



Eligibility for Pre-exposure Prophylaxis According to Different Guidelines in a Cohort of HIV-Negative Men Who Have Sex with Men in Lisbon, Portugal

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Abstract

Defining eligibility for preexposure prophylaxis (PrEP) is key to measuring the degree of PrEP implementation. While the clinical exclusion criteria are identical across different guidelines, definitions of substantial HIV risk are not. In this study, we aimed to estimate the proportion of men who have sex with men (MSM) being tested at a community-based voluntary human immunodeficiency virus (HIV) counseling and testing center in Lisbon that would be eligible for PrEP according to guidelines from the World Health Organization (WHO), the US Public Health Service and Centers for Disease Control and Prevention (US-CDC), the European AIDS Clinical Society (EACS), and the Portuguese National Health Service (PNHS). We used baseline data from 3392 HIV-negative MSM with valid information on eligibility for PrEP enrolled in the Portuguese Lisbon Cohort of MSM—an observational study designed as an open prospective, noninterval cohort—between March 2014 and March 2018. At baseline, the proportion of MSM eligible for PrEP was 67.7% according to the US-CDC, 60.6% according to the PNHS guidelines, 58.9% according to the WHO, and 46.5% according to the EACS guidelines. The most frequently met criteria were those related to condomless anal intercourse. In conclusion, in the same population, the proportion of men eligible for PrEP differed by guideline, ranging from 46.5% to 67.7%, though if they all seem to include the same well-known predictors of HIV seroconversion.

Keywords HIV · Preexposure prophylaxis · Men who have sex with men · Eligibility determination

Introduction

In Portugal, data from 2007 to 2015 showed a 3.2% mean annual increase in the number of human immunodeficiency

virus (HIV) notifications attributed to sex between men. In the same period, cases of HIV reportedly transmitted heterosexually, and due to unsafe drug injection decreased by 7.4% and 21.0%, respectively (Instituto Nacional de Saúde Doutor Ricardo Jorge 2017). This increase in HIV cases among men who have sex with men (MSM) in Portugal shows that, from the individual perspective the available tools to prevention are not used, and from a public health perspective are not sufficient.

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HIV preexposure prophylaxis (PrEP) is an antiretroviral therapy-based HIV prevention strategy for adolescents and adults at high risk of infection (European Medicines Agency 2019; US Food Drug Administration 2018). It is effective in reducing HIV acquisition among MSM, both when taken daily or on-demand (Grant et al. 2010; McCormack et al. 2016; Molina et al. 2015). In 2012, the US Food and Drug Administration approved the use of tenofovir disoproxil fumarate and emtricitabine for HIV PrEP, which is currently recommended by several national and international guidelines. In Portugal, PrEP use was approved in 2017, and it is provided free of charge in public hospitals since February 2018 without discrimination by legal status in the country. Taking into

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consideration primary and secondary prevention uptake (Carvalho et al. 2013; Gama et al. 2017; Rosińska et al. 2018), as well as prevalence and incidence estimates among MSM in Portugal (Martins et al. 2015; Gama et al. 2017; Marcus et al. 2012; Meireles et al. 2015a), a combination prevention tailored to them must include PrEP.

As of February 2019, 502 individuals were on PrEP (M. C. Machado, National Authority of Medicines and Health Products, personal communication, May 13, 2019) in Portuguese public hospitals, mainly in a daily regime (Valdoleiros et al. 2018; Ferreira Dias et al. 2018). MSM represented 86% to 98% of PrEP users in 3 Portuguese hospitals and were mainly referred by community-based voluntary HIV counseling and testing centers (CBVCT) (Valdoleiros et al. 2018; Granado et al. 2018; Ferreira Dias et al. 2018). The total number of MSM accessing PrEP outside the formal Portuguese National Health Service (PNHS) offer is unknown. However, it was reported that 64 MSM, using PrEP informally, were given counseling and follow-up services at CheckpointLX, a CBVCT in Lisbon, from May 2015 and May 2018 (Ribeiro and Rocha 2019). CBVCTs play a major role in PrEP awareness, in identifying MSM at higher risk and in providing support to MSM PrEP users, even before it was officially available.

The definition of eligibility for PrEP is key to measure the success of this prevention tool, given that one important metric will be the uptake among eligible individuals (Eakle et al. 2018). Clinical aspects of the eligibility criteria are common in all guidelines, such as being HIV negative and having a healthy renal function; however, risk ascertainment differs across the guidelines (Eakle et al. 2018; Hodges-Mameletzis et al. 2018). In general, the risk is measured considering the local and group-specific incidence of HIV and known behavioral predictors of HIV acquisition. Topics related to condom use, HIV-positive partners, use of postexposure prophylaxis (PEP), diagnosis of sexually transmitted infections (STIs) or use of psychoactive substances during sex, although differing in how they are specified, are included in the following guidelines: the World Health Organization's (WHO) Implementation Tool for Pre-exposure Prophylaxis of HIV Infection (WHO 2017a); the Centers for Disease Control and Preventions' US Public Health Service (US-CDC); Preexposure Prophylaxis for the Prevention of HIV Infection in the United States—2017 Update (CDC 2017); the European AIDS Clinical Society's (EACS) Guidelines Version 9 (EACS 2017); and the clinical guidelines from the PNHS (Ministry of Health Portugal 2018) (Table 1).

