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ELIGIBILITY FOR HIV PRE-EXPOSURE PROPHYLAXIS AMONG MEN WHO HAVE SEX WITH MEN: PORTUGUESE, PORTUGUESE MIGRANTS AND MIGRANTS IN PORTUGAL

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''HIV infection and AIDS is growing - but so too is public apathy. We have already lost too many friends and colleagues''

David Geffen

''The greatest grand challenge for any scientist is discovering how to prevent the spread of HIV and finding the cure or an effective vaccine for AIDS''

Philip Emeagwali

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AIDS – Acquired Immune Deficiency Syndrome
ARVs – Antiretrovirals
AVAC – AIDS Vaccine Advocacy Coalition
BMD – Bone Mineral Density
BMGF –Bill & Melinda Gates Foundation
CDC–Centers for Disease Control and Prevention
EMIS – European Men Who Have Sex with Men Internet Survey
FDA –Food and Drug Administration
FTC – Emtricitabine
HIV – Human Immunodeficiency Virus
MEMS – Medication Event Monitoring System
MSM – Men Who Have Sex With Men
NIH –National Institutes of Health
NYSDOH AI –New York State Department of Health AIDS Institute
PrEP – Pre Exposure Prophylaxis
STIs – Sexually Transmitted Infections
TasP – Treatment as Prevention
TDF – Tenofovir Disoproxil Fumarate
UAI – Unprotected Anal Intercourse
USAID –US Agency for International Development
WHO – World Health Organization

Abstract:

Human Immunodeficiency Virus (HIV) pre-exposure prophylaxis (PrEP) comprises the use of antiretroviral medications by HIV negative individuals to decrease infection risk. Men who have sex with men (MSM) have higher rates of HIV infection. Among MSM, migrants may face additional barriers related to certain types of cultures and stigma when seeking medical counseling that may increase the risk of acquiring the infection. This indicates an urgent need to develop alternative HIV prevention strategies. PrEP is a promising approach that can be part of an optimal comprehensive HIV prevention package targeted toward MSM in Portugal. This present study aims to estimate the proportions of eligible individuals for PrEP among a sample of 3 categories: 1) Portuguese-born living in Portugal, 2) non-Portuguese-born living in Portugal, and 3) Portuguese-born living abroad. Furthermore, it aims to identify predictors of eligibility in each group. This study was conducted among the Portuguese sample of The European Men-who-have-Sex-With-Men Internet Survey (EMIS), a cross sectional study that took place from June to August 2010. The sample included 5187 participants living in Portugal (80.7% Portuguese-born and 17.4% migrants) and 375 Portuguese-born living abroad (representing 8.1% of Portuguese-born and now living in other EMIS countries). Migrants were defined as men who were born in other country than their current country of residence. Information on HIV status, socio-demographic and behavioral characteristics was collected. Eligibility for PrEP was estimated according to the guidelines of the Centers for Disease Control and Prevention. Proportions were compared using the Chi-squared test and Odds Ratios (OR) with 95% confidence interval (95% CI) were computed using logistic regression to determine the predictors of PrEP at each group. The study found similar proportions of MSM eligible for PrEP among migrants living in Portugal (46.3%), Portuguese-born living in Portugal (44.4%) and Portuguese-born living abroad (45.1%) (p=0.621). Among migrants living in Portugal, participants from Latin America and the Caribbean region origin were more likely to be eligible for PrEP in comparison to Portuguese-born. The predictors of eligibility for PrEP were different among the 3 groups. Additional safe and effective approaches for HIV prevention in MSM such as PrEP are urgently needed.

KEYWORDS:

HIV, Pre-Exposure prophylaxis, MSM, Migrants

Resumo

A profilaxia pré-exposição (PrEP) para o VIH compreende o uso de medicamentos antirretrovíricos por indivíduos VIH negativos para diminuir o risco de infeção. Os homens que têm sexo com homens (HSH) têm maiores taxas de infeção por VIH. Entre os migrantes HSH, certos tipos de culturas, estigma e barreiras ao acesso ao aconselhamento médico, pode aumentar o risco de adquirir a infeção. Isto indica uma necessidade urgente de desenvolver estratégias alternativas de prevenção do VIH. A PrEP é uma abordagem promissora que pode ser utilizada como parte de uma estratégia abrangente de prevenção para o VIH dirigida aos HSH em Portugal. O presente estudo teve como objetivo estimar a proporção de indivíduos elegíveis para PrEP em três grupos: 1) nascidos e residentes em Portugal 2) nascidos noutro país e residentes em Portugal, e 3) nascidos em Portugal e residentes no estrangeiro. Para além disto, pretendeu-se identificar os preditores de elegibilidade em cada grupo. Para este estudo utilizaram-se dados da amostra portuguesa do estudo EMIS - *European Men-who-have-sex Internet survey*, um estudo transversal que teve lugar no período de junho a agosto de 2010. A amostra incluiu 5.187 participantes residentes em Portugal (80,7% nasceram em Portugal, 17,4% nasceram noutro país) e 375 indivíduos nascidos em Portugal residentes no estrangeiro (representando 8,1% dos HSH nascidos em Portugal e agora vivendo em outros países EMIS). Definiu-se como migrante os homens que nasceram num país diferente do seu país de residência atual. Recolheu-se informação sobre o estatuto serológico VIH, características sóciodemográficas e comportamentais. A elegibilidade para PrEP foi estimada de acordo com as orientações do Centro para o Controlo e Prevenção de Doenças dos Estados Unidos. Para comparar as proporções utilizou-se o teste do qui-quadrado e para determinar os preditores de profilaxia pré-exposição em cada grupo calcularam-se Odds Ratio (OR) com intervalos de confiança de 95% (IC95%) utilizaram-se modelos de regressão logística.. Encontraram-se proporções semelhantes de HSH elegíveis para PrEP entre os migrantes que vivem em Portugal (46,3%), os nascidos e residentes em Portugal (44,4%) e os migrantes nascidos em Portugal (45,1%) (p=0,621). Nos migrantes que vivem em Portugal, os participantes de origem região das Caraíbas e da América Latina eram mais provavelmente elegíveis para a PrEP em comparação com os nascidos em Portugal. Os preditores de elegibilidade para PrEP foram diferentes entre os três grupos. Abordagens seguras e eficazes adicionais para a prevenção do VIH em HSH, como PrEP são urgentemente necessários.

PALAVRAS-CHAVE:

HIV, profilaxia pré-exposição, HSH, Migrantes

INTRODUCTION

Human immunodeficiency virus (HIV) infection prevention had rapidly developed over the last decade, with several large-scale research studies and clinical trials showing that antiretrovirals (ARVs) can be used not only for the prevention of mother-to-child transmission, post-exposure prophylaxis and treatment as prevention (TasP) but also as HIV pre-exposure Prophylaxis (PrEP).

Daily oral PrEP with Tenofovir Disoproxil Fumarate-Emtricitabine (TDF–FTC) can safely and effectively reduce the risk of HIV infection among the not infected MSM and among heterosexual women and men. The recent Food and Drug Administration (FDA) approval for the use of Truvada® to prevent the acquisition of HIV infection and the release of interim guidance by the Centers for Disease Control and Prevention (CDC) for PrEP in men who have sex with men (MSM) (1) and heterosexually active individuals (2) ,at high risk of acquiring HIV, have increased the awareness and interest in PrEP as an important new addition to HIV infection prevention services.

On the other hand, and since the early beginning of the disease, MSM have been a core population affected by HIV infection (3). In spite of decades of public health efforts, in addition to community, medical and epidemiological research, HIV prevalence and incidence is still high and represent a heavy burden in MSM throughout the world(4). Even in high-income countries, the general HIV epidemic is declining except in MSM(5). Several factors play a role in aggravating the infection within the MSM community, starting from the biological factors, the stigma of the homosexuality and the denial of health services for MSM in several settings across the world, depriving them from the access to most of the basic HIV services and counseling (6).

Moreover, although several studies state about the relation between migration and HIV (7-11), there are only a few studies that showed in depth analysis or estimated the effect of the socio cultural effect in being involved in sexual risk behaviors in migrants MSM.

All of that make the recent optimism, that prevention methods such as the biomedical intervention chemoprophylaxis using a combination of TDF and FTC (Truvada®) having efficacy for MSM of paramount importance (12), and starts up real

opportunities for controlling the epidemics of HIV in MSM (6), bearing in mind that if we are aiming to achieve control of HIV infection, no population at high risk of infection can be excluded and no single HIV prevention strategy is going to be effective alone, knowing that several studies proved the cost effectiveness of PrEP in high epidemic settings (13).

As recently as 2012, Portuguese surveillance data reported that MSM in Portugal accounted for 24% of new HIV infection although representing only 3% of the Portuguese adult population (14). In addition, and according to national HIV prevalence data, the prevalence of HIV in MSM is around 11% among those ever tested (15). This data confirm that existing approaches to prevention have failed to control the HIV epidemic among MSM. A recent study, the iPrEX study, suggests that chemoprophylaxis PrEP could be a promising and effective approach to reduce the incidence of HIV in the MSM population. The study showed that a daily dose of TDF/FTC decreased HIV incidence in MSM (12) by 44% in general and by 73% among those who were highly adherent to daily dose. This suggests that HIV PrEP could have a potential role to effectively reduce the HIV epidemic in Portugal, where MSM have the highest annual incidence among all high-risk groups.

STATEMENT OF THE PROBLEM AND SIGNIFICANCE OF THE STUDY

In comparison to the current prevention methods such as condom use, lubricants, HIV voluntary counseling and testing, PrEP is an additional effective intervention, which had shown efficacy against HIV infection in MSM. Therefore detecting the prevalence and predictors of eligibility for HIV PrEP in the Portuguese sample of the European Men Who Have Sex with Men Internet Survey (EMIS), the largest sample of MSM ever studied in Portugal, will help us to better understand the magnitude of the problem prior to its adoption as a new effective HIV preventive method in Portugal. The study's significance lies in adding to efforts in controlling and curbing the spread and the rise in HIV infections at one of the most at high-risk population as well as detecting the determinants of being eligible for a new prevention method as PrEP in Portugal. This research is intended to add to the body of knowledge on PrEP in the Portuguese context. Moreover, it aims to stimulate more research and studies prior the adoption of PrEP in Portugal.

THEORETICAL BACKGROUND

Introduction

After more than thirty years of the first description of the HIV in MSM, the worldwide community is confronting a re-emerging and recent documented HIV epidemic among this population (16, 17). There is a need to start and scale up comprehensive sustained and effective HIV prevention methods among MSM in both the developing and the developed world. This goal can be achieved by a better acknowledgment of which method and intervention work best, and in what contexts.

Interventions and methods for decreasing acquisition of HIV infection among MSM included HIV testing to detect and treat HIV positive persons and decrease the risk of HIV transmission which is known as TasP**;** community-level behavioral interventions to reduce high risk behaviors (1); condom use**;** early detection and treatment of sexually transmitted Infections (STIs) (18); addiction and substance abuse counseling and mental health support when needed (19)**.** Recently, the FDA had approved PrEP as a new biomedical intervention to be added to the list of prevention methods for HIV. The efficacy of PrEP has been proven in four randomized control trials and the efficacy is high when the drug is used as directed in the term of adherence for the treatment (20).

