioned in our study is that there is a lack of availability and general knowledge about PrEP in many of the included countries. Women who may be at risk for HIV may not be accessing specialised clinics unless they have a condition which warrants examination [17]. Moreover, cultural, social and religious norms, such as patriarchal values and culturally prescribed gender roles, may contribute to women´s lack of knowledge about PrEP and access to PrEP services [31,32]. Thus, integrating PrEP into primary health and reproductive health services for women may enhance access and awareness of PrEP among women [12]. Goals for the future must include

making PrEP available and visible for women at risk of HIV acquisition. This would include improved knowledge but also require support to overcome barriers such as cost, low self-esteem and stigma, which still remain significant for women.

To our knowledge, this is the first study to explore PrEP access for women in Europe. It has several limitations. First, only 34 out of 51 countries within the WHO European Region responded to the survey. Although the survey invitation was sent to all members of WAVE, the aim was not for all invited participants to answer the survey, but to get one response per country completed by those who are prescribing PrEP in the country. Thus, the invitation targeted clinicians, researchers and community activists thought of as being in a good position to give relevant and trustful answers because of their expertise. However, it is unclear if the respondents have been able to capture fully accurate data on PrEP at a national level. Thus, our findings reflect clinician and community activists´ knowledge on PrEP for women in the responding country, rather than state-provided data from health authorities. Second, there is much variability in terms of the implementation of PrEP across Europe, making it difficult to describe the details of our results across the whole region. Finally, the survey included several open text answer options, making it difficult to categorize the different responses. However, the open text responses provided details elaborating the quantitative data.

Conclusion

Awareness and accessibility of PrEP for women in Europe are still very limited and not as equitable as for MSM. There is a general lack of information about the use of PrEP in women. Thus, it seems to be crucial to enhance understanding of how to increase PrEP awareness among women and healthcare professionals, to increase knowledge about PrEP for women and enable development of a successful prevention tool specifically designed for women.

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Conflict of Interests

No conflicts of interest declared by the authors in regard to this publication.

Contributors

BC, YG and KAP had the original concept of the study. JK, MV, MJPE, and GC contributed to the design of the study and the collection of data. EM wrote the first draft of the manuscript, and all authors contributed to the interpretation of data, writing the report, and approved the final version.

Table 1: Clinical follow-up among countries reporting PrEP accessibility

	All countries	West	East	Centre
	n=30	n=16	n=4	n=10
Formal follow-up of PrEP users, n (%)				
Yes	25 (83)	15 (94)	3 (75)	7 (70)
No	3 (10)	1 (6)	0	2 (20)
Unknown	2 (7)	0	1 (25)	1 (10)

Content of clinical follow-up in countries reporting formal clinical follow-up	**An adherence review**	**A side effects review**	**An HIV test**	**An HCV Test**	**Tests for bacterial STIs**	**A Serum creatinine/eGFR/urinalysis for kidneys**	**A pregnancy test, for women not using reliable contraception**	**A pregnancy test, for women using reliable contraception**	**Health promotion advice**
Center region									
Bosnia and Herzegovinia	■	■	■	■	■	■	■	■	■
Croatia	■	■	■	■	■	■	■	■	■
Czech Republic	■	■	■	■	■	■	■	■	■
Hungary	■	■	■	■	■	■	■	■	■
Poland	■	■	■	■	■	■	■	■	■
Romania	■	■	■	■	■	■	■	■	■
Slovenia	■	■	■	■	■	■	■	■	■
Eastern region									
Moldova	■	■	■	■	■	■	■	■	■
Russia	■	■	■	■	■	■	■	■	■
Ukraine	■	■	■	■	■	■	■	■	■
Western region									
Austria	■	■	■	■	■	■	■	■	■
Belgium	■	■	■	■	■	■	■	■	■
Denmark	■	■	■	■	■	■	■	■	■
Finland	■	■	■	■	■	■	■	■	■
France	■	■	■	■	■	■	■	■	■
Germany	■	■	■	■	■	■	■	■	■
Ireland	■	■	■	■	■	■	■	■	■
Isreal	■	■	■	■	■	■	■	■	■
Italy	■	■	■	■	■	■	■	■	■
The Netherlands	■	■	■	■	■	■	■	■	■
Portugal	■	■	■	■	■	■	■	■	■
Spain	■	■	■	■	■	■	■	■	■
Sweden	■	■	■	■	■	■	■	■	■
Switzerland	■	■	■	■	■	■	■	■	■
United Kingdom	■	■	■	■	■	■	■	■	■