We, therefore, aimed to estimate the proportion of MSM testing at a CBVCT center in Lisbon that would be eligible for PrEP using the WHO, US-CDC, EACS, and PNHS guidelines as a screening tool.

Methods

We used baseline data from the Lisbon Cohort of Men Who Have Sex with Men. Established in April 2011, this cohort is an ongoing observational prospective study conducted at CheckpointLX, a CBVCT in Lisbon for MSM whose entire team consists of trained peer community health workers (CHW), MSM themselves, who give support and peer education (recognized by European entities as a good practice center) (European Centre for Disease Prevention and Control 2012; WHO Regional Office for Europe 2016; WHO 2017b). A detailed description of the cohort has been provided elsewhere (Meireles et al. 2015a, b). Briefly, the Lisbon MSM Cohort was designed as an open, noninterval cohort, and inclusion criteria are: presenting for HIV testing at CheckpointLX, being a man, aged 18 years or older, reporting having sex with other men, and having a negative HIV test result at recruitment. All eligible men are invited to enter the cohort by a CheckpointLX peer CHW at their first visit. At each visit, this trained peer CHW administers a structured questionnaire and performs a rapid HIV test to all those who accepted to participate. Rapid syphilis and hepatitis C tests are also offered according to predefined eligibility criteria based on a risk assessment and the tests' characteristics (Simões et al. 2017). Data reported in this study refers to the period from March 2014 to March 2018.

Study Instruments and Variables

To compute eligibility for PrEP, we used the information collected in the structured baseline questionnaire of the cohort. This questionnaire collects sociodemographic characteristics, HIV testing history, and behavioral information such as sexual partners and practices, condom use, use of alcohol and drugs, knowledge and use of PEP and PrEP, and diagnosis of STIs. A detailed description is available elsewhere (Meireles et al. 2015b). An English translation of the currently used version of the questionnaire is available as a [supplement](#).

The operational definition of each eligibility criterion for PrEP in each guideline is presented in Table 2. We defined as eligible those meeting the operational definition of each criterion and those who did not as not eligible. Excluded from the analysis were participants with incomplete information, due to missing information or for having answered "I prefer not to answer" or "I don't know" in some questions that did not allow them to be classified as eligible or not eligible. We were unable to compute the EACS criterion related to chemsex, defined as "sex under the influence of recreational drugs taken predominantly intravenously immediately before and/or during sexual contacts," (EACS 2017) and the PNHS criterion related to "persons in situations of social vulnerability that may expose them to unprotected sex with individuals at high

Table 1 Overview of the WHO, US-CDC, EACS, and PNHS guidelines and specifications of their inclusion criteria by broad topic

Topic	Guideline			
	WHO (2017)	US-CDC (2017)	EACS (2017)	PNHS (2018)
Male partners	NA	Last 6 months, any	NA	NA
Relationship status	NA	Not monogamous with HIV-negative steady partner	NA	NA
Condomless anal intercourse	Last 6 months, > 1 partner	Last 6 months, ≥ 1 partner	≥ 1 casual partner	Last 6 months, ≥ 1 partner HIV-unknown
Use of psychoactive substances	NA	NA	Chemsex, intravenous	Any
STIs diagnosis	Last 6 months	Last 6 months	Recent	Last 6 months, CAI
Use of PEP	Last 6 months	NA	Ever	Last 6 months, CAI
Steady partners	HIV-positive, VL detectable	HIV-positive	HIV-positive, not on ART	HIV-positive, VL detectable
Sex work	NA	NA	NA	CAI

ART antiretroviral therapy; CAI Condomless anal intercourse; EACS European AIDS Clinical Society; HIV human immunodeficiency virus; NA Not applicable; PEP postexposure prophylaxis; PNHS Portuguese National Health Service; STI sexually transmitted infection; US-CDC United States–Centers for Disease Control and Prevention; VL Viral load; WHO World Health Organization

risk of acquiring HIV infection” (Ministry of Health Portugal 2018).

Participants and Ethics

From March 2014 to March 2018, 3713 adult MSM presented for testing and accepted to answer the Lisbon MSM Cohort baseline questionnaire. Among these, 148 (4.0%) had an HIV reactive result at their first visit and were excluded from the analysis. Among the remaining 3565, 18 (0.5%) had used PrEP, and 155 (4.3%) could not be classified by 1 or more guidelines and were excluded from this analysis. Among the 155 excluded, 66 (42.6%) were not classifiable according to the WHO guidelines, 62 (40.0%) according to the US-CDC, 112 (72.3%) the EACS and 82 (52.9%) the PNHS. We conducted the analysis among the remaining 3392 participants.