PrEP implies the use of an antiretroviral drug to reduce acquiring HIV infection by uninfected people. This concept had been settled in the laboratories by animal studies and in real world application by post-exposure prophylaxis and the prevention of mother-to-child transmission (21)**.** The safety of the two antiretroviral - FTC and TDF - being used for PrEP, has been proven through their use for treatment in HIV positive patients and in safety trials in uninfected people (22). Several clinical trials of effectiveness, Phase IIb and Phase III, had been organized in the last 10 years. These clinical trials focus on effectiveness of PrEP among high risk MSM, people who inject drugs, serodiscordant couples and heterosexual women (21).

The Epidemiology of HIV

In 2013, there were 35 million patients living with HIV (23). Since the early beginning of the epidemic 78 million has become infected with the virus and 39 million have died of AIDS- related illness (23). Worldwide, 2.1 million individual became infected with HIV in 2013 and 1.5 million died from AIDS-related causes around 12.9 million people living with HIV had access to ARV therapy in the same year (23) (Table 1). On the regional level, the majority, 24.7 million, of people living with HIV are in sub-Saharan Africa (table 2).

Table 1: 2013 HIV Global Statistics

	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
People living with HIV	**29.8 million** [28.1-31.9 million]	**30.7 million** [29.0-32.7 million]	**31.4 million** [29.7-33.3 million]	**31.8 million** [30.2-33.7 million]	**32.1 million** [30.5-34.0 million]	**32.4 million** [30.8-34.3 million]	**32.7 million** [31.2-34.6 million]	**33.1 million** [31.5-34.9 million]	**33.4 million** [31.8-35.2 million]	**33.8 million** [32.2-35.6 million]	**34.2 million** [32.5-36.2 million]	**34.6 million** [32.8-36.6 million]	**35.0 million** [33.2-37.2 million]
New HIV infections (Total)	**3.4 million** [3.3-3.6 million]	**3.3 million** [3.1-3.5 million]	**3.1 million** [3.0-3.3 million]	**3.0 million** [2.8-3.2 million]	**2.9 million** [2.7-3.1 million]	**2.8 million** [2.6-3.0 million]	**2.7 million** [2.5-2.9 million]	**2.6 million** [2.4-2.8 million]	**2.5 million** [2.3-2.7 million]	**2.5 million** [2.3-2.7 million]	**2.4 million** [2.2-2.6 million]	**2.2 million** [2.0-2.5 million]	**2.1 million** [1.9-2.4 million]
New HIV infections (adults)	**2.9 million** [2.7-3.0 million]	**2.7 million** [2.5-2.9 million]	**2.6 million** [2.4-2.7 million]	**2.4 million** [2.3-2.6 million]	**2.3 million** [2.2-2.5 million]	**2.2 million** [2.1-2.4 million]	**2.2 million** [2.1-2.4 million]	**2.2 million** [2.0-2.3 million]	**2.1 million** [1.9-2.3 million]	**2.1 million** [1.9-2.3 million]	**2.1 million** [1.9-2.3 million]	**2.0 million** [1.8-2.2 million]	**1.9 million** [1.7-2.1 million]
New infections (children)	**580 000** [530 000–640 000]	**580 000** [540 000–640 000]	**580 000** [540 000–630 000]	**570 000** [520 000–620 000]	**550 000** [510 000–600 000]	**520 000** [480 000–580 000]	**490 000** [450 000–540 000]	**460 000** [420 000–510 000]	**400 000** [370 000–450 000]	**360 000** [330 000–400 000]	**330 000** [290 000–370 000]	**270 000** [240 000–310 000]	**240 000** [210 000–280 000]
AIDS-related deaths	**2.0 million** [1.8-2.2 million]	**2.1 million** [2.0-2.4 million]	**2.3 million** [2.1-2.5 million]	**2.4 million** [2.2-2.6 million]	**2.4 million** [2.2-2.6 million]	**2.3 million** [2.1-2.5 million]	**2.2 million** [2.0-2.4 million]	**2.1 million** [1.9-2.3 million]	**2.0 million** [1.8-2.1 million]	**1.9 million** [1.8-2.1 million]	**1.8 million** [1.7–2.0 million]	**1.7 million** [1.5-1.8 million]	**1.5 million** [1.4-1.7 million]
People accessing treatment									**5.2 million**	**7.4 million**	**9.0 million**	**10.6 million**	**12.9 million**
Resources		**US$ 3.8 billion**	**US$ 4.6 billion**	**US$ 5.7 billion**	**US$ 7.4 billion**	**US$ 8.8 billion**	**US$ 10.5 billion**	**US$ 14.6 billion**	**US$ 15.5 billion**	**US$ 15.6 billion**	**US$ 17.1 billion**	**US$ 18.9 billion**	**US$19.1 billion**

Source: UNAIDS: Fact Sheet 2014

Table 2: 2013 HIV Regional and Global Statistics

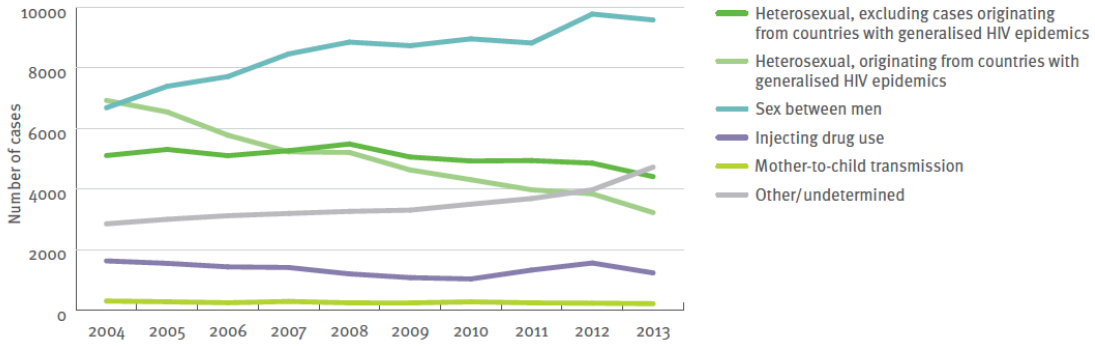
Region	People living with HIV 2013		New HIV infections 2013		AIDS-related deaths 2013 (total)
	total	children	total	children	
Sub-Saharan Africa	**24.7 million** [23.5 million–26.1 million]	**2.9 million** [2.6 million–3.2 million]	**1.5 million** [1.3 million–1.6 million]	**210 000** [180 000-250 000]	**1.1 million** [1.0 million–1.3 million]
Asia and the Pacific	**4.8 million** [4.1 million-5.5 million]	**210 000** [190 000-270 000]	**350 000** [250 000-510 000]	**22 000** [18 000-32 000]	**250 000** [210 000-290 000]
Latin America	**1.6 million** [1.4 million-2.1 million]	**35 000** [27 000-54 000]	**94 000** [71 000-170 000]	**1800** [<1000-7400]	**47 000** [39 000-75 000]
Western and Central Europe and North America	**2.3 million** [2.0 million-3.0 million]	**2800** [2300-3600]	**88 000** [44 000-160 000]	**<500** [<200-<500]	**27 000** [23 000-34 000]
Eastern Europe and Central Asia	**1.1 million** [980 000-1.3 million]	**14 000** [13 000-14 000]	**110 000** [86 000-130 000]	**<1000** [<1000-1200]	**53 000** [43 000-69 000]
Caribbean	**250 000** [230 000-280 000]	**17 000** [14 000-20 000]	**12 000** [9400-14 000]	**<1000** [<500-<1000]	**11 000** [8300-14 000]
Middle East and North Africa	**230 000** [160 000-330 000]	**16 000** [11 000-22 000]	**25 000** [14 000-41 000]	**2300** [1500-3400]	**15 000** [10 000-21 000]
Global	**35 million** [33.2 million-37.2 million]	**3.2 million** [2.9 million-3.5 million]	**2.1 million** [1.9 million-2.4 million]	**240 000** [210 000-280 000]	**1.5 million** [1.4 million-1.7 million]

Source: UNAIDS: Fact Sheet 2014

A global picture of HIV shows that the most common mode of transmission is through heterosexual intercourse (24). However, this picture differs in Europe. In most Europe, the HIV epidemic is highly concentrated in certain subpopulations including, MSM, people who inject drugs and migrants (specifically migrants from high HIV prevalence countries) (25-27). Available data shows that the prevalence of HIV among MSM is high and is continuing to increase in many countries throughout Europe (28).

In the West of Europe, there were 26 847 newly diagnosed cases with HIV infection in 2013 with a rate of 6.3 per 100 000 population (29). The most predominant mode of transmission was sex between men, followed by heterosexual sexual contact (Figure 1), accounting together for 77% of the new diagnosed cases (29). Sex between men accounted for 43% of the new diagnosed cases. Heterosexual contact accounted for 34% of the transmission. 4% of the acquired HIV infection were through injecting drug use and 0.7 % acquired through mother to child transmission (29).

Figure 1: New HIV diagnosis, by transmission mode and year of diagnosis in West of Europe, 2004-2013



Source: European Centre for Disease Prevention and Control/ WHO Regional Office for Europe. HIV/AIDS surveillance in Europe 2013. Stockholm: European Centre for Disease Prevention and Control; 2014

HIV prevalence among MSM in the 36 European countries that reported data, ranges from 0.5% to 17.7% (28). Prevalence is 5% or more in sixteen countries and 10% or more in 7 countries. The highest prevalence was reported by countries including France, Spain, Portugal, Belgium, Germany, Greece, Ireland, Italy and Switzerland (28).

The Concept of PrEP

The concept of providing a preventive medication prior to exposure to a certain germ or virus is not a new concept and had been used to prevent other infections and diseases (30, 31). For instance, when individuals travel to a place where malaria is endemic, they should take malaria medication before and during travel to prevent getting infected in case bitten by a mosquito infected by malaria parasite (32-34). However, the use of antiretroviral medications to prevent HIV infection had only recently been approved (30, 31). When used consistently with adherence to treatment, PrEP has shown to decrease the risk of HIV infection among adults who are at high risk of acquiring the infection through sex, including heterosexually active men and women and MSM. Current evaluation of PrEP's effectiveness in preventing HIV infection among people who inject drugs are underway, but those results are not yet available (30, 31).

PrEP as a recent HIV prevention method in which people who are HIV negative take daily dose of antiretroviral to reduce their risk of acquiring the infection. The daily dose contains medications that prevent HIV from making new virus when it enters the body. TDF and FTC are phosphorylated intracellularly to form active agents that inhibit HIV replication (35).By this way PrEP medicines can help keep the virus from establishing a permanent infection inside the body(30, 31).