Green = included in follow-up. Red = not included in follow-up

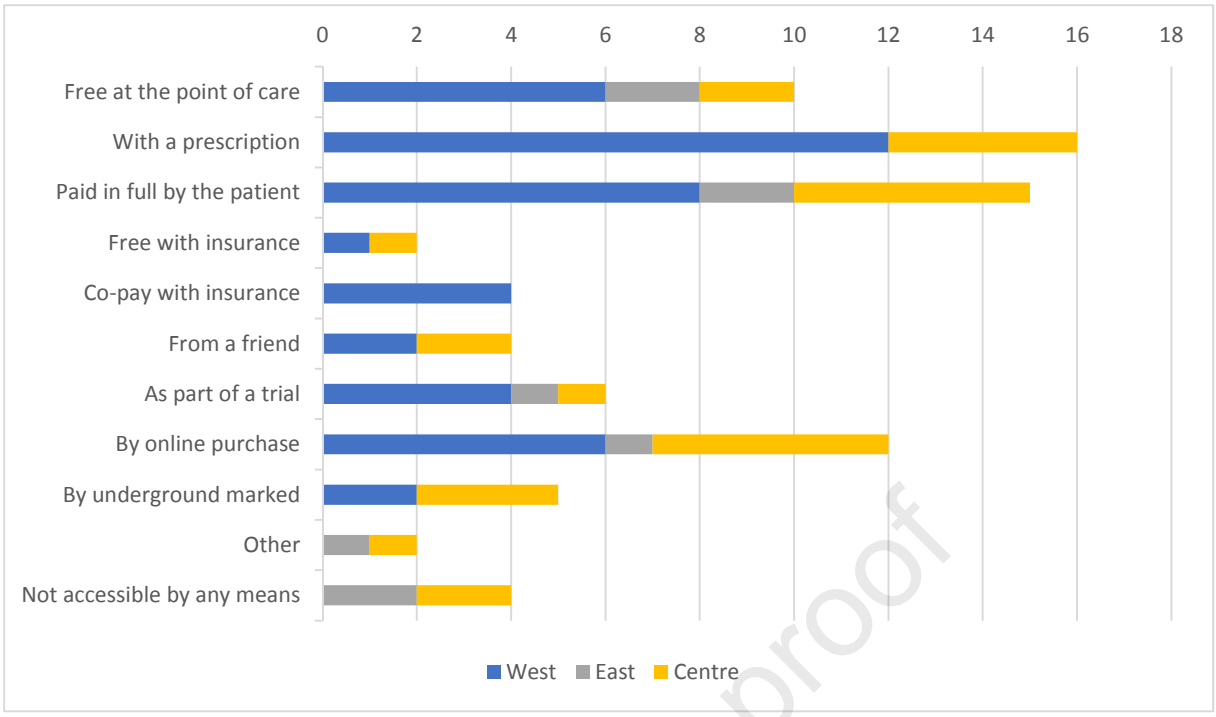

Figure 1: Main ways of accessing PrEP in the included 34 European countries reporting