All cohort participants gave written informed consent prior to inclusion and the study protocol was approved by the ethics committee of São João Hospital Center and Medical School, University of Porto (ID 104/12).

Statistical Analysis

A descriptive analysis of participants at cohort entry was performed. Eligibility for PrEP was described in terms of counts and proportions. All statistical analysis was computed with SPSS for Windows, version 23.0 (SPSS Inc., Chicago, IL).

Results

Participants had a median age of 27 years (25th–75th percentile, 23–35); most were born in Portugal, while most foreign-

born participants were from Brazil and other European countries. More than half of participants had a higher education degree, and 82.6% self-identified as gay. A previous HIV test was reported by 76.6% of participants. While the most reported reason for testing was to know the health status/part of routine care (89.8%), when we grouped the reasons for testing in terms of the perceived risk of HIV infection, the most reported reasons were related to risk exposure (64.8%). A detailed description is provided in Table 3.

The percentage of participants meeting each criterion and the additional proportion explained, as well as the total number and percentage of eligible participants are presented in Table 4. Eligibility was higher when computed according to the US-CDC guidelines, with 67.7% of participants being PrEP eligible, while according to the PNHS guidelines, 60.6% were eligible. According to the WHO guidelines, 58.9% of participants were eligible, while 46.5% were eligible considering the EACS guidelines. Criteria related to inconsistent condom use was the most frequently met, but its proportion varied depending on how it was defined: the US-CDC guideline defined it as any condomless anal sex, which was met by 69.2% of participants; the WHO guideline defined it as condomless anal sex with more than 1 partner, which was met by 55.0%; the PNHS guideline defined it as condomless sex and having sexual partners with unknown HIV status, which was met by 42.4%; and the EACS defined it as condomless anal sex with a casual partner, which was met by 39.5%. The criterion relating to illicit psychoactive substance use, included in the PNHS guidelines, was met by 29.7% of participants. The criteria related to having an HIV-positive sexual partner, a diagnosis of an STI, and PEP use, were less frequently met.

Table 2 Operational definition of each eligibility criterion in the WHO, US-CDC, EACS, and PNHS guidelines

<i>Topic</i>	<i>Criteria for eligibility</i>	<i>Operational definition of eligibility</i>
WHO (2017)		
Condomless anal intercourse	<i>Vaginal or anal sexual intercourse without a condom with more than 1 partner, or</i>	Any anal sex with steady or occasional partners without condom (“yes” to the questions: 1. In the last 12 months, did you have sexual intercourse with men?; and 2. In the last 12 months, did you have anal penetration with your steady partner?; or 3. In the last 12 months, did you have anal penetration with an occasional partner?; and “often,” “occasionally,” “rarely,” or “never” to the questions: 1. In the last 12 months, how often did you use condoms for anal penetration [insertive or receptive] with a steady partner?; or 2. In the last 12 months, how often did you use condoms for anal penetration [insertive or receptive] with an occasional partner?; or “no” to the questions: 1. During your last anal penetration with a steady partner, did you use a condom?; or 2. During your last anal penetration with an occasional partner, did you use a condom?) And More than 1 sexual partner (“yes” to the questions: 1. In the last 12 months, did you have a steady partner?; and 2. In the last 12 months, did you have sex [oral, anal, vaginal], and/or other sexual practices with occasional partners?; or reporting more than “one” to the following questions: 1. How many steady partners did you have in the last 12 months?; or 2. In the last 12 months, did you have anal sex [penetration] with how many occasional partners?)
STI diagnosis	<i>A recent history (in the last 6 months) of an STI by laboratory testing or self-report or syndromic STI treatment, or</i>	Self-report of syphilis, chlamydia, lymphogranuloma venereum, gonorrhea, trichomoniasis, genital herpes, condyloma or genital warts, or other STI diagnosis (“yes” to the questions: 1. Have you ever had an STI?; and 2. In the last 12 months, did you have the following STI? [syphilis, chlamydia, lymphogranuloma venereum, gonorrhea, trichomoniasis, genital herpes, condyloma or genital warts, or other STI].)
Use of PEP	<i>PEP for sexual exposure in the past 6 months, or</i>	Use of PEP (“yes” to the questions: 1. Have you ever used PEP?; and 2. Did you use PEP in the last 12 months?)
Steady partners	<i>Sexual partner with HIV who is not taking suppressive ART</i>	Anal sex with a steady partner (“yes” to the questions: 1. In the last 12 months, did you have a steady partner?; and 2. In the last 12 months, did you have anal penetration with your steady partner?) And having at least 1 HIV-positive steady partner (at least 1 response “HIV-positive” to the questions: Which of the following is your steady partner [1 to 5]?) And having at least 1 HIV-positive partner who is not on treatment or is not known (at least one response “no” or “I do not know” to the questions: Is your steady partner [1 to 5] currently taking ART?) Or who had a detectable or unknown viral load (at least on response “detectable” or “I do not know” to the questions: Your steady partner [1 to 5] last viral load was?)
US-CDC (2017)		
Male partners	<i>Any male sex partners in the past 6 months, and</i>	Any anal sex with steady or occasional partners (“yes” to the questions: 1. In the last 12 months, did you have sexual intercourse with men?; and 2. In the last 12 months, did you have anal penetration with your steady partner?; or 3. In the last 12 months, did you have anal penetration with your steady partner?)
Relationship status	<i>Not in a monogamous partnership with a recently tested, HIV-negative man, and any of the following</i>	Other than men reporting only 1 HIV-negative male steady partner and no occasional partners (other than men reporting “yes” to the question: In the last 12 months, did you have a steady partner?; and “one” to the question: How many steady partners did you