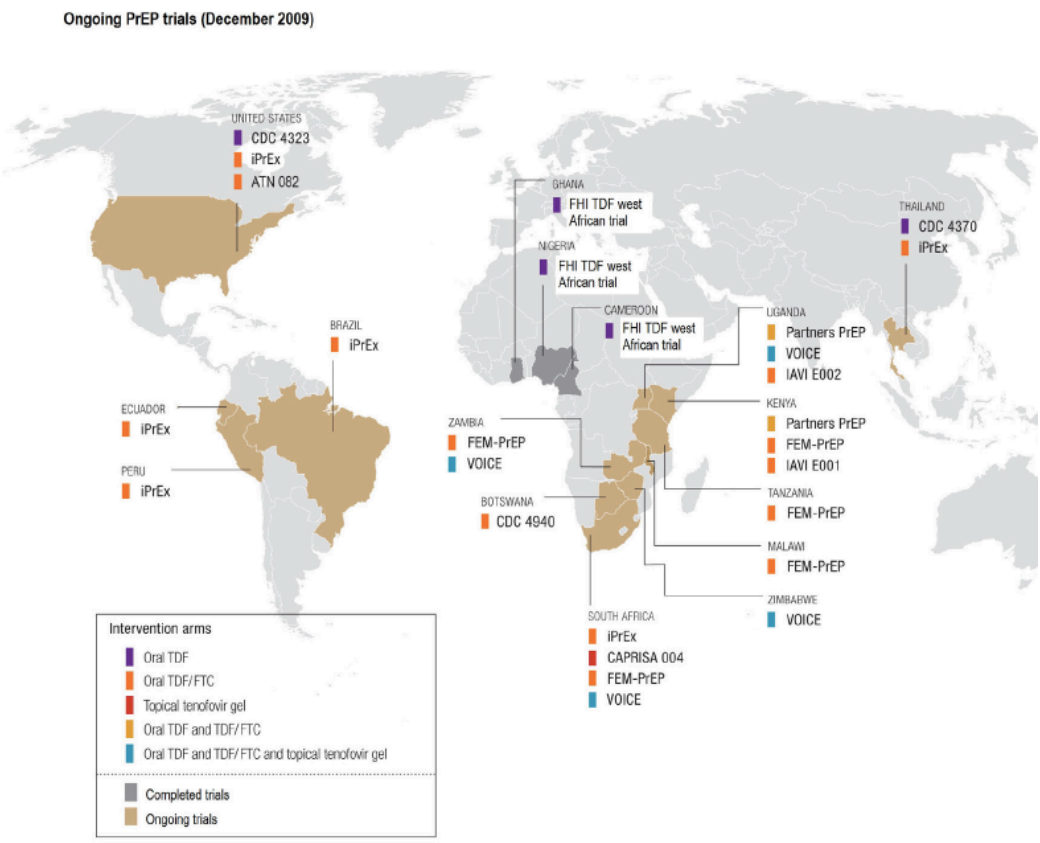
TDF/FTC for PrEP must only be used by individuals who are HIV-negative and who continue to be HIV-negative during use for that they should be tested at least every 3 months (35). PrEP is contraindicated in individuals with positive or unknown HIV status (30, 31)

For individuals who are at high risk for sexual exposure to HIV, PrEP may be considered an important additional prevention method. PrEP is a comprehensive approach that requires strict adherence to medication and HIV testing. PrEP is not intended to be used as a sole intervention, but in combination with other HIV prevention methods such as counseling for sexual health reduction, repeated condom provision and early diagnosis and treatment of sexually transmitted infection (STI) (30, 31). In case PrEP is used effectively by individuals who are at high risk, it can play an important role in reducing the number of new HIV infections.

Clinical Trials

Clinical trials of oral PrEP in different populations and settings started in 2005(34). Clinical trials of PrEP have been undertaken in more than 13 countries worldwide (Figure 2), including countries such as the US, Thailand, Peru, Ecuador, Brazil, Botswana, South Africa, Kenya, Uganda, Malawi, Tanzania, Zambia and Zimbabwe(36). The first generation of PrEP trials (Table 3) had enrolled more than 20,000 study subjects and were designed to produce results in different populations groups, representing different routes of HIV transmission in Africa, the Americas, and Asia (35). They focused on either 300mg TDF or 300mg TDF/200mg FTC taken once daily (34). These studies are mainly sponsored by the US National Institutes of Health (NIH), the Bill & Melinda Gates Foundation (BMGF), the CDC, and the US Agency for International Development (USAID) (37). Gilead Sciences manufactures both TDF and TDF/FTC and affords the drugs for these trials (37).

Figure 2: PrEP trials map worldwide - December 2009.



Source: AIDS Vaccine Advocacy Coalition (AVAC)

Table 3: The First Generation of PrEP Clinical Trials

Study name	Population and locations tested	Study sponsor; funder	Regimen	Major questions addressed	Study timelines
US extended safety trial	400 MSM in US	CDC	Daily oral TDF	Biological and behavioral safety of daily oral TDF	Enrollment began: Q1 2005 Fully enrolled: Q3 2007 Results presented: Q3 2010
Bangkok tenofovir study	2,400 injection drug users in Thailand	CDC	Daily oral TDF	Safety and efficacy of daily oral TDF in IDU (over 80% DOT)	Enrollment began: Q2 2005 Fully enrolled: Q2 2010 Results expected: 2011
TDF 2	1,200 heterosexual men and women in Botswana	CDC	Daily oral FTC/TDF	Safety and adherence in young heterosexual men and women in Africa	Enrollment began: Q2 2007 Enrollment stopped early Results expected: 2011
iPrEx	2,499 MSM in Peru, Ecuador, Brazil, US, Thailand, and South America	NIH; BMGF	Daily oral FTC/TDF	Safety and efficacy of daily oral Truvada in MSM globally	Enrollment began: Q3 2007 Fully enrolled: Q4 2009 Results published: Q4 2010
Partners PrEP	4,700 serodiscordant heterosexual couples in Kenya, Uganda	BMGF	Daily oral TDF; Daily oral FTC/TDF	Safety and efficacy of daily oral tenofovir and Truvada in serodiscordant couples in Africa	Enrollment began: Q3 2008 Enrolling Results expected: 2012
VOICE	5,000 heterosexual women in Malawi, South Africa, Uganda, Zambia, Zimbabwe	MTN, NIH	Daily oral TDF; Daily oral FTC/TDF; Daily topical tenofovir gel	Safety and efficacy of daily oral tenofovir, daily oral Truvada, and daily topical tenofovir in African women	Enrollment began: Q3 2009 Enrolling Results expected: 2013
FEM-PrEP	3,900 heterosexual women in Kenya, Malawi, South Africa, Tanzania, Zambia	FHI, USAID, BMGF	Daily oral FTC/TDF	Safety and efficacy of daily oral Truvada in African women	Enrollment began: Q2 2009 Enrolling Results expected: 2013
IAVI E001 and E002	150 serodiscordant couples and men and women in Kenya, Uganda	IAVI	Daily oral FTC/TDF; Intermittent oral FTC/TDF (twice weekly + post-coital dosing)	Safety and adherence of daily versus intermittent FTC/TDF	Enrollment began: Q2 2009 Fully enrolled Results presented: Q3 2010
PrEP in YMSM	99 young MSM in the US	ATN, NICHD	Daily oral FTC/TDF	Safety, acceptability, and feasibility in young US MSM	Enrollment began: Q2 2009 Enrolling Results expected: 2011

Source: AVAC's PrEP Trials Table

Several PrEP studies have focused on MSM populations, for example: a study for testing the safety of daily oral TDF in US MSM; a study to determine the efficacy of oral daily Truvada® in MSM in Brazil, Peru, Ecuador, the US, South Africa, and Thailand; and a study of PrEP safety, acceptability and feasibility in young MSM (36). In addition, other PrEP trials established exploring the safety and efficacy of TDF-based regimens in heterosexual men and women, heterosexual couples, and people who inject drugs. The chosen of TDF-based regimens based on the strength of pre-clinical trials**,** in addition to the proven safety, tolerability, and resistance profiles of these medication when used as HIV treatment. All of these clinical trials are examining substantial safety data and tolerability in these different populations. Moreover, some of these went further to conduct sub-studies to test specific safety concerns that include evaluation of renal toxicity and examination of bone mineral density. All the clinical trials will assess pill-taking activities via participant self-report**;** another studies will assess pill-taking practices through objective measures such as microchips that can record the number of opening of pill bottles, counting returned pills and drug levels in plasma, blood cells, or hair**.** The clinical trials also assessed sexual and drug-use practices during the course of the trial. These clinical trials are also aimed to evaluate PrEP efficacy. The majority of these drugs are evaluating a single daily oral dose regimen, while the Partners in Prevention trial are evaluating both daily oral Truvada® versus TDF, and the VOICE trial are evaluating daily Truvada®, TDF and daily vaginal TDF. On the other hand, neither of these clinical

trials aimed for a direct comparison of different regimens, but both will present comparative efficacy data through the same trial. Finally, among MSM who become HIV positive while receiving PrEP, these clinical trials will provide data on patterns of HIV resistance, the impact on HIV viral load set point and CD4 cell count. Most of these studies are also evaluating sexual and drug-use practices through the course of the clinical trial. Concern has been increased that individuals may increase their risk practices if they have access to effective prevention methods. This alteration in risk behavior could be due to a decrease in self-imposed limits to avoid risk**,** which is known as behavioral disinhibition, or decreasing awareness of risk, known as risk compensation, with the obtainability of the new prevention method (38, 39).

A website that contains updated data about the clinical PrEP trials is hosted by the AIDS Vaccine Advocacy Coalition: http://www.prepwatch.org.

Clinical Trials Among MSM

iPrEx

The iPrEx trial was the first clinical trial to produce results (12). It was a phase III large-scale study conducted in six countries that include the US, Ecuador, Brazil, Peru Thailand and South Africa and aimed to test whether a daily combination of FTC and TDF could prevent HIV infection among MSM in an effective and safe way among sexually active gay men and transgendered women who have sex with men (21). Research participants were at least 18 years old and HIV-negative at the time of enrolment and had been assessed for HIV infection monthly for the duration of their participation in the study. The results of the study had been published in November 2010 and showed that there was a 44% (95% CI 15% - 63%) reduction in risk among PrEP recipients (12). The study included 2,499 MSM and transgender women who have sex with men, who were at high risk of HIV infection. Half of the participants were given once-daily oral FTC-TDF, Truvada®, and the other half of participants was given a placebo. All subjects received risk-reduction counseling and monthly HIV testing. Among those taking daily oral FTC-TDF, 36 became infected with HIV during the study, compared to 64 in the placebo group. The protective effect was higher among participants with good pill adherence. The side effects of the drug were mild and included a transient nausea, which disappeared after several weeks. In addition, some participants who took the active drug experienced a mild elevation of creatinine. These new findings from the iPrEX study pertain only to the

effectiveness of PrEP among MSM and cannot be extrapolated to other populations (40).