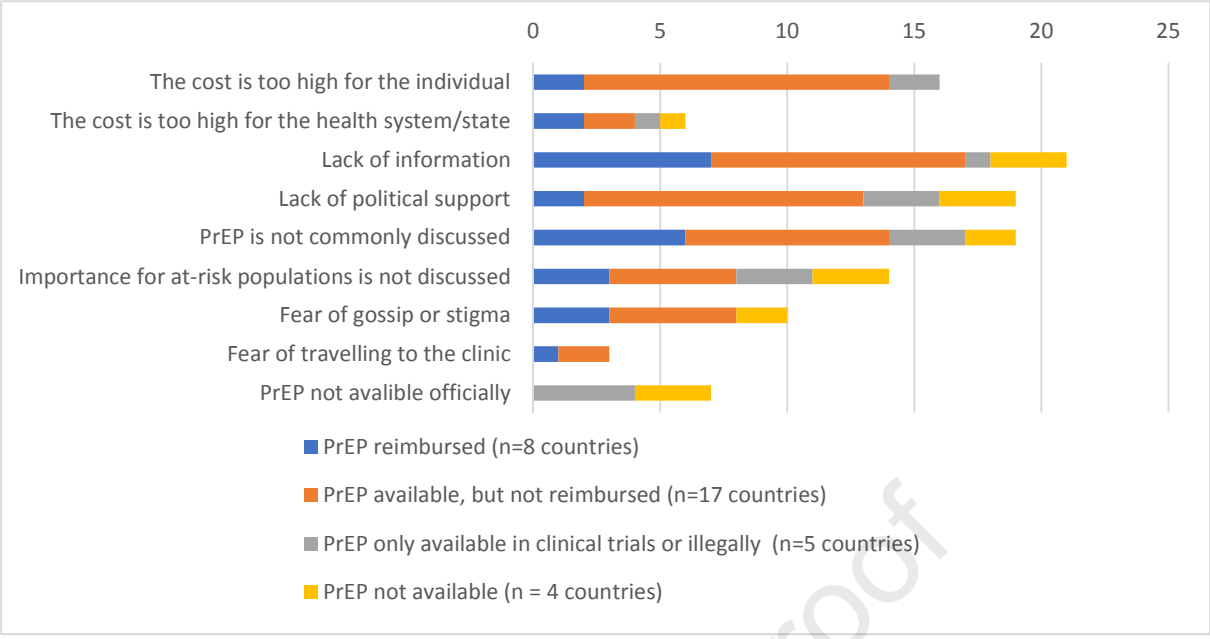

Figure 2: Obstacles to PrEP use in the 34 countries reporting

Dear Christina K Psomas,

We thank you for the opportunity to submit a revised version of our manuscript entitled

"*Achievements and gabs to provide Pre-Exposure Prophylaxis (PrEP) for women across the European Region – results from a European survey study"*

for publication in Journal of Virus Eradication.

We thank the reviewers for pointing out some important modifications needed in the manuscript. We found the comments both reviewers very helpful and constructive. We have addressed all the changes recommended.

These recent updates, as well as the recommendations from the reviewers, have been added to the revised version of the manuscript, and we are confident that the new version of the manuscript is easier to understand and has more fluent scientific discourse.

Please find our point-by-point responses to specific comments brought up by the reviewers (responses in italic) in the following pages. We have submitted a marked version of the manuscript, together with the other documents related to the manuscript.

We hope that these changes fulfill the requirements to make the manuscript acceptable for publication in Journal of Virus Eradication.

We look forward to hearing from you.

Yours sincerely,
Karoline Aebi-Popp

Reviewer comments

Reviewer #1

I also think it would be of great interest to understand, were EACS or relevant national, guidelines followed, what % of women diagnosed with HIV would have been offered PrEP had the guidelines for PrEP access been followed. My feeling is that even if guidelines were followed many women would not be offered PrEP as they would not meet high risk criteria - some discussion about this should be added please and if it is not possible to answer, it should still be raised as a possible limitation of PrEP roll out i.e. it's not just about failing to implement guidelines, it may also be much harder to reliably identify at risk women compared to, for example, MSM.

Thank you very much for this important comment. We are aware of the fact, that it is much harder to identify women who were eligible for PrEP compared to MSM. The WHO recommends that people at substantial risk of HIV infection should be offered PrEP, while the EACS guidelines state that PrEP may be considered in HIV negative heterosexual women (and men) who are inconsistent in their use of condoms and have multiple partners where some may be HIV positive and not on

treatment. Thus, the guidelines are quite vague on who should be offered PrEP, making it difficult to estimate how many women would be offered PrEP if the guidelines where followed. We agree with the reviewer that it is not only a question of implementing the guidelines, but also identifying women at risk and this is discussed in the discussion section of the manuscript.