Table 2 (continued)

Topic	Criteria for eligibility	Operational definition of eligibility
Condomless anal intercourse	<i>Any anal sex without condoms (receptive or insertive) in the past 6 months, or</i>	<p>have in the last 12 months?; and “HIV-negative” to the question: which of the following is your steady partner 1?; and “no” to the question: In the last 12 months, did you have sex [oral, anal, vaginal] and/or other sexual practices with occasional partners?)</p> <p>Any anal sex with steady or occasional partners without condom (“yes” to the questions: 1. In the last 12 months, did you have sexual intercourse with men?; and 2. In the last 12 months, did you have anal penetration with your steady partner?; or 3. In the last 12 months, did you have anal penetration with an occasional partner?; and “often,” “occasionally,” “rarely,” or “never” to the questions: 1. In the last 12 months, how often did you use condoms for anal penetration [insertive or receptive] with a steady partner?; or 2. In the last 12 months, how often did you use condoms for anal penetration [insertive or receptive] with an occasional partner?; or “no” to the questions: 1. During your last anal penetration with a steady partner, did you use a condom?; or 2. During your last anal penetration with an occasional partner, did you use a condom?)</p>
STI diagnosis	<i>Any STI diagnosed or reported in the past 6 months, or</i>	<p>Self-report of syphilis, chlamydia, lymphogranuloma venereum, gonorrhea, trichomoniasis, genital herpes, condyloma or genital warts, or other STI diagnosis (“yes” to the questions: 1. Have you ever had an STI?; and 2. In the last 12 months, did you have the following STI? [syphilis, chlamydia, lymphogranuloma venereum, gonorrhea, trichomoniasis, genital herpes, condyloma or genital warts, or other STI])</p>
Steady partners	<i>Is in an ongoing sexual relationship with an HIV-positive male partner</i>	<p>Anal sex with a steady partner (“yes” to the questions: 1. In the last 12 months, did you have a steady partner?; and 2. In the last 12 months, did you have anal penetration with your steady partner?)</p> <p>And</p> <p>having at least 1 HIV-positive steady partner (at least one response “HIV-positive” to the questions: Which of the following is your steady partner [1 to 5]?)</p>
EACS (2017)		
Condomless anal intercourse	<i>Inconsistent condom use with casual partners, or</i>	<p>Any anal sex with occasional partners without condom (“yes” to the questions: 1. In the last 12 months, did you have anal penetration with an occasional partner?; and “often,” “occasionally,” “rarely,” or “never” to the question: In the last 12 months, how often did you use condoms for anal penetration [insertive or receptive] with an occasional partner?; or “no” to the question: During your last anal penetration with an occasional partner, did you use a condom?)</p>
STI diagnosis	<i>Recent STI, or</i>	<p>Self-report of syphilis, chlamydia, lymphogranuloma venereum, gonorrhea, trichomoniasis, genital herpes, condyloma or genital warts, or other STI diagnosis (“yes” to the questions: 1. Have you ever had an STI?; and 2. In the last 12 months, did you have the following STI? [syphilis, chlamydia, lymphogranuloma venereum, gonorrhea, trichomoniasis, genital herpes, condyloma, or genital warts or other STI])</p>
Use of PEP	<i>Use of PEP, or</i>	<p>Use of PEP (“yes” to the question: Have you ever used PEP?)</p>
Steady partners	<i>Inconsistent condom use with HIV-positive partners who are not receiving treatment</i>	<p>Anal sex with a steady partner (“yes” to the questions: 1. In the last 12 months, did you have a steady partner?; and 2. In the last 12 months, did you have anal penetration with your steady partner?)</p> <p>And</p> <p>having at least 1 HIV-positive steady partner (at least one response “HIV-positive” to the questions: Which of the following is your steady partner [1 to 5]?)</p> <p>And</p>

Table 2 (continued)