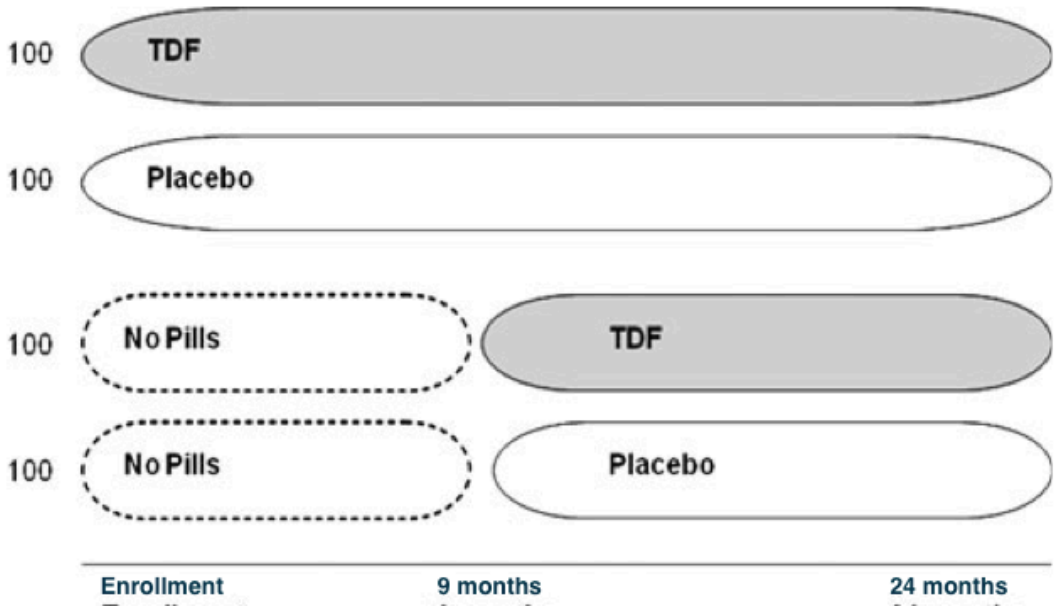
After the release of the trial results the CDC issued a guidance for using PrEP for the prevention of HIV infection among MSM (41). The guidance stated that for MSM at high risk for HIV infection, PrEP might represent an important additional prevention tool. PrEP in MSM should be used in combination with other HIV prevention methods and strategies and requires strict adherence (41).

US MSM SAFETY TRIAL

This trial was a phase II, randomized, placebo controlled, double blinded study of the behavioral effects and clinical safety of TDF as a PrEP among four hundred MSM participants (42). The study took place in 3 cities in the US that include Atlanta, Boston and San Francisco (43) had been sponsored by the CDC. The study subjects were assigned randomly 1:1:1:1 to receive a daily oral dose of TDF or placebo immediately or after nine month delay(42). Participants were assigned for follow-up visits one month after enrollment and 4 months after that. Medication adherence was high among participants without direct medication interruption (the adherence was up to 92% using pill count and up to 77% using pill bottle openings recorded by Medication Event Monitoring System caps (42). After running a multivariable analysis, the only adverse effect that was associated with TDF was back pain. In a portion of participants at the San Francisco (n=184) for whom bone mineral density (BMD) had been assessed, the receipt of TDF was found to be associated with small decrease in BMD (0.8% decrease for total hip and 1% decrease at the femoral neck) (44), but at the same time, the reception of TDF was not associated with bone fractures at any anatomical site. No HIV with mutations accompanied by TDF resistance was recorded among seven seroconversions (43). In addition, among participants who were given TDF, no HIV infections occurred**;** 3 seroconversions occurred in men while taking placebo, another 3 seroconversions occurred among men who were in the delayed TDF group but had not started receiving drug and one seroconversion occurred in a man who had been assigned randomly to receive placebo and was later on discovered to have had acute HIV infection at the enrollment visit (43).

This study evaluated the possibility for an alteration in sexual risk practices via its unique study scheme, which randomized half of the participants to take a daily pill of TDF or placebo upon enrollment, while the other half are randomly allocated to wait nine months prior to starting their daily study pill (Figure 3). This permits a direct comparison of risk behaviors and practices while men are or are not taking a daily pill, and may provide an early indication if there is likely to be significant risk compensation.

Figure 3: Study design of US CDC tenofovir (TDF) study



Source: Buchbinder SP, Liu A. Pre-exposure prophylaxis and the promise of combination prevention approaches. AIDS and behavior. 2011;15(1):72-9.

The PROUD study

The PROUD study took place in the UK and randomized participants to either immediate or deferred PrEP (after one year) using daily Truvada®. The data safety monitoring board recommended, on October 16 2014, to give daily PrEP to all trial participants because PrEP was highly protective against HIV (45).

The IPERGAY study

The IPERGAY study took place at six hospitals in France and one in Canada. It was used "on demand" prophylaxis only at the time sexual intercourse. A significant difference in incidence of HIV infection in the on demand PrEP group was found, and "on demand" Truvada® recommended to all trial participants (47).

Rationale for HIV Prophylaxis Using Antiretroviral Agents

Current efforts to prevent, control and treat HIV are starting to yield results. Noteworthy extension of antiretroviral therapy had led to reduced mortality. There had been some steadiness or decline in new HIV infections through several countries in sub-Saharan Africa, which is home of 67% of all individuals living with HIV(46). Data indicate that there were 400,000 less new infections in that area in 2008 than there were in 2001 (47). Although these promising progresses, much effort remains. Generally, HIV prevalence is disappointingly high and continues to rise in several parts of the world. HIV excessively affects MSM, PWID and sex workers (46). Despite that behavioral interventions are essential, and structural plans are needed to address the underlying factors of vulnerability to HIV, technology can also provide a much needed addition to the prevention methods. Developments in understanding of the pathogenesis of HIV have headed to more complex research on prevention strategies (37). Studies have revealed that early in infection, HIV targets and destroys cells of the immune system that are probably adapted to prevent establishing and control development of disease (48) .It is thus significant to intervene before infection is established and track all opportunities to develop a well-planned set of combination prevention. This set must contain effective and complementary modalities to reduce rates of HIV transmission to the highest degree possible (49, 50). One technological prevention choice that could be of great value is PrEP, which is an approach for HIV-negative individuals to decrease their risk of acquiring the infection by taking oral antiretroviral drugs used for HIV treatment.

As discussed earlier, this approach had been evaluated in a number of studies in different populations worldwide, but ‘‘Can a pill a day prevent HIV?’’ this was the tagline of recruitment campaign for HIV prevention trial to test whether a combination pill of TDF and FTC could reduce the number of HIV infections when taken daily among MSM (36). The general principle underlying PrEP is clear: medications that are offered as treatment can be used to prevent infection among persons highly exposed for HIV or those who are more susceptible to the infection, and as any infectious disease that can’t be controlled by antimicrobials alone, the control of HIV will be achieved through a combination of behavioral and biomedical methods and interventions (51). Even in chronic diseases such as coronary heart disease, 50 % decline in mortality was achieved in the US from 1980 to 2000 through a combination

of strategies that include modification of risk factors and biomedical interventions (52). Chloroquine was used to treat malaria and also to prevent it among individuals travelling to malarias districts (37). Another example is isoniazid, which is still used as prophylaxis in high-risk sets and as part of the treatment routine for tuberculosis. Observing the current epidemiology of the HIV epidemic, PrEP may be suitable targeted prevention strategy. Numerous accomplished pre-clinical studies in diverse animal models have shown promise. Macaques animals treated daily with FTC were less likely to be infected after rectal exposure to a simian version of HIV (SHIV) than untreated Macaques. Animals treated with oral FTC and TDF at similar doses to a human corresponding dose had an even lesser rate of seroconversion (37). Moreover, macaques treated daily with two antiretroviral drugs, FTC and TDF, at high doses were totally protected from HIV infection (53). HIV negative adults at high risk receive antiretroviral products formulated as pills or gels that prevent HIV replication during periods of HIV exposure as prophylaxis versus infection (54, 55).

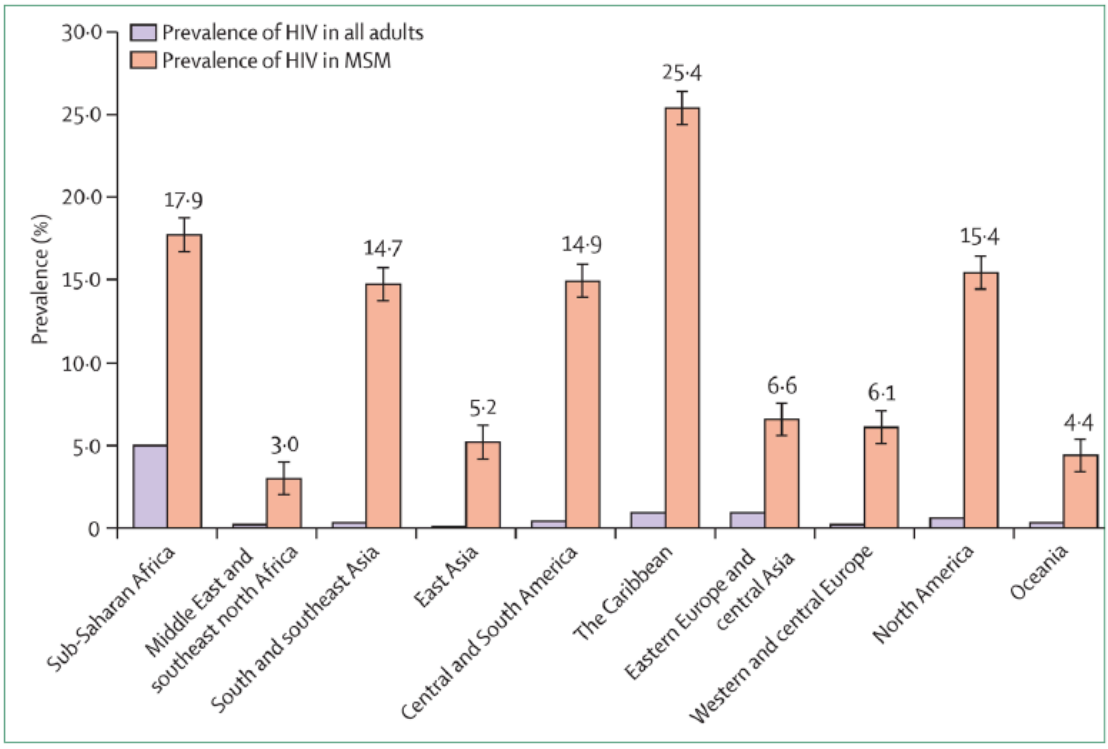
At population level, combination of different interventions that target different mechanisms of the HIV epidemic could be synergistic at a population level (56). For instance, in South Africa, a model that was testing the impact of combining male circumcision with a behavior change program found that male circumcision alone with 90% coverage would lead to one-third reduction in the incidence of HIV at population level. On the other hand, a behavior change program alone with 30% increase in condom use and 30% reduction in the rate of partner change would result to 2/3 reductions in HIV incidence rates. Nonetheless, in case we combined male circumcision with a behavior change program, HIV incidence would be nearly eliminated (57), and because PrEP is not 100% effective, therefore it needs to be combined with the other HIV prevention interventions to have the greatest impact.

Disease burden of HIV in MSM

Since the early beginning of HIV epidemic in the early 80s, MSM were one of the main populations affected by the disease (58, 59). Although there was important advanced and societal progress in the field of treatment, prevention and support in the past 3 decades, the epidemics of STIs and HIV in MSM are expanding worldwide, even in several countries with generalized HIV epidemics (60), because the effectiveness of this measures is dramatically affected by social and structural factors in the MSM groups (61). In addition, MSM face some political and structural

barriers to accessing services in many settings owing to their marginalized and stigmatized status (21). The substantial burden of HIV in MSM suggests that currently existing methods of HIV prevention are not sufficient and additional prevention methods should be considered (21). Worldwide, the odds of being infected with HIV are 19.3 times higher in MSM than for men in the general population (60). In many countries around the world, while there was an observed decline in HIV incidence, a steady increase in the number of new cases in MSM has been reported and documented (Figure 4) (62).

Figure 4: Global prevalence of HIV in MSM compared with regional adult prevalence reported by UNAIDS, 2010.

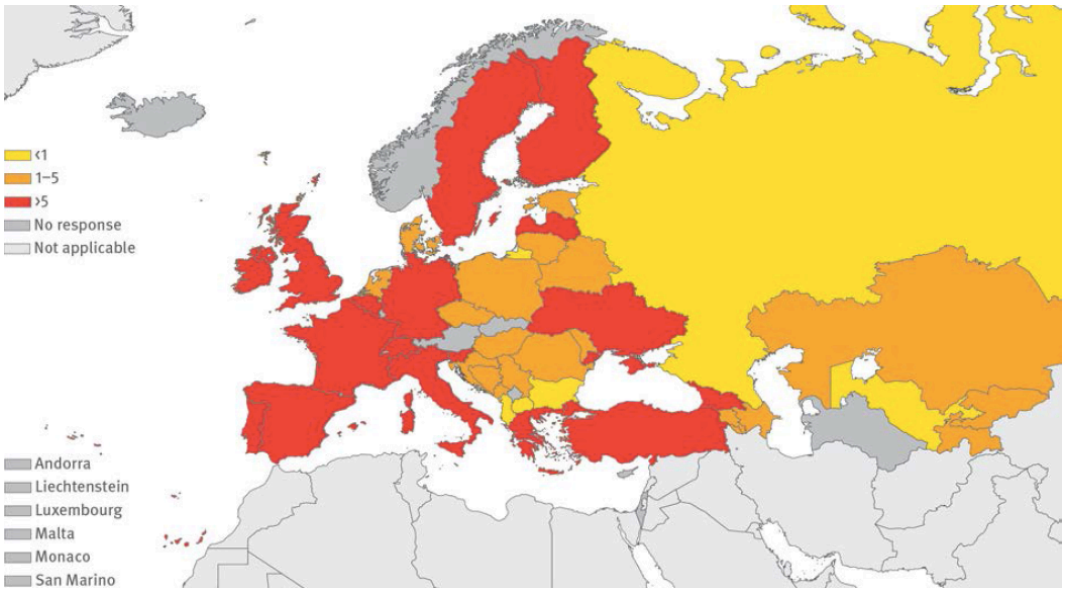


Source: McKeown E, Doerner R, Nelson S, Low N, Robinson A, Anderson J, et al. The experiences of ethnic minority MSM using NHS sexual health clinics in Britain. Sexually transmitted infections. 2012;88(8):595-600.

In the European Union, the largest increase in new infections was reported in MSM (64) (Figure 5). In several high-income countries like France, UK, USA and Australia, the overall epidemic trends are declining except in MSM (65, 66). There is a defect in understanding the worldwide epidemic. Total of 93 country from 196 had not provided any reports about the prevalence of HIV in MSM in the last 5 years by the end of the year 2011 (67). There are gaps in the data of the epidemiological characterization of the HIV infection in MSM, obstacles toward establishing

successful HIV research and surveillance because of the stigmatized and hidden nature of the MSM population in several countries, and of the continuous criminalization of same sex acts (67).

Figure 5: HIV prevalence among MSM in Europe and Central Asia



Source: European Centre for Disease Prevention and Control. Thematic report: Men who have sex with men. Monitoring implementation of the Dublin Declaration on Partnership to Fight HIV/AIDS in Europe and Central Asia: 2012 Progress Report. Stockholm: ECDC; 2013.

Migrants and HIV

Migration and mobility are main factors that affect a wide range of social outcomes and results (63). Migration plays a vital role as a key factor for HIV transmission worldwide (64, 65). Migration to Europe had risen dramatically in the past few decades, with a great burden and implications for public health services (66). With an estimation of about 72.6 million migrants now living in Europe, the region is an increasingly attracting one third of the world migrant population (67, 68). Infectious diseases are determined to be the main health issue for new migrants from middle and low income countries, with asylum seekers and refugees considered to be particularly affected (69). Multiple factors contribute to the vulnerability of new migrants to infectious diseases, with migrants known to face several barriers to healthcare, which may result in postponement to screening, diagnosis and treatment (70). Migrants may be affected concerning their ability to access and benefit from screening programs for infectious disease as they attempt to navigate a new health

system (71). In addition, they face individual, economic, socio-cultural, political and administrative barriers when using health services (66). Evidences from several studies suggest that epidemics of STIs are underway among MSM in developing countries (72). Developing countries are the main source of migrants worldwide (72, 73). Available data about MSM in Africa, Asia, south and central America, the former Soviet Union and the Caribbean are remarkably showing that MSM are at substantial risk for STIs (72).

Some of the migrant populations are highly expressed in the new cases of HIV in Europe (74), particularly in western countries. Migration plays a vital role as a key factor for HIV transmission worldwide (64, 65). An additional aggravating factor is the observation that migrants face individual, economic, socio-cultural, political and administrative barriers when using health services (66).

Although the epidemics of HIV in migrants in Europe is more visibly linked to heterosexual transmission, also migrant MSM from countries with generalized epidemics may be at higher risk of acquiring and transmit HIV post migration, a subject which has been comparatively neglected (75). Several factors such as the stigma associated with homosexuality in the country of origin, may interfere with knowledge about sexual health as well as with preventive behaviors of migrant MSM (75, 76).

Evidence accumulated thus far shows that in the US migrant MSM are at high risk for several poor health outcomes such as HIV and STI (77). MSM ethnic minorities in the US, especially African Americans and Latino, have the highest rates of new AIDS cases and STIs (77). Accordingly, a British study among MSM found that black men are 2.06 times as likely to be living with HIV infection in comparison to the white British majority, while Asian men are 0.32 times as likely to be infected (78). Another British study that aimed to examine rates of STIs and sexual behavior in black and minority ethnic including Caribbean, African or other MSM, showed that black and minority ethnic MSM were significantly more likely to report unprotected anal intercourse in the preceding three months, when white British were used as a comparison group (79).

Different cultures and the constrains of adapting to the country of residence can contribute to migrant MSM acquiring higher risk behavior (80). The EMIS study report showed that in general, migrant status was associated with some risk behavior that

may place migrants at higher risk of acquiring HIV (80). In addition, a greater prevalence of history of STIs or HIV infection with lower level of access to affordable HIV and STI testing was found among migrant participants (80).

Portugal has historically been a country of emigration and important immigration flows started much more recently (81). The country witnessed high inflow of Brazilian migrants, migrants from the African Portuguese-speaking countries, in addition to the labor migrants from Eastern Europe (82). In 2013, foreign population with regular residence as a percent of the resident population formed 3.8% of the total population (83).

HIV and MSM in Portugal

In Portugal, although the considerable health improvements in recent decades (84) and despite adopting many measures to improve the performance of the Portuguese healthcare system, including the reorganization of primary care and setting a long-term care networks (84), HIV infection continues to be of major public health importance in the country(85). MSM are substantially at high risk of being affected by the HIV epidemic (86). In Portugal, and according to national HIV prevalence data, the prevalence of HIV in men who have sex with men is 11% (15). In 2013, 4 369 cases of AIDS were diagnosed and reported by 29 EU/EEA countries, with a rate of 0.9 cases / 100 000 population. The highest rates were diagnosed and reported by Latvia (6.6) and then by Portugal (3.1) (29). In Portugal, as a part of West of Europe, the HIV epidemic is highly concentrated in three sub-groups: MSM, PWID and migrants (specifically migrants from high HIV prevalence countries) (6-8). The prevalence of HIV among adults can reach up to 0.9 % (87).

Portuguese official surveillance data showed an annual 9% increase in the number of newly diagnosed cases of HIV among MSM from 2005 to 2102, while there was a decrease by 2% in the new cases due to heterosexual intercourse and decrease by 18% in new cases due to unsafe injection behavior (85, 88). The proportion of MSM among all HIV cases diagnosed in 2013 amounted to 42.9 % while MSM represent approximately 3% of the male adult population (85, 88). This means that existing approaches to prevention have failed to control the HIV epidemic among MSM in Portugal; accordingly PrEP can be an additional new effective intervention against HIV infection in MSM that can control and curb the infection among MSM in Portugal.

The CDC Eligibility Criteria

Several organizations and Institutes such as CDC (30, 31), The New York State Department of Health AIDS Institute (NYSDOH AI) (89) and the World Health Organization (WHO) (90, 91) set certain guidelines and criteria to assist practitioners in assessing eligibility for PrEP, especially in key population such as serodiscordant couples, MSM and people who inject drugs (30, 31, 89-91). These guidelines are based on the results of the clinical trials, as well as on the review of published data (30, 31, 89-91). Our study estimated the Eligibility for PrEP using the criteria of the CDC, which follows the U.S. Public Health Service. IN 2014, the U.S. Public Health Service has published a comprehensive clinical practice guideline for the use of PrEP for the prevention of HIV infection in the US (92). The eligibility criteria for PrEP included; Unprotected anal intercourse, High number of sex partners, Sero-discordant sexual relationship with a known HIV-infected partner, Transactional sex and Recent bacterial STI (92).

OBJETIVES

- We aimed to estimate the proportion of MSM eligible for PrEP participating in the European MSM Internet Survey (EMIS) among: 1) Portuguese-born living in Portugal, 2) non-Portuguese-born living in Portugal, and 3) Portuguese-born living abroad.

- To identify predictors of eligibility among the 3 groups.

PAPER

ELIGIBILITY FOR HIV PREP AMONG MEN WHO HAVE SEX WITH MEN: PORTUGUESE, PORTUGUESE MIGRANTS AND MIGRANTS IN PORTUGAL

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Background:

HIV pre-exposure prophylaxis (PrEP) comprises the use of antiretroviral medications by HIV negative individuals to decrease infection risk. Men who have sex with men (MSM) have higher rates of HIV infection. Among migrants MSM, certain types of cultures, stigma, and barriers to seek medical advice, may increase the risk of acquiring the infection.

Objectives:

We aimed to estimate the proportion of MSM eligible for PrEP participating in the European MSM Internet Survey (EMIS) among: 1) Portuguese-born living in Portugal, 2) non-Portuguese-born living in Portugal, and 3) Portuguese-born living abroad, and to identify the predictors of eligibility.

Method:

Data were obtained through EMIS, a cross sectional study that took place from June to August 2010. An anonymous questionnaire was completed online (38 European countries using 25 languages) by 184 469 participants, of which 5187 lived in Portugal (80.7% Portuguese-born and 17.4% migrants) and 375 Portuguese-born lived abroad. Migrants were defined as men who were born in other country than

their current country of residence, while expatriates defined as men born in one of the 38 EMIS countries but currently living in one of the other 37 EMIS countries. The proportion of expatriates for a country is the number of men born there but not living there, compared to the total number of men born in the country. Information on HIV status, socio-demographic and behavioral characteristics was collected. Eligibility for PrEP was estimated according to the guidelines of the Centers for Disease Control and Prevention. Proportions were compared using the Chi-squared test and Odds Ratios (OR) with 95% confidence interval (95% CI) were computed using logistic regression.

Results:

Similar proportions of MSM eligible for PrEP were found among migrants living in Portugal (46.3%), Portuguese-born living in Portugal (44.4%) and Portuguese-born living abroad (45.1%) (p=0.621). In migrants living in Portugal, participants from Latin America and Caribbean region origin were more likely to be eligible for PrEP in comparison to Portuguese-born (OR=1.27; 95%CI 1.04-1.58; p=0.023). Portuguese-born living in Portugal showed the highest number of predictors for PrEP in comparison to the other 2 groups. In Portuguese-born living in Portugal, individuals who had ever undergone post-exposure prophylaxis were more likely to be eligible for PrEP (OR=2.26; 95% CI 1.30-3.93; p=0.004). In the same category having HIV test result in the last 12 months, having sex abroad with a man who was not from country of residence, consumption of any reactional drugs in the last 12 month or ever been tested for STIs other than HIV, increase the odds of being eligible for PrEP. Among migrants living in Portugal Migrants who reported having sex abroad with a man who was not from the country of residence in the previous 12 months were more likely to be eligible (OR=1.72; 95%CI 1.22-2.41; p=0.002). Migrant MSM who visited a social commercial venue in their country of residence were more eligible for PrEP in comparison to those who never sex venues (OR= 2.14; 95% CI 1.36-3.38; p=0.001). In Portuguese living abroad, individuals whose level of education was middle were more eligible for PrEP (OR= 1.74; 95% CI 1.06-2.86; p=0.029). Participants who received HIV test results in the last 12 months were more frequently eligible for PrEP in comparison to participates who didn't receive HIV results (OR= 1.84; 95%CI 1.17-2.90; p= 0.007).

Keywords:

HIV, Pre-Exposure prophylaxis, MSM, Migrants

Introduction:

Evidence from large-scale observational research and clinical trials conducted among multiple high-risk populations has demonstrated that Antiretrovirals (ARVs) can be used effectively as a PrEP to reduce the risk of acquiring HIV infection (1). In July 2012, on the basis of the results of these clinical trials, the U.S. Food and Drug Administration (FDA) approved the use of a combination of tenofovir + emtricitabine (TDF/FC) as pre-exposure prophylaxis to reduce the risk of HIV in adults at high risk(2).

The Centers for Disease Control and Prevention (CDC) (3, 4), The New York State Department of Health AIDS Institute (NYSDOH AI) (5) and the World Health Organization (WHO) (6, 7) set certain guidelines and criteria to assist practitioners in assessing eligibility for PrEP, especially in key population such as serodiscordant couples, MSM and people who inject drugs (3-7). These Guidelines are based on the results of the clinical trials, as well as on the review of published data (3-7).

In most Europe, the HIV epidemic is highly concentrated in certain subpopulations including men who have sex with men, people who inject drugs and migrants (specifically migrants from high HIV prevalence countries) (8-10). Available data show that the prevalence of HIV among MSM is high and is continuing to increase in many countries throughout Europe (11). In West of Europe, there were 26 847 newly diagnosed case with HIV infection in 2013 with a rate of 6.3 per 100 000 population (12). The most predominant mode of transmission was sex between men, followed by heterosexual sexual contact, accounting together for 77% of the new diagnosed cases (12). Sex between men accounted for 43% of the new diagnosed cases. Heterosexual contact accounted for 34% of the transmission. Four percent of the acquired HIV infection were through injecting drug use and 0.7 % acquired through mother to child transmission (12).

HIV prevalence among men who have sex with men (MSM) differs across Europe but is considered high in many western and southern European countries: in the 36 European countries that reported data, prevalence estimates range from 0.5% to

17.7% (11). Prevalence is 5% or more in sixteen countries and 10% or more in 7 countries. The highest frequency was reported by countries including France, Spain, Portugal, Belgium, Germany, Greece, Ireland, Italy and Switzerland (11). In Portugal, men who have sex with men are at high risk of being affected by the HIV epidemic (13) and, using self-reported information on serological status, the prevalence of HIV in men who have sex with men was estimated at 11%(14).

Some of the Migrant populations are highly expressed in the new cases of HIV in Europe (15), particularly in western countries. Migration plays a vital role as a key factor for HIV transmission worldwide (16, 17). An additional aggravating factor is the observation that migrants face individual, economic, socio-cultural, political and administrative barriers when using health services (18).

Although that the epidemics of HIV in migrants in Europe is more visibly linked to heterosexual transmission, also migrant men who have sex with men from countries with generalized epidemics may be at higher risk of acquiring and transmit HIV post migration, a subject which has been comparatively neglected (19). Several factors such as the stigma associated with homosexuality in the country of origin, may interfere with knowledge about sexual health as well as with preventive behaviors of migrant MSM (19, 20).

Evidence accumulated thus far shows that in the US of America migrant MSM are at high risk for several poor health outcomes such as HIV and STI (21). MSM ethnic minorities in the US, especially African Americans and Latino, have the highest rates of new AIDS cases and STIs (21). Accordingly, a British study among MSM found that black men are 2.06 times as likely to be living with HIV infection in comparison to the white British majority, while Asian men are 0.32 times as likely to be infected (22). Another British study that aimed to examine rates of STIs and sexual behavior in black and minority ethnic including Caribbean, African or other men who have sex with men (MSM), showed that black and minority ethnic MSM were significantly more likely to report unprotected anal intercourse in the preceding three months, when white British were used as a comparison group (23).

Portugal has historically been a country of emigration and important immigration flows started much more recently (24). The country witnessed high inflow of Brazilian migrants, migrants from the African Portuguese-speaking countries, in addition to the

labour migrants from Eastern Europe (25). In 2013, foreign-born population with regular residence in the country formed 3.8% of the total resident population(26).

In comparison to the current prevention methods such as voluntary counseling, testing, condom use and lubricants, PrEP is an additional effective intervention, which had shown efficacy against HIV infection in MSM. Therefore detecting the prevalence and predictors of eligibility for HIV PrEP in the Portuguese sample of the European Men Who Have Sex with Men Internet Survey (EMIS), the largest sample of MSM ever studied in Portugal, will help to better understanding of the magnitude of the problem prior to its adoption as a new effective HIV preventive method in Portugal. We aimed to estimate the proportion of MSM eligible for PrEP participating in the European MSM Internet Survey (EMIS) among: 1) Portuguese-born living in Portugal, 2) non-Portuguese-born living in Portugal, and 3) Portuguese-born living abroad, and to identify the predictors of eligibility. The study's significance lies in adding to efforts in controlling and withholding the spread and the rise in HIV infections at one of most at high-risk population as well as knowing the determinants of a new prevention method as PrEP in Portugal.

Methods:

The EMIS Study

The EMIS is a multilingual Internet-based survey for MSM and living in Europe (27). The study included 184466 participants. MSM across 38 European countries, including the 27 EU Member countries, filled in an online questionnaire on their several domains of their sexual health, which was made available in 25 different languages.

The survey had been developed through collaboration between 5 primary and 77 secondary partners working in MSM sexual health through public health, academic and community organizations in Europe (27-29). The recruitment method and data collection had been designed to attract a large sample of MSM in Europe and was promoted through a wide variety of 235 trans-national websites for MSM, nongovernmental organizations and gay online social media that include Gaydar, PlanetRomeo, Manhunt and other gay community organizations(27).

Individuals who confirmed that they had read and understood the goal of the study and were legally of age to have consensual sex with men in their country of residence were directed to the survey questions. Upon choice of the language, the study website explained the research in the chosen language. Men who confirmed they had read and understood the purpose of the study and were lawfully of age to have sex with men in their country of residence were directed to the survey questions (28). The survey questions were the outcome of more than a year's effort of investigating scientific literature, agreed indicators, consulting a large number of NGOs and exploring preceding questionnaires (30). The study was initially conducted for comprehension and length by MSM in 21 collaborating countries (29). This was an extensive procedure because EMIS needed questions, which were appropriate for the whole European MSM population irrespective of their sexual identity, or the social and political background in which they existed. The final form of self-completion survey comprised of about 280 questions, but was customized using intra-survey filters, which based on the respondent's answer to preceding questions (28). Guidelines for answering the survey and descriptions of terms were offered within the survey. Slang language had been used because it is supposed to increase reporting of socially unwanted behavior (31). The median accomplishment time was about 20 min, which was calculated from the accurate completion time for each survey, which was auto-captured as an integral segment of the survey software used (28, 29). The survey software installed no cookies or left any other trace files on computers, and no IP-addresses were saved or no other data that could be used to recognize computers and hence participants (28). This guaranteed that survey was completely anonymous. The respondent had to accomplish the survey in one sitting. The answers were only recorded by the respondent ticking through to the final page and selecting the submit button. The survey was accessible for online completion within 12 weeks in June through August 2010, and all processes were approved by the Research Ethics Committee of the University of Portsmouth, United Kingdom (27). For further information about the EMIS survey and methodology the following sources are recommended www.EMIS-project.eu and the EMIS final report (27).

Participants

For this study, we examined several sociodemographic, behavioral characteristics and testing behaviors measured in EMIS. The outcome of interest, eligibility for HIV PrEP, was measured within the three-group categories: 1) Portuguese-born living in Portugal, 2) non-Portuguese-born living in Portugal, and 3) Portuguese-born living abroad. The sample included 5187 participant lived in Portugal (80.7% Portuguese-born and 17.4% migrants) and 375 Portuguese-born lived abroad (representing 8.1% of Portuguese-born and now living in other EMIS countries).

Migrants

In the EMIS survey, migrants were defined as men who were born in another country than their current country of residence (27). Based on this definition**,** through Europe, 11.9% of respondents were migrants**.** The highest proportion of migrants was recorded in Luxembourg (50%) and the highest proportion of migrants by sub-region was in West of Europe (22%). The proportion of migrants in Portugal was 17.4% (27). In most sub-regions, the largest proportion of migrants came from the same sub-region, nevertheless in Southwest the largest proportion of migrants was from Latin America (27).

Expatriates

EMIS defined expatriates as men born in one of the 38 EMIS countries but currently living in one of the other 37 EMIS countries (27). The proportion of expatriates for a country is the number of men born there but not living there, compared to the total number of men born in the country which is an another way of looking at migration by considering the country of birth, rather than taking the perception of the current country of residence, and observing at the percentage of people born abroad (27). The EMIS stated that these figures should be treated with carefulness, because they eliminate men born in EMIS countries but now living outside those countries (27). Germany had the lowermost proportion of expatriates: only 4% of all EMIS respondents born in Germany were living in one of the other 37 EMIS countries, the highest proportions of expatriates were recorded in Bosnia and Herzegovina (56%) and Cyprus (34%), while it was (8.1%) in Portugal which also shows the countries with the percentages of expatriates distributed across the sub-regions.

Statistical analysis

Eligibility for PrEP was estimated according to the guidelines of the CDC that includes individuals with HIV-positive sexual partner, recent bacterial STI, high number of sex partners and Transactional Sex (3-5). The individuals are considered clinically eligible if they are HIV negative and so exclusion of HIV positive cases had been made. According to these criteria a list of variables, which have been used in the EMIS Portuguese sample, were selected after matching it with the previous CDC criteria (3-5). Proportions of eligibility for HIV PrEP in the 3 groups categories were compared using the Chi-squared test and odds Ratios (OR) with 95% confidence interval (95% CI) were computed using logistic regression to determine the indicators for PrEP. These indicators included several characteristics such as HIV and STIs testing behaviors, consumption of drugs, attendance of sex venues, exposure to post exposure prophylaxis and having sex abroad.

Results:

Stratifying the eligibility for PrEP according to the CDC's eligibility criteria (table1) show that Non-monogamous relations with unprotected anal intercourse (UAI) in the last 6 months accounts for 96.2% of the eligibility for PrEP in Portuguese-born living in Portugal, 93.3% in non-Portuguese-born living in Portugal, and 93.0% of the Portuguese-born living abroad.

Similar proportions of MSM eligible for PrEP (table 2) were found among migrants living in Portugal (46.3%), Portuguese-born living in Portugal (44.4%) and Portuguese-born living abroad (45.1%) (P=0.621), but after classifying migrants living in Portugal according to region of origin (table 3), we found that participants from Latin America and Caribbean were more likely to be eligible for PrEP in comparison to Portuguese-born (OR=1.27; 95%CI 1.04-1.58; p=0.023) and among migrants who were eligible for PrEP 38.6% were from Latin America and Caribbean region.

In Portuguese-born living in Portugal (table4), being Ever tested for STIs other than HIV was associated with increase the eligibility for PrEP (OR= 1.35; 95% CI 1.17-1.54; p<0.001). Individuals who had ever undergone post-exposure prophylaxis were more likely to be eligible for PrEP (OR=2.26; 95% CI1.30-3.93; p=0.004). In the same category, participates who identified themselves as homosexuals were more like to be eligible for PrEP in comparison to individuals who identified themselves as bisexual or other, (OR= 1.46; 95%CI 1.26-1.69; p= <0.001). In addition, having HIV

test result in the last 12 months, having sex abroad with a man who was not from country of residence or the consumption of any reactional drugs in the last 12 month increase the odds of being eligible for PrEP. In migrants living in Portugal, participants from Latin America and Caribbean were more likely to be eligible for PrEP in comparison to Portuguese-born (OR=1.27; 95%CI 1.04-1.58; p=0.023). Among migrants who were eligible for PrEP (n=359) (table 5), 71.2% identified themselves as homosexuals, 57.5% of high educational level and 74.1% were employed. Migrants who reported having sex abroad with a man who was not from the country of residence in the previous 12 month were more likely to be eligible (OR=1.72; 95%CI 1.22-2.41; p= 0.002). Migrant MSM who visited a social commercial venue in their country of residence were more eligible for PrEP in comparison to those who never sex venues (OR= 2.14; 95% CI 1.36-3.38; p=0.001). In Portuguese-born living abroad (table4), individuals whose level of education were middle were more frequently eligible for PrEP (OR= 1.74; 95% CI 1.06-2.86 P=0.029). In the same category, 62.2% of participants who received HIV results in the last 12 month were eligible for PrEP. Participants who received HIV test results in the last 12 months, after exclusion of HIV positive cases, were more frequently eligible for PrEP in comparison to participates who didn't receive HIV results (OR= 1.84; 95%CI 1.17-2.90; p= 0.007).

Table1: Eligibility criteria for HIV PrEP among MSM in Portugal according to place of birth and migration status after exclusion of HIV positive cases.

	CDC Eligibility Criteria for PrEP			**Total n (%)**
	Non-monogamous w HIVneg and UAI last 6 months n(%)	Non-monogamous w HIVneg. and diagnosed with an STI last 6 months n (%)	Steady partner with HIV n (%)	
Portuguese-born living in Portugal	1562 (96.2)	20 (1.2)	42 (2.6)	1624 (100)
Non-Portuguese-born living in Portugal (Migrant)	335 (93.3)	12 (3.3)	12 3.3	359 (100)
Portuguese-born living abroad	133 (93.0)	5 (3.5)	5 (3.5)	143 (100)
Total	2030 (95.5)	37 (1.7)	59 (2.8)	2126 (100)

Table 2 Eligibility for HIV PrEP among MSM in Portugal according to place of birth and migration status after exclusion of HIV positive cases.

		CDC Eligibility criteria for PrEP		
	Eligible n (%)	Not Eligible n (%)	OR (95% CI)	P-value
Portuguese-born living in Portugal	1624 (44.4)	2032 (55.6)	1	
Non-Portuguese-born living in Portugal (Migrant)	359 (46.3)	416 (53.7)	1.080 (0.92-1.26)	0.333
Portuguese-born living abroad	143 (45.1)	174 (54.9)	1.028(0.81-1.29)	0.812
Total	2126(44.8)	2622 (55.2)		

Table 3 Eligibility for HIV PrEP after classifying Migrants according to their region of origin.

	CDC Eligibility for PrEP			
	Not Eligible n(%)	Eligible n(%)	OR (95% CI)	P-value
Country/Region of origin (regionorigin)				
Born in Portugal	2032 (77.5)	1624 (76.4)	1	
West Europe	55 (2.1)	46 (2.2)	1.04(0.70-1.55)	0.823
Northwest Europe	3 (0.1)	1 (0.0)	0.41(0.43-4.01)	0.449
Central-west Europe	25 (1.0)	14 (0.7)	0.70(0.363-1.35)	0.289
Southwest Europe	197 (7.5)	152 (7.1)	0.96(0.77-1.35)	0.755
Central-East Europe	4 (0.2)	3 (0.1)	0.93(0.21-4.19)	0.934
Southeast (EU) Europe	5 (0.2)	0(0.0)	0.00	0.999
Southeast (non-EU) Europe	1(0.0)	0(0.0)	0.00	1
East Europe	5(0.2)	4(0.2)	1.00(0.26-3.73)	0.999
WHO Region of the Americas: Canada, USA	12(0.5)	8(0.4)	0.83(0.34-2.04)	0.692
WHO Region of The Americas: Latin America and Caribbean	190(7.2)	194(9.1)	1.27(1.03-1.57)	0.023
WHO Eastern Mediterranean Region	1(0.0)	0(0.0)	0.00	1
WHO African Region	88(3.4)	76(3.6)	1.08(0.79-1.47)	0.628
WHO Western Pacific Region: Australia and New Zealand	2(0.1)	1(0.0)	0.62(0.05-6.90)	0.702
WHO Western Pacific Region: (excl. Australia and New Zealand)	2(0.1)	3(0.1)	1.87(0.31-11.24)	0.491
Total	2622(100)	2126 (100)		

Table 4: Predictors for the eligibility for HIV PrEP according to participants' characteristics, results from EMIS 2010

Predictors for the eligibility for HIV PrEP in Portuguese-born living in Portugal according to participants' characteristics, results from EMIS 2010				
	Not Eligible n (%)	Eligible n (%)	OR (95% CI)	P-value
Age				
<25	604 (29.7)	453 (27.9)	1	
25-39	1054 (51.9)	848 (52.2)	1.07 (0.92-1.24)	0.364
>or =40	374(18.4)	323 (19.9)	1.15 (0.95-1.39)	0.151
Sexual Identity				
Bisexual/other	687(33.9)	419 (25.9)	1	
Homosexual	1342(66.1)	1198 (74.1)	1.46(1.26-1.69)	<0.001
Education level				
Low	155(7.7)	137 (8.5)	1.13(0.88-1.45)	0.309
Mid	663(32.9)	540 (33.5)	1.04(0.90-1.20)	0.532
High	1200(59.5)	934 (58.0)	1	
Job situation				
Employed	1348(66.8)	1143 (70.8)	1	
Unemployed	136(6.7)	113 (7.0)	0.98(0.75-1.27)	0.879
No Response	535(26.5)	358 (22.2)	0.78(0.670-.92)	0.003
HIV test result in the previous 12 months				
No	1149(56.5)	802 (49.4)	1	
Yes	883(43.5)	882 (50.6)	1.33(1.17-1.52)	<0.001
Ever been treated with PEP				
NO	1940(96.7)	1501 (93.8)	1	
Yes	20(1.0)	35 (2.2)	2.26(1.30-3.93)	0.004
I don't Know	46(2.3)	64(4.0)	1.79(1.22-2.64)	.003
Having sex abroad with a man who was not from country of residence				
No	1228 (60.6)	877(54.2)	1	
Yes, more than 12month ago	483(23.9)	395(24.4)	1.14(0.97-1.34)	0.094
Yes, in the last 12 months	314(15.5)	346(21.4)	1.54(1.29-1.83)	<0.001

Sex Venues: visited a social commercial venue in their country of residence: café, bar, disco, or nightclub				
Never	437(21.5)	229(14.1)	1	
Ever	1595(78.5)	1395(85.9)	1.66(1.40-1.98)	<0.001
Ever tested for STIs				
Never tested for STIs other than HIV	1143(61.2)	807(53.8)	1	
Ever tested for STIs other than HIV	726(38.8)	692(46.2)	1.35(1.17-1.54)	<0.001
Consumption of any drugs typically associated with sex and parties in the last 12 month				
Never/Before 12 Month	1614(80.0)	1232(77.0)	1	
In the last 12 Month	403(20.0)	369(23.0)	1.20(1.02-1.40)	0.025

Predictors for the eligibility for HIV PrEP in non-Portuguese-born living in Portugal according to participants' characteristics, results from EMIS 2010

	Not Eligible	Eligible	OR (CI)	P.value
Age				
<25	85(20.4)	88 (24.5)	1	
25-39	221(53.1)	191(53.2)	0.83(0.585-1.19)	0.319
>or =40	110(26.4)	80(22.3)	0.70(0.46-1.06)	0.095
Sexual Identity				
Bisexual/other	120(28.8)	97(27.2)	1	
Homosexual	296(71.2)	260(72.8)	1.08(0.79-1.48)	0.605
Education level				
Low	26(6.3)	22(6.2)	1.08(0.59-1.97)	0.785
Mid	124(30.1)	129(36.3)	1.33(0.98-1.81)	0.064
High	262(63.6)	204(57.5)	1	
Job situation				
Employed	306(74.1)	252(70.8)	1	
Unemployed	24(5.8)	28(7.9)	1.41(0.80-2.50)	0.231
No Response	83(20.1)	76(21.3)	1.11(0.78-1.58)	0.556
HIV test result in the last 12 months				
No	206(49.5)	175(48.7)	1	
Yes	210(50.5)	184(51.3)	1.03(0.77-1.36)	0.830
Ever been treated with PEP				

NO	386(94.1)	328(92.7)	1	
Yes	8(2.0)	8(2.3)	1.17(0.43-3.17)	0.747
I don't Know	16(3.9)	18(5.1)	1.32(0.66-2.63)	0.425
Having sex abroad with a man who was not from country of residence				
No	174(42.1)	119(33.3)	1	
Yes, more than 12month ago	121(29.3)	99(27.7)	1.19(0.84-1.70)	0.320
Yes, in the last 12 months	118(28.6)	139(38.9)	1.72(1.22-2.41)	0.002
Sex Venues: visited a social commercial venue in their country of residence: café, bar, disco, or nightclub				
Never	68(16.4)	30(8.4)	1	
Ever	347(83.6)	329(91.6)	2.14(1.36-3.38)	0.001
Ever tested for STIs				
Never tested for STIs other than HIV	190(48.6)	168(50.0)	1	
Ever tested for STIs other than HIV	201(51.4)	168(50.0)	0.94(0.70-1.26)	<0.705
Consumption of any drugs typically associated with sex and parties in the last 12 month				
Never/Before 12 Month	343(83.1)	279(79.7)	1	
In the last 12 Month	70(16.9)	71(20.3)	1.24(0.86-1.79)	0.237

Predictors for the eligibility for HIV PrEP in Portuguese-born living abroad according to participants' characteristics, results from EMIS 2010

	Not Eligible	Eligible	OR (CI)	P.value
Age				
<25	33(19.0)	23(16.1)	1	
25-39	112(64.4)	105(73.4)	1.34(0.74-2.43)	0.329
>or =40	29(16.7)	15(10.5)	0.74(0.32-1.68)	0.476
Sexual Identity				
Bisexual/other	44(25.3)	28(19.7)	1	
Homosexual	130(74.7)	114(80.3)	1.37(0.80-2.35)	0.241
Education level				
Low	18(10.5)	19(13.5)	1.62(0.80-3.31)	0.170
Mid	46(26.7)	52(36.9)	1.74(1.06-2.86)	0.029

High	108(62.8)	70(49.6)	1	
Job situation				
Employed	136(79.0)	108(75.5)	1	
Unemployed	12(7.0)	17(11.9)	1.78(0.81-3.89)	0.146
No Response	24(14.0)	18(12.6)	0.94(0.48-1.83)	0.865
HIV test result in the last 12 months				
No	92(52.9)	54(37.8)	1	
Yes	82(47.1)	89(62.2)	1.84(1.17-2.90)	0.007
Ever been treated with PEP				
NO	165(95.9)	133(94.3)	1	
Yes	5(2.9)	6(4.3)	1.48(0.44-4.98)	0.519
I don't Know	2(1.2)	2(1.4)	1.24(0.17-8.92)	0.830
Having sex abroad with a man who was not from country of residence				
No	44(25.6)	35(24.5)	1	
Yes, more than 12month ago	56(32.6)	31(21.7)	0.696(0.37-1.29)	0.255
Yes, in the last 12 months	72(41.9)	77(53.8)	1.344(0.77-2.32)	0.290
Sex Venues: visited a social commercial venue in their country of residence: café, bar, disco, or nightclub				
Never	14(8.0)	15(10.5)	1	
Ever	160(92.0)	128(89.5)	0.74(0.34-1.60)	0.454
Ever tested for STIs				
Never tested for STIs other than HIV	76(46.3)	69(50.7)	1	
Ever tested for STIs other than HIV	88(53.7)	67(49.3)	0.83(0.53-1.32)	0.449
Consumption of any drugs typically associated with sex and parties in the last 12 month				
Never/Before 12 Month	151(86.8)	124(86.7)	1	
In the last 12 Month	23(13.2)	19(13.3)	1.00(0.52-1.93)	0.986

Discussion:

High-risk groups are one of the biggest obstacles toward eradication of the HIV infection. MSM and migrant are within the most vulnerable groups. Since the beginning of HIV epidemic in the early 80s, MSM are one of the main populations affected by the disease (32, 33). The present study used data from the EMIS to

investigate the eligibility for HIV PrEP among MSM in Portugal. Our results revealed a high prevalence of eligibility for HIV PrEP. Since almost half of the participants in the 3 categories seem to be eligible for PrEP, attention to the question of how PrEP may affect the national HIV epidemic among MSM should be considered. Overall, the perception of difference in the proportions of eligible individuals among the 3 groups was not statistically significant, but after classifying migrants living in Portugal according to region of origin, we found that participants from Latin America and Caribbean were more likely to be eligible for PrEP in comparison to Portuguese-born (OR=1.27; 95%CI 1.04-1.58; p=0.023). Among migrants who were eligible for PrEP 38.6% were from Latin America and Caribbean region. This finding can probably be explained by the substantial population of Brazilian migrants in Portugal. A study from Spain in a convenience sample of MSM in Catalonia found that immigrants from the same region of origin, Latin America, were more likely to have UAI in the previous 12 months, which is one of the eligibility criteria for PrEP, in comparison to the Spanish MSM (OR= 2.28; 95%CI 1.43-3.64; p= 0.001)(34). In studies conducted among MSM in the US, MSM from Latin America reported the higher rates of UAI, when compared to the other minority groups (35).This evidence supports that we are not only observing the effect of host country but also the effect of contextual specificities of the region of origin, which highlights the need of focusing on specific migrant populations according to their region of origin.

Non-monogamous relations with UAI in the last 6 months accounts for 96.2% of the eligibility for PrEP in Portuguese-born living in Portugal, 93.3% in non-Portuguese-born living in Portugal, and 93.0% of the Portuguese-born living abroad. Since PrEP is not a sole intervention and it should be prescribed as part of a comprehensive prevention plan (5) that encompasses emphasis on condom use. Even though lack of consistent use of barrier protection is not a contraindication to PrEP(5).

Among migrant MSM living in Portugal, participants who reported having sex abroad with a man who was not from the country of residence in the previous 12 month were more likely to be eligible (OR=1.72; 95%CI 1.22-2.41; p= 0.002). A study from Belgium found that MSM residing in Belgium who had sexual contact abroad were more likely to be also expatriates too (36).

The final results from the EMIS total European sample showed that, and compared with non-migrants, migrants were more likely to be over 25 years of age**,** to live in a large city, have a higher university degree, be more open about their sexual

orientation and feel lonely (27). Moreover, migrants use more drugs associated with sex and parties, more usually reported having more partners in the last 12 months, and more likely to be diagnosed with HIV/STIs in the last 12 months (27). Different cultures and strains in adapting into the country of residence may contribute to higher risk behavior among migrant MSM (27). Associations were found between certain types of risk behavior that might increase the danger of their acquiring HIV infection and STIs among migrant MSM (27). The study concluded that, a greater self-reported prevalence of HIV and STIs among migrant MSM together with lesser access to free or affordable HIV and STI testing services proposes that prevention interventions should be customized and tailored for this category (27). Social and community support could be included in these specific interventions since studies established an association between social isolation and sexual risk behaviour among MSM (27).

On the other hand, our Portuguese study sample study showed that Portuguese-born living in Portugal showed the highest number of predictors for eligibility in comparison to non-Portuguese-born living in Portugal (migrants) and Portuguese-born living abroad. Portuguese official surveillance data showed an annual 9% increase in the number of newly diagnosed cases of HIV among MSM from 2005 to 2102, while there was a decrease by 2% in the new cases due to heterosexual intercourse and decrease by 18% in new cases due to unsafe injection behavior(37, 38). The proportion of MSM among all HIV cases diagnosed in 2013 amounted to 42.9 % while MSM represent approximately 3% of the male adult population(37, 38). This means that existing approaches to prevention have failed to control the HIV epidemic among MSM in Portugal; accordingly PrEP can be an additional new effective intervention against HIV infection in MSM that can control and curb the infection among MSM in Portugal.

Among Portuguese-born living in Portugal, consumption of any reactional drugs in the last 12 months showed a clear association with the eligibility for the PrEP, that was in line with several studies that showed an association between unprotected sexual relation, and the use of drugs (39-41). All of that highlights the crucial need to include drugs and substance use in any prevention program if we would like to avoid or decrease PrEP use among the target population.

The same category showed a strong association between PrEP and being ever tested for STDs other than HIV and the eligibility for HIV PrEP. That makes

prevention and screening programs that address STDs in MSM of paramount important. Some MSM avoid seeking healthcare because they expect disapproval regarding their lifestyle (42), this behavior can be exaggerated in certain populations such as migrants due to some cultural barriers and stigma, so it is particularly important for the healthcare personnel to become culturally competent toward this issues. This highlights the need for establishing screening programs for STDs that can play a crucial role in the early diagnosis of STDs and decrease the transmission.

Limitations:

Taking into consideration the self-reported nature of the survey, limitations such as social desirability bias and recall bias may affect some findings. Exclusion of MSM who don't have an access to the Internet, who may show different socio-demographic characteristics, make the data biased toward participants with higher level of education and an access to the internet. The social desirability bias and the bias of data toward participants with higher education level may therefore have influenced the results in that it underestimates levels of eligibility for HIV PrEP, but despite this type of biases, this is the largest sample of MSM ever studied in Portugal. Although being Internet-based survey which recruited participants through internet and individuals in such samples tend to be more educated, urban and younger, EMIS was able to recruit the world's largest sample of MSM, including about 180,000 MSM from 38 countries. In addition, this is the largest study to date to examine not only the proportions of eligible individuals but also the predictors of eligibility for PrEP among MSM in Portugal. This research represents an important step in investigating the proportion of eligible individuals for HIV PrEP in the largest sample of MSM ever studied in Portugal.

Conclusion:

No differences were found for PrEP eligibility between the three groups, but the predictors for PrEP were different among them. Accordingly, further analysis of the predictors in each category will help to customize tailored prevention programs for each group. Moreover, additional subgroup analysis of migrant MSM in Portugal is mandatory to address migration experiences and determine which migrant population needs more support. Further analysis of migration and mobility is needed, taking into consideration a more advanced definition of migrant and mobility dynamics.

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Conclusion:

- No differences were found for PrEP eligibility between the three groups, but the predictors for PrEP were different among them. Accordingly, further analysis of the predictors in each category will help to customize tailored prevention programs for each group. A

- Additional subgroup analysis of migrant MSM in Portugal is mandatory to address migration experiences and determine which migrant population needs more support. Further analysis of migration and mobility is needed, taking into consideration a more advanced definition of migrant and mobility dynamics.

- In the light of the high proportions of eligibility for HIV PrEP within the 3 groups, there is a necessity for moving from research in to policy, management and practical application, and for integration of research and policy to acquire a comprehensive implementation framework for PrEP in Portugal. It is essential for public health decision makers to formulate a collective, coordinated and rational response to the results of the last official reports that showed substantial burden of HIV among MSM in Portugal.

- Because pills alone will never entirely control the HIV epidemic among MSM in Portugal, we also need an effective combination prevention approaches that may combine PrEP with other prevention strategies and to combine PrEP with behavioral and social interventions to curb down HIV incidence in MSM in Portugal.

- The high transmission for HIV in MSM proposes that prevention methods that can decrease possibilities of per-act transmission such as PrEP will possibly be needed in a population-based national level, to produce considerable reductions in new infections and to produce substantial results.

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