Specific comments:

1) Abstract: please include denominator i.e. how many countries received questionnaire

We have added more detail in the conclusion, as suggested by the reviewer.

2) Abstract: please add a little more detail to the conclusion

We have added more detail in the conclusion, as suggested by the reviewer.

3) Methods: who was the survey sent to? Clinicians? Commissioners? Activists? Did the survey ask for the role of the person completing it, and if so please include that data, if not could this be a limitation i.e. is it possible that the person completing the survey did not know the answers for the whole country? How confident can you be that a clinician answering the survey could represent all services beyond their own?

The survey was sent to all members of WAVE. A WAVE membership is open to junior and senior healthcare professionals, members of the community and advocacy groups, industry employees, and others that may qualify based upon interest or expertise, regardless of gender and geographical location. All WAVE members must be EACS members. The survey did not ask for the role of the person completing it, only the name and institution. We agree with the reviewer that it is a limitation that the person completing the survey may not have knowledge about PrEP use in the whole country and this is highlighted in the limitation paragraph.

4) Results: did the 4.4% who opened the survey complete it? If you had 86 responses (assuming the 4.4% who clicked the link completed it?) and 38 countries responded presumably some countries yielded >1 response - how did you deal with conflicting answers if that happened? Please include number of responses per country in the appendix

The survey invitation was sent to all members of WAVE. We received a response from 38 countries, of which several responses where received from four countries (France, Italy, Spain and Greece). The respondents from countries that provided several responses were contacted and asked to provide one consensus answer from that country. As the community of researchers and clinicians involved in the PrEP is small, the respondents often had collaborations and knew each other.

5) Results: what about legal online purchase? It's not all illegal and the wording of your question may not captre this?

We agree with the reviewer´s comment and have changed the wording accordingly.

6) Results: for points i-iiii please also add %

The percentage has been added accordingly

7) Importing PrEP - what's the denominator for the 13 and 11 countries? Please include

The denominator has been added to this section accordingly

8) Obstacles for PrEP use - in the text you divide this by countries with and without access to PrEP but not in the table - it's impt to understand both so please amend the table accordingly and add some specific figures to the text

We agree with the reviewer that the difference between text and figure may be confusing. We have therefore amended the table according and rewritten some of the text to increase consensus between text and figure.

9) Discussion: lots of detail about HIV testing, please frame this in the context of opportunities to offer PrEP ig test negative

We agree that the paragraph about HIV testing may be confusing and not in line with the focus of the study. We have therefore deleted this paragraph from the discussion to make room for the additional information/data requested by the reviewers.

Reviewer #2

IN GENERAL:

* The article should be proof read for long and complex sentences, and sometimes missing words, especially in the abstract.

Thank you for pointing this out. We have proofread the article accordingly.

* Reporting should be clear and concise. I recommend being explicit about which countries reported what, instead of using more vague terms such as 'the majority of the countries...' and 'most countries said...'

We have tried to make the reporting more concise throughout the manuscript.

* In relation to my previous remark, it would help to be transparent and include the survey questions in the main manuscript. This way, the reader also has an idea in which way data were collected (phrasing of questions can help understand what exactly was requested from participants).

Thank you for highlighting the need for clarification. We have added some more details to the methods and material section of the manuscript and added the survey questions as supplement 1.

* While I believe strongly in the core message the authors want to bring ('we need to focus more on women in PrEP research and policy), the findings of this study rely a great deal on self-reported data from a very limited sample of non-specified respondents. This makes it very hard to draw any original conclusions from this research as such. An appraisal of existing evidence on PrEP for women by reviewing available data reports and literature (e.g. systematic review) would add strength and body to the message the authors want to deliver.

A systematic review is beyond the scope of the study. Several systematic reviews have been published on the efficacy, safety and barriers of PrEP use among women. We have added this information to the introduction. We agree with the reviewer that a limitation of the study is the use of self-reported data. However, the aim was not to assess the implementation of current national PrEP guidelines and access to PrEP in general (This has been done by the ECDC), but rather to explore PrEP availability and implementation for women specifically across the European region. In

our opinion this is the basis to be more prepared to improve access to prep for women, including different policies according to each setting. Part of WAVEs mission is to increase understanding of what works for women and what we can learn from each other. Furthermore, we believe that awareness can be raised by exchange of knowledge, which is why this manuscript is highly relevant for clinicians and others working with prevention of HIV.