Topic	Criteria for eligibility	Operational definition of eligibility
PNHS (2018)	<i>Persons who have had condomless sex in the past 6 months and sexual partners with unknown HIV status, or</i>	<p>having at least 1 HIV-positive partner who is not taking treatment (at least one response “no” to the questions: Is your steady partner [1 to 5] currently taking ART?)</p> <p>And</p> <p>Any anal sex with steady partners without condom (“often,” “occasionally,” “rarely,” or “never” to the questions: 1. In the last 12 months, how often did you use condoms for anal penetration [insertive or receptive] with a steady partner?; or “no” to the questions: 1. During your last anal penetration with a steady partner, did you use a condom?)</p>
Condomless anal intercourse	<i>Persons who have had condomless sex in the past 6 months and sexual partners with unknown HIV status, or</i>	<p>Any anal sex with steady or occasional partners without condom (“yes” to the questions: 1. In the last 12 months, did you have sexual intercourse with men?; and 2. In the last 12 months, did you have anal penetration with your steady partner?; or 3. In the last 12 months, did you have anal penetration with an occasional partner?; and “often,” “occasionally,” “rarely,” or “never” to the questions: 1. In the last 12 months, how often did you use condoms for anal penetration [insertive or receptive] with a steady partner?; Or 2. In the last 12 months, how often did you use condoms for anal penetration [insertive or receptive] with an occasional partner?; or “no” to the questions: 1. During your last anal penetration with a steady partner, did you use a condom?; or 2. During your last anal penetration with an occasional partner, did you use a condom?)</p> <p>And</p> <p>having at least 1 sexual partner for whom the HIV status is unknown (at least one response “I do not know” to the questions: 1. Which of the following is your steady partner [1 to 5]?; or 2. Are any of the occasional partners you have had in the last 12 months HIV positive?)</p>
Use of psychoactive substances	<i>People who refer to the use of psychoactive substances during sexual intercourse, or</i>	<p>Used at least 1 psychoactive substance during sex, including cannabis, heroin, cocaine, ecstasy, amphetamines, poppers, LSD, ketamine, GHB, methadone, substances commonly sold at smart shops, methamphetamines, mephedrone, or other (“yes” to the questions: 1. In the last 12 months, did you use alcohol or drugs?; and 2. Did you have sex under the influence of [cannabis, heroin, cocaine, ecstasy, amphetamines, poppers, LSD, ketamine, GHB, methadone, substances commonly sold at smart shops, methamphetamines, mephedrone or other]?)</p>
STI diagnosis	<i>Persons who have had condomless sex in the past 6 months and had a STI diagnosis, or</i>	<p>Any anal sex with steady or occasional partners without condom (“yes” to the questions: 1. In the last 12 months, did you have sexual intercourse with men?; and 2. In the last 12 months, did you have anal penetration with your steady partner?; or 3. In the last 12 months, did you have anal penetration with an occasional partner?; and “often,” “occasionally,” “rarely,” or “never” to the questions: 1. In the last 12 months, how often did you use condoms for anal penetration [insertive or receptive] with a steady partner?; or 2. In the last 12 months, how often did you use condoms for anal penetration [insertive or receptive] with an occasional partner?; or “no” to the questions: 1. During your last anal penetration with a steady partner, did you use a condom?; or 2. During your last anal penetration with an occasional partner, did you use a condom?)</p> <p>And</p> <p>Self-report of syphilis, chlamydia, lymphogranuloma venereum, gonorrhea, trichomoniasis, genital herpes, condyloma or genital warts, or other STI diagnosis (“yes” to the questions: 1. Have you ever had an STI?; And 2. In the last 12 months, did you have the following STI? [syphilis, chlamydia, lymphogranuloma</p>

Table 2 (continued)

Topic	Criteria for eligibility	Operational definition of eligibility
Use of PEP	<i>Persons who have had condomless sex in the past 6 months and used PEP for HIV, or</i>	<p>venereum, gonorrhea, trichomoniasis, genital herpes, condyloma, or genital warts or other STI])</p> <p>Any anal sex with steady or occasional partners without condom (“yes” to the questions: 1. In the last 12 months, did you have sexual intercourse with men?; and 2. In the last 12 months, did you have anal penetration with your steady partner?; or 3. In the last 12 months, did you have anal penetration with an occasional partner?; and “often,” “occasionally,” “rarely,” or “never” to the questions: 1. In the last 12 months, how often did you use condoms for anal penetration [insertive or receptive] with a steady partner?; or 2. In the last 12 months, how often did you use condoms for anal penetration [insertive or receptive] with an occasional partner?; or “no” to the questions: 1. During your last anal penetration with a steady partner, did you use a condom?; or 2. During your last anal penetration with an occasional partner, did you use a condom?)</p> <p>And</p> <p>Use of PEP (“yes” to the questions: 1. Have you ever used PEP?; and 2. Did you use PEP in the last 12 months?)</p>
Steady partners	<i>People whose partner is infected with HIV, without medical care or ART or without virologic suppression and do not use condoms consistently, or</i>	<p>Anal sex with a steady partner (“yes” to the questions: 1. In the last 12 months, did you have a steady partner?; and 2. In the last 12 months, did you have anal penetration with your steady partner?)</p> <p>And</p> <p>having at least 1 HIV-positive steady partner (at least one response “HIV-positive” to the questions: Which of the following is your steady partner [1 to 5]?)</p> <p>And</p> <p>having at least 1 HIV-positive partner who is not taking treatment or is not known (at least one response “no” or “I do not know” to the questions: Is your steady partner [1 to 5] currently taking ART?)</p> <p>Or</p> <p>who had a detectable or unknown viral load (at least on response “detectable” or “I do not know” to the questions: Your steady partner [1 to 5] last viral load was?)</p> <p>And</p> <p>Any anal sex with steady or occasional partners without condom (“yes” to the questions: 1. In the last 12 months, did you have sexual intercourse with men?; and 2. In the last 12 months, did you have anal penetration with your steady partner?; or 3. In the last 12 months, did you have anal penetration with an occasional partner?; and “often,” “occasionally,” “rarely,” or “never” to the questions: 1. In the last 12 months, how often did you use condoms for anal penetration [insertive or receptive] with a steady partner?; or 2. In the last 12 months, how often did you use condoms for anal penetration [insertive or receptive] with an occasional partner?; or “no” to the questions: 1. During your last anal penetration with a steady partner, did you use a condom?; or 2. During your last anal penetration with an occasional partner, did you use a condom?)</p>
Sex work	<i>People who engage in sexual intercourse to obtain money or goods or illicit substances and do not use condoms consistently</i>	<p>People who report having received money, goods, or drugs in exchange for sex (“yes” to the question: In the last 12 months, did you have sex [oral, anal, vaginal] for the purpose of getting money, goods, or drugs?)</p> <p>And</p> <p>Any anal sex with steady or occasional partners without condom (“yes” to the questions: 1. In the last 12 months, did you have sexual intercourse with men?; and 2. In the last 12 months, did you have anal penetration with your steady partner?; or 3. In the last 12 months, did you have anal penetration with an occasional partner?; and “often,” “occasionally,” “rarely,” or “never” to the</p>