INTRODUCTION:

* First paragraph: when talking about HIV diagnoses in the WHO EU region, please specify when you are talking about women only and when about the population in general. This is not clear upon reading right now.

This has been amended accordingly

* Second paragraph: when referring to the meta-analysis by Fonner et al, please clarify that no differences with regard to effectiveness of PrEP among different populations was found when PrEP was used daily. For event-driven PrEP regimens, evidence is less conclusive.

This point has been added to the text.

* Third parapgraph: please expand a bit further upon what WAVE exactly is. Is it community-based, is it a NGO, or rather a research project, or a bit of a mix?

Women Against Viruses in Europe (WAVE) is a working group of European AIDS Clinical Society (EACS). WAVE's mission is to promote the welfare of HIV-positive women in Europe. The initiative involves healthcare professional, researchers s and community representatives. WAVE endeavors to promote equality of access to care and excellence in standards of care for women living with HIV, including HIV prevention for women. This information has been added to the introduction.

METHODS:

* Please include the survey content (i.e. the survey questions and corresponding response categories)

The survey questions and response categories have been added in supplement 1.

* Overall the methods section requires more justification for why certain decisions were made by the investigators. I added some questions below:

- It says that the survey was sent to all EACS and WAVE members. Who are these people? What is their typical background and (professional) profile? Also, why was the survey sent to all members (quite a large group) and not more purposively to those thought of as being in a good position to give relevant and trustful answers because of their expertise (e.g. access to data reports etc.)?

WAVE is explained in the answer above. The European Aids Clinical Society (EACS) includes a large number of specialists across the region and of course we did not send it to be answered by all the members, but those, who are prescribing PrEP in the country/setting as mostly they know each other.

WAVE (women against viruses in Europe) is under the umbrella of EACS to focus on women specific issues like PrEP for women and also includes community members.

- Invited participants were encouraged to send only one response of their country. How could respondents make sure only one answer per country was sent? Do they know each other? How could they organize themselves for this? Also why would you only want one response per country, it would be interesting to see the variations they provide as a validity check?

Yes, actually we are sure, that HIV drug prescribing doctors know each other and in terms of PrEP there are mostly less people involved. We understand that it would have been interesting to have more than one answer, but for the purpose of the study we tried to get an overview about the whole region instead of also analyzing specific variations within each country. But sure, this could be done in more detail in the future.

- Quantitative data do not require the same methods of analysis compared to qualitative data. How did you deal with this issue?

The quantitative data was presented descriptively in terms of number and percentage or naming the relevant countries. The qualitative text was used to elaborate these quantitative finding. Thus, a qualitative analysis as such was not completed, but the text was used for elaboration, clarification or as a supplement to the quantitative results. We have tried to clarify this in the methods section.

RESULTS:

* How many respondents completed the survey? Also 38 (one per country), or did you receive more completed surveys?

The total number of responses were 42. We received more than one response from 4 countries (France, Greece, Italy and Spain). In this case, the respondents from these countries were contacted and asked to provide one consensus answer.

* The response rate is rather low. Reporting the response rate per country might be a bit misleading. Was it the aim from the beginning to include only one response per country? If so, please justify why you chose this approach.

The aim was not for all invited participants to answer the survey, but to get one response per country. This was chosen to get a good overview over the situation, as PrEP in women is not established at all and we were not so much focusing on the roll out in men, rather on the attitude towards PrEP for women.

* Why were the 4 non-WHO EU countries included in this study? How were they selected, on what basis?

They were answering the survey as they are members of EACS /WAVE. We deleted this part as it was too difficult to integrate in the overall results.

* Throughout the results section, please specify which countries reported which results instead of using more vague terms such as 'the majority said...' or 'two thirds of the countries...'. Now it is often impossible to know for a specific country what they have responded because there is no overview of this. If I would be interested in what e.g. Italy answered, how can I find this?