Table 2 (continued)

Topic	Criteria for eligibility	Operational definition of eligibility
		<p>questions: 1. In the last 12 months, how often did you use condoms for anal penetration [insertive or receptive] with a steady partner?; or 2. In the last 12 months, how often did you use condoms for anal penetration [insertive or receptive] with an occasional partner?; or “no” to the questions: 1. During your last anal penetration with a steady partner, did you use a condom?; or 2. During your last anal penetration with an occasional partner, did you use a condom?)</p>

ART antiretroviral therapy; *US-CDC* United States–Centers for Disease Control and Prevention; *EACS* European AIDS Clinical Society; *GHB* gamma-hydroxybutyric acid; *HIV* human immunodeficiency virus; *LSD* lysergic acid diethylamide; *PEP* postexposure prophylaxis; *PNHS* Portuguese National Health Service; *STI* sexually transmitted infection; *WHO* World Health Organization

Discussion

In a community-based cohort of HIV-negative MSM, a large proportion of participants would be eligible for PrEP based on current guidelines. It varied from 46.5% according to the EACS guidelines to 67.7% according to the US-CDC guidelines, a difference of more than 20 percentage points.

The proportion of eligible participants follow the scope of each guideline set of criteria, even though they all included almost the same behavioral indicators of risk. The US-CDC guidelines had broader criteria, while the EACS guidelines were narrower. Regarding condomless anal intercourse, the EACS guidelines were more restrictive, defining as eligible those who did not use condoms consistently with casual partners or with HIV-positive partners who are not receiving treatment. In turn, the US-CDC criteria defined as eligible participants who reported any condomless anal sex, and the WHO considered as eligible those who reported any condomless vaginal or anal sex with more than 1 partner. Further, the PNHS guidelines considered as eligible participants who reported any condomless sex and any of the following risk indicators: sexual partners with unknown HIV status; an STI diagnosis; use of PEP; having an HIV-infected partner not receiving treatment or not virally suppressed; and having sexual intercourse to obtain money, goods, or illicit substances. Regarding the use of PEP, it was included in the EACS, WHO, and PNHS guidelines, but with some differences regarding the time frame. The US-CDC guidelines do not include the use of PEP in its criteria, but because this criterion was less frequently met, it did not increase the number of eligible participants according to the other guidelines. Psychoactive substance use was only included in the PNHS guidelines and contributed to a higher proportion of eligibility, given that it was also broadly defined. If a narrower definition had been used, as restricting to drugs typically associated with chemsex (i.e., excluding alcohol, cannabis, and poppers), this criterion would be met by 10.4% and the proportion of eligible MSM would be 51.1%.

These results give us a magnitude of the potential needs of PrEP among MSM in Portugal, under different guidelines, and are helpful for health decision-makers to design an appropriately dimensioned response. It also shows us that definitions are not concordant even though all guidelines are intended to identify people at higher risk of HIV. This means that some people will inevitably be defined as not at risk, while if another set of criteria was used, they would have been defined as at risk. So, both the allocation of resources and the approaches to individual risk prediction are highly dependent on the chosen guideline. PrEP needs to be seen as part of a comprehensive response to HIV prevention that includes multiple options. Moving the focus from PrEP eligibility assessment by using risk prediction tools to assess whether PrEP is a suitable option for a given individual in a given moment of his life, as already suggested (Golub and Myers 2019), might help to overcome guidelines limitations and create more equitable access.

Nevertheless, the number of PrEP users in Portugal, as of February 2019, was far less than what we estimated to be the number of potential beneficiaries. The European MSM Internet Survey that showed 33 (1.5%) MSM among those recruited in Portugal (excluding the HIV-positive) on current PrEP (The EMIS Network 2019) and the small number of exclusions in this analysis due to PrEP use reinforce that the PrEP needs in Portugal are not being met. Increasing access and use of PrEP will require more than the ability to identify those who are eligible. On the side of the candidates to PrEP, previous studies have shown that there are discrepancies between being eligible, perceiving a need, and using PrEP (Shover et al. 2018) or being willing to consider using PrEP (Parsons et al. 2017). In Portugal, awareness of PrEP among MSM varied from 41.0% in 2014 to 71.8% in 2017, and willingness to use PrEP was 57% (Rocha et al. 2014; The EMIS Network 2019). It is expected that at the initial phase of any innovation implementation, such as PrEP implementation, only a small proportion of the total population, described as “early adopters,” (Berwick 2003) on the side of both providers and users, are using PrEP (Krakower and

Table 3 Baseline description of participants ($n = 3392$)

Characteristics	Participants
Age (years)	
Mean (SD) age	29.9 (9.49)
Median (25th–75th percentile) age	27 (23–35)
Minimum–maximum age	18–77
Country/region of origin, n (%)	
Portugal	2490 (73.4)
Brazil	398 (11.7)
Other European countries	305 (9.0)
African country	90 (2.7)
Other American countries (North, Central, or South)	65 (1.9)
Asia/Middle East/Oceania	43 (1.3)
Missing	1 (0.0)
Educational level, n (%)	
Basic education or less	170 (5.0)
Secondary education	1093 (32.2)
Professional training	94 (2.8)
Postsecondary	40 (1.2)
Bachelor	1302 (38.4)
Master or doctoral	689 (20.3)
Rather not say	3 (0.1)
Missing	1 (0.0)
Sexual identity, n (%)	
Gay	2803 (82.6)
Bisexual	468 (13.8)
Heterosexual	44 (1.3)
Other/does not use a term/does not know	72 (2.1)
Rather not say	5 (0.1)
Previous HIV testing, n (%)	
No	794 (23.4)
Yes	2598 (76.6)
Reason for the index test, n (%)	
Reasons related to symptoms ^a	225 (6.6)
Reasons related to risk exposure ^b	2198 (64.8)
Reasons not related to symptoms or risk exposure ^c	949 (28.0)
Missing	20 (0.6)
Calendar year of entry	
2014	618 (18.2)
2015	770 (22.7)
2016	887 (26.1)
2017	924 (27.2)
2018	193 (5.7)

HIV human immunodeficiency virus

^a Participants reported “Symptoms/Medical indication”

^b Participants did not report “Symptoms/Medical indication” and reported at least 1 of the following reasons: “Anonymous partner notification,” “partner was diagnosed with HIV/disclosed HIV status,” “window period in the previous test,” “accident with condom use,” “perception of recent exposure to HIV,” or “perception of exposure to HIV more than 3 months”

^c Participants did not report “Symptoms/Medical indication” and did not report any of the reasons coded as related to risk exposure and reported at least 1 of the following reasons: “Asked by a sexual partner,” “before discontinuing using the condom with my partner,” “beginning of a new relationship,” “end of relationship with my usual partner,” or “to know health status/routine”

Mayer 2016; Mayer et al. 2015). However, to enhance the diffusion of PrEP, it is important to create demand, particularly among potential users who are at high risk but may not be initially motivated to use it (Eakle et al. 2018). This can be done by focusing strategies on the additional benefits of PrEP

besides HIV prevention (Golub and Myers 2019). Further, it is important to promote interventions, such as increasing the visibility of successful early adopters, to support widespread acceptance of PrEP by larger numbers of providers (Berwick 2003). On the side of provision, PrEP coverage has been shown to be the single greatest contributor to incidence reduction in a scenario of PrEP indication according to the US-CDC guidelines and eligibility defined similarly to our study (Jenness et al. 2016). To increase coverage in the Portuguese legal framework, it is necessary to increase the number of involved hospitals and their ability to meet demand in due time, by increasing the involved workforce. Making PrEP prescription and follow-up less burdensome and explicitly simpler in the guidelines, by for instance, including same-day initiation, may also contribute to increasing its uptake (Golub and Myers 2019; Kamis et al. 2019). It is also very important to be aware of inequities in access to PrEP, of PrEP-related stigma, and pay special attention to groups more disadvantaged. Additionally, PrEP delivery outside the hospitals, at the primary healthcare units, community pharmacies, or community-based organizations, should be considered.

The next steps in research should assess whether differences in how eligibility is defined influence the correct identification of those at higher risk, should evaluate how time changes in individual life context and behaviors might affect the need for PrEP and how to incorporate exposure modification in the guidelines and PrEP delivery. Users, providers, and key informant’s views should be included in participatory research toward the definition of the appropriate strategies to increase coverage and to an easier delivery of PrEP.

Limitations

Our study is subject to some limitations. Few criteria in each of the 4 guidelines could not be matched directly to the variables collected in the Lisbon MSM Cohort, and 2 of the criteria were impossible to measure. For instance, inconsistent condom use with HIV-positive partners who are not receiving treatment had to be defined as: (1) reporting to have had anal sex with a steady partner; and (2) having at least 1 HIV-positive steady partner; and (3) having at least 1 HIV-positive partner who is not receiving treatment; and (4) having had any anal sex with steady partners without condoms (in the previous 12 months). It is possible that participants may have had more than 1 steady partner in the previous 12 months and that either anal sex or inconsistent condom use had not happened with the HIV-positive steady partner. In the same way, the cohort variables refer to behaviors in the previous 12 months, while the WHO, US-CDC, and PNHS guidelines used a time period of 6 months. Both concessions we had to make to compute PrEP eligibility led to its overestimation, and the bias can differ by guidelines and contribute to explaining some of the differences found. The proportion of

Table 4 Proportion of participants ($n = 3392$) enrolled in the cohort meeting each of the eligibility criterion and additional proportion explained by each criterion according to the WHO, US-CDC, EACS, and PNHS guidelines and proportion of eligible participants

Topic, % (additional %)	Guideline			
	WHO (2017)	US-CDC (2017)	EACS (2017)	PNHS (2018)
Male partners	NA	96.5%	NA	NA
Relationship status	NA	93.7% (− 6.0)	NA	NA
Condomless anal intercourse	55.0%	69.2% (− 25.9)	39.5%	42.4%
Use of psychoactive substances	NA	NA	Not measured	29.7% (+16.1)
STI diagnosis	8.5% (+1.1)	8.5% (+1.5)	8.5% (+4.0)	6.9% (+1.4)
Use of PEP	2.1% (+0.7)	NA	5.0% (+2.5)	1.5% (+0.3)
Steady partners	2.6% (+2.2)	5.1% (+1.7)	0.8% (+0.5)	1.1% (+0.3)
Sex work	NA	NA	NA	1.4% (+0.1)
<i>Total eligible, n (%)</i>	<i>1999 (58.9%)</i>	<i>2298 (67.7%)</i>	<i>1576 (46.5%)</i>	<i>2056 (60.6%)</i>

EACS European AIDS Clinical Society; HIV human immunodeficiency virus; NA Not applicable; PEP postexposure prophylaxis; PNHS Portuguese National Health Service; STI sexually transmitted infection; US-CDC United States–Centers for Disease Control and Prevention; WHO World Health Organization

eligible MSM according to the US-CDC or other national guidelines were lower in other studies (Coyer et al. 2018; Dubin et al. 2018; Hoots et al. 2016; Nic Lochlainn et al. 2017); but it might only reflect different study populations. We did not include alcohol to fulfill the PNHS criterion on the psychoactive substances. We took this decision because it is not explicit in the guideline, and alcohol use during sex was frequently reported (48.7%), which would lead to a proportion of eligible of 73.0%. Data are inconclusive regarding the association of alcohol use during sex and HIV incidence, particularly without a measure of quantity (Woolf and Maisto 2009). So we decided to consider only the illicit psychoactive substances. On the other hand, guidelines are intended for use at an individual level in an appointment with one's physician. Thus, we may be missing relevant information to classify participants. For instance, any contraindication for PrEP could not be evaluated. We computed eligibility using the information provided during an interview with a peer CHW not specifically designed to assess eligibility. The structured questionnaire used covered all the topics but, in some cases, phrased differently. Additionally, for research purposes, we needed a strict yes or no classification of criteria, which is not expected in the clinical practice. Having data collected in front of an interviewer can also lead to bias related to social desirability, even if reduced by the fact that the interviewer is also an MSM.

These guidelines' discrepancies are not generalizable to the entire MSM population, even in Portugal. We know that participants in the cohort were more often self-identified as gay, were more educated, and were perhaps more aware of HIV risk, as they been tested for HIV more frequently in the past and as they were recruited at an HIV testing site (Meireles et al. 2015b), than other MSM populations studied in Portugal (Martins et al. 2015; Carvalho et al. 2013; Ferreira and Cabral 2010; Gama et al. 2017). Finally, among

CheckpointLX users, we can only report data from those who agreed to participate in the cohort, whom we know to be different in terms of sociodemographic characteristics (e.g., reported being born outside of Portugal, had lower levels of education, and self-identified less as gay) but probably with a similar perceived high risk of acquiring HIV as the frequency of a prior HIV testing was similarly high (Meireles et al. 2015b).

Conclusions

In conclusion, the proportion of men eligible for PrEP differed according to the guideline used, ranging from 46.5% to 67.7%. It makes the allocation of resources and the approaches to individual risk prediction highly dependent on the chosen guideline even if they all seem to include the same well-known predictors of HIV seroconversion.

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