We have tried to be more specific throughout the results section, as per reviewer´s comment

* PrEP ACCESSIBILITY IN EUROPE:

- "...though a minority of PrEP users do buy it privately" : how do we know the frequency of this practice? Is it based only upon what one respondent says? Also who is this respondent? (knowing the background of the respondents would help us judge their credibility).

We agree with the reviewer that this sentence is vague and depend on the respondent's knowledge and experience. We har therefore deleted it from the text.

- "Spain commented that some individuals got PrEP for free by asking for PEP" : is this a rumor or a policy?

The was a free text comment from the respondent from Spain. We have highlighted this in the text.

- Albania is categorized as a country where PrEP is not available. Yet sero-discordant people use it. So is it available then for this indication?

Based on the answers provided by the respondent from Albania, PrEP is not officially accessible in the country, but has been used for sero-discordant couples trying to become pregnant. We have tried to clarify this in the text.

* IMPORTING PrEP

- Importing was legal in 13 countries: which countries? Also, does this refer to a general law on importing medication, or is this for PrEP specifically?

We have specified the countries in this paragraph. As this was a response to a yes/no question of whether importing PrEP was legal in their country, we do not know if this refers to a general law or to PrEP specifically. We have specified the data source to clarify this point.

* NATIONAL GUIDELINES

- Be specific on which countries reported what

We have specified the countries accordingly

- I don't understand the difference between prescription guidelines and provision guidelines, even not when reading the definition you gave. Do you mean eligibility criteria by prescription guidelines? And do provision guidelines more refer to how PrEP should be implemented? Please clarify.

Thank you for this question. Yes, prescription relates to the drug prescription itself and is more the medical part. Provision relates more to the social/ political part of the role out and attitude towards offering PrEP (which includes, availability, social and political circumstances). This clarification has been added to the text.

- "Five countries reported having not only national guidance but specific reommendations for PrEP in women..." : what were these recommendations? Between brackets are 6 countries, not 5. Please homogenize.

Thank you for pointing this out. We have corrected the text accordingly. We only know that the specific recommendations relate to women at high risk of HIV acquisition based on the free text comments from Austria and France, and have highlighted this in the text.

* PrEP ELIGIBILITY

- "PrEP was accessible to all groups" : which groups do you mean when saying 'all' groups?

The question was related to PrEP accessibility in all groups irrespective of gender or sexuality. This has been specified in the text.

- availability at the hospital and cost are barriers to access to care and should be mentioned in the paragraph on 'obstacles to PrEP use'

We agree that availability to PrEP use may be seen as an obstacle to PrEP use, however, these comments relate to the question of why PrEP might not be accessible to all groups. Thus, the comments elaborate on the quantitative yes/no response on PrEP eligibility. Because cost is also mentioned as a barrier in the "obstacles to PrEP use" section, we have deleted the sentence here.

* NUMBER OF PEOPLE ACCESSING PrEP

- How reliable are these numbers? Did you perform the survey at the clinical departments yourself?

Thanks for this question, it was meant to be an estimate and we are aware that those numbers are maybe not correct. Although we believe it is important to know. We have clarified the source of the data in the text.

* FORMAL CLINICAL FOLLOW-UP

- The previous paragraph mentioned PrEP was accessible for all persons at risk in only 18 countries while the Table 1 says 28 countries, and the first line of this paragraph says 24 countries. Please homogenize.

We agree the wording may be confusing and have revised the text and table accordingly.

- An overview of which country recommended what practices for follow-up would be helpful.

The country specific content of clinical follow-up of PrEP has been added to table 1.

* OBSTACLES TO PrEP USE

- Lack of knowledge: among potential users, health care providers, policy makers? Please specify throughout the paragraph.

The respondents were asked to provide yes or no answers to a predefined list of obstacles. One of these was lack of information (not lack of knowledge), without further specification. We have changed the wording, so that it corresponds to the text provided in the survey.

- Cost : for the user, for the health care provider, for insurance companies? Please specify throughout the paragraph.

This has been specified throughout the text.

- Lack of political will : to do what exactly? Expand access?

One of the obstacles mentioned in the survey was lack of political support (not will), without further specification. We have changed the wording, so that it corresponds to the text provided in the survey.

* EFFORTS TO ENCOURAGE ACCESS

- The findings presented here are very respondent-dependent and drawn from a very small convenience sample that is not further specified. More efforts might exist that were failed to be identified here. For

instance I could also name from the top of my head efforts being done in Belgium to reach women for PrEP despite Belgium not being mentioned here.

We agree with the reviewer that this is a limited description on efforts to encourage access to PrEP among women based on the survey respondents experience and knowledge. However, this is the results reported in the survey and the scope of the study has not been to gather country specific information beyond this survey.

* NON-EU COUNTRIES
- Why were they included?

They were answering the survey as they are members WAVE: We deleted this part as it was too difficult to integrate in the message.

DISCUSSION
* I would recommend starting this section with a quick recap of the study's objectives and methods used

Thank you for this recommendation. We have started the discussion with a short summary of the study aim and methods.

* "...less than 10% of PrEP users in Europe are women" : are there estimates available about the % of women that would be eligible for PrEP? If yes, you have an idea of the eligibility-usage gap. If not, this is a gap in evidence that you can mention as a future recommendation.

Thank you for the comment. As far as we know, there are no exact numbers about this issue. There is also a problem to define eligibility in women. This seems easier in MSM, but women are a much more heterogenous group, including sex workers for example.

* There is a paragraph about (access to) HIV testing among women that appears a bit 'lost' in the discussion section. How does this relate to PrEP exactly?

We agree with the reviewer that this paragraph might not be relevant to the current study and have deleted the text accordingly

* "Our results show that women in many countries are not considered a risk group of HIV acquisition..." : do you feel that women in general should then be regarded as a risk group for HIV? One could argue against this. I would consider re-phrasing, especially since you later on mention that risk should not be based on groups of people per se.

Thank you for this comment. We do not believe that all women should be considered a risk group of HIV acquisition and have rewritten some of the wording to avoid any confusion.

* Limitations: you mention (correctly) the limited ability to generalize from this study. Was this, however, the aim of the study? To come up with generalizable data?

Thank you. Of course, the data is not generalizable, but it well provides a start to think, where the next steps of research as well as implementation of PrEP should go. We know that the number of newly infected young women is far too high, and in our opinion, it will be a challenge to end AIDS if we have so many new infections. Women are even more vulnerable and might have their own

children with the risk of vertical transmission. Therefore, we wanted to reach out to see, where we could improve prevention measures for women. The text has been rewritten accordingly.

* Limitations: the low response rate in general (not per country) should also be mentioned as a limitation I feel

The aim was not for all invited participants to answer the survey, but to get one response per country. This was chosen to get a good overview over the situation, as PrEP in women is not established at all and we were not so much focusing on the roll out in men, rather on the attitude towards PrEP for women. Thus, providing a response rate of related to all those invited would be misleading. We have rewritten some of the text, to avoid any confusion.

* How exactly were the qualitative data analyzed? There is not reporting of this in the manuscript.

The qualitative data was not analyzed per se. The free text comments were used descriptively to elaborate on the quantitative answers. This has been highlighted in the methods section.

* While the discussion section offers many interesting elements related to (disparities in) access to PrEP for women, I think the authors could built even a stronger case by reviewing the literature systematically, and requesting for data reports that are available (ECDC for instance). Also, I would have expected the authors to refer to (even recent) research studies on PrEP excluding cis-gender women and mainly focusing on MSM and transgender women (e.g. recent Cabotegravir study).

A systematic review of the literature on PrEP for women is beyond the scope of this study. We have referenced to the current reviews completed within this area. We have also referenced to ECDC report on PrEP throughout the manuscript. We have updated the references in the background section of the manuscript to include some of the more recent PrEP studies among women and transgender women. We are aware that a major barrier for PrEP implementation is maintaining adequate adherence and persistence over time. However, we did not ask about this in the survey and can therefore not say if this is a barrier experienced by the country representatives. Thus, we have not focus on either the efficacy of PrEP or adherence issues in the discussion, as neither is within the scope of the study.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: