**Programa Doutoral em Saúde Pública**

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# Preexposure prophylaxis for HIV prevention among men who have sex with men:

# *understanding eligibility and early uptake*

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II. Rocha M, Deniel A, Meireles P, Fuertes R, Barros H, Bernier A. Urgent need for demonstration projects in Portugal to produce pre-exposure prophylaxis-related data. International Journal of STD & AIDS. 2016;27(10):920-1. DOI: 10.1177/0956462416645245

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VI. Meireles P, Fernandes F, Rocha M, Plankey M, Barros H. Provision of preexposure prophylaxis at the Portuguese National Health Service and uptake in the Lisbon Cohort of men who have sex with men (under review).

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**Abbreviations:**

AIDS: Acquired immunodeficiency syndrome

ART: Antiretroviral therapy

BASHH: British Association for Sexual Health and HIV

BHIVA: British HIV Association

CAI: Condomless anal intercourse

CBVCT: Community-based voluntary HIV counseling and testing

CHW: Community health workers

CI: Confidence interval

CSW: Commercial sex workers

EACS: European AIDS Clinical Society

ECDC: European Centre for Disease Prevention and Control

EEA: European Economic Area

EMA: European Medicines Agency

EU: European Union

GAT: *Grupo de Ativistas em Tratamentos*

GBD: Global Burden of Diseases

HBsAg: Hepatitis B virus surface antigen

HBV: Hepatitis B virus

HCV: Hepatitis C virus

HIV: Human immunodeficiency virus

INSA: Portuguese National Institute of Health, Dr. Ricardo Jorge

ISPUP: Institute of Public Health of the University of Porto

MSM: Men who have sex with men

NGO: Non-governmental organization

NHS: National Health Service

P25: 25th percentile

P75: 75th percentile

PEP: Postexposure prophylaxis

PLHIV: People living with HIV

PNHS: Portuguese National Health Service

PNSE: Spanish National Plan on AIDS

PrEP: Preexposure prophylaxis

PWID: People who inject drugs

PWUD: People who use drugs

SD: Standard deviation

SDG: Sustainable Development Goals

STI: Sexually transmitted infections

TAF/FTC: Tenofovir alafenamide/emtricitabine

TDF/FTC: Tenofovir disoproxil fumarate/emtricitabine

UNAIDS: Joint United Nations Programme on HIV/AIDS

US: United States

US-CDC: United States Public Health Service, Centers for Disease Control and Preventions

US-FDA: United States, Food and Drug Administration

VL: Viral load

WHO: World Health Organization

**ABSTRACT**

**Introduction**

There are several effective strategies in the HIV prevention armamentarium that, in a combination approach, have the potential to reverse the epidemic. One of those is preexposure prophylaxis (PrEP), a highly effective antiretroviral therapy-based HIV prevention strategy for individuals at high risk, including men who have sex with men (MSM). PrEP is now available in several countries. In Portugal, it is financially covered by the National Health Service (NHS) and available since February 2018.

Clinical guidelines for the use of PrEP were designed to help clinicians to deliver PrEP by providing the criteria to identify those at higher risk for eligibility. However, while the clinical exclusion criteria are identical across different guidelines, definitions of substantial HIV risk are not. This has implications both in the quantification of the eligible population and in the HIV prediction ability. Furthermore, ascertainment of eligibility leads to a dichotomous classification, having or not an indication for PrEP at a given moment. However, behavior and life circumstances change, and so does eligibility for PrEP. Finally, data regarding PrEP uptake in Portugal are incipient and mostly about the use before PrEP implementation.

**Objectives**

In this work, we aimed:

1. To describe the assembling of the Lisbon Cohort of MSM (Paper I);
2. To raise awareness for PrEP relevance in the Portuguese setting (Paper II);
3. By using and comparing four different guidelines – the World Health Organization (WHO), the United States 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):
    a. To estimate the proportion of MSM eligible for PrEP (Paper III);
    b. To provide real-world evidence of their ability in predicting HIV seroconversion by comparing HIV incidence according to each set of eligibility criteria for PrEP and measuring the association between guideline-specific eligibility and seroconversion (Paper IV);
4. To describe the transitions between PrEP eligibility states and from these to HIV infection, and to estimate the intensity and probability of those transitions (Paper V);

5. To assess the time-trends in the uptake of PrEP comparing the period before and after PrEP implementation in Portugal, to compare PrEP users with non-users and, among users, to compare those who started before and after PrEP implementation (Paper VI).

**Methods**

We used data from the Lisbon Cohort of MSM, an open, noninterval, prospective cohort study of adult men who report having sex with men, and who have an HIV-negative test result at baseline. Recruitment and data collection takes place at CheckpointLX, a community-based voluntary counseling and testing center (CBVCT) in Lisbon devoted to MSM, whose services are provided by trained peers community-health workers (CHWs). Follow-up visits occur according to participants' convenience, but ideally with 6-month intervals. At each visit, a structured questionnaire is administered, and an HIV rapid testing is performed by peer CHWs. We used data from April 2011 to February 2014 in paper I, from March 2014 and March 2018 in paper III, IV and V, and from March 2014 to July 2019 in paper VI.

Characteristics of participants enrolled were described using absolute frequencies and proportions in the case of categorical variables. Means and standard deviation or median and $25^{th}$-$75^{th}$ percentiles were used to describe continuous variables. Comparisons between groups were performed using the Student's *t*-test for independent samples or the Mann-Whitney U test for continuous variables and the Pearson Chi-Square or the Fisher exact test for categorical variables.

Incidence rates (IR) with 95% confidence intervals (CI) were estimated using as the denominator the sum of person-years (PY) and were computed for participants defined as eligible and as ineligible at baseline, according to each guideline. To measure the magnitude of the associations, we computed crude incidence rate ratios (IRRs) and 95% CI using generalized linear models with Poisson regression. We have also computed the sensitivity and specificity of guidelines, and the number needed to treat to prevent one HIV infection among eligible individuals under three scenarios of risk reduction.

A time-homogeneous Markov multi-state model was applied to estimate the frequencies, intensities, and probabilities of transitions between PrEP eligibility states (eligible/ineligible) and from these to HIV infection.

**Results**

*Paper I*

From April 2011 to February 2014, 3106 MSM were eligible to enter the cohort of whom 923 (29.7%) refused to participate. The remaining 2183 (70.3%) individuals were enrolled, and 804 had at least one follow-up evaluation, for a total of 893 person-years of observation. Participants had a median age of 29 years, 75.7% were born in Portugal, and 58.1% had a high-education degree. Eighty-four percent self-identified as gay. HIV testing prior to cohort entry was reported by 81.9%. Twelve percent of MSM reported sexual intercourse with HIV-positive men in the previous 12 months, and approximately eight percent of those in a steady relationship had an HIV-positive partner. Of those with a steady partner, 71.4% reported inconsistent condom use over the previous 12 months. Eighty-five percent reported at least one occasional partner in the same period, of whom 46.4% did not use condoms consistently. The most referred reason for engaging in condomless anal intercourse was sex with a steady partner (66.2%). The use of alcohol or drugs before or during sex, in the previous 12 months, was reported by 59.5% of participants. Slightly over one-third of participants knew about postexposure prophylaxis, and 2.7% used it. Finally, approximately 10% presented symptoms compatible with a sexually transmitted infection or had it diagnosed in the previous 12 months.

*Paper III*

At the baseline visit of 3392 participants in the period of March 2014 to March 2018, 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.

*Paper IV*

From March 2014 to March 2018, 1254 participants were followed in the cohort for a total of 1724.54 person-years. During this period, we identified 28 HIV incident cases, of whom those defined as eligible at baseline varied from 60.7% (according to the EACS guidelines) to 85.7% (according to the PNHS guidelines). Being found eligible by any guideline was associated with an increased HIV incidence. However, the IR was higher among those defined as eligible according to the PNHS guidelines (2.46/100 PY; IRR: 4.61 [95% CI: 1.60-13.27]), and lowest among those defined considering the WHO guidelines (1.89/100 PY; IRR: 1.52 [95% CI: 0.69-3.35]). Assuming different relative reductions, the lowest number needed to take PrEP for one year to avert one HIV infection varied from 42 to 53, with the PNHS guidelines resulting in the lowest values across all scenarios.

*Paper V*

Among 1177 participants with valid information to be classified according the PNHS guidelines and that had at least two visits from March 2014 to March 2018, the transitions' intensities were similar for ineligible–eligible (I–E) (1.591) and eligible–ineligible (E–I) (1.493) while the transition eligible–HIV infection (E–HIV) was 22.0 times more likely than ineligible–HIV infection (I–HIV) (0.032 vs. 0.001). The transition's probabilities for 90 days were similar for the transition I–E and E–I (0.275 vs. 0.258) while the transition E–HIV was 4.4 times more likely than I–HIV (0.007 vs. 0.002). The transition probabilities increased with time; they were similar between the two eligibility states, but the ratios between the transition's probabilities to HIV infection decreased.

*Paper VI*

From March 2014 to July 2019, 198 (3.2%) participants reported having used PrEP in the previous 12 months or between visits. Approximately one third started after its introduction in the Portuguese NHS. PrEP uptake increased from 0.15% (95% CI 0.02-0.55) in 2014 to 5.36% (95% CI 4.29-6.60) in 2019. Out of the 122 (61.6%) that provided additional information on their first PrEP use, 86 (70.5%) used it daily, 31 (25.4%) as event-driven, and 5 (4.1%) reported other regimens. How PrEP was obtained varied according to the timing of the initial PrEP experience – prescribed by a physician in Portugal (11.1% before vs. 68.8% after implementation), and online (40.7% before vs. 14.1% after implementation). The presence of eligibility criteria was higher among users than non-users (76.3% vs. 56.4%) and did not change significantly after PrEP implementation (73.8% vs. 78.1%).

**Conclusions**

The implementation and follow-up of the Lisbon Cohort of MSM have been a valuable tool to monitor HIV incidence and trends in primary and secondary prevention among HIV-negative MSM testing at a CBVCT center in Lisbon. It is also a privileged setting to study the introduction of new prevention tools such as HIV PrEP in Portugal. Our results highlighted the potential for missing people who need PrEP when a strict risk-based approach is used to define eligibility. We also showed that the indication for PrEP was likely to change over time and that being ineligible was only a short-time indicator of a lower probability of acquiring HIV. The anticipation or timely detection of changes to an eligible state demands a well-timed delivery of PrEP. Finally, we detected an increase in PrEP uptake, particularly after its introduction to the Portuguese NHS, after which there was also a shift in how MSM obtained PrEP with physician prescription in Portugal becoming the most frequent mean. This can contribute to a safer and more equitable access to a highly effective HIV prevention tool.

**RESUMO**

**Introdução**

O arsenal de prevenção atual do VIH possui várias estratégias eficazes que, em prevenção combinada, têm o potencial de reverter a epidemia. Uma dessas ferramentas é a profilaxia pré-exposição (PrEP), uma estratégia altamente eficaz de prevenção do VIH baseada na terapêutica antirretrovírica para indivíduos de alto risco, incluindo homens que têm sexo com homens (HSH). A PrEP está agora disponível em vários países, incluindo Portugal, onde é disponibilizada de forma gratuita no Serviço Nacional de Saúde (SNS) desde fevereiro de 2018.

As *guidelines* clínicas para o uso da PrEP auxiliam os clínicos na disponibilização da PrEP através de, entre outros, fornecerem os critérios de elegibilidade para identificar os indivíduos em maior risco. No entanto, embora os critérios de exclusão clínica sejam idênticos nas diferentes *guidelines,* as definições de risco substancial para o VIH não são. Essa diferença tem implicações tanto na quantificação da população elegível quanto na predição do VIH. Além disso, a determinação da elegibilidade leva a uma classificação dicotómica de ter ou não indicação para a PrEP num determinado momento. No entanto, tanto o comportamento como os contextos de vida mudam e, em consequência, a elegibilidade para a PrEP. Finalmente, os dados sobre a utilização da PrEP em Portugal são ainda incipientes e referem-se, sobretudo, ao uso antes da implementação da PrEP.

**Objetivos**

Os objetivos deste trabalho foram:

1. Descrever a implementação da *Lisbon Cohort of MSM* (Coorte de Lisboa dos homens que têm sexo com homens – HSH) (Artigo I);

2. Sensibilizar para a relevância da PrEP no cenário português (Artigo II);

3. Usando e comparando quatro *guidelines* diferentes – da Organização Mundial de Saúde (OMS), do Serviço de Saúde Pública dos Estados Unidos e Centros de Controlo e Prevenção das Doenças (US-CDC), da *European AIDS Clinical Society* (EACS) e do Serviço Nacional de Saúde Português (SNSP):

   a. Estimar a proporção de HSH elegíveis para a PrEP (Artigo III);
   b. Fornecer evidência da sua capacidade em predizer a seroconversão para o VIH comparando a incidência do VIH de acordo com os diferentes conjuntos de critérios de

elegibilidade para a PrEP e a associação entre a elegibilidade para cada uma das *guidelines* e a seroconversão (Artigo IV);

4. Descrever as transições entre os estados de elegibilidade para a PrEP e a transição desses para a infeção por VIH e estimar a intensidade e a probabilidade dessas transições (Artigo V);

5. Avaliar as tendências temporais na utilização da PrEP comparando o período antes e depois da implementação em Portugal, comparar os utilizadores da PrEP com os não utilizadores e, entre os que usam, comparar aqueles que começaram antes e depois da implementação da PrEP (Artigo VI).

**Métodos**

Utilizamos dados da Coorte de Lisboa dos HSH, um estudo de coorte prospetivo, aberto, não intervalar, de homens adultos que reportam ter sexo com homens e que têm um resultado negativo para o teste do VIH na entrada. O recrutamento e a recolha de dados ocorrem no CheckpointLX, um centro de base comunitária de aconselhamento e teste do VIH (*community-based voluntary counseling and testing center* – CBVCT), em Lisboa, dedicado aos HSH, cujos serviços são prestados por técnicos pares, indivíduos também HSH, treinados. As visitas de seguimento ocorrem de acordo com a conveniência dos participantes, mas idealmente em intervalos de 6 meses. Em cada visita é realizado um questionário estruturado e um teste rápido de VIH pelos técnicos pares. Utilizamos dados de abril de 2011 a fevereiro de 2014 no artigo I, de março de 2014 a março de 2018 nos artigos III, IV e V, e de março de 2014 a julho de 2019 no artigo VI.

As características dos participantes foram descritas usando frequências absolutas e proporções no caso das variáveis categóricas, e médias e desvio padrão ou mediana e percentis 25 e 75 no caso de variáveis contínuas. As comparações entre os grupos fizeram-se com recurso ao teste *t* de Student para amostras independentes ou teste de Mann-Whitney no caso das variáveis contínuas, e usando o teste qui-quadrado de Pearson ou exato de Fisher no caso das variáveis categóricas.

Estimamos as taxas de incidência e os intervalos de confiança a 95% (IC 95%) para os participantes definidos como elegíveis e inelegíveis na primeira visita de acordo com cada *guideline* usando como denominador a soma de pessoas-ano em risco. Para medir a magnitude das associações calculamos as razões de taxas de incidência brutas (IRR) e os IC 95% usando modelos de regressão linear generalizada com a distribuição de Poisson. Também calculamos a

sensibilidade e a especificidade das *guidelines* e o número necessário tratar para prevenir uma infeção pelo VIH entre os indivíduos elegíveis, em três cenários de redução de risco.

Para estimar as frequências, intensidades e probabilidades das transições entre os estados de elegibilidade para a PrEP (elegível/inelegível) e destes para a infeção pelo VIH usamos um modelo multi estado de Markov com tempo homogéneo.

**Resultados**

*Artigo I*

De abril de 2011 a fevereiro de 2014, 3106 HSH eram elegíveis para entrar na coorte, dos quais 923 (29,7%) se recusaram a participar. Os restantes 2183 (70,3%) indivíduos foram incluídos na coorte e 804 tiveram pelo menos uma avaliação de seguimento num total 893 pessoas-ano de observação. Os participantes tinham uma idade mediana de 29 anos, 75,7% nasceram em Portugal e 58,1% tinham o ensino superior. Quase 84% autoidentificaram-se como gay. Ter feito o teste de VIH antes da entrada na coorte foi reportado por 81,9% dos participantes. Doze por cento relataram relações sexuais com homens VIH-positivos nos 12 meses anteriores, e aproximadamente oito por cento daqueles num relacionamento estável tinham um parceiro VIH-positivo. Entre os participantes com parceiro estável, 71,4% relataram uso inconsistente de preservativo nos últimos 12 meses. Oitenta e cinco por cento dos participantes relataram pelo menos um parceiro ocasional no mesmo período, dos quais 46,4% não usaram o preservativo de forma consistente. O motivo mais referido para não usar preservativo foi ter relações sexuais com um parceiro estável (66,2%). O uso de álcool ou drogas antes ou durante relações sexuais nos 12 meses anteriores foi reportado por 59,5% dos participantes. Pouco mais de um terço dos participantes conhecia a profilaxia pós-exposição e 2,7% tinham-na usado. Finalmente, aproximadamente 10% apresentaram sintomas ou diagnóstico de uma infeção sexualmente transmissível nos 12 meses anteriores.

*Artigo III*

Na primeira visita de 3392 participantes no período de março de 2014 a março de 2018, a proporção de HSH elegíveis para a PrEP foi de 67,7% de acordo com os critérios do US-CDC, 60,6% de acordo com os do SNSP, 58,9% de acordo com os da OMS, e 46,5% de acordo com os da EACS. Os critérios mais frequentemente reportados foram os relacionados com o sexo anal sem preservativo.

*Artigo IV*

De março de 2014 a março de 2018, 1254 participantes foram seguidos na coorte num total de 1724,54 pessoas-ano. Durante esse período, ocorreram 28 casos incidentes de VIH, dos quais os definidos como elegíveis na primeira visita variaram entre 60,7% (de acordo com as *guidelines* da EACS) e 85,7% (de acordo com as *guidelines* do SNSP). Ser considerado elegível por qualquer *guideline* esteve associado a um aumento da incidência do VIH. No entanto, a incidência foi maior entre aqueles definidos como elegíveis de acordo com as diretrizes do SNSP (2,46/100 pessoas-ano; IRR: 4,61 [IC 95%: 1,60-13,27]) e menor entre os definidos considerando as *guidelines* da OMS (1,89/ 100 pessoas-ano; IRR: 1,52 [IC 95%: 0,69-3,35]). O número necessário tratar com PrEP por um ano para evitar uma infeção pelo VIH, assumindo diferentes reduções de risco, mostrou que as estimativas mais baixas variaram de 42 a 53, com as *guidelines* do SNSP a mostrarem os valores mais baixos em todos os cenários.

*Artigo V*

Entre os 1300 participantes com informação válida para as *guidelines* do SNSP que tiveram pelo menos duas visitas de março de 2014 a março de 2018, as intensidades das transições foram semelhantes para inelegível–elegível (I–E) (1,591) e elegível-inelegível (E–I) (1.493) enquanto que a intensidade da transição elegível–infeção VIH (E–VIH) foi 22,0 vezes maior que a transição inelegível–infeção VIH (I–VIH) (0,032 vs. 0,001). As probabilidades da transição aos 90 dias foram semelhantes para I-E e E-I (0,275 vs. 0,258), enquanto a probabilidade da transição E-VIH foi 4,4 vezes maior que I-VIH (0,007 vs. 0,002). As probabilidades de transição aumentaram com o tempo; sendo semelhantes entre os dois estados de elegibilidade, enquanto as razões entre as probabilidades da transição para a infeção pelo VIH diminuíram.

*Artigo VI*

De março de 2014 a julho de 2019, 198 (3,2%) participantes relataram ter usado a PrEP nos últimos 12 meses ou no tempo entre as visitas. Aproximadamente um terço começou a usar após a sua introdução no SNS Português. O uso de PrEP aumentou de 0,15% (95% IC 0,02-0,55) em 2014 para 5,36% (95% CI 4,29-6,60) em 2019. Dos 122 (61,6%) utilizadores que forneceram informações adicionais sobre a primeira vez que usaram PrEP, 86 (70,5%) usaram-na diariamente, 31 (25,4%) de acordo com as práticas sexuais e 5 (4,1%) reportaram outros regimes. A forma de obtenção da PrEP variou de acordo com o momento da experiência inicial – prescrita por um médico em Portugal (11,1% antes vs. 68,8% após a implementação) e online (40,7% antes vs. 14,1% após a implementação). A presença de critérios de elegibilidade foi maior

entre os utilizadores do que entre os não utilizadores (76,3% vs. 56,4%) e não mudou significativamente após a implementação da PrEP (73,8% vs. 78,1%).

**Conclusões**

A implementação e o seguimento da Coorte de Lisboa dos HSH tem sido uma ferramenta valiosa na monitorização da incidência e das tendências na prevenção primária e secundária do VIH entre os HSH VIH-negativos que vão fazer o teste do VIH num centro de base comunitária em Lisboa. Este é também um cenário privilegiado para estudar a introdução de uma nova ferramenta de prevenção do VIH, como é a PrEP, em Portugal. Os resultados deste trabalho chamam a atenção para o potencial de perder pessoas que precisam de PrEP quando se usa uma abordagem estritamente baseada no risco para determinar a sua elegibilidade. Também mostrámos que é provável que a indicação da PrEP mude ao longo do tempo e que ser classificado como inelegível foi apenas um indicador de curto prazo de uma menor probabilidade de adquirir o VIH. A antecipação ou deteção atempada da mudança para um estado de elegível exige uma disponibilização oportuna da PrEP. Finalmente, foi possível detetar um aumento na utilização de PrEP, principalmente após a sua introdução no SNS Português, após o qual houve também uma mudança na forma como os HSH obtiveram PrEP, tendo a prescrição médica em Portugal tornado o meio mais frequente. Este facto pode contribuir para um acesso mais seguro e equitativo a uma ferramenta de prevenção de VIH altamente eficaz.

## 1. INTRODUCTION

The Joint United Nations Programme on HIV/AIDS (UNAIDS) has set the ambitious goal for the response to the human immunodeficiency virus (HIV) epidemic, aligned with the Sustainable Development Goals (SDG) of ending the epidemic by 2030 (SDG 3.3) (1, 2). The necessary tools to achieve this goal, both in terms of prevention and treatment are currently available. If widely accessible and used, ending the HIV epidemic is possible.

While the promise of a vaccine has not yet come to reality and all possible outcomes must be anticipated from efficacy-stage studies in the near future (3), nor a broad cure strategy is available (4), we can only aim to reach the elimination of HIV by stopping transmission.

Long-standing HIV prevention strategies such as condom use, behavioral risk reduction, male circumcision, harm reduction interventions for people who inject drugs (PWID), prevention, diagnosis and treatment of other sexually transmitted infections (STI), postexposure prophylaxis (PEP), and more recently preexposure prophylaxis (PrEP), are effective in reducing the risk of HIV acquisition and can be tailored to people from different populations, at different levels of risk, preferences, and needs. Routine HIV testing, as an essential tool for secondary prevention, is the gateway to early detection of HIV and immediate linkage to care, whether it is social support services, provision of antiretroviral therapy (ART), and counseling. Finally, early ART initiation and viral suppression are key to the better possible prognosis, and to stop the transmission of HIV. The combination of the available preventive strategies to maximize its effects, also known as combination HIV prevention, has the potential to bend the epidemic (5-8).

To end the HIV epidemic as a public health threat by 2030, the Fast-Track approach – an agenda for quickening the pace of implementation, at the global, regional, country, province, district and city levels, was defined (9). Its milestones by 2020 are (2, 10):

- The 90-90-90 targets: 90% of people (children, adolescents, and adults) living with HIV knowing their status; 90% of people living with HIV who know their status receiving ART; and 90% of people on ART having suppressed viral load;
- To reduce new HIV infections to fewer than 500 000;
- To reduce AIDS-related death to fewer than 500 000;
- To eliminate HIV-related stigma and discrimination.

By reaching these targets in 2020, we would be firmly on track towards ending the epidemic by 2030 (2).

### 1.1 HIV/AIDS progress towards elimination

The state of the epidemic in 2018 showed, however, that there is still a long way to reach the targets. The UNAIDS estimated that in 2018, 1.7 million (95% CI 1.4 million–2.3 million) people became newly infected with HIV, and 770 000 (95% CI 570 000–1.1 million) people died from AIDS-related illnesses (11). Globally, there were 37.9 million (95% confidence interval (CI) 32.7 million–44.0 million) people living with HIV (PLHIV), of whom 95.5% were adults (≥ 15 years of age) (11).

The number of new HIV infections has been declining since the peak of 2.9 million (2.3-3.8 million) in 1997, but these declines have grown smaller each year. Since 2010 a 16% reduction of new HIV infections was observed, which is not enough to reach the target of fewer than 500 000 in 2020 (Figure 1) (11). Regarding the number of AIDS-related deaths, after the peak in 2004 of 1.7 million (1.3-2.4 million) deaths, a reduction by 33% since 2010 was observed. However, reaching the 2020 milestone of fewer than 500 000 deaths will require further reductions in deaths at a pace of 135 000 per year (Figure 2) (11). The Global Burden of Diseases (GBD) forecasted that fewer than ten countries would meet the incidence or mortality targets in 2020 and 2030 (12).

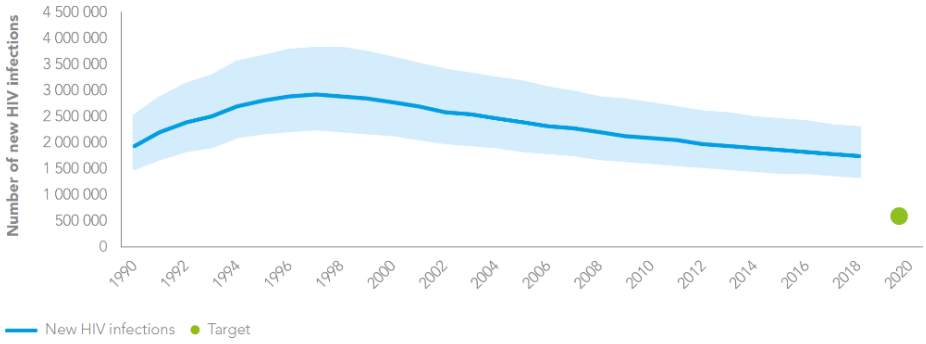



*Figure 1: Number of new HIV infections, global, 1990–2018 and 2020 target. Reproduced from: UNAIDS 2019 estimates.*

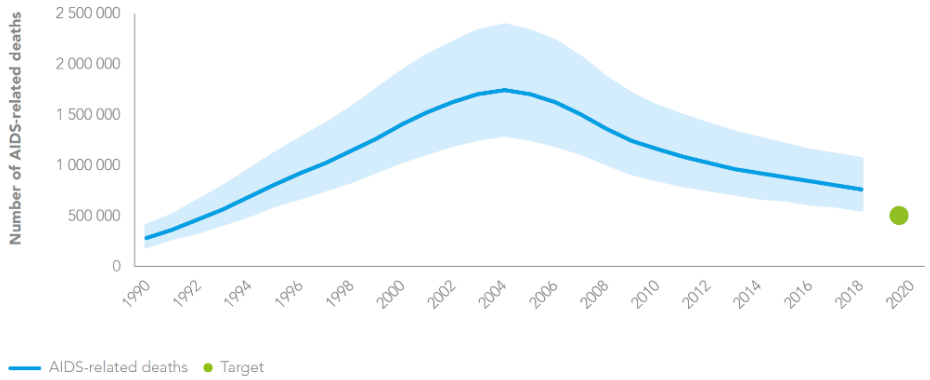



*Figure 2: Number of AIDS-related deaths, global, 1990–2018 and 2020 target. Reproduced from: UNAIDS 2019 estimates.*

Moreover, this global picture hides huge differences among countries and regions. The largest reductions in annual new HIV infections and AIDS-related deaths have occurred in eastern and southern Africa, where 54% of the PLHIV live; while in eastern Europe and central Asia, in the Middle East and North Africa, and Latin America there have been rises in, either or both, annual new HIV infections and AIDS-related mortality (11, 12).

The widespread use, since 1996, of combination antiretroviral therapy, has substantially improved the survival of HIV-positive patients, as depicted in Figure 3 (13). The early initiation of ART was found to have an individual benefit by improving the health of those receiving treatment, but also public health benefits by the preventive effect of viral load suppression (14-21). These findings were major breakthroughs in the road to elimination leading to global public policy and guidelines to focus on HIV testing and immediate treatment regardless of CD4 cell count (22).

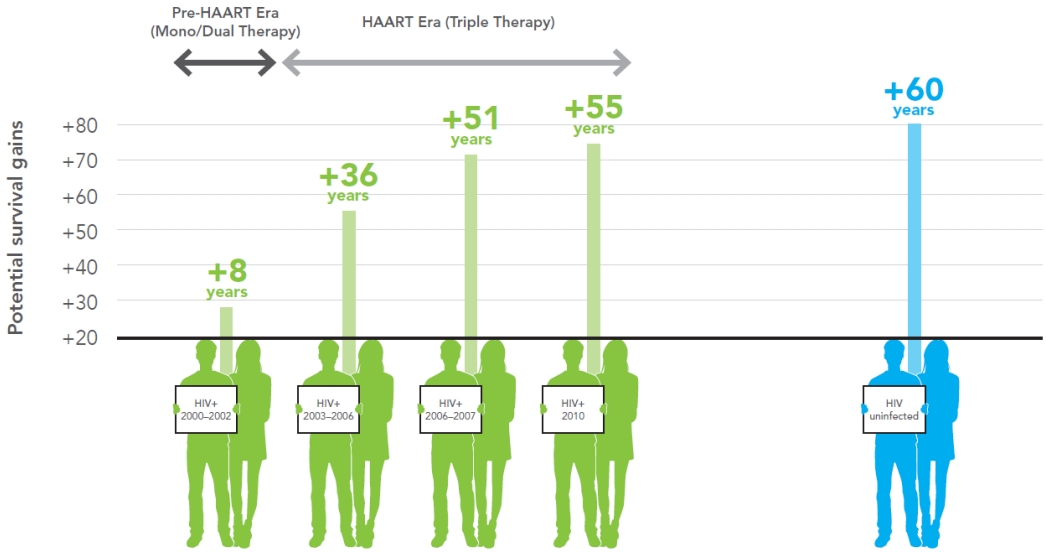



*Figure 3: Expected impact of HIV treatment in the survival of a 20 years old person living with HIV in a high-income setting (different periods). Reproduced from: UNAIDS, 90-90-90 An ambitious treatment target to help end the AIDS epidemic 2014, using data from Samji H et al., PLoS ONE, 2013.*

The 90-90-90 targets, focusing on the HIV continuum of care, are in line with the maximization of treatment and prevention benefits of ART (10, 22) and are a useful tool to measure the progress towards the ending of HIV as public health threat. In 2018, worldwide, an estimated 79% (67-92%) of PLHIV knew their status. Of those, 78% (69-82%) were accessing ART, and among those, 86% (72-92%) had their viral load suppressed (Figure 4) (23). If we use the same denominator for each metric, we verify that of all PLHIV, 79% (67-92%) knew their status, 62% (47-74%) were accessing treatment, and 53% (43-63%) were virally suppressed (23). This means that the target of 73% of PLHIV virally suppressed by 2020 is far off and that approximately 17.8 million people living with HIV do not have their disease controlled – 8.1 million are still undiagnosed, 6.4 million are not accessing ART, and 3.4 million are not virally suppressed. Estimates from the GBD were more pessimistic and showed, for 2017, that 40.5% (95% CI 37.8–43.7) of the 36.8 million (95% CI 34.8–39.2) people estimated to be living with HIV worldwide were not on ART (12). They also showed that 54 countries were on track to meet the 2020 target of 81% ART coverage, and only 12 countries would meet the 2030 target of 90% ART coverage (12).

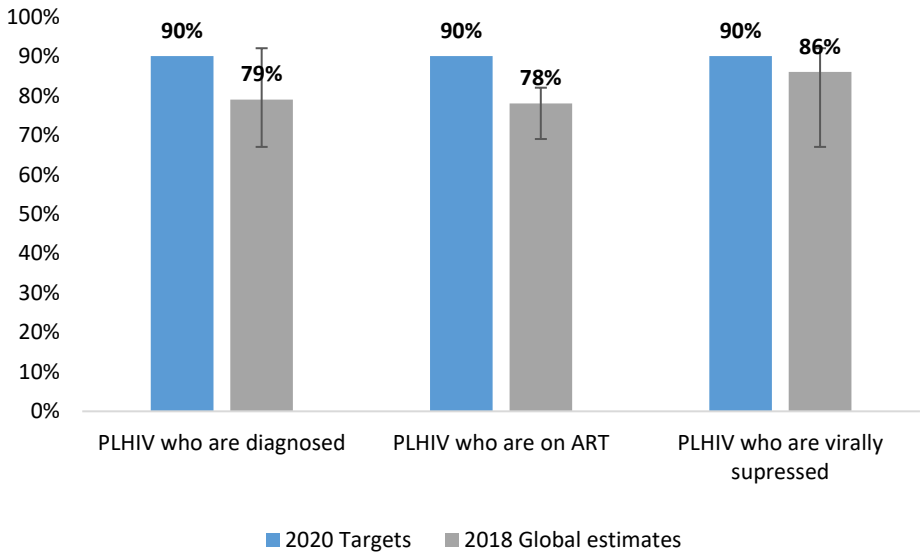



*Figure 4: The 2020 treatment targets and 2018 global estimates. Source: UNAIDS 2019 estimates.*

A more regional perspective showed that in the 31 countries from the European Union/European Economic Area (EU/EEA) region, there were 26 164 people newly diagnosed with HIV, in 2018, corresponding to a rate of 5.8 per 100 000 inhabitants when adjusted for reporting delay (24). Even if this represents a decline from a 6.6 per 100 000 observed in 2009, it still seems to be insufficient to meet the target of 5000 or less new HIV infections by 2020 in this region (Figure 5) (24).

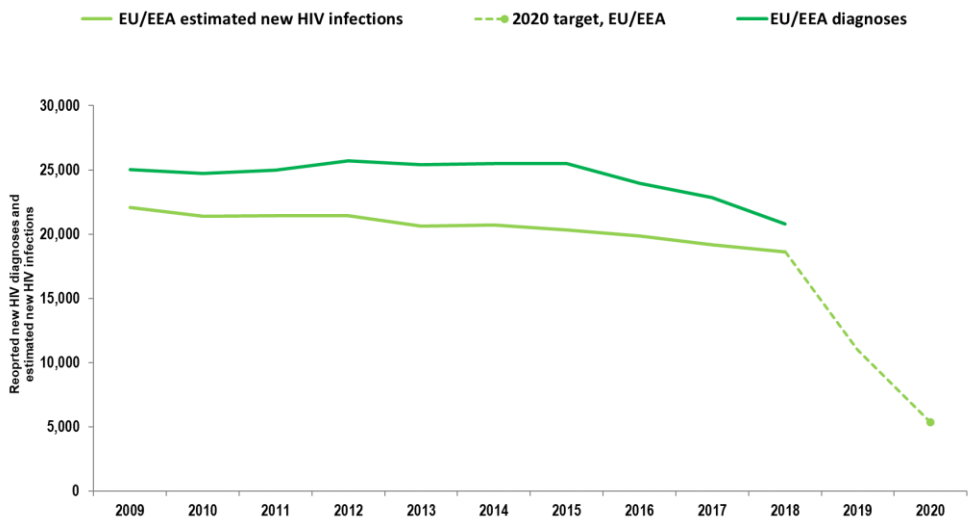



*Figure 5: Estimated new HIV infections and reported diagnoses, EU/EEA, 2018. Reproduced from: ECDC/WHO (2019). HIV/AIDS Surveillance in Europe 2019 – 2018 data.*

This decline was likely driven by substantial declines in new infections in some countries, including Austria, Belgium, Denmark, France, Estonia, Italy, Luxembourg, the Netherlands, Norway, Portugal, Slovenia, Spain, and the United Kingdom (24). For which the main cause was pointed as the decline in diagnoses among men who have sex with men (MSM) in certain countries (24-26). These decreases of new cases among MSM can be explained by more frequent and targeted testing aiming at promoting earlier diagnosis, rapid linkage to care, and immediate initiation of ART for those found to be positive, as well as by the formal and informal use of PrEP (24-27).

Regarding the progress towards the 90-90-90 targets in countries in the EU/EEA, in 2018, the overall figures were 86–91–92, with 86% of all PLHIV diagnosed, 91% of people living with diagnosed HIV on treatment, and 92% of those on treatment virally suppressed (28). Although overall, 73% of all PLHIV were virally suppressed, 13 out of the 31 countries were still not able to reach this target (28). The proportion of people living with HIV who are virally suppressed in each country clearly shows the high variability in countries' progress (Figure 6).

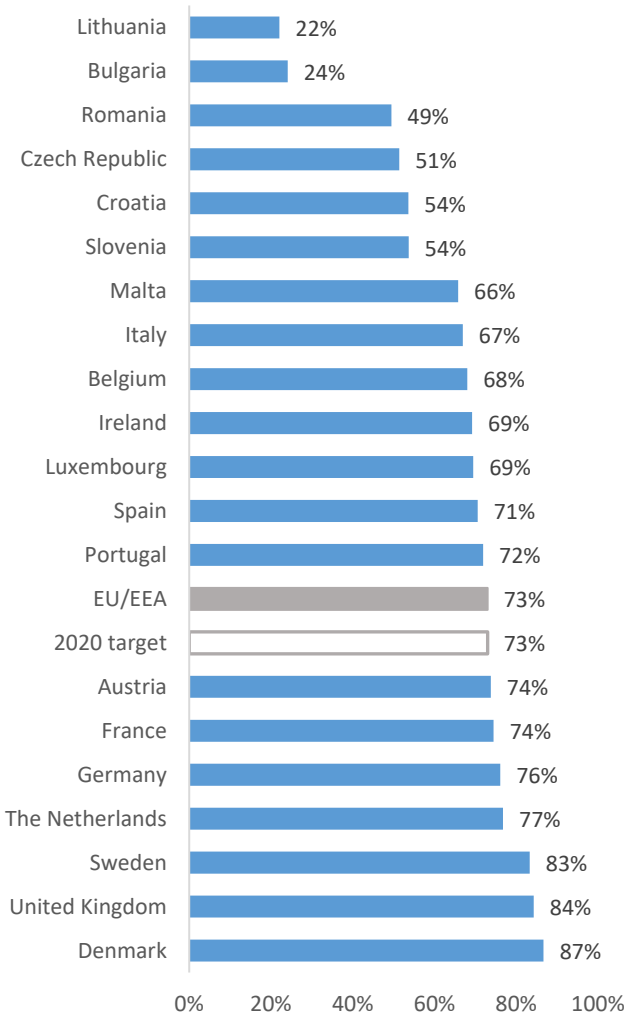



*Figure 6: Proportion of people living with HIV who are virally suppressed by EU/EEA country in 2018 (n=22). Source: Brown et al., 2018.*

In Portugal, 973 new HIV infections were reported in 2018, corresponding to a rate of 13.0 new cases per 100 000 inhabitants, after adjusting for reporting delay (24, 29). In 2018, 38 959 people were living with HIV in Portugal, of those 35 709 (92%) were diagnosed, 31 000 (87%) of those diagnosed were receiving ART, and 28 007 (90%) of those on ART had undetected viral load (Figure 7) (28). This puts the country on track to meet the treatment targets by 2020, showing important improvements such as a decrease in the undiagnosed fraction from 23.6% in 2008 to 8% in 2018 (28, 29). This decrease cannot be fully explained by increased investment in testing and treating, but also by changes in how estimates of PLHIV were computed. These figures also show that there are still around 11 000 people with transmissible levels of virus, and that the rate of new HIV infections is more than the double of the one for the EU/EEA.

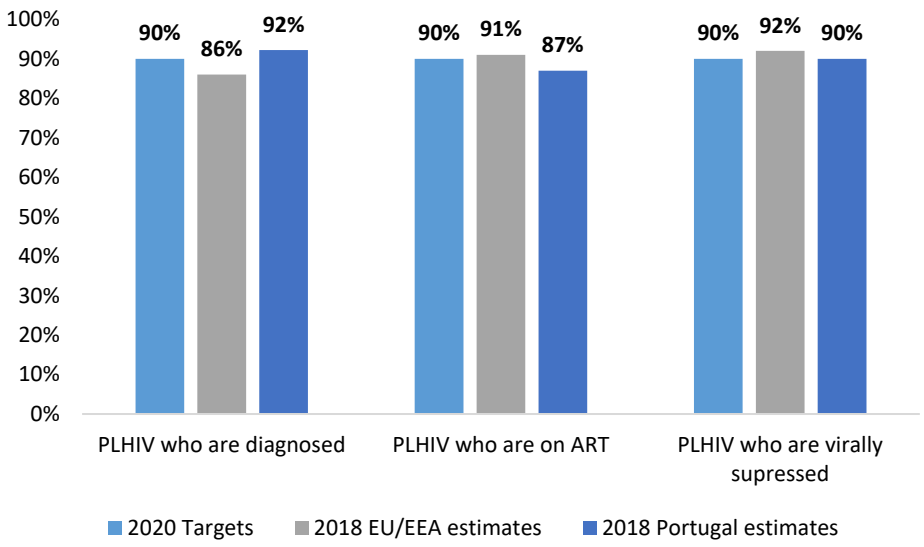



*Figure 7: Continuum of HIV care and progress towards the global 90–90–90 targets, EU/EEA countries and, Portugal, 2018 (n=20). Source: Brown et al., 2018.*

Substantial progress has been made globally in decreasing the number of new HIV cases and AIDS-related deaths and in reaching the 90-90-90 targets by 2020. Yet, that progress does not seem to be enough to put the world on track to end the HIV epidemic as a public health threat. Key issues from a public health perspective need to be addressed in the global response to HIV – the persistence of major disparities between regions and countries and within countries, when and where the targets are achieved, the "last 10 percent" will include people especially marginalized from healthcare services for whom continued, and innovative strategies will be needed (28), while the progress towards the zero discrimination targets remains to be measured.

### 1.2 Preexposure prophylaxis

The use of antiretroviral therapy to prevent transmission of HIV infection includes not only treatment of HIV-positive persons, to reduce the risk of transmission, but also pre- and postexposure prophylaxis for uninfected people exposed to HIV.

The preexposure prophylaxis is an antiretroviral therapy-based HIV prevention strategy to avoid or reduce the risk of HIV infection in adolescents and adults at high risk of infection. Results from a recent systematic review analyzed the effects of PrEP on HIV acquisition from 12 randomized controlled trials (30). Eleven trials evaluated PrEP against a placebo (31-41), and one evaluated immediate vs. delayed PrEP (42). All trials enrolled persons at increased risk for HIV infection – six enrolled persons at increased risk because of heterosexual contact (31, 33, 35-37, 40), four

trials enrolled MSM or transgender women (32, 38, 41, 42), one trial enrolled high-risk women and MSM (34), and one enrolled PWID (39). Five trials evaluated tenofovir disoproxil fumarate (TDF) monotherapy (300 mg) (31, 33, 38-40), eight trials tenofovir disoproxil fumarate (300 mg)/emtricitabine (FTC) (200 mg) (32-37, 40, 41), and one trial tenofovir disoproxil fumarate (245 mg)/emtricitabine (200 mg) (42). Eleven trials evaluated daily PrEP (31-40, 42), and three evaluated intermittent dosing or event-driven (34, 37, 41), but only one reported results for event-driven (before and after sex[1]) (41). In all trials, all patients received HIV risk reduction and adherence counseling. Table 1 summarizes the main characteristics of the studies, including one more recent study not included in the systematic review and meta-analysis (43).

*Table 1: Study characteristics of 13 randomized controlled trials for PrEP. Adapted from: Chou et al. 2019.*

| Study | Country | Intervention | HIV Risk Group: Risk-Based Inclusion Criteria |
|---|---|---|---|
| **Study of TDF Peterson et al., 2007 (31)** | Cameroon, Ghana, Nigeria | A. Tenofovir disoproxil fumarate (300 mg) (n=469)<br>B. Placebo (n=467) | High-risk women: Mean of ≥3 coital acts per week and ≥4 sexual partners per month |
| **iPrEx Grant et al., 2010 (32)** | Brazil, Ecuador, Peru, Thailand, South Africa, United States | A. Tenofovir disoproxil fumarate (300 mg)/emtricitabine (200 mg) (n=1251)<br>B. Placebo (n=1248) | MSM: Anal sex with ≥4 male partners, a diagnosis of STI, history of transactional sex activity, condomless anal sex with an HIV-infected partner or of unknown infection status in previous 6 months |
| **Partners PrEP Baeten et al., 2012 (33)** | Kenya, Uganda | A. Tenofovir disoproxil fumarate (300 mg) + placebo tenofovir disoproxil fumarate/emtricitabine (n=1571)<br>B. Tenofovir disoproxil fumarate (300 mg)/emtricitabine (200 mg) + placebo tenofovir disoproxil fumarate (n=1565)<br>C. Placebo tenofovir disoproxil fumarate + placebo tenofovir disoproxil fumarate/emtricitabine (n=1570) | High-risk heterosexual men and women: ART-naïve HIV-infected partner |
| **IAVI Kenya Study Mutua et al., 2012 (34)** | Kenya | A. Tenofovir disoproxil fumarate (300 mg)/emtricitabine (200 mg) (n=24)<br>B. Intermittent tenofovir disoproxil fumarate/emtricitabine (n=24)<br>C. Daily placebo (n=12)<br>D. Intermittent placebo (n=12) | MSM and high-risk women: Current or previous STI, multiple episodes of unprotected vaginal or anal sex, or engaging in transactional sex in the previous 3 months |
| **TDF2 Thigpen et al., 2012 (35)** | Botswana | A. Tenofovir disoproxil fumarate (300 mg)/emtricitabine (200 mg) (n=611)<br>B. Placebo (n=608) | High-risk heterosexual men and women: Sexually active in high-prevalence area |
| **FEM PrEP Van Damme et al., 2012 (36)** | Kenya, South Africa, Tanzania | A. Tenofovir disoproxil fumarate (300 mg)/emtricitabine (200 mg) (n=1062)<br>B. Placebo (n=1058) | High-risk women: >1 vaginal sex act in the previous 2 weeks or >1 sex partner in previous months |

[1] The dosing scheme used in the ANRS IPERGAY trial was 2 pills 2 to 24 hours before sex, followed by a third pill 24 hours after the first drug intake and a fourth pill 24 hours later. In case of multiple consecutive episodes of sexual intercourse, participants were instructed to take one pill per day until the last sexual intercourse and then to take the two postexposure pills.

| | | | |
|---|---|---|---|
| **CDC Safety Study Grohskopf et al., 2013 (38)** | United States | A. Tenofovir disoproxil fumarate (300 mg) (n=201)<br>B. Placebo (n=199) | MSM: Biological male engaging in anal sex with another man in the previous 12 months |
| **IAVI Uganda Study Kibengo et al., 2013 (37)** | Uganda | A. Tenofovir disoproxil fumarate (300 mg)/emtricitabine (200 mg) (n=24)<br>B. Intermittent tenofovir disoproxil fumarate/emtricitabine (n=24)<br>C. Daily placebo (n=12)<br>D. Intermittent placebo (n=12) | High-risk heterosexual men and women: Unprotected vaginal sex with ART-naïve HIV-infected partner in the previous 3 months |
| **Bangkok Tenofovir Study Choopanya et al., 2013 (39)** | Thailand | A. Tenofovir disoproxil fumarate (300 mg) (n=1204)<br>B. Placebo (n=1209) | PWID: Injection drug use in the previous 12 months |
| **IPERGAY Molina et al., 2015 (41)** | France, Canada | A. On-demand Tenofovir disoproxil fumarate (300 mg)/emtricitabine (200 mg) (n=199)<br>B. Placebo (n=201) | MSM: Unprotected anal sex with ≥2 partners in the previous 6 months |
| **VOICE Marrazzo et al., 2015 (40)** | South Africa, Uganda, Zimbabwe | A. Tenofovir disoproxil fumarate (300 mg) + placebo (n=1007)<br>B. Tenofovir disoproxil fumarate (300 mg)/emtricitabine (200 mg) + placebo (n=1003)<br>C. Placebo only (n=1009) | High-risk women: Sexually active in a high-prevalence area |
| **PROUD McCormack et al., 2016 (42)** | England | A. Immediate tenofovir disoproxil fumarate (245 mg)/emtricitabine (200 mg) (n=275)<br>B. Tenofovir disoproxil fumarate/emtricitabine deferred for 1 year (n=269) | MSM: Anal intercourse without a condom in the previous 90 days and likely to have anal intercourse without a condom in the next 90 days |
| **DISCOVER Hare et al., 2019 (43)** | United States, Austria, Canada, Denmark, France, Germany, Ireland, Italy, Netherlands, Spain, United Kingdom | A. Tenofovir alafenamide (25 mg) /emtricitabine (200 mg) + placebo tenofovir disoproxil fumarate/emtricitabine (n=2694)<br>B. Tenofovir disoproxil fumarate (300 mg)/emtricitabine (200 mg) + placebo tenofovir alafenamide/emtricitabine (n=2693)<br>C. Tenofovir alafenamide (25 mg)/emtricitabine (200 mg) deferred for 96 weeks | MSM and transgender women: CAI with at least two unique male partners in the past 12 weeks (either HIV-positive or unknown) or documented history of syphilis, or rectal gonorrhea or chlamydia in the past 24 weeks |

ART, antiretroviral therapy; CAI, condomless anal intercourse; HIV, human immunodeficiency virus; MSM, men who have sex with men; STI, sexually transmitted infections.

PrEP was associated with an overall 56% decreased risk of acquiring HIV infection (risk ratio: 0.44; 95% CI: 0.29-0.65) (30). The effectiveness of PrEP varied significantly according to the level of adherence (Figure 8) (30). When adherence was 70% or greater, the reduction in risk was 73% (risk ratio: 0.27; 95% CI, 0.19-0.39), with a number needed to treat with PrEP for one year to avert one HIV infection of approximately 33 (30).

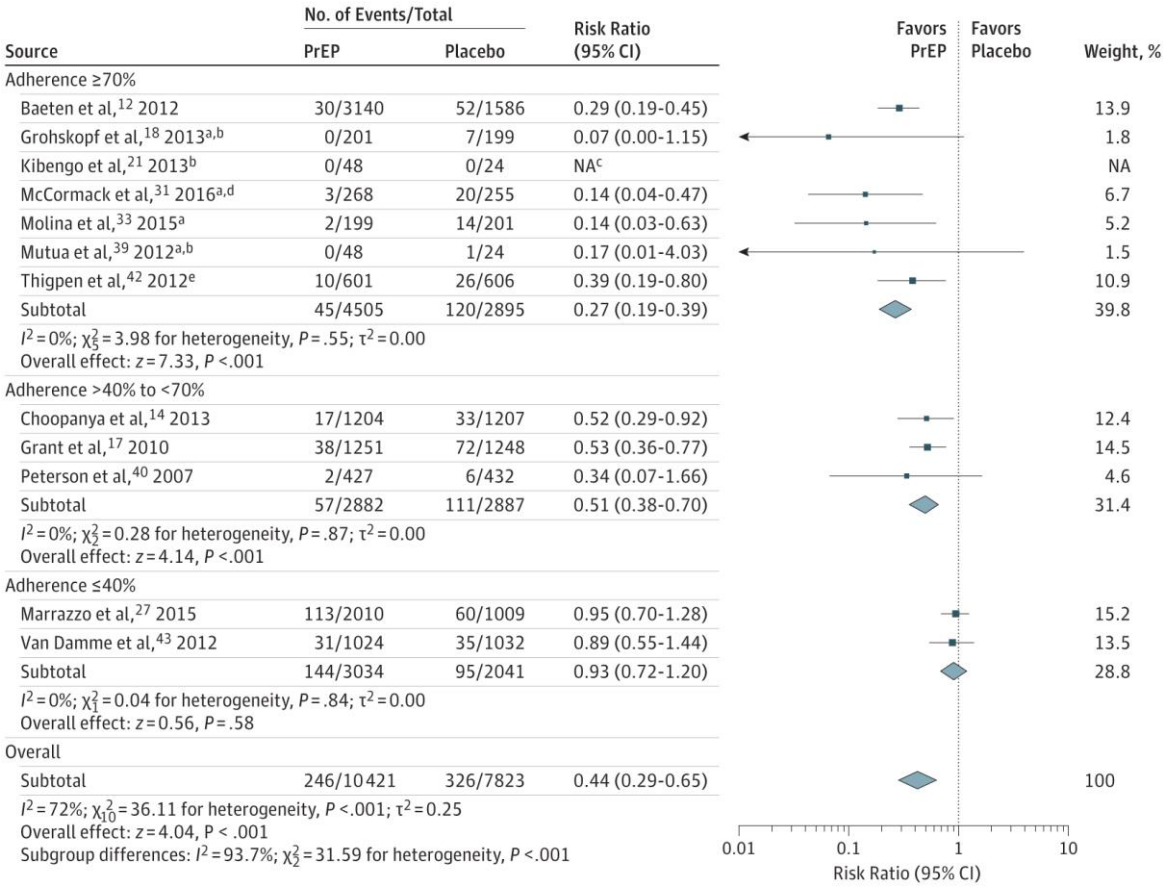



*Figure 8: Meta-analysis: HIV infection stratified by adherence. Source: Chou et al., 2019.*

Adherence was based on plasma testing unless otherwise noted. The area of each square represents the weight given to the study in the meta-analysis. The area of each diamond represents the sample size for each pooled estimate (subgroup or overall analysis), and the width of each diamond represents the confidence interval for the pooled estimate. The Mantel-Haenszel method was used to calculate the heterogeneity ($I^2$) test statistic. NA indicates not available; PrEP, preexposure prophylaxis. [a] Study conducted in the United States, Canada, or Europe. [b] Assessed using medication event monitoring system. [c] Not estimable. [d] Assessed by self-report, confirmed by plasma sample. [e] Assessed by self-report (30).

Among MSM, the use of PrEP has shown a relative risk reduction in HIV incidence of 73% (risk ratio: 0.23; 95% CI 0.08-0.62) both when taken daily or event-driven (30, 32, 38, 41, 42). An open-label extension of the ANRS IPERGAY trial confirmed and extended the effectiveness of event-driven PrEP (44). Indeed, a relative reduction of HIV incidence of 97% (95% CI 81–100) was found (44). In demonstration projects, as well as in real-life clinical settings, PrEP has also been shown to be effective in preventing HIV infection (45-50).

PrEP was also found to be effective for heterosexual men and women (risk ratio: 0.54; 95% CI 0.31-0.97) and PWID (risk ratio: 0.52; 95% CI 0.29-0.92) (30).

More recently, the DISCOVER trial - a phase 3, randomized, double-blind study evaluated the safety and efficacy of another drug combination, tenofovir alafenamide (25 mg) and emtricitabine (200mg) (TAF/FTC) as PrEP, for daily use. The trial enrolled 5387 men and

transgender women who have sex with men at risk of HIV-1 infection recruited from 94 sites across 11 countries in Europe and North America. The study demonstrated the noninferiority of TAF/FTC to TDF/FTC and showed improved biomarkers of renal function and bone mineral compared with TDF/FTC at 48 weeks (43, 51, 52).

Besides the efficacy and effectiveness of PrEP, which has been demonstrated, time to clinical protection is an important issue regarding PrEP uptake, but it is not yet definitively established. The most conservative estimates are that after 7 days of daily dosing of TDF/FTC optimal protection is achieved for rectal exposure, for genital and blood exposure protection is most likely achieved also after 7 days, but optimal protection is achieved after 20 days of daily dosing for all sites of exposure (53). Taking 2 pills of TDF/FTC on the day of initiation might decrease the time needed to achieve protective concentrations for all sites of exposure (53). Regarding the time to protection for TAF/FTC, data are insufficient to make an estimate (53). The recommendations from the British HIV Association and the British Association for Sexual Health and HIV (BHIVA/BASHH) for starting and stopping PrEP, are (54):

- if the HIV risk is through anal sex, PrEP can be started with a double dose of TDF/FTC taken 2 to 24 hours before sex and continued daily until 48 hours after the last sexual exposure;
- if PrEP for anal sex has been interrupted within less than 7 days since the last TDF/FTC dose then PrEP can be re-started with a single dose of TDF/FTC;
- if the risk of HIV acquisition is through vaginal sex, PrEP should be started as a daily regimen 7 days ahead of the likely risk and continued daily for 7 days after the last sexual exposure.

This is particularly important given that PrEP is not expected to be used indefinitely; sexual behavior and life circumstances change, and so would the need for PrEP (55-57). While for some persons PrEP may even be used only in short episodes of anticipated increased risk, such as vacations (58).

#### *1.2.1 PrEP availability and use*

The use of Truvada® (TDF/FTC) as PrEP, was first approved by the United States (US) Food and Drug Administration (FDA) in 2012 (59). In 2014, the World Health Organization (WHO) recommended offering PrEP to MSM as an additional HIV prevention choice (60). This recommendation was expanded to include all population groups at substantial risk of HIV infection in 2015 (61). In this same year, the European Centre for Disease Prevention and Control (ECDC) recommended that EU Member States should consider offering PrEP in addition to the existing HIV prevention package for those most at-risk, starting with MSM (62). In 2016, the

European Medicines Agency (EMA) recommended granting a marketing authorization in the EU for Truvada® for PrEP to reduce the risk of HIV-1 infection in adults at high risk (63). In 2019, the US-FDA approved the use of Descovy® (TDF/TAF) as PrEP in adults and adolescents at-risk for sexually acquired HIV, with the exception of individuals at-risk from receptive vaginal sex (64).

Regarding the use of PrEP, a systematic review and meta-analysis of self-reported HIV PrEP identified 72 primary studies reporting PrEP use published from 2006 through 2018 (65). The majority of studies were from the United States (n=55) and mostly from MSM (n=58) (65). The pooled prevalence of global self-reported PrEP use was 2.6% (95% CI: 1.3–4.8) and increased significantly following US-FDA approval in 2012 (Figure 9) (65).

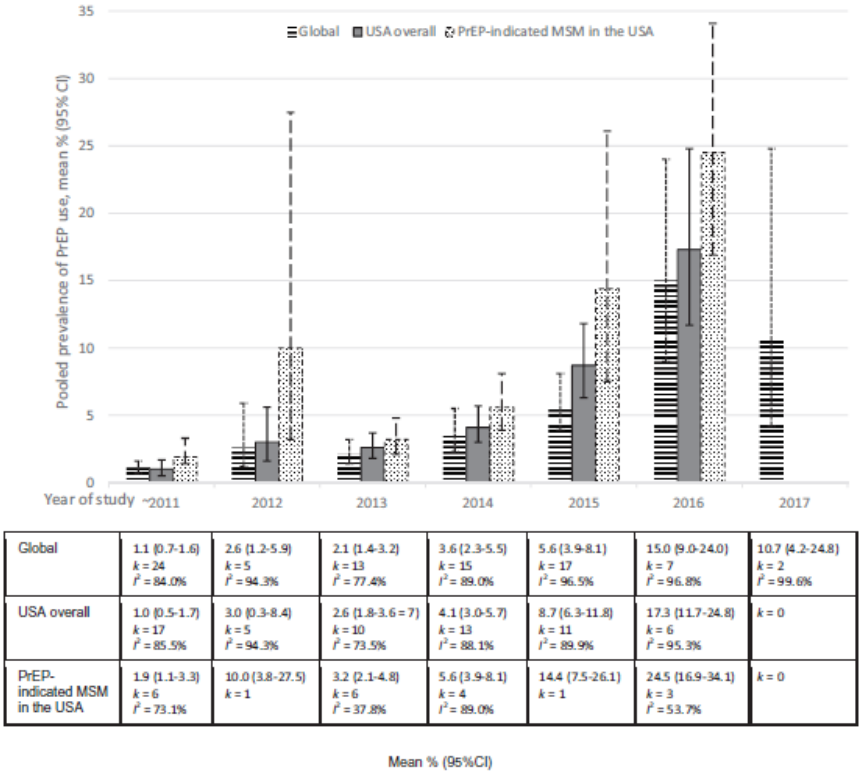



*Figure 9: Pooled prevalence of self-reported preexposure prophylaxis use in study participants: global vs. USA overall vs. MSM meeting CDC's PrEP indications in the USA (n=72).*

In absolute terms, as of October 2019, according to the Global PrEP Tracker, a quarterly survey sent by AVAC: Global Advocacy for HIV Prevention – a coalition of civil society, researchers, policymakers and many other stakeholders working in HIV prevention research and implementation, to partners known to be working on PrEP demonstration projects, implementation initiatives and other programs, there were 380 000 to 385 000 people on PrEP in 72 countries, of whom slightly over one third were in the United States (66). A further 36.6% were in sub-Saharan Africa, overwhelmingly concentrated in a handful of countries: Kenya, South Africa, Zimbabwe, Uganda, and Lesotho (66) (Figure 10). These estimates are far from the UNAIDS global target of three million people accessing PrEP annually by 2020 (2).

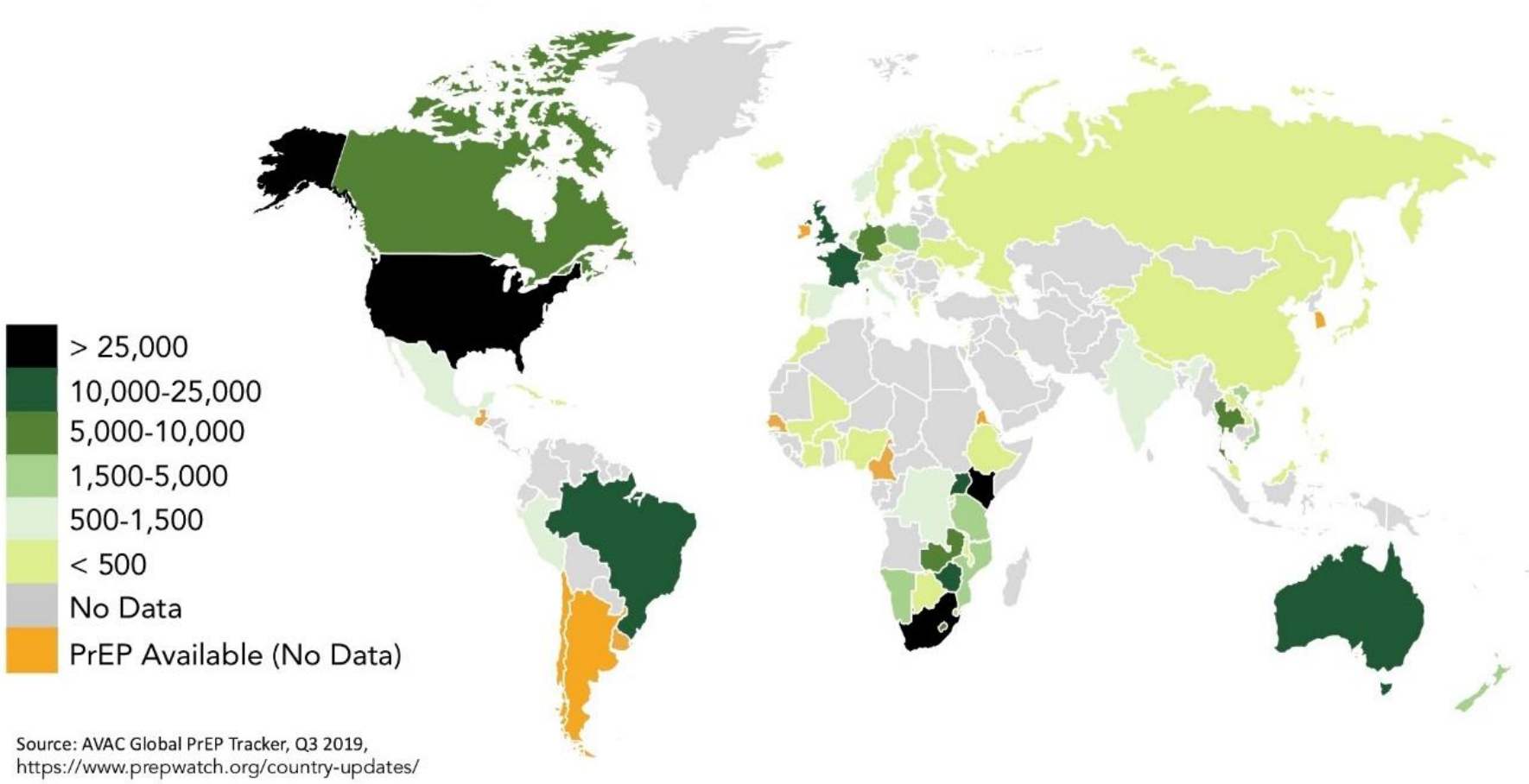



*Figure 10: PrEP initiations by country, October 2019. Source: AVAC Global PrEP Tracker, Q3 2019.*

Data from European and Central Asian countries reported to ECDC/WHO in the framework of the Dublin Declaration monitoring, showed that PrEP was reimbursed within the national health service in 16 out of 53 countries in this region in 2019 (Belgium, Bosnia and Herzegovina, Croatia, Denmark, France, Germany, Iceland, Ireland, Luxembourg, Moldova, the Netherlands, Norway, Portugal, Spain, Sweden, and Scotland within the United Kingdom); it was available in healthcare settings, but not fully reimbursed in nine countries (Armenia, Austria, the Czech Republic, Finland, Israel, Italy, Malta, Poland, and Switzerland); and available through pilot, research or demonstration projects at national or sub-national level in five countries (Georgia, Greece, Slovenia, Ukraine, and England, Northern Ireland and Wales within the United Kingdom) (67). In total, 32 613 people reported to have used PrEP at least once; the majority received PrEP for the first time in the last 12 months (67). Figure 11 shows the number and rate per 100 000 inhabitants of people receiving PrEP in 20 reporting countries from Europe and Central Asia. Portugal did not provide data on PrEP users but reported later in 2019 to have one thousand PrEP users at the Portuguese National Health Service (NHS) (29).

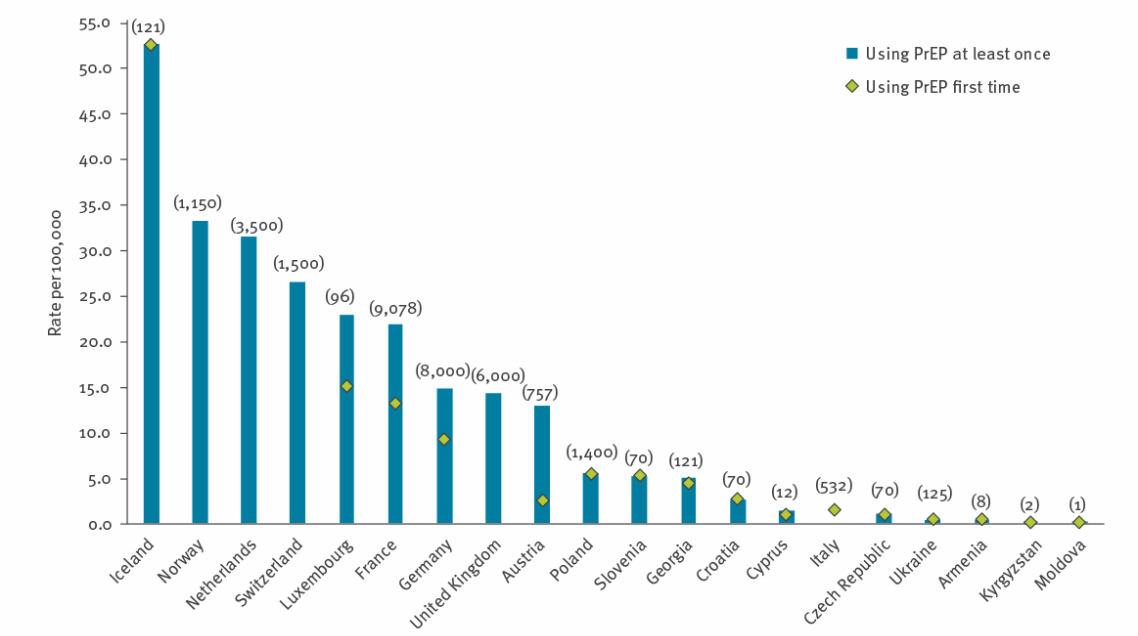



*Figure 11: Number and rate per 100 000 inhabitants of people receiving PrEP, Dublin Declaration monitoring in Europe and Central Asia reported in 2019 (n=20 countries). Reproduced from Hayes et al., 2019.*

The described availability of PrEP excludes the informal use of PrEP by people who access it online or by other means outside countries' health systems.

First reports of the use of PrEP among MSM were from earlier 2000s in the United States when PrEP efficacy was unproven (68, 69). Informal use of PrEP was the way individuals, mostly MSM, found to overcome the lack of availability in their countries. Several strategies were, and are, used to access PrEP informally, or also called "wild PrEP", these include buying online generics

of versions of Truvada®. In several European countries, webpages such as www.iwantprepnow.co.uk, or Facebook groups were created to help MSM ordering PrEP and obtaining information regarding how to use it. Other means of obtaining PrEP include partners and friends living with HIV or participants in clinical trials, using leftovers from a non-occupational PEP treatment, or obtain non-occupational PEP for PrEP (70-76).

The informal use of PrEP challenges the proper clinical evaluation before starting PrEP, especially the exclusion of HIV infection, the monitoring of HIV, STIs and renal function while on PrEP, the assurance that the proper drugs are being taken and the continuity of PrEP due to drug availability, delay in shipping or affordability (73, 75, 77). In response to these challenges, there were cases of an organized response, for instance, in Lisbon, a community-based HIV testing service began offering counseling and follow-up services for PrEP users, and in England, an innovative service offering plasma TDF/FTC therapeutic drug monitoring for people buying generic PrEP online was established (74, 78). Informal PrEP-users were associated with being tied to a higher socio-economic background, well informed about prevention tools, and highly exposed to HIV (72, 79). This is indicative of proper self-selection for PrEP but also of some level of inequality in access since only those knowledgeable and able to afford the costs associated with acquiring PrEP outside the formal system can access it.

In European countries where PrEP was available through their public health services, accessing PrEP outside the formal health system was lower than in countries where it is not available (76, 80). Also, in these countries, the unmet need for PrEP described as “PrEP gap” was smaller (81). The PrEP gap corresponds to the difference between the proportion of respondents who were using PrEP and those who would be ‘very likely’ to use PrEP if they could access it (81). This was estimated to vary from 44.8% in Russia to 4.3% in Portugal, while the overall estimate for the EU was 17.4% (81). In absolute terms, authors estimated that 500 000 (95% CI: 420 000–610 000) MSM were not using PrEP but would be very likely to do so if they could access it (81).

But as in the United States, where the PrEP uptake has been slower than expected (82), reasons for the gap between needs and access may also be related to limited awareness, or ability to afford co-payments where PrEP is not fully reimbursed, concerns related to stigma and discrimination especially in settings where there is a cultural and institutional stigma associated with sexuality, substance use and HIV (83). The “little blue pill” (Truvada) is, in some contexts, a synonym of being HIV-infected and so maybe a disincentive for an HIV-negative person to take PrEP, along with the fears of ‘‘risk compensation’’, i.e., increases in sexual risk behavior

counteracting the benefit provided a given prevention tool, that have fueled new sexual moralism (83).

From the side of providers in the EU/EEA, the main reported barrier to implement PrEP was the cost of the drug (Figure 12). Concerns about the impact of PrEP on sexual behaviors and on the HIV and STIs epidemiology persisted in 18 countries (81).

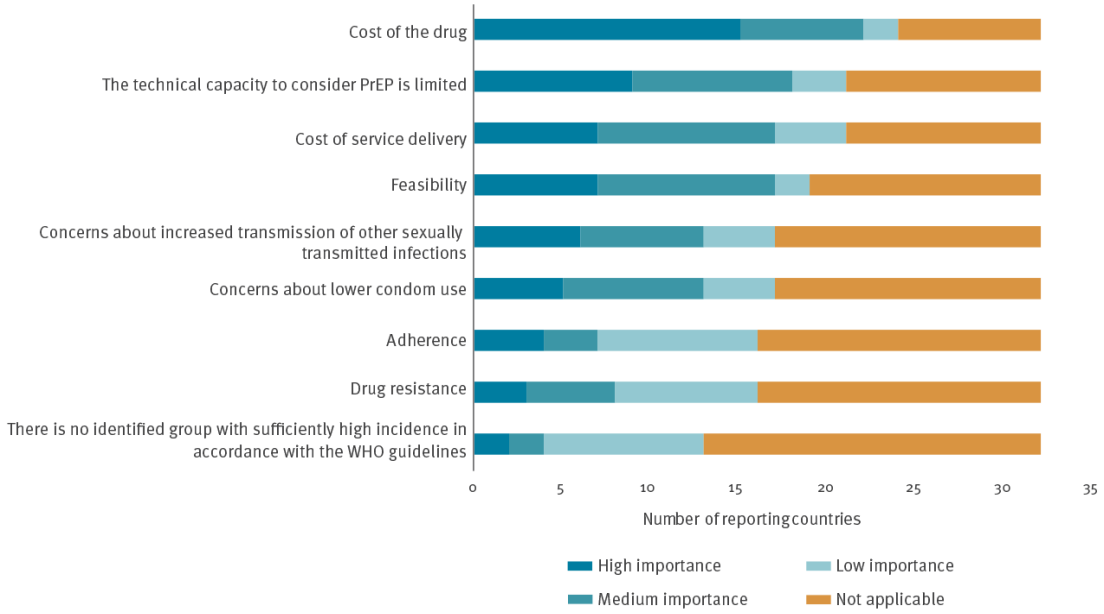



*Figure 12: Country reported barriers to implementing PrEP, Dublin Declaration monitoring in Europe and Central Asia, 2018 (n=32 countries). Reproduced from: Hayes et al. 2019.*

Efforts to decrease the costs of drugs and expand PrEP delivery within provision strategies that are friendly, close, and easy to access, and in which out-of-pocket costs are minimum seem to be key to overcome the challenges of informal use and the unmet needs for PrEP.

### *1.2.2 Indications for preexposure prophylaxis*

To ensure a successful implementation of PrEP, decision-makers must determine who can benefit most from PrEP, how PrEP can be provided safely and efficiently, and in what kind of health system support (84). Informed guidance regarding testing, new treatments, and innovations in disease prevention are essential to physicians and policymakers in rapidly evolving areas of medical care, such as this one (85). Several screening tools exist to help health care providers identify high-risk individuals based on HIV predictors (86-89). However, they had only moderate discrimination (30).

Still, the definition of eligibility for PrEP, mostly based on a risk assessment, is likely to be key to measure the success of this prevention tool (90). Several PrEP cascades or continuum of care

have been proposed with slight differences in the included steps, but they all start with the identification of those at high risk for HIV (91-94), and thus one important metric will be the uptake among eligible individuals (90).

Major reference entities have issued either implementation or clinical guidelines for the use of PrEP. These include the World Health Organization's Implementation Tool for Pre-exposure Prophylaxis of HIV Infection (95), 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 (96), or the European AIDS Clinical Society's (EACS) Guidelines (97), the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine HIV pre-exposure prophylaxis: clinical guidelines (98), among others .

Several countries issued their guidelines. In Europe in Central Asia, in 2019, 21 countries stated that PrEP guidelines had been developed or are being implemented; five countries stated that PrEP guidelines had been developed but are not yet implemented, and 21 countries stated that PrEP guidelines were not developed (67). Portugal is one of the countries where clinical guidelines were issued by the Portuguese National Health Service (PNHS) and are being implemented (99), as well as the Spanish National Plan on AIDS – Consensus Document on pre-exposure prophylaxis for HIV in Spain (PNSE) (100), or the British HIV Association and the British Association for Sexual Health and HIV guidelines on the use of HIV pre-exposure prophylaxis (BHIVA/BASHH) (54).

Guidelines intend to lead health care providers in the provision of PrEP. They provide eligibility criteria to identify those who have an indication for PrEP. 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 guidelines (90, 101). In general, the risk is measured considering the local and group-specific incidence of HIV and known behavioral predictors of HIV acquisition. Issues related to condom use, HIV-positive partners, use of PEP, previous diagnosis of STIs, or the use of psychoactive substances during sex are included in almost all guidelines. However, there is room for variation or ambiguity on how they specify each of these issues, such as the type and number of partners with whom condom was not used, or whether the HIV-positive sexual partner is virally suppressed or on treatment, or the timeframe for which the assessment is done. The discretion of clinicians in prescribing PrEP to individuals not meeting the criteria, but deemed appropriate candidates, is also clearer in some guidelines than others. Table 2 presents an overview of the different guidelines' specifications regarding their eligibility criteria by broad topic.

*Table 2: Overview of the WHO, US-CDC, EACS, Australasian, PNHS, BHIVA/BASHH, and PNSE guidelines and of their inclusion criteria by broad topic.*

| | Guideline | | | | | | |
|---|---|---|---|---|---|---|---|
| **Topic** | **WHO (2017)** | **US-CDC (2017)** | **EACS (2017)** | **Australasian (2018)[2]** | **PNHS (2018)** | **BHIVA/BASHH (2018)[2]** | **PNSE (2018)** |
| **Male partners** | n.a. | Last 6 months, any | n.a. | n.a. | n.a. | n.a. | Last 12 months, >10 |
| **Relationship status** | n.a. | Not monogamous with HIV-negative steady partner | n.a. | n.a. | n.a. | n.a. | n.a. |
| **Condomless sex** | Last 6 months, > 1 partner | Last 6 months, ≥1 partner | ≥1 casual partner | Last 3 months, ≥ male casual HIV-positive or unknown AND Next 3 months, >1 CAI | Last 6 months, ≥1 partner HIV-unknown | Last 6 months and on-going | Last 12 months, any |
| **Use of psychoactive substances** | n.a. | n.a. | Chemsex, intravenous | Methamphetamine | Any, PWID sharing paraphernalia | n.a. | Last 12 months, any, CAI |
| **STIs diagnosis** | Last 6 months | Last 6 months | Recent | Last 3 months or at screening for PrEP | Last 6 months, CS | n.a. | Last 12 months |
| **Use of PEP** | Last 6 months | n.a. | Ever | n.a. | Last 6 months, CI | n.a. | Last 12 months, ≥1 |
| **HIV-positive partners** | Last 6 months, VL detectable | Any | Not on ART | Not on ART or VL detectable and CAI in the last 3 months | Not on care, or not on ART, or VL detectable, CS | Last 6 months, not on ART or VL detectable, CS | n.a. |
| **Sex work** | n.a. | n.a. | n.a. | n.a. | CAI | n.a. | n.a. |

ART, antiretroviral therapy; BHIVA/BASHH, British HIV Association and the British Association for Sexual Health and HIV; CAI, Condomless anal intercourse; CS: Condomless sex; EACS, European AIDS Clinical Society; HIV, human immunodeficiency virus; n.a., Not applicable; PEP, postexposure prophylaxis; PNHS, Portuguese National Health Service; PNSE, Spanish National Plan on AIDS, Group of PrEP Experts; STI, sexually transmitted infection; US-CDC, United States – Centers for Disease Control and Prevention; VL, Viral load; WHO, World Health Organization.

[2] Only high-risk criteria.

More recently, approaches to assess indication for PrEP suggest a movement away from a risk-based indication to adequacy to one's prevention strategy, options, preferences, or needs. This is framed in a rights-based, culturally adapted, and more holistic approach to PrEP as part of sexual health (102-104), while acknowledging and valuing the additional benefits of PrEP besides preventing HIV. PrEP was found to have effects on sexual wellbeing, such as happiness and fulfillment of sex life and reduction in anxieties and fears of HIV among MSM (76, 102, 105, 106). PrEP can also provide an opportunity to have a discussion on sexual behavior, drug use, and other sexual health needs (107-109). PrEP is also about empowering individuals to protect themselves by conferring levels of agency and control over prevention options not generally achieved with condoms (83, 110). Additionally, a modeling study showed that high PrEP coverage among MSM could also lead to an important decline in other STIs incidence, mainly due to routine testing, which allows for early detection and treatment of asymptomatic STIs (111). On the other hand, risk prediction tools are imperfect, as already mentioned, they have only a moderate discriminatory ability; therefore, they will inevitably exclude some people at risk (30, 104). In fact, some studies reported an unsatisfactory sensitivity of the US-CDC guidelines (112-114).

### 1.3 The Portuguese epidemic

Throughout the first 35 years of the HIV epidemic in Portugal, changes in the patterns of transmission have been observed. During the initial 20 years, the epidemic was predominantly associated with unsafe injection practices. In the early 2000s, with the scaling up of drug treatment structures and harm reduction strategies in Portugal, as well as, possibly, an avoidance of injection use, a steep decrease in cases among people usually injecting drugs was observed. The epidemic transited then to an apparently heterosexual mode of transmission, still the main mode, but with a high male to female ratio (26). Since the early 2000s, an increase in the absolute number of notified cases related to sexual transmission between men was observed, which was consistent with other high-income countries with concentrated epidemics (115, 116). Figures 13 and 14 show the number of HIV cases by transmission mode by year of diagnosis.

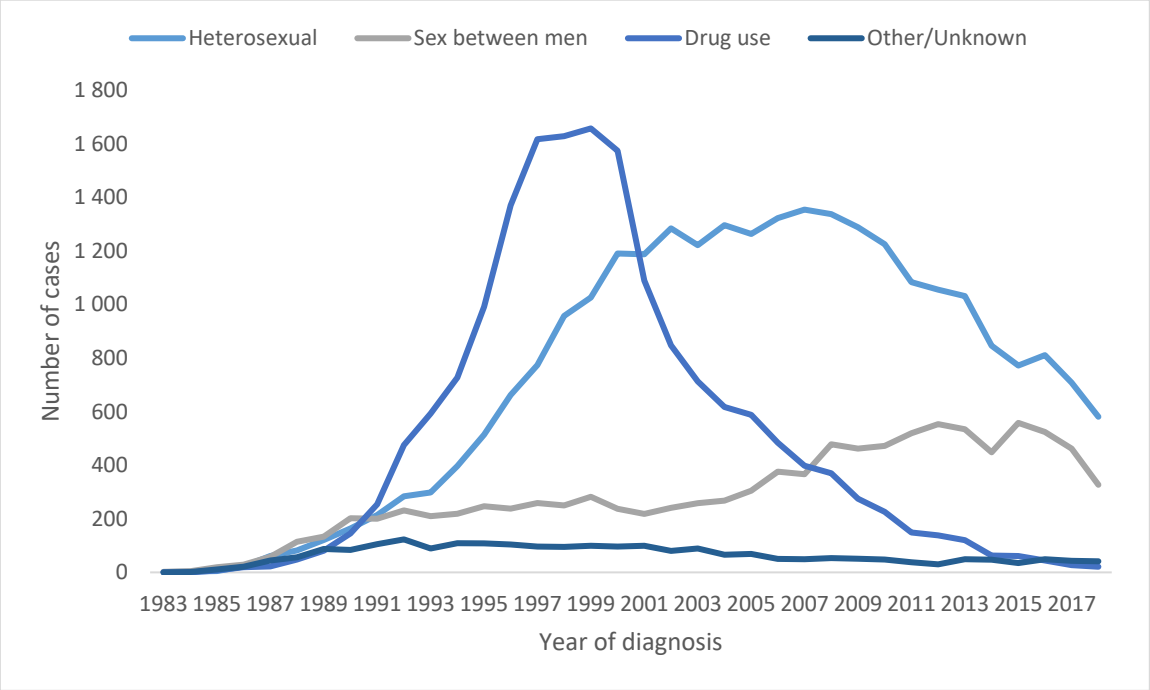



*Figure 13: Number of HIV cases by transmission mode by year of diagnosis (1983-2018). Source: INSA, 2019.*

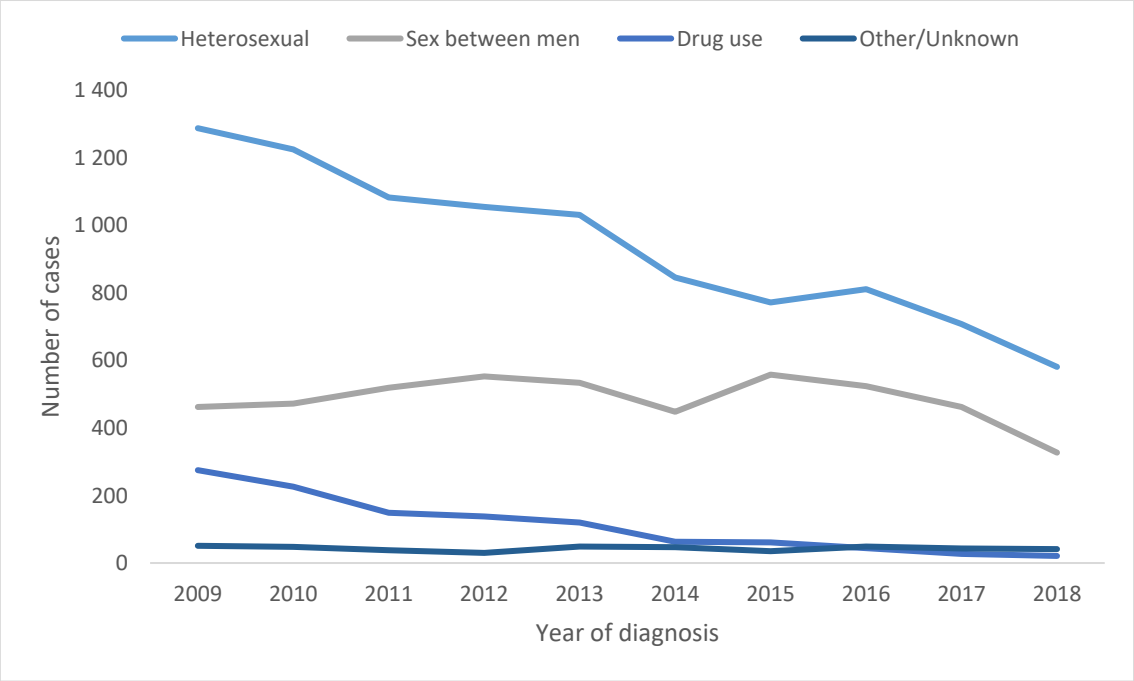



*Figure 14: Number of HIV cases by transmission mode per year (2009-2018). Source: INSA, 2019.*

From 2013 to 2017, the number of cases associated with the sharing of drug injection material continued to decrease (-26.0% on average per year), there was also a continued decrease in cases associated with heterosexual transmission (-7.3% on average per year), and in cases among MSM (-2.6% on average per year) after two five-year periods in an increasing trend (Figure 15). The data for most recent years should be regarded with caution due to delays in reporting new HIV cases.

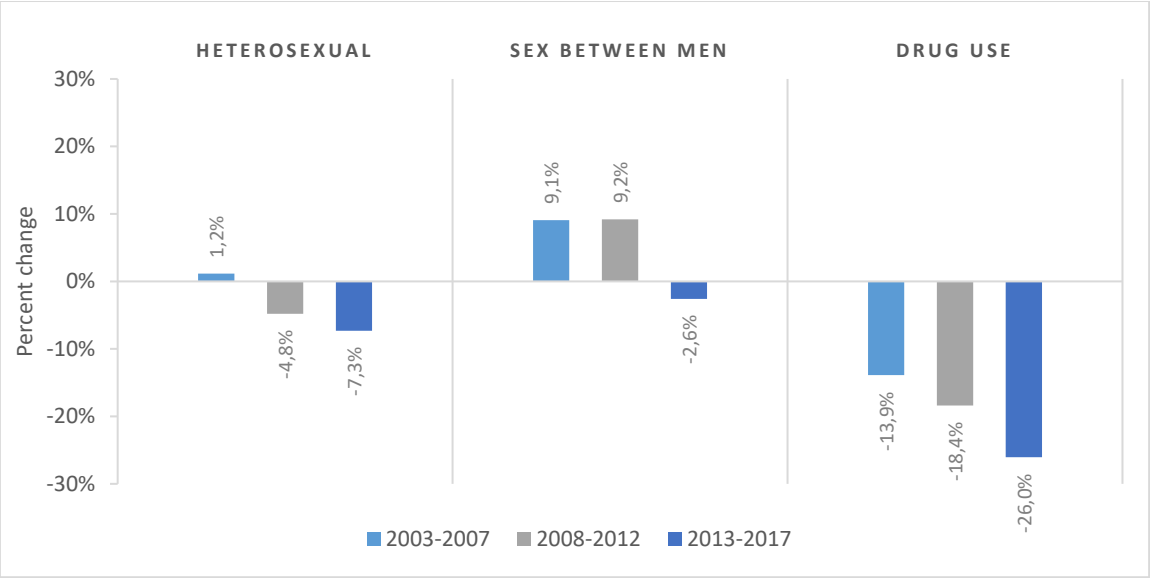



*Figure 15: Mean annual percentage change in HIV notifications by mode of transmission by a five-year period. Source: INSA, 2019.*

### *1.3.1 HIV among MSM in Portugal*

In Portugal, gay and other MSM never were, based on surveillance figures, the major driver of the epidemic. However, like in other western countries since the beginning of the epidemic in 1981, when the first cases were described in previously healthy gay men in the United States (117), MSM have been a key population at higher risk for HIV infection.

Overall, the available data for 2018 suggest that the risk of HIV acquisition among gay and other MSM was 22 times higher than among all adult men (11). Likewise, the risk of HIV for PWID was 22 times higher than for people who do not inject drugs, and 21 and 12 times higher for sex workers and transgender people, respectively, compared to adults aged 15–49 years (11).

In Portugal, previous estimates among patients attending an STI clinic in Lisbon in 2004 highlighted that gay and other MSM had an approximately 3 times higher proportion of HIV-positive tests than heterosexuals (17.4% vs. 5.2%) (118). More recent studies recruited MSM using diverse techniques such as snowball sampling (119), venue-based sampling (120), time-location sampling (121), and online internet surveys (80, 122). This makes comparisons difficult but allowed for the generation of estimates for HIV prevalence and uptake of primary and secondary prevention in this group, as presented in Table 3.

*Table 3: Study characteristics of five cross-sectional studies recruiting MSM in Portugal.*

| Study | The EMIS Network 2013 (122); Carvalho et al. 2013 (123); Martins et al. 2015 (124) | Gama et al. 2012 (119) | Gama et al. 2017 (120) | SIALON II 2016 (121) | The EMIS Network 2019 (80) |
|---|---|---|---|---|---|
| **Data collection period** | June-August 2010 | 2010-2011 | January-September 2011 | 2013-2014 | October 2017-January 2018 |
| **Sampling method** | Online | Snowball sampling | Venue-based sampling | Time-Location Sampling | Online |
| **Sample size (included in the analysis)** | 5391; 5187 | 1046 | 1011 | 409 | 2555 |
| **Place of data collection** | National | Lisbon | Lisbon | Lisbon | National |
| **Age** | Mean (SD): 32.3 (10.6) Median: 30 | Mean (SD): 31.9 (9.9) | 18-24: 24.5% 25-34: 43.2% 35-44: 20.4% >=45: 11.9% | Mean (SD): 37.9 (1.19) Median: 36 Min-Max: 19-76 | Median: 34 |
| **Portuguese-born** | 82.3% | 90.3% | - | 88.3% | - |
| **High-education degree** | 56.8% | 39.6% | 39.6% | 79.10% | - |
| **History of HIV testing** | 72.3% | 88.30% | 88.4% | 60.90% | - |
| **HIV-positive status** | 10.9% (among those ever tested) | 10.3% (among those ever tested) | 8.8% | 17.1% (95% CI 12.4-23.0) | 14.3% |
| **Inconsistent condom use with steady partner** | 60.3% (last 12 months) | - | 47.5% (last 12 months) | 87.5% (last 6 months) | - |
| **Inconsistent condom use with occasional partner** | 23.4% (last 12 months) | - | 18.5% (last 12 months) | 39.4% (last 6 months) | 23.9% (last 12 months) |
| **PEP use** | 1.6% | - | - | - | - |
| **PrEP use** | - | - | - | - | 1.5% |
| **Drug use associated with sex** | - | - | 356 (35.2%) | - | - |

HIV: human immunodeficiency virus; PEP: postexposure prophylaxis; PrEP: preexposure prophylaxis; SD: Standard deviation.

It was possible to estimate HIV incidence in the first longitudinal study among MSM in Portugal. Among the 804 MSM followed for a total of 893 person-years between April 2011 and February 2014 in the Lisbon Cohort of MSM, the overall HIV incidence was 2.80/100 person-years (95% CI: 1.89–4.14) (57). Predictors of HIV seroconversion included short-term contextual and behavioral changes during follow-up such as partner disclosure of HIV status, newly adopted

condomless anal sex with a steady partner, and being newly diagnosed with syphilis during follow-up. Sexual intercourse with HIV-positive men, having an HIV-positive steady partner at least once during follow-up and persistent condomless anal sex with occasional partners were also predictors of seroconversion (57). This study showed the high HIV incidence among MSM in Portugal, even compared with other European settings (125-127), and confirmed the need for tailored responses *to MSM in Portugal*.

### *1.3.2 Tailored responses to MSM in Portugal*

Community-based HIV testing and counseling approaches have been developed that target specific population groups at higher risk and involve community stakeholders as peer-counselor and key informants (128). In Portugal, the first community-based voluntary HIV counseling and testing (CBVCT) center opened in 2011 in Lisbon, specifically targeted at MSM and delivered in a peer-based approach (129). CheckpointLX led the way for wider implementation of community-based HIV testing in Portugal, where now several similar CBVCT centers exist targeting specific key populations, such as people who use drugs (PWUD), commercial sex workers (CSW), migrants, transgender people. More recently, in 2016, one other CBVCT opened in Northern Portugal also targeted at MSM.

These are privileged settings for capturing HIV trends and behavioral changes among MSM, as for instance, the early uptake of PrEP and also for prospective research on the incidence and drivers of the HIV epidemic, which can be used to inform preventive strategies.

## 2. OBJECTIVES

The overarching aim of this thesis was to provide evidence to understand PrEP eligibility and uptake in the Portuguese setting by addressing the population of men who have sex with men that participate in the Lisbon Cohort of MSM.

We used cross-sectional and prospective data from the cohort of HIV-negative MSM recruited while testing at CheckpointLX – a community-based HIV voluntary counseling and testing center in Lisbon, to provide answers to the following objectives (Figure 16):

1. To describe the assembling of Lisbon Cohort of MSM (Paper I);

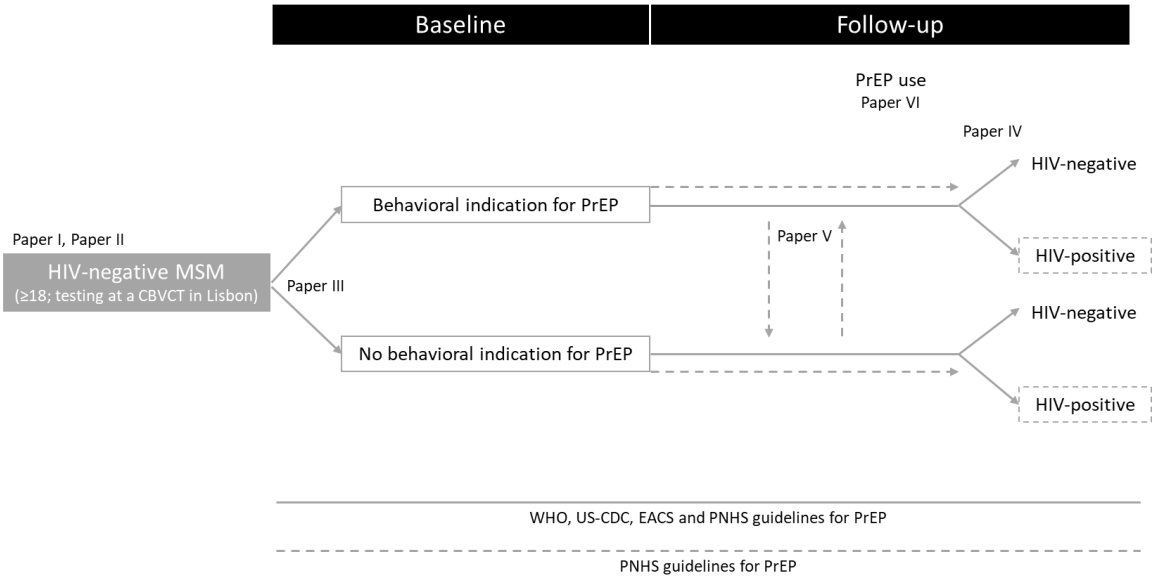
2. To raise awareness for PrEP relevance in the Portuguese setting (Paper II);

3. To estimate the proportion of MSM eligible for PrEP using different international and national guidelines as a screening tools [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)] (Paper III);

4. To provide real-world evidence of the ability of different guidelines in predicting HIV seroconversion by comparing HIV incidence according to their eligibility criteria for PrEP [WHO, US-CDC, the EACS, and the PNHS] and measuring the association between guideline-specific eligibility and seroconversion (Paper IV);

5. To describe the transitions between PrEP eligibility states and the transition from these states to HIV infection, and to estimate the intensity and probability of those transitions (Paper V);

6. To assess the time-trends in the uptake of PrEP comparing the period before and after PrEP implementation in Portugal, to compare PrEP users with non-users and, among users, to compare those who started before and after PrEP implementation (Paper VI).




CBVCT: community-based voluntary counseling and testing center; EACS: European AIDS Clinical Society; HIV: human immunodeficiency virus; MSM: men who have sex with men; PNHS: Portuguese National Health Service; PrEP: preexposure prophylaxis; US-CDC: United States, Centers for Disease Control and Prevention; WHO: World Health Organization.

*Figure 16: Scheme of the objectives presented in this work.*

## 3. METHODS AND PARTICIPANTS

### 3.1 Study setting

CheckpointLX was launched as a CBVCT center in Lisbon. It was a longtime cherished project of GAT Portugal – *Grupo de Ativistas em Tratamentos* (GAT), a Portuguese non-governmental organization (NGO) advocating legal and political changes for a positive effect on the rights and quality of life of people living with HIV, or those most at risk (129, 130) which was finally supported by the official health structures. CheckpointLX and GAT have an active and open-minded position as a community-based and activist organization that voices the importance of bringing together science, training, advocacy, and high-quality services that follow the evidence and best practices. GAT's projects, including CheckpointLX, have been highlighted and recognized by the WHO and European entities as good practices (131-134).

Currently, CheckpointLX offers multiple sexual health services such as point-of-care testing for HIV, Syphilis, viral hepatitis B and C, and runs a STI clinic called "Checklist". Pretest and posttest counseling are offered at every visit, in an opt-out strategy. Rapid testing sessions at CheckpointLX are anonymous (or confidential, in case users opt to disclose their identity) and free of charge (129). The service is purposely directed at MSM, and all procedures are delivered by peers – whether peer community health workers[3] (CHW) or peer health professionals; the latter are mostly allocated to the STI clinic (129). CheckpointLX also provides a referral to the public hospital with an HIV or infectious diseases department most convenient to its users. Although the center is directed to MSM, it also receives anyone seeking their services. These, although more limited than those available for MSM, include rapid testing for HIV pre- and posttest counseling, condoms and lubricant provision, and referrals to the appropriate specialized services.

The opening of CheckpointLX led to prolonged discussions regarding the ability of the national law to accommodate for community-based HIV testing outside formal health structures. This important debate allowed to change national practices and brought community responses, so much needed, closer to the community. As a consequence, similar CBVCT centers were opened directed specifically at other key populations. CheckpointLX is also part of the Portuguese Community Screening Network – a network of 27 CBVCT structures from 18 NGOs targeting

[3] CHWs were defined as "people who provide sexual health and other health-related support (whether being paid or unpaid) to gay, bisexual and other MSM. A CHW may deliver health promotion and/or public health activities outside of formal health settings. They may be members of, or connected to, the communities they serve (peers)." (Lorente N et al. European Community Health Worker Online Survey Report. Edited by CEEISCAT, Barcelona, 2019. Publications Office of the European Union, Luxembourg, 2019)

MSM, transgender people, PWUD, CSW, and migrants, offering tailored prevention and detection of HIV, viral hepatitis B, and C and Syphilis and supporting them to access diagnosis, treatment or prophylaxis in the Portuguese NHS (134-136).

CheckpointLX is located at a Lesbian Gay Bisexual Transgender socializing quarter promoting walk-ins (Figure 17); it is publicized in MSM socializing sites such as bars, discos, saunas, sex shops, and guesthouses, at parties and events of the gay community, at cruising areas and online social networks. Promotion materials include flyers, videos, stickers, banners at online social networks, and prevention kits containing condoms, lubricant, and an information card about CheckpointLX. CheckpointLX is also usually present at the Gay Parades in Lisbon (Figure 18).

*Figure 17: CheckpointLX front-shop and facilities by Lucas Moura.*


*Figure 18: CheckpointLX staff at the Lisbon Gay Parade in 2017 advocating for PrEP delivery at community-based HIV testing centers, by Luís Costa.*

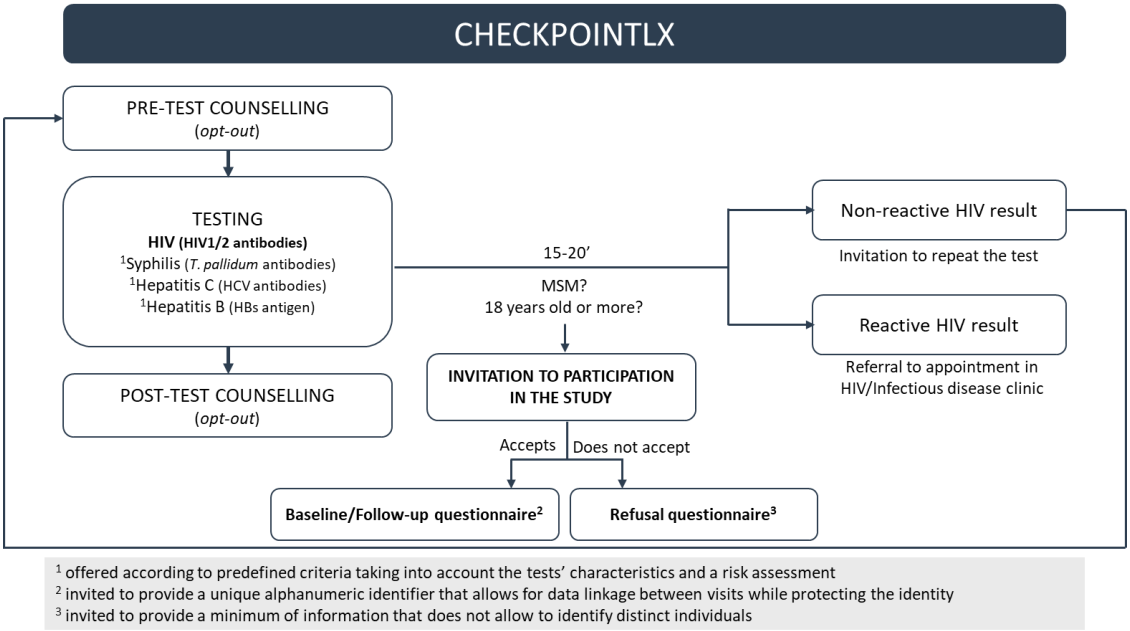
The Lisbon Cohort of Men who have Sex with Men was designed taking CheckpointLX as the recruitment base and following its privileged anchorage in the community. It is a joint project of GAT and the Institute of Public Health of the University of Porto (ISPUP). The cohort was implemented at the same time as CheckpointLX and started recruiting the day the center opened its activity in April 2011 (Figure 19). These initiatives were a response to the rising HIV prevalence among MSM in Portugal, to the limited targeted health promotion on HIV/AIDS, and the barriers in access including high levels of stigma and concerns over confidentiality (132) (Paper I). Recruitment and data collection takes place at CheckpointLX by their peer CHWs, while ISPUP provides scientific support, data management, and analysis. All institutions were involved in the design and implementation of the cohort protocol and share the commitment to the follow-up of cohort participants and the dissemination and evaluation of research outputs (Paper I). All institutions are equally represented at the Lisbon Cohort of MSM Executive Committee.

*Figure 19: Upper side: CheckpointLX staff and the Minister of Health at the opening of CheckpointLX in April 2011, by João Pádua. From left to right: Ricardo Fuertes, Hugo Machado, João Brito, Júlio Esteves, Luís Mendão, Ana Jorge, Maria José Campos, Ricardo Abrantes, Nuno Pinto. Lower side: Opening of CheckpointLX in April 2011, by João Pádua. From left to right: Luís Mendão (President of GAT); Ana Jorge (Minister of Health), and Henrique Barros (President of ISPUP)*

The Lisbon Cohort of MSM is an ongoing observational study designed as an open, prospective, and noninterval cohort (Paper I). Eligibility criteria to be enrolled in the cohort study are being a cisgender man, aged 18 or more, regardless of nationality or residence, having had sex with

men, and having an HIV-negative test result at enrollment (Paper I). The main objectives of the cohort, a major research structure for life-sciences and social-sciences, are: on a first stage, to quantify the frequency of the disease by estimating the incidence of HIV infection among MSM, and monitoring trends in primary (for instance, condom use) and secondary prevention (early detection); and, in a later stage, to identify strategies to improve the provision of HIV testing and linkage to care (Paper I).

A scheme of enrollment in the cohort study is presented in Figure 20.




[1] offered according to predefined criteria taking into account the tests' characteristics and a risk assessment
[2] invited to provide a unique alphanumeric identifier that allows for data linkage between visits while protecting the identity
[3] invited to provide a minimum of information that does not allow to identify distinct individuals

*Figure 20. Scheme of enrollment in the Lisbon Cohort of MSM.*

Eligibility for the cohort, as well as the tests to be proposed, are assessed during the pretest counseling using a short screening form (Annex 1). Then, the tests are performed and, while waiting for results, if it is the first visit to CheckpointLX, eligible users (before testing results, i.e., MSM, aged 18 or older) are presented all information about the study and are invited to enter the cohort. Those who accept to participate are asked to provide informed consent and are administered a baseline questionnaire in a face-to-face interview. In subsequent visits, also while waiting for the test results, CHWs assess whether the individual has been enrolled in the cohort previously. If yes, they are given information regarding their participation in the study and are asked to provide additional informed consent. Then the peer CHW administers the follow-up questionnaire. Most participants remember being part of the cohort. However, if someone does not remember, the peer CHW gives some external cues. If someone has refused to participate in their first or earlier visits but accepts to participate in any subsequent visit, he is enrolled in the cohort and fills a baseline questionnaire. Those who refuse to participate in any visit are asked to provide a limited set of information as part of the refusal questionnaire.

Those with a non-reactive HIV test result are invited to come back for a follow-up visit in the context of the cohort study. Timing to the next visit is proposed tailored to the risk assessed during the testing session; it can be 30 days, three, or six months later. However, no fixed time between visits is established, and participants can return whenever they want, mostly responding to their self-perception of risk. At each visit, users undergo a similar process. Those with a reactive HIV test are offered referral and an appointment at a public hospital with an HIV or infectious diseases department, respecting their geographical or any other personal convenience. Participants diagnosed with HIV are no longer eligible for follow-up at the Lisbon Cohort of MSM, and in fact, for the time being, are not subjected to any follow-up in the context of CheckpointLX.

## 3.2 Study procedures

Participation in the cohort involves a face-to-face interview with the peer CHW comprising a structured questionnaire and an HIV test. Other rapid tests, for syphilis, viral hepatitis B and C are also offered according to an individual risk assessment, which is explained in detail below.

### *3.2.1 Interviews with structured questionnaires*

At each visit, a structured questionnaire is administered by the peer CHW and completed as part of the global interview. There are three types of questionnaires – one for the baseline evaluation, another one to be completed at follow-up, and one designed to obtain a limited amount of information if there is a refusal. Each questionnaire is identified using a sequential number, and participants are identified with a six-digit and four-letter unique code corresponding to their date of birth (YYMMDD) and the first two letters of their first and last names. This alphanumeric code allows the linkage of successive visits while protecting personal identity. Those who refuse participation are asked to provide a minimum of anonymous information. This option precludes to separate individuals and leave on individual test records.

The baseline and follow-up questionnaires cover the same main topics. These include:

- **Identification** (questionnaire's ID, type of questionnaire, peer CHW initials, how were they knowledgeable about CheckpointLX, participant's code, status regarding the acceptance of receiving reminders for their participation);
- **Sociodemographic characteristics** (age, gender, country of residence, country of birth, year of arrival to the country of residence, level of education, employment status);
- **HIV testing** (previous HIV testing and information about the test result, reasons for not testing or not having the HIV test result, number of previous HIV tests, place, date, and

results of the last HIV test, reasons for the index test, previous testing at CheckpointLX, number and date of last test at CheckpointLX);

- **Sexual life and partners** (sexual orientation, history of sexual or physical abuse due to sexual orientation, anal sex with a man, age at first anal sex, role in anal sex, characteristics of sexual partners and those with whom condomless sex occurred, time since last risk situation for HIV);
    - **Steady partner** (number of steady partners, date of the relationship beginning, steady partners' gender, HIV status, uptake of antiretrovirals and last viral load of the HIV-positive steady partner, sexual practices with steady partners, condom use at last anal sex and frequency of condom use at anal sex);
    - **Occasional partner** (sex in exchange for money, goods or drugs, number of occasional partners with whom anal sex occurred, perceived HIV status and viral load of occasional partners, sexual practices with occasional partners, condom use at last anal sex and frequency of condom use at anal sex, usual places to meet occasional partners);
- **Condom use** (reasons for condomless anal sex, lubricant use during anal sex and type);
- **Use of alcohol and drugs** (alcohol or drugs consumption, time since last consumption of alcohol or drugs by type of substance[4], sex under the influence of alcohol or drugs by type of substance, injection of substances, and date of the last injection),
- **Postexposure prophylaxis** (knowledge about PEP, use of PEP, being denied PEP);
- **Preexposure prophylaxis** (knowledge about PrEP, use of PrEP, the regimen of PrEP, date of beginning and end of PrEP for each regimen, means of obtaining PrEP, willingness to use PrEP, places of preference for PrEP delivery, main reasons for not willing to use PrEP);
- **Sexually transmitted infections and viral hepatitis** (history of symptoms[5], history of STI diagnosis, ever been tested for an STI or viral hepatitis[6], usual frequency of STI or viral hepatitis testing, knowledge about any health problem concerning the MSM community).
- **Syphilis testing** (test result, referral, and place of referral, reasons for not being tested);
- **Hepatitis C testing** (test result, referral, and place of referral, reasons for not being tested);
- **Hepatitis B testing** (test result, referral, and place of referral, reasons for not being tested);
- **HIV testing** (test result, referral, and place of referral);

[4] Alcohol; Cannabis; Smart-shop substances; Cocaine; Ecstasy; Poppers; Viagra, Cialis (or similar); Amphetamines; Lysergic acid diethylamide (LSD); gamma-hydroxybutyric Acid (GHB); Ketamine; Heroin; Methadone; Mephedrone; Methamphetamines; Others.

[5] Burning sensation when urinating; Discharge; Lesions; Warts; Other.

[6] Syphilis; Chlamydia; Genital herpes; Gonorrhea; Condylomas or genital warts; Trichomonas; Lymphogranuloma venereum; Human papillomavirus; Other (including Hepatitis A virus, Hepatitis B virus, Hepatitis C virus)

At the baseline questionnaire, information is asked regarding the lifetime and the past 12 months, while at the follow-up questionnaire, information is asked regarding the period between visits. There are some questions only asked at the baseline visit, such as sexual orientation or usual places to meet occasional partners, as the follow-up questionnaire is intended to be shorter and to update information that is likely to change. Refusal forms collect what was considered to be the minimum of sociodemographic and behavioral information that could allow us to compare participants and non-participants.

From 2011 to 2017 the questionnaire was revised three times, to include or rephrase questions, in order to answer the specific objectives of the cohort, and because of the inclusion of the Lisbon Cohort of MSM in the COBA-cohort study – a prospective cohort of HIV-negative MSM, attending community-based HIV testing services in five European countries (137) and the need to harmonize questionnaires. The current English translated version of the questionnaire is available as Annex 2.

A paper and pen questionnaire was used from inception to March 2014. These questionnaires were periodically sent to ISPUP where they were processed into a computer-based data management system, and where data were stored and analyzed. Since March 2014, the questionnaires are computer-assisted, available through Limesurvey, an online tool made available by the University of Porto. Data are stored in the University of Porto servers and are periodically downloaded for storage into the main dataset.

### *3.2.2 Rapid testing*

**HIV**

Rapid testing for HIV-1 and HIV-2 is performed at each visit by the same peer CHW who conducts the interview. From April 2011 to April 2012, the third-generation test Retrocheck HIV (QUALPRO DIAGNOSTICS; manufacturer reported sensitivity=100.00% and specificity=99.75%) was used. Then, the Alere Determine HIV-1/2 (Alere Medical Co Ltd.; manufacturer reported sensitivity=100.00% and specificity=100.00%) was used up to October 2016 and again from November 2017 to April 2018. The Alere Determine, HIV-1/2 Ag/Ab Combo fourth-generation test (Alere Medical Co Ltd.; manufacturer reported HIV-1 sensitivity=99.90%; HIV-2 sensitivity=100.00%; overall specificity=99.80%) was used from October 2016 to October 2017. The third-generation test INSTI® HIV-1/HIV-2 Rapid Antibody Test (bioLytical Laboratories; manufacturer reported sensitivity=99.6% and specificity 99.3%) was used from April 2018 to December 2018. Since then, the Anti-HIV 1/2 Rapid Test (Turklab Tibbi Malzemeler San. Tic. A.S;

manufacturer reported sensitivity=100% and specificity=100%) is used. All tests used capillary (fingerstick) whole blood samples.

**Syphilis**

Rapid testing for the detection of *Treponema pallidum* antibodies is offered to participants reporting no prior diagnosis of syphilis infection or unaware of a previous infection. The test was introduced at CheckpointLX in May 2012. From then to May 2018, the Alere Determine Syphilis TP (Alere Medical Co, Ltd.; manufacturer reported sensitivity=92.31% and specificity=100.00%) was used. From May 2018 to March 2019, the ACCU-TELL Rapid Syphilis Test Cassette (AccuBiotech Co., Ltd.; manufacturer reported relative sensitivity=>99.90%; relative specificity=99.70%) was used. Since March 2019, the NADAL Syphilis Test (Human GmbH; manufacturer reported sensitivity=99.6% and specificity=99.1%) is used. All tests used capillary (fingerstick) whole blood samples.

**Hepatitis C**

Rapid testing for detection of Hepatitis C virus (HCV) antibodies is proposed to participants reporting no prior diagnosis of Hepatitis C infection or unaware of a previous infection and reporting risk behavior for Hepatitis C. These include:

- Receptive anal sex, with internal ejaculation, with a partner with HCV or unknown status;
- Receptive or insertive anal sex in a group, without using a condom or a new condom between partners;
- Fisting, receptive or insertive, without using a glove or a new glove between partners;
- Sharing of lubricant jar at group fisting;
- Sharing material for internal rectal washing (*douching*);
- Sharing sex toys, used for anal penetration, without using a condom or new condom between partners;
- Sharing a tube, straw or banknote for snorting drugs (including poppers' bottle, if leaning against the nose);
- Sharing injecting drugs paraphernalia (including steroids' bottle);
- Having piercings or tattoos done with shared materials (at home, on the street, prison or military service);
- Hemodialysis, blood transfusions, or surgery before 1992.

The test was introduced at CheckpointLX in September 2012. From then to April 2015, the OraQuick HCV test was used (OraSure Technologies, Inc. manufacturer reported

sensitivity=99.70%, specificity=99.90%) either using oral fluid or capillary (fingerstick) whole blood samples. Since April 2015, the Info anti-HCV rapid test (Türklab; manufacturer reported sensitivity=100.00%, specificity=100.00%) is being used at capillary (fingerstick) whole blood samples.

**Hepatitis B**

Rapid tests for the detection of Hepatitis B virus (HBV) surface (HBs) antigen is proposed to unvaccinated participants, to those born in Portugal before 1991, or those who were born in a country with a prevalence higher than 2% for HBs antigen[7] (138). The test was introduced at CheckpointLX in March 2018. The Info HBsAg Rapid Test (Türklab; manufacturer reported sensitivity=100.00%, specificity=100.00%), either using capillary (fingerstick) whole blood samples, is being used.

### *3.2.3 Linkage to care and prevention*

In case of a reactive test for HIV, HCV, and HBV, an outpatient appointment is offered at a public hospital with an HIV, Infectious diseases clinic or Gastroenterology department most convenient to the participant. The appointment is usually arranged during the visit to CheckpointLX. The confirmation of diagnosis and enrollment in care, when appropriate, are supposed to occur at the hospital level. The peer CHW offers to go with the participant to the first appointment.

In case of a non-reactive test for HIV, if eligible to PrEP and after the consent, an outpatient appointment is offered at a public hospital with an HIV or infectious disease clinic.

In case of a non-reactive test for HBs antigen, a medical prescription for Hepatitis B vaccine is sent to the client's email the day after, so that the complete course for Hepatitis B vaccines can be done, free of charge, at any primary health center in the NHS (139).

In the case of a reactive syphilis test, a same-day nurse appointment is proposed, as part of the Checklist STI clinic, where the triage of syphilis stage is performed, and blood is drawn. The requisition of laboratory tests and prescription of treatment according to the triage is performed

[7] Albania, Algeria, Angola, Azerbaijan, Bangladesh, Belarus, Belize, Benin, Bhutan, Brunei Darussalam, Bulgaria, Burkina Faso, Burundi, Cambodia, Cameroon, Cape Verde, Central African Republic, China, Colombia, Congo, Côte d'Ivoire, Cyprus, Djibouti, Dominican Republic, DR Congo, Ecuador, Equatorial Guinea, Eritrea, Ethiopia, Federated States of Micronesia, Fiji, Gabon, Gambia, Georgia, Ghana, Guinea, Haiti, Italy, Jamaica, Kazakhstan, Kenya, Kiribati, Kosovo, Kyrgyzstan, Laos, Liberia, Libya, Madagascar, Malawi, Mali, Marshall Islands, Mauritania, Moldova, Mongolia, Mozambique, Myanmar, Namibia, Nauru, New Zealand, Niger, Nigeria, Niue, Oman, Pakistan, Palau, Papua New Guinea, Peru, Philippines, Romania, Russia, Rwanda, Samoa, Saudi Arabia, Senegal, Sierra Leone, Singapore, Solomon Islands, Somalia, South Africa, South Korea, South Sudan, Sri Lanka, Sudan, Suriname, Swaziland, Syria, Tahiti, Tajikistan, Tanzania, Thailand, Togo, Tonga, Tunisia, Turkey, Tuvalu, Uganda, Uzbekistan, Vanuatu, Vietnam, Yemen, Zambia, Zimbabwe

by a physician. In case of a non-reactive syphilis test, but in the presence of signs or symptoms of primary syphilis, a sexual partner diagnosed in the last 3 months, or an anonymous partner notification in the last three months, a similar same-day nurse appointment is offered, and epidemiological treatment is prescribed by the physician the day after.

#### *3.2.4 Reminders*

Participants in the cohort are asked to provide an email contact to be reminded of their participation in the cohort. The first invitation to this reminder system occurs at the baseline visit, but the contacts are confirmed, and informed consent to store this information is asked in every visit. This is also very useful in assessing the type of visit of each participant – a first or a follow-up visit, and, in case of a follow-up visit, determining the time since the previous one.

These data, together with the participant's unique code, questionnaire number, and date of visit, are stored in a separate dataset, which is located at CheckpointLX's hard drive and only accessible to peer CHWs. Reminders to participation in the cohort are tailored to what has been counseled during the testing session about the appropriate time for the next visit, which can be at 30 days, three months, or six months. The three possible scheduling options are presented in Table 4. Participants will receive their first reminder at 30 days in case of suspected window period and less than 45 days since possible exposure, at three months in case of suspected window period and more than 45 days since possible exposure, or six months later given it's the desirable time between visits.

| | 1st reminder | 2nd reminder | 3rd reminder | 4th reminder | 5th reminder |
|---|---|---|---|---|---|
| **Option 1** | 30 days | 3 months | 6 months | 7 months | 12 months |
| **Option 2** | 3 months | 6 months | 7 months | 12 months | n.a. |
| **Option 3** | 6 months | 7 months | 12 months | n.a. | n.a. |

*Table 4: Time since the previous visit according to scheduling options of reminders' system.*

### 3.3 Participants

From April 2011 to July 2019, there were 24 423 records from adult MSM in the cohort. Of those, 18 324 were of participations in the cohort – 7626 baseline visits and 10 698 follow-up visits, and 6099 were refusal registries. Figure 21 shows the type of visit according to the year and trimester.

Among the 7626 MSM aged 18 or older who accepted to participate in the cohort until the end of July 2019, 275 (3.6%) were found HIV-reactive at baseline (228 (82.9%) accepted the referral to care). The remaining 7351 were invited for follow-up, of whom 3523 (47.9%) had at least one

follow-up visit by July 2019. The median number of visits was 3 (25th percentile-75th percentile: 2-5); the maximum was 65 visits. The total time of follow-up was 9099.7 person-years.

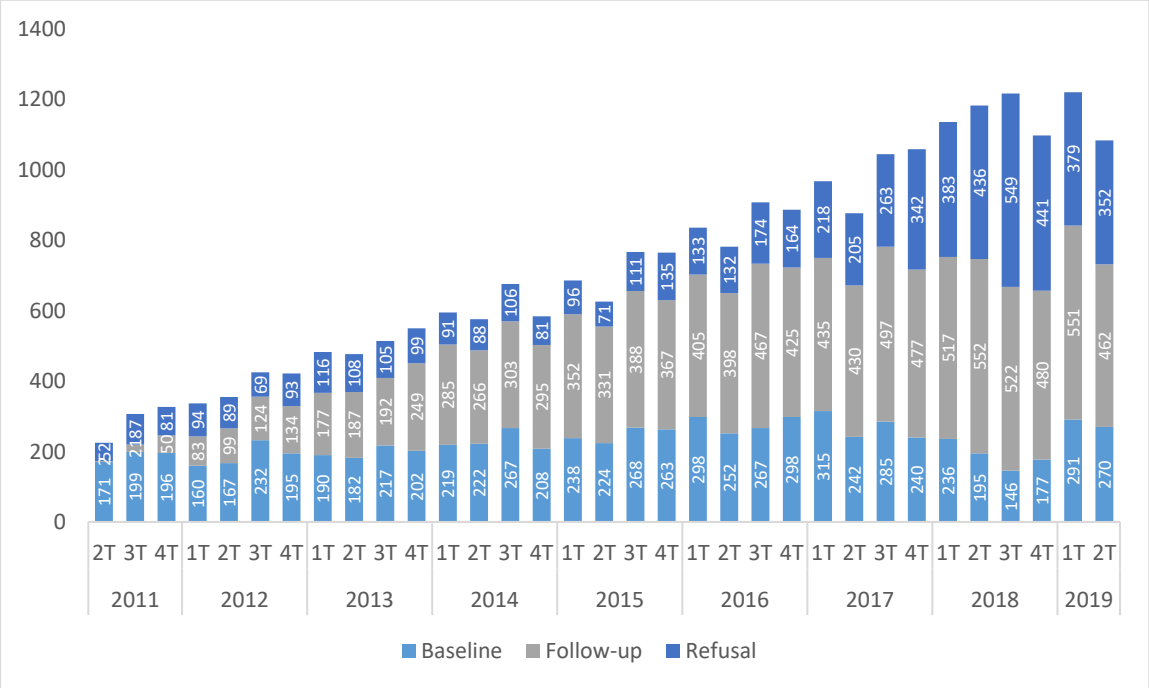



*Figure 21: Type of visit in the cohort by year and trimester.*

### 3.4 Ethics

This study was approved by the Ethics Committee for Health of São João Hospital Center and Medical School, University of Porto, in 2012 (ID 104/12). Later, two extension requests for data collection were submitted and approved (April 2013 and March 2018). Additionally, there were two amendments. The first regarding the participation and communication of data to the Work Package 5 of the EURO HIV EDAT Project (Operational knowledge to improve HIV early diagnosis and treatment among vulnerable groups in Europe) (140) in April 2016, and the second to a change to the informed consent (January 2019). The current version of the informed consent is provided as Annex 3.

The data treatment authorization from the Portuguese Data Protection Authority was received in 2013 (authorization number 3897/2013).

The Ethical Principles for Medical Research in Humans expressed in the Declaration of Helsinki are being followed (141). Those who accept to participate are asked to sign the informed consent and given a duplicate of the document at each visit. As mentioned previously, all participants with reactive results are offered a referral to a hospital in the Portuguese National Health Service, or an internal referral to Checklist, the STI clinic at CheckpointLX.

# 4. RESULTS

## 4.1 The Lisbon Cohort of men who have sex with men (Paper I)

Paula Meireles, Raquel Lucas, Ana Martins, Ana Cláudia Carvalho, Ricardo Fuertes, João Brito, Maria José Campos, Luís Mendão, Henrique Barros

*(BMJ Open 2015;5:e007220. doi:10.1136/bmjopen-2014-007220)*

BMJ Open

# The Lisbon Cohort of men who have sex with men

Paula Meireles,[1,2] Raquel Lucas,[1,2] Ana Martins,[1,2] Ana Cláudia Carvalho,[1,2] Ricardo Fuertes,[3] João Brito,[3] Maria José Campos,[3] Luís Mendão,[3] Henrique Barros[1,2]

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## ABSTRACT

**Purpose:** Newly diagnosed HIV infections among men who have sex with men (MSM) are rising in many European countries. Surveillance tools must be tailored to the current state of the epidemic, and include decentralised prospective monitoring of HIV incidence and behavioural changes in key populations. In this scenario, an open prospective cohort study was assembled—The Lisbon Cohort of MSM—aiming to dynamically monitor the frequency of disease and its predictors.

**Participants:** The Lisbon Cohort of MSM is an ongoing observational prospective study conducted at a community-based voluntary HIV counselling and testing centre in Lisbon, Portugal (CheckpointLX). Men testing negative for HIV, aged 18 or over and reporting having had sex with men are invited to follow-up visits every 6 months. At each evaluation, a face-to-face interview using a structured questionnaire is conducted, and HIV and syphilis rapid tests are performed by trained peer counsellors. From April 2011 to February 2014, 3106 MSM were eligible to the cohort of whom 923 (29.7%) did not participate. The remaining 2183 (70.3%) MSM were enrolled and 804 had at least one follow-up evaluation, for a total of 893 person-years of observation.

**Future plans:** The study findings will be disseminated in peer-reviewed journals and presented at national and international conferences. The follow-up of this cohort of HIV-negative MSM will be a valuable tool for monitoring HIV incidence in a setting where limited prospective information existed. Moreover, it will allow for a deeper analytical approach to the study of population time trends and individual changes in risk factors that currently shape the HIV epidemic among MSM.

## Strengths and limitations of this study

- Enables the dynamic monitoring of the frequency of the disease and its predictors.
- Enables the comparison of the findings with other cohorts.
- Limited representativeness of the sample.
- Selection and participation bias.
- Possible Hawthorne effect.

## INTRODUCTION

Since the beginning of the HIV/AIDS epidemic in the early 80s, gay, bisexual and other men who have sex with men (MSM) have been a core population affected by the disease, but also key contributors to the response to it.[1 2] During the past three decades, significant scientific advances and societal efforts in the fields of prevention, treatment, care and support have renewed the hope of achieving an AIDS-free generation. However, in many high-income countries where a decline in overall HIV diagnoses have been observed, a concurrent increase in the number of new cases among MSM has also been documented.[3] In the European Union/European Economic Area (EU/EEA) the largest increase in new diagnoses in the last decade was observed among young MSM, aged 20–29 years old.[4]

In Portugal, as in most EU/EEA countries, the HIV epidemic is concentrated in certain key populations, such as MSM, people who inject drugs, prisoners and commercial sex workers.[5] A large internet survey on Portuguese MSM found a prevalence of self-reported HIV infection of 10.9% among participants with a previous HIV test.[6] Although with different methodology, a previous interview survey found a very similar prevalence of 10.3% of self-reported HIV infection among participants ever tested (Gama A, 2013, personal communication).

Portuguese official surveillance data show a 9% annual increase in the number of newly diagnosed HIV cases among MSM from 2005 to 2012, while cases due to unsafe injection behaviour and heterosexual intercourse decreased by 18% and by 2%, respectively, in the same period.[7] In 2013, sex between men accounted for 42.9% of all HIV cases reported in men and 30.3% of all cases.[7] Hence, there is an urgency to establish dynamic instruments to monitor HIV

incidence and determinants in this population if, in fact, we want to succeed in the response to HIV among MSM.[1]

HIV surveillance must be tailored to the state of the epidemic in each setting, and this includes the promotion of decentralised surveillance tools that are capable of capturing HIV trends and behavioural changes in a more timely and analytical fashion than national surveillance systems, which are necessarily heavier structures with a resulting limited applicability for behavioural research.[8]

Community-based studies of MSM present great challenges, namely when it comes to defining a sampling frame,[9] due to the clear difficulty in establishing the boundaries of the target population itself because of cultural, anthropological and sociological reasons. Traditional sampling strategies designed to ensure representativeness and external validity, such as simple, random or cluster sampling, are often not efficient enough to recruit and follow MSM.[8–11] Alternative sampling techniques such as convenience sampling in community-based facilities devoted to MSM can be substantially more feasible and improve crucial attributes for the success of integrated epidemiological surveillance such as simplicity, acceptability of participants and stability.[8–12]

The Lisbon Cohort of MSM was assembled as a facility-based open prospective cohort in a community-based voluntary HIV counselling and testing service directed at MSM. The main objectives of the study are: on a first stage, to quantify the frequency of the disease by estimating the incidence of HIV infection in MSM, and monitoring trends in primary (condom use for anal intercourse (AI)) and secondary prevention (early detection); and, in a subsequent stage, to identify strategies to improve the provision of HIV testing.

## Cohort description

The Lisbon Cohort of MSM is an ongoing observational prospective study established in April 2011, designed as an open cohort. Eligible participants are MSM, aged 18 or older, regardless of nationality or residence, who voluntarily attend CheckpointLX for HIV testing and counselling, and who have a negative HIV test result at the time of recruitment.

## Setting

The cohort is a joint project of GAT Portugal (GAT) and the Institute of Public Health of the University of Porto (ISPUP). GAT is a non-governmental organisation advocating legal and political changes that can have a positive effect on the rights and quality of life of those living with HIV, or those most at risk of acquiring the infection. One of GAT's projects has materialised in CheckpointLX, where the Lisbon Cohort of MSM is recruited. CheckpointLX is a community-based centre for anonymous and free rapid HIV testing and counselling, targeted at MSM, and provided by trained peer MSM counsellors. ISPUP is an advanced training and research institution in the Public Health domain. With respect to the cohort study, CheckpointLX is responsible for recruitment and data collection, while ISPUP provides scientific support, data management and analysis. Both institutions were involved in the design and implementation of the cohort protocol, and both have established an official partnership to guarantee a shared commitment to the follow-up of cohort participants, and to the periodic dissemination and evaluation of research outputs.

## Ethics

The collected data are confidential, and the participants give their written informed consent prior to inclusion. Furthermore, in accordance with the ethical guidelines for surveillance in populations at higher risk for HIV, the Lisbon Cohort of MSM offers all participants: timely results, information about HIV and AIDS, counselling on HIV prevention and with regard to other health or social needs, linkage to treatment, and care to the extent possible with local resources and protocols with health services for referrals.[9]

## Funding

From April 2011 to March 2014, there was no specific funding for this study. All direct costs with human resources and materials were supported through CheckpointLX as part of its daily activity. Since April 2014, additional specific funding has been obtained as part of the European Commission DG SANCO—Health and Consumers funded Euro HIV EDAT project (grant number 20131101). From inception, ISPUP has provided pro bono contribution through the allocation of research staff time and information technology support (programming, software and hardware) to the project.

## Recruitment and follow-up of participants

Recruitment is generally made on the first visit to CheckpointLX, where peer counsellors invite all eligible individuals to enter the cohort. Eligibility criteria for entering the cohort are being a male aged 18 or over, regardless of nationality or residence, reporting having had sex with other men and having a HIV-negative test result. CheckpointLX is publicised in MSM socialising sites such as bars, discos, saunas, sex shops and guesthouses, parties and events of the gay community, cruising areas and online social networks. The centre itself, since it is located at a Lesbian Gay Bisexual Transgender socialising quarter, promotes walk-ins. Promotional materials include flyers, videos, stickers, banners at online social networks and prevention kits containing condoms, lubricant and an information card about CheckpointLX.

Follow-up is intended to take place at intervals of 6 months, although the exact time between visits is adjusted according to the convenience of the participant. Men who leave their contact details are invited to come back for follow-up visits through text messages or

email from CheckpointLX staff. All the remaining participants are interviewed and tested for HIV whenever they decide to appear again for testing. Repeat visits are identified by asking if the individual has already been invited to enter the cohort. Most participants do not have trouble remembering if they are part of the cohort. However, if someone does not remember being enrolled in the cohort, the peer counsellor usually gives him some external cues.

End points for follow-up are the acquisition of HIV infection or death. Recruitment began almost 3 years ago; since then, we have followed 804 participants for a total of 893 person-years. Median time between visits was 208 days (approximately 7 months) and 25th–75th centiles were 148–308 days (approximately 5–10 months).

## Study procedures

### Questionnaire

At each visit, a face-to-face interview is performed by a trained CheckpointLX peer counsellor and data are recorded using a structured questionnaire. The questionnaire applied at cohort entry is divided into the following sections: sociodemographic characteristics, HIV testing history, sexual life and partners, condom use, use of alcohol and drugs, postexposure prophylaxis (PEP) and other sexually transmitted infections (STIs). Follow-up questionnaires update time-varying information on all sections. The questionnaire is provided as an online supplementary file; detailed content is presented in table 1.

Information is collected from those eligible MSM who decline to participate but agree to provide some baseline data, concerning age, gender, country of origin, educational level, HIV testing history, date and result of previous HIV test, sexual identity, screening for HIV and syphilis at the index visit to CheckpointLX, and reasons for declining participation. Questionnaires are identified through a sequential number, and each participant is identified with a six-digit and four-letter unique code corresponding to their date of birth (YYMMDD), and the first two letters of their first and last names, which allows for data linkage during follow-up while protecting personal identity.[9] Periodically, questionnaires are sent to ISPUP where they are processed into a computer-based data management system, and where data are stored and analysed.

### Rapid HIV testing

Rapid testing for HIV-1 and HIV-2 is performed at each visit by the same peer counsellor who conducts the interview. From April 2011 to April 2012, two rapid tests were used, namely the *Retrocheck HIV* (QUALPRO DIAGNOSTICS, Goa, India; manufacturer reported sensitivity=100.00% and specificity=99.75%) *and Hexagon HIV* (Human GmbH, Wiesbaden, Germany; manufacturer reported sensitivity=100.00% and specificity=99.50%). Since then, only the Alere Determine HIV-1/2 (Alere Medical Co, Ltd, Chiba, Japan; manufacturer reported sensitivity=100.00% and specificity=100.0%, although some studies refer lower specificity[13 14]) has been used according to the instructions provided by the manufacturer. In case of a reactive test, an outpatient appointment is scheduled for every participant that accepts it at the HIV/Infectious diseases clinic at Santo António dos Capuchos Hospital in Lisbon, where a confirmatory test is performed. The peer counsellor offers to accompany the participant to that appointment. Pretest and post-test counselling is offered at every visit.

### Syphilis rapid testing

Rapid testing for detection of *Treponema pallidum* antibodies is proposed to every individual who reports with no prior history of syphilis infection or who is unaware of a previous infection; in this instance the *Alere Determine Syphilis TP* (Alere Medical Co, Ltd, Chiba, Japan; manufacturer reported sensitivity=92.31% and specificity=100.00%) is used according to the instructions provided by the manufacturer. In the case of a reactive test, a medical appointment is proposed and scheduled at CheckpointLX as part of the Checklist STI clinic, where a confirmatory test is performed and treatment is prescribed, if needed.

## Statistical procedures

Characteristics of participants at cohort entry were described using absolute and relative frequencies in the case of categorical variables. Medians and percentiles, 25 and 75 (P25-P75), were used to describe continuous variables. Comparisons between groups were performed using the $\chi^2$ test or Fisher's exact test when variables were categorical. For continuous variables the Mann-Whitney test was used. In data analysis, all possible answer categories are described, but the missing answers are excluded from the denominator of proportions for each item since no information at all was provided. This is due to the fact that the question was not asked or not recorded in the questionnaire form. The 'rather not say' answers were included in the denominator since they provide valid information reported by the participants.

## Characteristics of enrolled population between April 2011 and February 2014

Between April 2011 and February 2014, there were 3301 potential eligible individuals, 195 (5.9%) of whom had a HIV reactive test at entry and therefore were not included in the cohort. The remaining 3106 were eligible to the cohort. Among those, 923 (29.7%) declined to participate, and 2183 (70.3%) were enrolled in the cohort. As of February 2014, 804 of the 2183 participants had been re-evaluated at least once, yielding approximately 2300 questionnaires (figure 1). The most common reasons for declining participation were having no interest in the study (25.7%), not having the time (23.5%) and not living in Portugal (18.0%). No additional information was collected on this topic.

**Table 1** Content of the questionnaire

| | Entry | Follow-up |
|---|---|---|
| 1. Sociodemographic characteristics | | |
| Date of birth | ✓ | – |
| Gender | ✓ | – |
| Country of birth | ✓ | – |
| Educational level | ✓ | ✓ |
| Employment status | ✓ | – |
| 2. HIV testing | | |
| Ever tested for HIV | ✓ | – |
| Access to HIV testing result | ✓ | – |
| Reasons for not testing or not having HIV test result | ✓ | – |
| Number of previous HIV tests | ✓ | – |
| Place, date and result of previous HIV test | ✓ | ✓ |
| Reasons for index test | ✓ | ✓ |
| 3. Sexual life and partners | | |
| Sexual identity | ✓ | ✓ |
| Age at first anal intercourse | ✓ | – |
| Role in anal intercourse | ✓ | ✓ |
| Characteristics of sexual partners in the previous 12 months/since the previous visit* | ✓ | ✓ |
| A. Steady partner | | |
| Steady partner in the previous 12 months/since the previous visit | ✓ | ✓ |
| Duration of the relationship with steady partner | ✓ | ✓ |
| Gender of steady partner | ✓ | ✓ |
| Sexual practices with steady partner | ✓ | ✓ |
| Sexual intercourse with other partners | ✓ | ✓ |
| HIV status of the steady partner | ✓ | ✓ |
| B. Occasional partner | | |
| Occasional partner in the previous 12 months/since the previous visit | ✓ | ✓ |
| Number of occasional partners in the previous 12 months/since the previous visit | ✓ | ✓ |
| Sexual practices with an occasional partner | ✓ | ✓ |
| Venues used to meet occasional partners | ✓ | ✓ |
| C. Sex work | | |
| Having sex for money or drugs in the previous 12 months/since previous visit | ✓ | ✓ |
| 4. Condom use | | |
| Condom use with a steady partner in the previous 12 months/since the previous visit | ✓ | ✓ |
| Condom use with a steady partner in the last anal intercourse | ✓ | ✓ |
| Condom use with an occasional partner in the previous 12 months/since the previous visit | ✓ | ✓ |
| Condom use with an occasional partner in the last anal intercourse | ✓ | ✓ |
| Condom use for oral sex | ✓ | ✓ |
| Reasons for not using condom | ✓ | ✓ |
| Lubricant use for anal intercourse | ✓ | ✓ |
| 5. Alcohol and drugs | | |
| Lifetime use of alcohol or drugs before or during intercourse | ✓ | – |
| Frequency of use of alcohol or drugs before or during intercourse in the previous 12 months/since the previous visit | ✓ | ✓ |
| Perception of reduction in condom use due to use of alcohol or drugs | ✓ | ✓ |
| 6. Postexposure prophylaxis | | |
| Knowledge of PEP | ✓ | – |
| Lifetime use of PEP | ✓ | – |
| Use of PEP in the previous 12 months/since the previous visit | ✓ | ✓ |
| 7. STIs and hepatitis | | |
| Lifetime history of STI (symptoms or diagnosis) | ✓ | – |
| Symptoms of STI in the previous 12 months/since the previous visit | ✓ | ✓ |
| Lifetime history of STI diagnosis | ✓ | – |
| Diagnosis of STI in the previous 12 months/since the previous visit | ✓ | ✓ |
| Immunisation status for hepatitis A and hepatitis B | ✓ | ✓ |
| Lifetime history of hepatitis virus A, B or C diagnosis | ✓ | ✓ |

*Bisexual men; men with different partners; sex workers; HIV-positive men; injecting drug users; women; trios/group sex.
PEP, postexposure prophylaxis; STI, sexually transmitted infection.

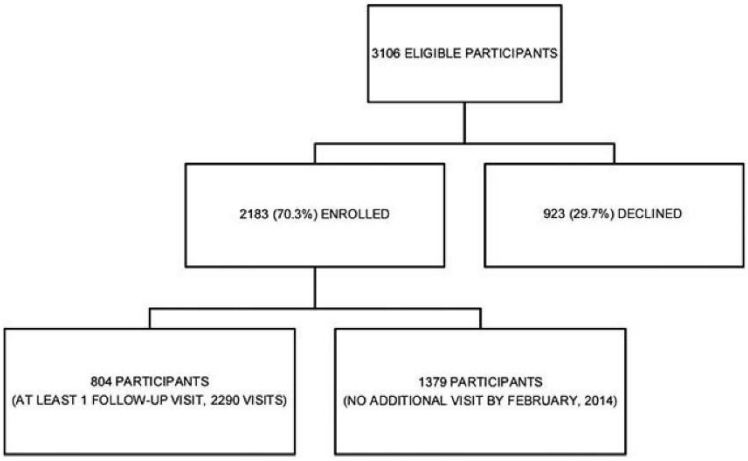


**Figure 1** Flow chart of enrolments between April 2011 and February 2014.

As summarised in table 2, there were significant differences between participants and those who declined to participate: participants self-identified more frequently as homosexual (83.9% vs 78.3%, p<0.001); participants were more frequently born in Portugal (75.7% vs 59.0%, p<0.001); and 58.1% of participants had a university degree compared with 51.4% among those who declined to participate. The proportion of individuals

**Table 2** Comparison of sociodemographic characteristics between participants in the cohort and those who declined to participate

| | Participants 2183 (70.3) | Declined to participate 923 (29.7) | p Value |
|---|---|---|---|
| Sexual identity, n (%) | | | <0.001 |
| Homosexual | 1831 (83.9) | 709 (78.3) | |
| Bisexual | 306 (14.0) | 151 (16.7) | |
| Heterosexual | 28 (1.3) | 37 (4.1) | |
| Other/did not know/rather not say | 17 (0.8) | 8 (0.9) | |
| Missing | 1 | 18 | |
| Age, median (P25-P75) | 29 (23–36) | 30 (24–38) | 0.074 |
| Country/region of origin, n (%) | | | <0.001 |
| Portugal | 1573 (75.7) | 539 (59.0) | |
| Brazil | 231 (11.1) | 160 (17.5) | |
| Other European country | 139 (6.7) | 141 (15.4) | |
| African country | 89 (4.3) | 27 (3.0) | |
| Other American country | 31 (1.5) | 30 (3.3) | |
| Asia/Middle East/Oceania | 9 (0.4) | 16 (1.8) | |
| Rather not say | 5 (0.2) | 1 (0.1) | |
| Missing | 106 | 9 | |
| Educational level, n (%) | | | <0.001 |
| Basic education or less | 78 (3.6) | 101 (11.3) | |
| Secondary education | 564 (25.9) | 288 (32.3) | |
| Professional training | 260 (11.9) | 36 (4.0) | |
| Bachelor | 896 (41.0) | 341 (38.2) | |
| Master or Doctoral | 373 (17.1) | 118 (13.2) | |
| Other/rather not say | 10 (0.5) | 9 (1.0) | |
| Missing | 2 | 30 | |
| Previous HIV testing, n (%) | | | 0.167 |
| Yes | 1650 (81.9) | 766 (83.8) | |
| No | 354 (17.6) | 145 (15.9) | |
| Did not know | 11 (0.5) | 2 (0.2) | |
| Rather not say | 0 (0.0) | 1 (0.1) | |
| Missing | 168 | 9 | |

who had a previous HIV test was similar between groups (81.9% in participants vs 83.8% in those who declined to participate).

### Characteristics of cohort participants

Median (P25-P75) number of HIV tests prior to cohort entry was 3 (2–6) and the most common reasons for the index HIV test were: to check health status/routine (81.3%), perception of exposure to HIV more than 3 months before (50.5%) and within the previous 3 months (40.7%; table 3).

**Table 3** Characteristics related with HIV testing

| HIV testing | N (%) | Missing |
|---|---|---|
| Previous HIV testing (n=2183) | | 168 |
| Yes | 1650 (81.9) | |
| No | 354 (17.6) | |
| Did not know | 11 (0.5) | |
| Rather not say | 0 (0.0) | |
| Number of previous tests, median (P25-P75) | 3 (2–6) | 31 |
| Place of last HIV test (n=1650) | | 2 |
| Public network of VCT centres (CAD) | 506 (30.7) | |
| Family doctor (National health service) | 311 (18.9) | |
| Public hospital (National health service) | 182 (11.0) | |
| Abroad | 152 (9.2) | |
| Private laboratory | 150 (9.1) | |
| Private hospital or clinic | 144 (8.7) | |
| CheckpointLX | 79 (4.8) | |
| Blood donation | 45 (2.7) | |
| Mobile unit | 28 (1.7) | |
| Other | 49 (3.0) | |
| Did not know | 2 (0.1) | |
| Reasons for index test (n=2183)* | | |
| To check health status/routine | 1736 (81.3) | 49 |
| Perception of HIV exposure more than 3 months before | 1084 (50.5) | 38 |
| Perception of HIV exposure in the previous 3 months | 884 (40.7) | 9 |
| Accident with condom use (rupture/left inside) | 183 (8.6) | 56 |
| My partner asked me to test for HIV | 158 (7.4) | 57 |
| To stop using condom with my partner | 149 (7.0) | 64 |
| Partner diagnosed HIV +/disclosed HIV+ status | 138 (6.5) | 56 |
| Possible window period by the time of the last test | 136 (6.4) | 61 |
| Symptoms/medical indication | 58 (2.7) | 61 |
| Other reason | 159 (7.3) | – |

*Percentage of participants that answered 'yes' at each option after excluding missing answers. The remaining participants answered no, did not know or rather not say.
CAD, Centro de Aconselhamento e Deteção Precoce do VIH; VCT, voluntary counselling and testing.

Median (P25-P75) age at first AI (receptive or insertive) was 18 (16–22) years, and 1409 (65.2%) men reported having a versatile role on AI, while 553 (25.6%) reported having only an insertive role and 177 (8.2%) only a receptive role. Twelve per cent reported sexual intercourse with HIV-positive men in the previous 12 months (table 4).

In the previous 12 months, 1373 (63.0%) participants had at least one steady partner, of whom 108 (7.9%) had a HIV-positive partner, 338 (24.8%) were unaware

**Table 4** Characteristics related with sexual life and partners

| Sexual life and partners | N (%) | Missing |
|---|---|---|
| Age at first anal intercourse, median (P25-P75) | 18 (16–22) | 216 |
| Role on anal intercourse | | 22 |
| Only insertive | 553 (25.6) | |
| Only receptive | 177 (8.2) | |
| Versatile | 1409 (65.2) | |
| Did not know | 2 (0.1) | |
| Rather not say | 20 (1.0) | |
| *Intercourse with at least one of the following in the previous 12 months* | | |
| Bisexual men | | 31 |
| Yes | 732 (34.0) | |
| No | 1145 (53.2) | |
| Did not know | 262 (12.2) | |
| Rather not say | 13 (0.6) | |
| Men with different sex partners | | 32 |
| Yes | 1475 (68.6) | |
| No | 491 (22.8) | |
| Did not know | 172 (8.0) | |
| Rather not say | 13 (0.6) | |
| Sex workers (even if not paid) | | 32 |
| Yes | 133 (6.2) | |
| No | 1920 (89.3) | |
| Did not know | 85 (4.0) | |
| Rather not say | 13 (0.6) | |
| HIV-positive men | | |
| Yes | 259 (12.0) | 32 |
| No | 1181 (54.9) | |
| Did not know | 698 (32.5) | |
| Rather not say | 13 (0.6) | |
| Injecting drug users | | 32 |
| Yes | 16 (0.7) | |
| No | 1958 (91.0) | |
| Did not know | 164 (7.6) | |
| Rather not say | 13 (0.6) | |
| Women | | 32 |
| Yes | 287 (13.3) | |
| No | 1851 (86.1) | |
| Did not know | 0 (0.0) | |
| Rather not say | 13 (0.6) | |
| Trios/group sex | | 33 |
| Yes | 585 (27.2) | |
| No | 1549 (72.0) | |
| Did not know | 1 (0.0) | |
| Rather not say | 15 (0.7) | |

Table 5 Characteristics related with steady partners

| Steady partner | N (%) | Missing |
|---|---|---|
| Steady partner in the previous 12 months (n=2183) | | 2 |
| Yes, one | 1254 (57.5) | |
| Yes, more than one | 119 (5.5) | |
| No | 798 (36.6) | |
| Did not know | 0 (0.0) | |
| Rather not say | 10 (0.5) | |
| HIV status of steady partner (n=1373) | | 11 |
| HIV negative | 913 (67.0) | |
| HIV positive | 108 (7.9) | |
| Did not know | 338 (24.8) | |
| Rather not say | 3 (0.2) | |
| *Condom use with steady partner* | | |
| In the last sexual encounter (n=1373) | | 70 |
| Yes | 572 (43.9) | |
| No | 718 (55.1) | |
| Did not know | 5 (0.4) | |
| Rather not say | 8 (0.6) | |
| Frequency in the previous 12 months (n=1373) | | 69 |
| Always | 364 (27.9) | |
| Often/occasionally/rarely/never | 931 (71.4) | |
| Rather not say | 9 (0.7) | |
| Frequency in the previous 12 months with HIV-positive steady partner (n=108) | | 5 |
| Always | 57 (55.3) | |
| Often/occasionally/rarely/never | 45 (43.7) | |
| Rather not say | 1 (1.0) | |
| Frequency in the previous 12 months with unknown HIV status steady partner (n=338) | | 10 |
| Always | 95 (29.0) | |
| Often/occasionally/rarely/never | 233 (71.0) | |
| Rather not say | 0 (0.0) | |

Table 6 Characteristics related with occasional partners

| Occasional partners | N (%) | Missing |
|---|---|---|
| Occasional partners in the previous 12 months (n=2183) | | 0 |
| Yes | 1860 (85.2) | |
| No | 312 (14.3) | |
| Rather not say | 11 (0.5) | |
| Number of occasional partners in the previous 12 months: median (P25-P75) (n=1860) | 4 (2–10) | 45 |
| Being paid for sex with money or drugs in the previous 12 months (n=1860) | | 1 |
| Yes | 62 (3.3) | |
| No | 1796 (96.6) | |
| Did not know | 1 (0.1) | |
| *Condom use with occasional partner* | | |
| In the last sexual encounter (n=1860) | | 124 |
| Yes | 1360 (78.3) | |
| No | 367 (21.1) | |
| Did not know | 8 (0.5) | |
| Rather not say | 1 (0.1) | |
| Frequency in the previous 12 months (n=1860) | | 123 |
| Always | 925 (53.3) | |
| Often/occasionally/rarely/never | 806 (46.4) | |
| Did not know | 2 (0.1) | |
| Rather not say | 4 (0.2) | |
| Venues used to meet occasional partners (n=1860)* | | |
| Internet | 1338 (72.2) | 8 |
| Discos and gay bars | 897 (48.4) | 7 |
| Cruising sites | 430 (23.2) | 10 |
| Saunas | 356 (19.3) | 11 |
| Gym | 232 (12.6) | 14 |
| 'Dark rooms' (including sex shops) | 129 (7.0) | 11 |
| Sex clubs | 92 (5.0) | 10 |
| Other | 445 (23.9) | – |

*Percentage of participants that answered 'yes' at each option after excluding missing answers. The remaining participants answered no, did not know or rather not say.

of their steady partner's HIV status and the remaining 913 (67.0%) stated that their steady partner was HIV-negative. More than half of the men who had at least one steady partner reported no condom use with the steady partner in the last sexual encounter (LSE) and approximately 72.0% reported inconsistent use over the previous 12 months. Among those in a serodiscordant relationship, 43.7% reported inconsistent use of condoms and that proportion was 71.0% among those unaware of their steady partner's HIV status (table 5).

Sexual intercourse with at least one occasional partner in the previous 12 months was reported by 1860 (85.2%) participants and the median (P25-P75) number of partners was 4 (2–10). Twenty-one per cent of men who had at least one occasional partner reported no condom use with an occasional partner in the LSE and 46.4% reported inconsistent use in the previous 12 months. The most referred venues where participants usually met their occasional partners were the internet (72.2%), discos and gay bars (48.4%), and cruising sites (23.2%; table 6).

Condoms were always used for oral sex by 2.3% of participants. Always using condoms for AI in lifetime was reported by 652 (32.9%) participants. Among the 1318 (66.5%) participants who reported not having always used condoms for AI, the most common reasons for engaging in unprotected AI were a steady partner (66.2%), a steady partner after testing negative for HIV (47.9%), 'reliable' persons (39.8%) and being too aroused (37.1%; table 7).

Lifetime use of alcohol (regardless of the amount) or drugs before or during intercourse was reported by 1520 (69.7%) participants, and 1262 (59.5%) reported consumption in the previous 12 months. The most frequently

Table 7 Characteristics related with condom use

| Condoms | N (%) | Missing |
|---|---|---|
| Lifetime condom use on oral sex (n=2183) | | 7 |
| Always | 49 (2.3) | |
| Often/occasionally/rarely/never | 2106 (96.8) | |
| Rather not say | 21 (1.0) | |
| Lifetime condom use on anal intercourse (n=2183) | | 202 |
| Always | 652 (32.9) | |
| Often/occasionally/rarely/never | 1318 (66.5) | |
| Rather not say | 11 (0.6) | |
| Reasons for not using condom on anal intercourse (n=1318)* | | |
| With steady partner | 870 (66.2) | 3 |
| With steady partner after testing for HIV and both were negative | 629 (47.9) | 5 |
| With a 'reliable' person | 523 (39.8) | 3 |
| Being too aroused | 487 (37.1) | 6 |
| Condom reduces pleasure | 360 (27.4) | 5 |
| With a partner who declares he is HIV negative | 303 (23.1) | 7 |
| Not having condoms at that moment | 261 (19.9) | 5 |
| If the participant has used alcohol or drugs | 226 (17.2) | 5 |
| Condom interrupts sexual intercourse | 201 (15.3) | 5 |
| Does not like using condoms | 205 (15.6) | 5 |
| Condom makes the participant lose erection | 188 (14.3) | 4 |
| With a partner who does not want to use | 124 (9.4) | 5 |
| Being in a sex venue without condoms available | 59 (4.5) | 6 |
| Condoms are expensive | 40 (3.0) | 6 |
| With a partner who declares undetectable viral load† | 19 (9.5) | 5 |
| Allergy to latex | 24 (1.8) | 6 |
| Other reasons | 77 (5.8) | – |

*Percentage of participants that answered 'yes' at each option after excluding missing answers. The remaining participants answered no, did not know or rather not say.
†Among men who have sex with men who reported sexual intercourse with HIV-positive men in the previous 12 months.

reported psychoactive substances were alcohol (57.6%), poppers (17.8%) and cannabis (15.9%; table 8).

A little over one-third of participants had heard about PEP, and 54 participants (2.7%) knew about and had used PEP (table 9).

A lifetime history of STI symptoms or diagnoses was reported by 37.1% of respondents; and 9.9% reported STI symptoms/diagnoses in the past 12 months. The most commonly reported STI in the past 12 months was gonorrhoea (2.5%), followed by syphilis (1.7%). In total, 0.5% of respondents reported a lifetime history of hepatitis C diagnosis (none of whom reported injection drug use; table 10).

## STRENGTHS AND LIMITATIONS

The Lisbon Cohort of MSM is the first Portuguese prospective study of MSM in the context of HIV incidence and testing. As an open prospective study, it will provide information on the trends of HIV infection and other STIs among MSM in Portugal, and it will contribute to identify and monitor determinants of infection, including risk-taking behaviours.

Until recently, serological and behavioural evidence relating to HIV among MSM in Portugal was scarce, apart from the necessarily succinct indicators obtained through routine national HIV surveillance. Two recent cross-sectional studies[15 16] targeting MSM in Portugal provided the first population-based estimates of self-reported prevalence among MSM with a previous HIV test: 10.9%[6] and 10.3% (Gama A, 2013, personal communication). In addition to these alarming estimates, both studies have raised important concerns regarding the future of the epidemic in Portugal supporting the need for closer monitoring of behavioural and serological indicators within a dynamic framework.

A few cohorts follow HIV-negative MSM internationally with different recruitment strategies and settings. For instance, the Amsterdam Cohort Studies (ACS) on HIV infection and AIDS, which started shortly after the first cases of AIDS had been diagnosed in the Netherlands,[17] and the Multicenter AIDS Cohort Study (MACS), initiated in 1983 in four universities in the USA;[18] both are based at formal health or academic facilities. The Omega Cohort Study in Montreal, Canada, was carried out from October 1996 to July 2003 at formal health facilities and at community organisations.[19] The Health in Men (HIM) in Sydney, Australia, was established in July 2001[20] and, recently, in 2008, The ITACA cohort–HIV negative MSM cohort study for early diagnosis of HIV and other STIs and their determinants was established in Barcelona. Both of these are community-based open cohorts.[21] These cohorts have significantly contributed to our understanding of the HIV/AIDS epidemic,

Table 8 Characteristics related with alcohol and drug use before or during intercourse

| Alcohol and drugs | N (%) | Missing |
|---|---|---|
| Lifetime use of alcohol or drugs before or during intercourse (n=2183) | | 1 |
| Yes | 1520 (69.7) | |
| No | 662 (30.3) | |
| Use of alcohol or drugs before or during intercourse in the previous 12 months (n=2183) | | 62 |
| Yes | 1262 (59.5) | |
| No | 837 (39.4) | |
| Did not know | 4 (0.2) | |
| Rather not say | 19 (0.9) | |
| Ever used alcohol or drugs before or during intercourse in the previous 12 months (n=2183)* | | |
| Alcohol | 1256 (57.6) | 4 |
| Poppers | 389 (17.8) | 2 |
| Cannabis | 329 (15.9) | 114 |
| Cocaine | 236 (10.8) | 1 |
| Ecstasy | 123 (5.6) | 3 |
| Viagra/cialis/similar | 89 (4.1) | 2 |
| Mephedrone | 76 (3.5) | 3 |
| Amphetamines | 72 (3.3) | 3 |
| GHB | 37 (1.7) | 2 |
| Ketamine | 32 (1.5) | 2 |
| LSD | 31 (1.4) | 3 |
| Heroin | 7 (0.3) | 3 |
| Methadone | 8 (0.4) | 2 |
| Others | 49 (2.2) | – |

*Percentage of participants that answered 'yes' at each option after excluding missing answers. The remaining participants answered no, did not know or rather not say.
GHB, gamma-hydroxybutyric acid; LSD, lysergic acid diethylamide.

and the HIM and ITACA cohorts, especially, will enable comparisons of their findings with those of our newly developed infrastructure. Additionally, the Lisbon Cohort of MSM has the potential to serve as a modern decentralised surveillance structure that will provide dynamic information about the frequency of the disease and its determinants in this group. Within our geographical setting, this study has the potential to enable locally adapted responses in terms of service provision, namely on the development of effective strategies to anticipate diagnosis. The cohort will also allow for comparisons of behavioural indicators drawn from entry and follow-up questionnaires within the international context, since it collects the set of indicators for behavioural surveillance among MSM defined by the European Centre for Disease Control and Prevention (ECDC).[22] Finally, a set of specific analytical research objectives will be pursued, with strong emphasis on how contextual and behavioural trajectories throughout follow-up may be used to predict the risk of seroconversion.

Table 9 Characteristics related with PEP

| PEP (n=2183) | N (%) | Missing |
|---|---|---|
| Did not know about PEP | 1228 (61.2) | 175 |
| Knows but never used | 726 (36.2) | |
| Knows and used | 54 (2.7) | |

PEP, postexposure prophylaxis.

The Lisbon Cohort of MSM has a relevant strength in the peer-based approach provided by CheckpointLX. Peer-based services attempt to promote an adequate response to MSM needs, to be non-judgemental and inclusive, which has been reported as the preference of gay and other MSM for testing services.[23] From a research point of view, we believe this approach can also help in reducing social desirability bias with regard to the information collected, and can be more cost-effective than interventions based on clinical staff.[24] Another strength of the cohort is the assurance of anonymity, which is expected to influence completeness of reporting and disclosure of risk.[9] Furthermore, CheckpointLX peer counsellors accompany newly identified HIV-positive participants to their first appointment at a HIV/Infectious disease clinic to boost linkage to care. This strategy is in common with that of other community-based centres dedicated to MSM in European countries that have shown to have high efficiency in HIV detection and linkage to care.[25 26]

The Lisbon Cohort of MSM, as a facility-based structure, is unlikely to result in a representative sample of the source MSM population, which limits the generalisability of our findings to the whole community. This is a frequent concern in studies with non-probabilistic samples, but it should not be used as an argument for not attempting to generate the best scientific evidence possible within real-world constraints. In addition, by following only MSM who actively seek HIV testing, we are arguably selecting a subgroup that might be on average at a higher risk of infection than the general MSM community. Consequently, this focuses our attention onto a priority subset of the population (even if potentially more aware than those not reached by the service). The following comparisons are useful to assess the extent of selection bias (table 11). In the 2007 National Health and Sexuality Survey (HSS),[27] which included a representative sample of the Portuguese population, 4.7% of adult male individuals reported some kind of sexual contact with other men in their lifetime, 3.0% of sexually active men had sex with men in the previous 12 months, and 0.9% reported homosexual identity. Despite the heteronormative frame still persistent in Portuguese society,[27] the proportion of men reporting sex with other men is quite similar to that estimated by Marcus *et al*, where approximately 3.0% of the adult male population living in Portugal were estimated to be MSM.[28] Men in our sample are clearly younger than in the HSS, where about 31% were less than 25 years old, whereas men who have had some kind of sexual contact

Table 10 Characteristics related with STIs

| STIs and hepatitis | N (%) | Missing |
|---|---|---|
| Lifetime history of STI (symptoms or diagnosis) (n=2183) | | 6 |
| Yes, in the previous 12 months | 216 (9.9) | |
| Yes, more than 12 months before | 593 (27.2) | |
| No | 1368 (62.8) | |
| *STI diagnosed (n=2183)* | | |
| History of gonorrhoea | | 3 |
| Yes, in the previous 12 months | 57 (2.5) | |
| Yes, more than 12 months before | 169 (7.8) | |
| No | 1946 (89.3) | |
| Did not know | 8 (0.4) | |
| History of syphilis | | 1 |
| Yes, in the previous 12 months | 38 (1.7) | |
| Yes, more than 12 months before | 116 (5.3) | |
| No | 2026 (92.9) | |
| Did not know | 2 (0.1) | |
| History of condyloma or genital warts | | 3 |
| Yes, in the previous 12 months | 68 (3.1) | |
| Yes, more than 12 months before | 22 (1.0) | |
| No | 2088 (95.6) | |
| Did not know | 2 (0.1) | |
| History of chlamydia | | 2 |
| Yes, in the previous 12 months | 64 (2.9) | |
| Yes, more than 12 months before | 14 (0.6) | |
| No | 2096 (96.1) | |
| Did not know | 7 (0.3) | |
| History of genital herpes | | 3 |
| Yes, in the previous 12 months | 4 (0.2) | |
| Yes, more than 12 months before | 21 (1.0) | |
| No | 2153 (98.8) | |
| Did not know | 2 (0.1) | |
| History of *Trichomonas* | | 1 |
| Yes, in the previous 12 months | 3 (0.1) | |
| Yes, more than 12 months before | 1 (0.0) | |
| No | 2176 (99.7) | |
| Did not know | 2 (0.1) | |
| History of lymphogranuloma venereum | | 1 |
| Yes, in the previous 12 months | 0 (0.0) | |
| Yes, more than 12 months before | 2 (0.1) | |
| No | 2178 (99.8) | |
| Did not know | 2 (0.1) | |
| *Lifetime history of hepatitis diagnosis (n=2183)* | | 12 |
| History of hepatitis A | | |
| Yes | 127 (5.8) | |
| No | 1897 (87.4) | |
| Did not know | 137 (6.3) | |
| Rather not say | 10 (0.5) | |
| History of hepatitis B | | 13 |
| Yes | 52 (2.4) | |
| No | 2002 (92.3) | |
| Did not know | 106 (4.9) | |
| Rather not say | 10 (0.5) | |
| History of hepatitis C | | 15 |
| Yes | 10 (0.5) | |
| No | 2032 (93.7) | |
| Did not know | 116 (5.4) | |
| Rather not say | 10 (0.5) | |
| *Vaccination (n=2183)* | | 8 |
| Hepatitis A | | |
| Yes | 827 (38.0) | |
| No | 742 (34.1) | |
| Did not know | 596 (27.4) | |
| Rather not say | 10 (0.5) | |
| Hepatitis B | | 6 |
| Yes | 1603 (73.6) | |
| No | 312 (14.3) | |
| Did not know | 252 (11.6) | |
| Rather not say | 10 (0.5) | |

STI, sexually transmitted infection.

Table 11 Comparison of the Lisbon Cohort of MSM with previous studies in Portugal

| | Lisbon Cohort of MSM | HSS* | EMIS Portugal† |
|---|---|---|---|
| Age | | | |
| Median (P25-P75) | 29 (23–36) | Not available | 32 (25–40) |
| Up to 24 (%) | 30.9 | 9.8 | 28.0 |
| University degree (%) | 58.1 | Not available | 61.9 |
| Self-reported homosexual identity (%) | 83.9 | 35.9 | 73.6 |
| HIV previous test (%) | 81.9 | 61.0 | 77.0 |
| Lifetime use of PEP (%) | 2.7 | Not available | 2.1 |

*Between only those men who have had some kind of sexual contact with men.
†Subanalysis of participants aged 18 years or more living in the Lisbon region.
EMIS, European men who have sex with men internet survey; HSS, Health and Sexuality Survey; MSM, men who have sex with men; PEP, postexposure prophylaxis.

with men in that age strata represent only 9.8% in the HSS. Men in the Lisbon Cohort reported more frequently of having had a previous HIV test (81.9% vs 61.0% in HSS). When compared with the European MSM internet survey results[15] from a subanalysis including only participants aged 18 or more living in the Lisbon region, men in our sample have lower median age (29 vs 32) and lower educational level (58.1% with an university degree vs 61.9%), but report homosexual identity more frequently (83.9% vs 73.6%), previous HIV test (81.9% vs 77.0%) and lifetime use of PEP (2.7% vs 2.1%).

We may assume that we are capturing men who are more self-identified as homosexual, which was expected once CheckpointLX was targeted to this group, and perhaps more aware of HIV risk as the frequency of uptake of HIV testing is higher than in the previous studies. It is important to stress that since CheckpointLX promotion strategies remained similar during follow-up, we do not expect a change in the extent of selection bias over time, which is particularly important for the estimation of secular trends of infection and behaviours in the source population.[8–10]

Participation bias is also a key methodological issue in epidemiological studies. In fact, participants in our study are more self-identified as homosexual, more frequently born in Portugal and more educated than those who declined to participate. This implies that important data may be missing on a harder to reach subset of the target population. However, it is interesting to note that the proportion of a previous HIV test is similar between groups, suggesting that both groups may have similar perceived high risk of acquiring HIV.[29 30]

Attrition is a main concern in prospective investigations; due to the fact that this is not an interval cohort with fixed follow-up times, the ability to estimate attrition in a short time frame is limited. However, efforts have been made in order to minimise dropout rates. CheckpointLX peer counsellors ask all participants to provide their email or mobile phone contact details on their first visit and to update their contact details in the follow-up assessments. These details are then used, with the consent of the participants, in order to send reminders within the month of an intended follow-up.

One other ongoing challenge is the possible behavioural modification by cohort participants due to their participation in an investigation, known as the Hawthorne effect. This aspect also relates to the dual role of CheckpointLX as a healthcare/counselling provider and research structure. Checkpoint's first priority is that appropriate and high-quality pretest and post-test information or counselling is offered, and hopefully that will produce a change towards better health empowerment, likely to influence the risk of the outcomes being studied.[31]

## COLLABORATION

We invite scientists, researchers and students from graduation or postgraduation to get involved in data collection and/or analyses, and to raise new scientific questions in the scope of the Lisbon Cohort of MSM. Requests for data analysis, presentation or publication, must be submitted to the Lisbon Cohort of MSM scientific coordination, and will require acknowledgement that Lisbon Cohort of MSM has the property of the data. Information is available at http://www.checkpointLX.com.

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**Contributors** PM drafted the manuscript and performed the descriptive data analysis. RL participated in the study design, helped draft the manuscript, participated in analysis and interpretation of data, and reviewed the manuscript for important intellectual content. AM participated in analysis and interpretation of data, and reviewed the manuscript for important intellectual content. ACC reviewed the manuscript for important intellectual content. RF and JB participated in the study design and data collection, and reviewed the manuscript for important intellectual content. MJC, LM and HB conceived the study, participated in the study design and coordination, and reviewed the manuscript for important intellectual content.

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**Ethics approval** Ethics Committee of São João Hospital and Medical School, University of Porto (ID 104/12).

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### 4.2 Urgent need for demonstration projects in Portugal to produce pre-exposure prophylaxis-related data (Paper II)

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## Urgent need for demonstration projects in Portugal to produce pre-exposure prophylaxis-related data

Dear Editor,

In Portugal, the HIV epidemic is concentrated in key populations (KP), e.g. people who inject drugs, men having sex with men (MSM) as well as male/female sex workers.[1–3] In the last decade, HIV prevention activities for KPs were implemented, such as CheckpointLX. This community-based facility in Lisbon, run by the non-governmental organization (NGO) GAT, offers, in an MSM-friendly atmosphere, free testing for HIV and other sexually transmitted infections (STIs), medical consultations, and peer counseling. Despite these initiatives, the epidemic is still uncontrolled, in particular among MSM, whose incidence rate was recently estimated at 2.8/100 person-years.[4] Consequently, Portugal urgently needs additional strategies to control HIV.

Oral pre-exposure prophylaxis (PrEP) is a prevention tool, directed at seronegative people highly exposed to HIV. Numerous clinical trials showed that the combination of antiretroviral drugs tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) protected participants who took the drugs as recommended from HIV infection, with a very high efficacy (>90%). The level of adherence was the main factor associated with PrEP efficacy.[5] PrEP is now recommended by many organizations, in the framework of a combination prevention package. As of March 2016, Truvada® has been authorized as a preventative biomedical intervention in six countries worldwide (i.e. Canada, Israel, France, South Africa, Kenya, and the United States).[6]

Despite these encouraging results, many political, legal, economic, and social issues regarding PrEP need to be better understood. The WHO encourages countries to implement trials, in particular demonstration projects, to identify how to include PrEP in real life. Each country must now identify the best strategy for the introduction and the scaling-up of PrEP.

Several PrEP initiatives have recently been launched in various cities around the world (e.g. San Francisco, Baltimore, Sao Paulo, and Amsterdam). In Europe, the Netherlands and Belgium initiated demonstration projects in 2015 (AmPREP and Be-PrEP-ared). In addition, the British PROUD study is still going on as an open-label project, offering PrEP to participants of both arms. Finally, Paris will also be launching its initiative in the next few months.

Regarding PrEP in Portugal, data are scarce. A PrEP acceptability study, conducted in Lisbon during the 2014 gay pride fair and involving 110 HIV-negative MSM, concluded that 57% of participants would be willing to take PrEP if available in Portugal and 66% would participate in a clinical trial in Portugal. Among the MSM of the Lisbon cohort (2183 individuals between 2011 and 2014), 80% were eligible for PrEP according to the Centres for Disease Control and Prevention recommendations. The country now needs a demonstration project to identify the target and the best way to deliver PrEP. Considering the role of civil society in HIV prevention, it would be essential to involve the community and community-based NGOs in this process, ensuring a good acceptability of PrEP in the community. Community-based facilities, like the CheckpointLX, would be good settings to implement a PrEP demonstration project for MSM. There is now an urgent need to produce data about PrEP in Portugal and consider the introduction of PrEP for the most at-risk seronegative people!

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**4.3 Eligibility for preexposure prophylaxis according to different guidelines in a cohort of HIV-negative men who have sex with men in Lisbon, Portugal (Paper III)**

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

Paula Meireles[1] · Michael Plankey[2] · Miguel Rocha[3,4] · Jesus Rojas[3,4] · João Brito[3,4] · Henrique Barros[1,5]



## Abstract

**Objectives** 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).

**Methods** 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.

**Results** 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.

**Conclusions** 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.

**Policy implications** These results show that both the allocation of resources and the approaches to individual risk prediction are highly dependent on the chosen guideline. Moving the focus from assessing risk to assessing whether PrEP is a suitable option for a given individual in a given moment of his life might help to overcome guidelines limitations and create more equitable access.

**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.

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

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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 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

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

| | Guideline | | | |
|---|---|---|---|---|
| Topic | 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

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 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.

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

| *Topic* | *Criteria for eligibility* | *Operational definition of eligibility* |
|---|---|---|
| WHO (2017) | | |
| Condomless anal intercourse | *Vaginal or anal sexual intercourse without a condom with more than 1 partner, or* | 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?)<br>And<br>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 | *A recent history (in the last 6 months) of an STI by laboratory testing or self-report or syndromic STI treatment, or* | 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 | *PEP for sexual exposure in the past 6 months, or* | 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 | *Sexual partner with HIV who is not taking suppressive ART* | 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?)<br>And<br>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]?)<br>And<br>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?)<br>Or<br>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 | *Any male sex partners in the past 6 months, and* | 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 | *Not in a monogamous partnership with a recently tested, HIV-negative man, and any of the following* | 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* |
|---|---|---|
| | | 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?) |
| Condomless anal intercourse | *Any anal sex without condoms (receptive or insertive) in the past 6 months, or* | 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?) |
| STI diagnosis | *Any STI diagnosed or reported in the past 6 months, or* | 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]) |
| Steady partners | *Is in an ongoing sexual relationship with an HIV-positive male partner* | 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?)<br>And<br>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]?) |
| EACS (2017) | | |
| Condomless anal intercourse | *Inconsistent condom use with casual partners, or* | 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?) |
| STI diagnosis | *Recent STI, or* | 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 | *Use of PEP, or* | Use of PEP ("yes" to the question: Have you ever used PEP?) |
| Steady partners | *Inconsistent condom use with HIV-positive partners who are not receiving treatment* | 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?)<br>And<br>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]?)<br>And |

**Table 2** (continued)

| *Topic* | *Criteria for eligibility* | *Operational definition of eligibility* |
|---|---|---|
| | | 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?)<br>And<br>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?) |
| PNHS (2018) | | |
| Condomless anal intercourse | *Persons who have had condomless sex in the past 6 months and sexual partners with unknown HIV status, or* | 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?)<br>And<br>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?) |
| Use of psychoactive substances | *People who refer to the use of psychoactive substances during sexual intercourse, or* | 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]?) |
| STI diagnosis | *Persons who have had condomless sex in the past 6 months and had a STI diagnosis, or* | 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?)<br>And<br>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 |

**Table 2** (continued)

| *Topic* | *Criteria for eligibility* | *Operational definition of eligibility* |
|---|---|---|
| | | venereum, gonorrhea, trichomoniasis, genital herpes, condyloma, or genital warts or other STI]) |
| Use of PEP | *Persons who have had condomless sex in the past 6 months and used PEP for HIV, or* | 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?)<br>And<br>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 | *People whose partner is infected with HIV, without medical care or ART or without virologic suppression and do not use condoms consistently, or* | 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?)<br>And<br>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]?)<br>And<br>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?)<br>Or<br>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?)<br>And<br>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?) |
| Sex work | *People who engage in sexual intercourse to obtain money or goods or illicit substances and do not use condoms consistently* | 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?)<br>And<br>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 |

**Table 2** (continued)

| *Topic* | *Criteria for eligibility* | *Operational definition of eligibility* |
|---|---|---|
| | | 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?) |

*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

The criteria related to having an HIV-positive sexual partner, a diagnosis of an STI, and PEP use, were less frequently met.

## 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

**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 reported 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"

(Krakower and 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) |
| *Total eligible, n (%)* | *1999 (58.9%)* | *2298 (67.7%)* | *1576 (46.5%)* | *2056 (60.6%)* |

*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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## 4.4 Different guidelines for preexposure eligibility result in different HIV risk estimates: an incidence study in a Portuguese cohort of HIV-negative men who have sex with men, 2014-2018 (Paper IV)

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*(accepted for publication in Eurosurveillance)*

The following is a post-peer-review, pre-copyedit version of the article accepted for publication in *Eurosurveillance*.

**Abstract**

**Introduction:** Guidelines for preexposure prophylaxis (PrEP) provide the criteria to identify individuals at higher risk of HIV. We compared HIV incidence according to eligibility for PrEP using four guidelines—the World Health Organization (WHO), the US Public Health Service and Centers for Disease Control and Prevention, the European AIDS Clinical Society (EACS), and the Portuguese National Health Service (PNHS) —and measured the association between guideline-specific eligibility and HIV seroconversion.

**Methods:** We studied 1254 participants from the Lisbon Cohort of men who have sex with men with at least two visits from March 2014 to March 2018, corresponding to 1724.54 person-years (PY) of follow-up. We calculated incidence rates (IRs) according to each guideline eligibility definition and incident rate ratios (IRRs) to test the association between eligibility at baseline and HIV seroconversion.

**Results:** We found 28 incident cases, of whom those defined as eligible at baseline varied from 60.7% (EACS) to 85.7% (PNHS). Being found eligible by any guideline was associated with an increased HIV incidence. However, the IR was higher among those defined as eligible according to the PNHS guidelines (2.46/100 PY; IRR: 4.61 [95% CI: 1.60-13.27]), and lowest among those defined considering the WHO guidelines (1.89/100 PY; IRR: 1.52 [95% CI: 0.69-3.35]).

**Conclusions:** Being identified as eligible for PrEP was associated with a higher risk of getting infected, the magnitude of the risk varying according to the guideline used. However, the number of HIV infections identified among ineligible participants highlights the potential for missing people who need PrEP and the need to improve guidelines' performance.

**Keywords:** HIV; incidence; preexposure prophylaxis; men who have sex with men; eligibility

**Introduction**

The current prevention armamentarium for human immunodeficiency virus (HIV) has several effective strategies—such as treatment as prevention, medical male circumcision, condom use, behavioral change, preexposure prophylaxis (PrEP), and postexposure prophylaxis (PEP) — which, when used in combination, have the potential to reverse the epidemic.[1-3] One key aspect of a public health approach to combination prevention is the ability to identify those at higher risk correctly.[4] While some strategies are intended to reach the highest number of individuals, such as condom use, other strategies, such as PrEP, primarily target individuals at higher risk to maximize its cost-effectiveness.[5] Several screening tools and guidelines exist that help health care providers identify high-risk individuals based on HIV predictors.[6-9] However, their ability to discriminate is only moderate.[10]

PrEP is the use of antiretroviral therapy, usually tenofovir disoproxil fumarate and emtricitabine, to prevent HIV in adolescents and adults at high risk of infection, including men who have sex with men (MSM).[11-13] It was first approved by the United States (US) Food and Drug Administration in 2012, then, in 2016, by the European Medicines Agency (EMA) and is now available in several countries, including Portugal. In Portugal, PrEP is available through the National Health Service (NHS) fully reimbursed since February 2018.

PrEP has been shown to be very effective in reducing HIV incidence. The pooled relative risk reduction of randomized clinical trials conducted among MSM was estimated at 77% but highly correlated with adherence.[10] Clinical guidelines were designed to help health care professionals in the provision of PrEP by defining the eligibility criteria to identify those at higher risk.

Guidelines recommend the use of PrEP for sexually active individuals without acute or established HIV infection who are at high risk of acquiring HIV. Their specific criteria include known predictors of HIV seroconversion such as condomless anal intercourse, having an HIV-positive sexual partner who is not virally suppressed, and a diagnosis of a sexually transmitted infection. However, only some published guidelines include the number of partners, substance use, or history of PEP. This results in different proportions of eligibility in the same population by using different guidelines, as we previously showed.[14] And, we hypothesize that it may also result in different ability in predicting HIV seroconversion.

HIV incidence is expected to be higher among those eligible for PrEP. However, some studies reported an unsatisfactory sensitivity of the United States, Centers for Disease Control and Prevention (US-CDC) guidelines.[15-17] Additionally, the classification of ineligible is difficult to

ascertain because it can vary largely with time and because monitoring is more intense among those ever defined as eligible, HIV incidence is also harder to measure.

We wanted to provide real-world evidence of the ability of different international guidelines in predicting HIV seroconversion using data from a cohort of HIV-negative MSM testing at a community-based voluntary HIV counseling and testing (CBVCT) center in Lisbon, Portugal. Thus, we compared HIV incidence according to eligibility for PrEP defined by the World Health Organization (WHO), the US Public Health Service and CDC, the European AIDS Clinical Society (EACS), and the Portuguese National Health Service (PNHS) and we measured the association between guideline-specific eligibility and HIV seroconversion.

**Methods**

The Lisbon Cohort of MSM is an ongoing prospective cohort study conducted at a CBVCT in Lisbon, Portugal (CheckpointLX). A description of the cohort was provided elsewhere.[18, 19] In brief, the Lisbon Cohort of MSM is an open, noninterval, cohort of men aged 18 years or older reporting having sex with men, presenting for an HIV test at CheckpointLX, and having an HIV-negative test result at recruitment. All individuals meeting these criteria are invited to enter the cohort by CheckpointLX's peer community health workers (CHWs) at their first visit. Follow-ups occur when participants come for another HIV test; no fixed time between visits is defined. At each visit, a structured questionnaire is administered using an online form, and a rapid HIV test is performed by a trained CheckpointLX peer CHW. Pretest and posttest counseling were offered at every visit in an opt-out strategy. Recruitment started in April 2011, but data reported in this study refer to the period from March 2014 to March 2018.

***Participants and ethics***

For this study, we considered the 3713 adult MSM who presented for a first test at CheckpointLX and accepted to complete a baseline questionnaire between March 2014 to March 2018. 148 (4.0%) had an HIV reactive result and were not eligible for follow-up. Among the remaining 3565, 1347 came for at least one follow-up visit. Of those, 93 were excluded from the analysis because they reported use of PrEP (n=46), could not be classified as eligible or ineligible by one or more guidelines at baseline (n=46), of for both reasons (n=1). Thus, we analyzed 1254 participants, corresponding to a total follow-up of 1724.54 person-years (PY), with a median number of visits of 2 and a median time between visits of 7 months and 18 days.

All participants provided 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).

*Study instruments and variables*

PrEP eligibility was defined according to four different guidelines: (1) module 1 of the WHO's Implementation Tool for Preexposure Prophylaxis of HIV Infection[20]; (2) the CDC/US Public Health Service's Preexposure Prophylaxis for the Prevention of HIV Infection in the United States–2017 Update[21]; (3) the EACS' Guidelines Version 9[22]; and (4) the Portuguese clinical guidelines from the National Health Service.[23] The criteria were matched with the behavioral information collected in the Lisbon Cohort of MSM baseline questionnaire (available on request) and were operationally defined as described in Table 1. A more detailed description is available elsewhere.[14] Information regarding the previous 12 months before the baseline was used, except for the EACS criterion regarding the use of PEP, for which lifetime information was used. The EACS criterion related to chemsex, defined as "sexual intercourse under the influence of recreational drugs taken predominantly intravenously immediately before and/or during sexual contacts,"[22] and the PNHS criterion related to "persons in situations of social vulnerability that may expose them to unprotected sexual intercourse with individuals at high risk of acquiring HIV infection"[23] were not possible to compute using our collected information. Participants were defined as eligible according to each guideline when they met the respective criteria and were defined as ineligible otherwise. We excluded those with incomplete information due to missing information or having answered "rather not say" or "do not know." We also collected information on age, country birth (then categorized in regions except for Portugal and Brazil), educational level, sexual identity, history of a previous HIV test, and reasons for the index test (a list of 12 reasons is provided of which more than one reason can be chosen, for this analysis we have categorized hierarchically the reasons in terms of self-perception of risk as follows: related to symptoms, related to risk exposure, and not related to symptoms or risk exposure).

**Table 1: Operational definition of each eligibility criterion in the WHO, US-CDC, EACS, and PNHS guidelines.**

HIV testing was performed using rapid tests. A third-generation test (Alere Determine HIV-1/2, Alere Medical Co Ltd, Chiba, Japan) was used up to October 2016 and again since November 2017. A fourth-generation test (Alere Determine, HIV-1/2 Ag/Ab Combo, Alere Medical Co Ltd, Chiba, Japan) was used from October 2016 to October 2017. In case of a reactive test result, a referral was offered to the public hospital HIV/infectious diseases clinic most convenient to the participant, where a confirmatory test would be performed. Results from the confirmation of infection were not provided to CheckpointLX; however, two participants informed that their

result did not confirm. Therefore, seroconversions were defined as having a reactive result, unless the participant informed CheckpointLX that his infection did not confirm.

*Statistical analysis*

We described the participants using counts and proportions, and computed incidence rates (IRs) for participants defined as eligible and ineligible at baseline according to each guideline and by each criterion. Time at risk was computed as the period between recruitment and the most recent follow-up visit. For those MSM who seroconverted, we subtracted half of the period between the last HIV-negative test result and the HIV-positive test result. To measure the magnitude of the association between being eligible for PrEP at baseline and acquiring HIV during follow-up, we computed crude incidence rate ratios (IRRs) and respective 95% confidence intervals (CIs) using generalized linear models with Poisson regression, with the default log link and offset in the variable time at risk. Statistical analysis was computed with SPSS for Windows, version 23.0 (SPSS Inc, Chicago, IL). To evaluate guidelines' performance in identifying participants who seroconverted, we computed the sensitivity (i.e., the proportion of eligible individuals among participants who seroconverted) and the specificity (i.e., the proportion of ineligible participants among those who did not seroconvert). We also computed the number needed to treat (NNT) to prevent one HIV infection among eligible individuals under three scenarios: (1) a relative risk reduction of 97% as reported in the open-label extension of the ANRS IPERGAY study[24]; (2) a relative risk reduction of 86% as in the ANRS IPERGAY trial and PROUD study[12, 13]; and (3) a relative risk reduction of 77% as the results of a meta-analysis of randomized clinical trials among MSM.[10] We used this relative reduction to calculate the expected IR had PrEP been given to eligible individuals. Then the NNT could be computed as the reciprocal of the IR difference.

**Results**

The description of the overall sample and by HIV status at the end of follow-up is presented in Table 2. At baseline, participants had a median age of 27.1 years (25th-75th percentiles, 23.0-35.3), 965 (77.0%) were born in Portugal, and foreign-born individuals were mostly from Brazil (n=122, 9.7%) and other European countries (n=111, 8.9%). Participants who seroconverted reported more frequently than those who remained negative to have been born in Brazil (6 of 28; 21.4% vs. 116 of 1226; 9.5%) or an African country (2 of 28; 7.1% vs. 30 of 1226; 2.4%). More than 80% of participants self-identified as gay, and more than half had a higher education degree (among participants that seroconverted this percentage was less than 50%, 13 of 28). The most reported reasons for testing were related to the perception of being exposed to a risk situation

for HIV (66.6%); this proportion was higher (71.4%) among participants who seroconverted. Having a previous HIV test was reported by 958 participants (76.4%).

At baseline, 61.0% of participants were eligible for PrEP according to the WHO guidelines, 68.4% according to the US-CDC guidelines, 48.8% according to the EACS guidelines, and 60.5% according to the PNHS guidelines. Among those who acquired HIV during follow-up, the proportion of eligible participants (sensitivity) varied from 60.7% (17 of 28), according to the EACS guidelines, to 85.7% (24 of 28), according to the PNHS guidelines. The WHO and US-CDC guidelines showed a sensitivity of 67.9% (19 of 28) and 78.6% (22 of 28), respectively. The proportion of ineligible participants among those who remained HIV negative (specificity) varied from 31.8%, according to the US-CDC guidelines, to 51.5%, according to the EACS guidelines. The specificity of the WHO and PNHS guidelines were 40.0% and 39.8%, respectively (Table 2).

**Table 2: Description at baseline of the overall sample (N=1254) and by HIV status at the end of follow-up.**

Table 3 presents the results concerning HIV incidence and the association with eligibility for PrEP. During follow-up, there were 28 incident infections in a total of 1724.54 PY at risk, yielding an incidence rate of 1.62 (95% CI: 1.12-2.35) per 100 PY. More seroconversions were observed among those defined as eligible for PrEP according to the PNHS guidelines, corresponding to an HIV incidence per 100 PY of 2.46 (95% CI: 1.65-3.67). The HIV incidence among eligible participants defined according to the US-CDC guidelines was 1.96 (95% CI: 1.29-2.98), while it was 1.89 (95% CI: 1.21-2.97) according to the WHO guidelines and 2.13 (95% CI: 1.33-3.43) according to the EACS guidelines. The incidence per 100 PY among ineligible participants was 0.53 (95% CI: 0.20-1.42) according to the PNHS guidelines, 1.00 (95% CI: 0.45-2.22) according to the US-CDC, 1.25 (95% CI: 0.65-2.40) according to the WHO, and 1.19 (95% CI: 0.66-2.14) according to the EACS.

A strong association (IRR: 4.61 [95% CI: 1.60-13.27]) was found between being eligible according to the PNHS guidelines at baseline and HIV seroconversion. Being eligible according to the other guidelines was associated with a 52% increase in HIV incidence in the case of the WHO guidelines (IRR: 1.52 [95% CI 0.69-3.35]), 80% in the case of the EACS guidelines (IRR: 1.80 [95% CI: 0.84-3.84]), and 96% in the case of the US-CDC guidelines (IRR: 1.96 [95% CI: 0.80-4.85]) (Table 3). However, for all but the PNHS guidelines, the CI overlapped 1.

**Table 3: Association between eligibility for PrEP according to the WHO, US-CDC, EACS, and PNHS guidelines and HIV incidence (N=1254)**

Table 4 shows the participant's distribution by each guideline criterion; the most frequently met were those related to condom use. HIV incidence was higher among those meeting the EACS's

criterion of “Inconsistent condom use with casual partners” (IR: 2.37, 95% CI 1.45-3.87) and the PNHS criterion of “Persons who have had condomless sex in the past six months and sexual partners with unknown HIV status” (IR: 2.76, 95% CI 1.74-4.38) and the criterion of “People who refer to use of psychoactive substances during sexual intercourse” (IR: 2.49, 95% CI 1.41-4.38). These criteria also presented the highest lower bound of the confidence interval.

**Table 4: HIV incidence by criteria for eligibility for PrEP according to the WHO, US-CDC, EACS, and PNHS guidelines.**

Table 5 presents the estimates for the number needed to take PrEP for one year to avert one HIV infection, assuming different relative reductions. The lowest estimates varied from 42 to 53, with the PNHS guidelines having the lowest values across all scenarios.

**Table 5: Estimates for the expected incidence rate and number needed to treat for one year under different scenarios of relative risk reduction and eligibility defined according to the WHO, CDC, EACS, and PNHS guidelines.**

## Discussion

Using these four guidelines for PrEP, the proportion of incident cases that would be eligible for PrEP at baseline varied from 60% to more than 85%, meaning that, in the worst scenario of PrEP eligibility identification and relative reduction, at least half of the infections could have been avoided. HIV incidence was 1.62 per 100 PY; this was higher among participants defined as eligible for PrEP, independently of the guideline used, varying from 1.89 per 100 PY when the WHO guidelines were used to 2.46 per 100 PY when the PNHS guidelines were used.

The PNHS guidelines were able to identify the highest number of seroconverters (85.7%) and showed the strongest association with seroconversion (IRR: 4.61 [95% CI: 1.60-13.27]). Being eligible according to the other guidelines was also associated with an increased HIV incidence, but the magnitude of those associations was lower, and all confidence intervals included 1. Even when approximately the same number of eligible participants at baseline resulted from different guidelines, their discriminating ability was different, leading to a range of NNT varying from 42 to 69. These estimates of NNT are higher than the one estimated by the PROUD study,[13] but the baseline HIV incidence rates are very different, being much lower in this Portuguese setting. We chose to use these three scenarios to be able to provide estimates under a range of relative reductions that are mainly dependent on adherence to treatment.

These differences among guidelines can be due to the differences in the eligibility criteria and their relevance or ability to capture the drivers of HIV transmission. The predictors of HIV seroconversion in this cohort have been previously described and were similar to those found in other MSM cohorts.[18, 25-28] All these aspects were generally included in the guidelines. However, for instance, condomless anal sex with a steady partner, independent of HIV status, is

not included in the WHO and EACS guidelines and can lead to missing those MSM to whom the steady partner had not yet disclosed his HIV status (whether previously diagnosed or not). Reportedly not knowing the HIV status of the sexual partners with whom condomless sex occurred and having used psychoactive substances during sexual intercourse were included as criteria only in the PNHS guidelines, which may explain their strong association with seroconversion as both criteria have two of the highest incidence rates. These parameters should receive consideration in defining or updating guidelines for PrEP use among MSM.

A study conducted in Madrid, Spain, among MSM and transgender women (97.8% were men) recently diagnosed as having HIV, found that 86.6% had an indication for PrEP according to the national AIDS study group guidelines, a sensitivity similar to the one showed by the best operating guidelines.[29] Yet, our ability to make comparisons with previous studies is limited because most evaluated guidelines' ability to identify HIV seroconversion in the United States using the US-CDC guidelines.

Our results show that the eligibility criteria were able to identify a high number of MSM who, in fact, seroconverted. However, having as much as 39% of seroconversions among participants defined as ineligible at baseline should be highlighted. This suggests that people who do not fill the eligibility criteria may still need PrEP. However, we must acknowledge that changes in the eligibility status may have occurred during follow-up, which we have previously shown to influence seroconversion risk.[18] Nevertheless, it is important to highlight that there was a substantial number, varying according to the guideline used, of HIV seroconversions among ineligible participants. It was previously shown that the US-CDC criteria failed to identify a considerable proportion of individuals at risk for HIV,[9, 16, 17] and the same was observed in this study and for the other guidelines. Previous research also suggests that people not meeting the eligibility criteria may be at risk of HIV seroconversion.[30, 31] Having a person requesting PrEP, while not meeting the eligibility criteria, may be one of the cases.[30, 32] In line with this, the Australasian guidelines state that clinicians may deem a person at risk and recommend or consider PrEP, even though the candidate does not meet their criteria.[33] Also, changes to improve guidelines' performance in identifying HIV seroconverters among specific populations of MSM have been suggested; these were to include psychosocial components, as well as network or other population-level factors besides individual-level factors.[9, 16, 34] All these factors highlight the tension between what guidelines recommend, what clinicians think is best, and what individuals want.

Our study has limitations that need to be acknowledged. First, exposure ascertainment can lead to misclassifications for two main reasons: (1) the variables collected in questionnaires of the cohort are not exactly phrased as the criteria and (2) our analysis was grounded in behavioral risk and not on clinical eligibility, with the exception of the HIV antibody determination; therefore, there was no clinical information to assess any contraindication for PrEP, which may overestimate the expected advantages. The timing of exposure ascertainment should also be discussed. We opted to use baseline information for two main reasons: 1. we wanted to guarantee a longitudinal design, and make sure that the ascertainment of eligibility preceded the seroconversion; and 2. to be closer to a scenario in which MSM may not be at an imminent risk of HIV acquisition but seeking for PrEP (as they did for HIV testing) and are classified as eligible or not. This approach, however, does not account for changes in eligibility during follow-up and, in some cases, may be a distant predictor. Nevertheless, about 50% had only two visits and a median time between visits of 7 and a half months. Second, taking into consideration the number of seroconversions observed and the related effect on precision, estimates need to be cautiously considered. We were not able to determine eligibility according to the PNHS guidelines for the period from inception to March 2014, which was possible for the other three guidelines. When they were evaluated using the entire period, the direction and magnitude of the associations for the WHO, US-CDC, and EACS guidelines were similar to the results presented here (data provided in Supplementary Table 1). Third, external validity might be limited if the drivers of the epidemic are different in other settings and time periods. Information bias due to a high number of losses to follow-up may also influence the association between eligibility and seroconversion. Although participants with follow-up visits presented different socio-demographic characteristics at baseline from those with no follow-up in terms of country of birth, and educational level, there were no differences in the mean age, sexual orientation, previous HIV test, reasons for the index test, and eligibility for PrEP, except for the EACS guidelines(Supplementary table 2). Another source of bias to our estimates may be related to social desirability and recall of information. We aimed to reduce these by the peer-based approach provided by CheckpointLX. Nevertheless, we cannot exclude the possibility of underreporting of risk behaviors.

In conclusion, the observed number of new HIV cases and the incidence rate were highest among those defined as being eligible for PrEP according to the PNHS guidelines, suggesting their adequacy identifying MSM at high risk of HIV infection. Still, all guidelines were able to identify those at higher risk. Nonetheless, the substantial number of HIV infections among ineligible participants should highlight the potential of missing people in need of PrEP. This study

shows that further work is needed to improve the performance of guidelines or alternative approaches to assess candidacy for PrEP.

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**Table 1: Operational definition of each eligibility criterion in the WHO, US-CDC, EACS, and PNHS guidelines.**

| Guideline and criteria for eligibility [a] | Operational definition of eligibility |
|---|---|
| *WHO criteria (2017)* | |
| 1. Vaginal or anal sexual intercourse without a condom with more than one partner, or | Any anal intercourse with steady or occasional partners without a condom<br>AND<br>more than one sexual partner |
| 2. A recent history (in the last six months) of an STI by laboratory testing or self-report or syndromic STI treatment, or | Self-report of syphilis, chlamydia, lymphogranuloma venereum, gonorrhea, trichomoniasis, genital herpes, condyloma or genital warts, or other STI diagnosis |
| 3. PEP for sexual exposure in the past six months, or | Use of PEP |
| 4. Sexual partner with HIV who is not taking suppressive ART. | Anal intercourse with steady partner<br>AND<br>having at least one HIV-positive steady partner<br>AND<br>having at least one HIV-positive partner who is not taking treatment<br>OR whose HIV status is not known<br>OR<br>who had detectable or unknown viral load |
| *US-CDC criteria (2017)* | |
| 1. Any male sex partners in the past six months, and | Any anal intercourse with steady or occasional partners |
| 2. Not in a monogamous partnership with a recently tested, HIV-negative man, and any of the following | Other than men reporting only one HIV-negative male steady partner and no occasional partners |
| 3. Any anal sex without condoms (receptive or insertive) in the past six months, or | Any anal intercourse with steady or occasional partners without a condom |
| 4. Any STI diagnosed or reported in the past six months, or | Self-report of syphilis, chlamydia, lymphogranuloma venereum, gonorrhea, trichomoniasis, genital herpes, condyloma or genital warts, or other STI diagnosis |
| 5. Is in an ongoing sexual relationship with an HIV-positive male partner. | Anal intercourse with steady partner<br>AND<br>having at least one HIV-positive steady partner |
| *EACS criteria (2017)* | |
| 1. Inconsistent condom use with casual partners, or | Any anal intercourse with occasional partners without a condom |
| 2. Recent STI, or | Self-report of syphilis, chlamydia, lymphogranuloma venereum, gonorrhea, trichomoniasis, genital herpes, condyloma or genital warts, or other STI diagnosis |
| 3. Use of PEP, or | Use of PEP (lifetime) |
| 4. Inconsistent condom use with HIV-positive partners who are not receiving treatment. | Anal intercourse with steady partner<br>AND<br>having at least one HIV-positive steady partner<br>AND<br>having at least one HIV-positive partner who is not taking treatment<br>AND<br>any anal intercourse with steady partners without a condom |
| *PNHS criteria (2018)* | |
| 1. Persons who have had condomless intercourse in the past six months and sexual partners with unknown HIV status, or | Any anal intercourse with steady or occasional partners without a condom<br>AND |

| | |
|---|---|
| | having at least one sexual partner for whom the HIV status is unknown |
| 2. People who refer to the use of psychoactive substances during sexual intercourse, or | Used at least one psychoactive substance during intercourse, including cannabis, heroin, cocaine, ecstasy, amphetamines, poppers, LSD, ketamine, GHB, methadone, substances sold at smart shop, methamphetamines, mephedrone, or other |
| 3. Persons who have had condomless intercourse in the past six months and had an STI diagnosis, or | Any anal intercourse with steady or occasional partners without a condom<br>AND<br>self-report of syphilis, chlamydia, lymphogranuloma venereum, gonorrhea, trichomoniasis, genital herpes, condyloma or genital warts, or other STI diagnosis |
| 4. Persons who have had condomless intercourse in the past 6 months and used PEP for HIV, or | Any anal intercourse with steady or occasional partners without a condom<br>AND<br>use of PEP |
| 5. People whose partner is infected with HIV, without medical care or ART, or without virologic suppression and do not use condoms consistently, or | Anal intercourse with steady partner<br>AND<br>having at least one HIV-positive steady partner<br>AND<br>having at least one HIV-positive partner who is not taking treatment or whose HIV status is not known<br>OR<br>who had detectable or unknown viral load<br>AND<br>any anal intercourse with steady or occasional partners without a condom |
| 6. People who engage in sexual intercourse to obtain money or goods or illicit substances and do not use condoms consistently. | People who report having received money, goods, or drugs in exchange for sexual intercourse<br>AND<br>any anal intercourse with steady or occasional partners without a condom |

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.

**Table 2: Description at baseline of the overall sample (N=1254) and by HIV status at the end of follow-up.**

| Characteristics | Participants N=1254 | | HIV status at the end of follow-up | | | |
|---|---|---|---|---|---|---|
| | | | HIV negative n=1226 | | HIV positive n=28 | |
| **Age (years)** | | | | | | |
| Mean, SD | 30.0 | 9.34 | 30.0 | 9.39 | 29.6 | 6.99 |
| Median, 25th-75 percentile | 27.1 | 23.0-35.3 | 27.1 | 22.9 - 35.4 | 28.5 | 23.4-34.0 |
| Range | 18.0-69.0 | | 18.0-69.1 | | 19.9-43.5 | |
| **Country/region of origin, no., %** | | | | | | |
| Portugal | 965 | 77.0% | 948 | 77.3% | 17 | 60.7% |
| Brazil | 122 | 9.7% | 116 | 9.5% | 6 | 21.4% |
| Other European country | 111 | 8.9% | 108 | 8.8% | 3 | 10.7% |
| African country | 32 | 2.6% | 30 | 2.4% | 2 | 7.1% |
| Other American country | 16 | 1.3% | 16 | 1.3% | 0 | 0.0% |
| Asia / Middle east / Oceania | 8 | 0.6% | 8 | 0.7% | 0 | 0.0% |
| **Educational level, no., %** | | | | | | |
| Basic education or less | 50 | 4.0% | 50 | 4.1% | 0 | 0.0% |
| Secondary education | 428 | 34.1% | 414 | 33.8% | 14 | 50.0% |
| Professional training | 40 | 3.2% | 39 | 3.2% | 1 | 3.6% |
| Postsecondary | 14 | 1.1% | 14 | 1.1% | 0 | 0.0% |
| Bachelor | 452 | 36.0% | 442 | 36.1% | 10 | 35.7% |
| Master or doctoral | 269 | 21.5% | 266 | 21.7% | 3 | 10.7% |
| Rather not say | 1 | 0.1% | 1 | 0.1% | 0 | 0.0% |
| **Sexual identity, no., %** | | | | | | |
| Gay | 1037 | 82.7% | 1014 | 82.7% | 23 | 82.1% |
| Bisexual | 177 | 14.1% | 172 | 14.0% | 5 | 17.9% |
| Heterosexual | 12 | 1.0% | 12 | 1.0% | 0 | 0.0% |
| Other/does not use a term/does not know | 27 | 2.2% | 27 | 2.2% | 0 | 0.0% |
| Rather not say | 1 | 0.1% | 1 | 0.1% | 0 | 0.0% |
| **Previous HIV testing, no., %** | | | | | | |
| No | 296 | 23.6% | 290 | 23.7% | 6 | 21.4% |
| Yes | 958 | 76.4% | 936 | 76.3% | 22 | 78.6% |
| **Reason for the index test, no., %** | | | | | | |
| Reasons related to symptoms[a] | 76 | 6.1% | 74 | 6.0% | 2 | 7.1% |
| Reasons related to risk exposure[b] | 835 | 66.6% | 815 | 66.5% | 20 | 71.4% |
| Reasons not related to symptoms or risk exposure[c] | 333 | 26.6% | 327 | 26.7% | 6 | 21.4% |
| Missing | 10 | 0.8% | 10 | 0.8% | 0 | 0.0% |
| **Eligible for PrEP, no., %** | | | | | | |
| **WHO** | | | | | | |
| Ineligible | 489 | 39.0% | 480 | 39.2%[d] | 9 | 32.1% |
| Eligible | 765 | 61.0% | 746 | 60.8% | 19 | 67.9%[e] |
| **US-CDC** | | | | | | |
| Ineligible | 396 | 31.6% | 390 | 31.8%[d] | 6 | 21.4% |
| Eligible | 858 | 68.4% | 836 | 68.2% | 22 | 78.6%[e] |
| **EACS** | | | | | | |
| Ineligible | 642 | 51.2% | 631 | 51.5%[d] | 11 | 39.3% |
| Eligible | 612 | 48.8% | 595 | 48.5% | 17 | 60.7%[e] |
| **PNHS** | | | | | | |
| Ineligible | 495 | 39.5% | 491 | 40.0%[d] | 4 | 14.3% |
| Eligible | 759 | 60.5% | 735 | 60.0% | 24 | 85.7%[e] |

US-CDC: United States Centers for Disease Control and Prevention; EACS: European AIDS Clinical Society; HIV: human immunodeficiency virus; PNHS: Portuguese National Health Service; PrEP: preexposure prophylaxis; SD: Standard deviation; WHO: World Health Organization.

[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," "Condom failure," "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."

[d] These values represent the specificity of the guidelines.

[e] These values represent the sensitivity of the guidelines.

**Table 3: Association between eligibility for PrEP according to the WHO, US-CDC, EACS, and PNHS guidelines and HIV incidence (N=1254)**

| | HIV cases | Person-years | IR per 100 person-years (95% CI) | IRR (95% CI) |
|---|---|---|---|---|
| **Overall** | 28 | 1724.54 | 1.62 (1.12-2.35) | |
| **Eligibility for PrEP at baseline** | | | | |
| **WHO (2017)** | | | | |
| Ineligible | 9 | 720.95 | 1.25 (0.65-2.40) | Reference |
| Eligible | 19 | 1003.59 | 1.89 (1.21-2.97) | 1.52 (0.69-3.35) |
| **US-CDC (2017)** | | | | |
| Ineligible | 6 | 601.66 | 1.00 (0.45-2.22) | Reference |
| Eligible | 22 | 1122.87 | 1.96 (1.29-2.98) | 1.96 (0.80-4.85) |
| **EACS (2017)** | | | | |
| Ineligible | 11 | 928.01 | 1.19 (0.66-2.14) | Reference |
| Eligible | 17 | 796.53 | 2.13 (1.33-3.43) | 1.80 (0.84-3.84) |
| **PNHS (2018)** | | | | |
| Ineligible | 4 | 748.85 | 0.53 (0.20-1.42) | Reference |
| Eligible | 24 | 975.69 | 2.46 (1.65-3.67) | 4.61 (1.60-13.27) |

US-CDC: United States, Centers for Disease Control and Prevention; CI: confidence interval; EACS: European AIDS Clinical Society; HIV: human immunodeficiency virus; IR: incidence rate; IRR: incidence rate ratio; PNHS: Portuguese National Health Service; PrEP: preexposure prophylaxis; WHO: World Health Organization.

**Table 4: HIV incidence by criteria for eligibility for PrEP according to the WHO, US-CDC, EACS, and PNHS guidelines.**

| Guideline and criteria for eligibility [a] | Participants' distribution | HIV cases | Person-years | IR per 100 person-years (95% CI) |
|---|---|---|---|---|
| **WHO criteria (2017)** | | | | |
| 1. Vaginal or anal sexual intercourse without a condom with more than one partner | 713 (56.9) | 19 | 937.47 | 2.03 (1.29-3.18) |
| 2. A recent history (in the last six months) of an STI by laboratory testing or self-report or syndromic STI treatment | 116 (9.3) | 3 | 149.16 | 2.01 (0.65-6.24) |
| 3. PEP for sexual exposure in the past six months | 30 (2.4) | 0 | 32.88 | 0.00 (0.00-11.22) |
| 4. Sexual partner with HIV who is not taking suppressive ART | 35 (2.8) | 0 | 40.82 | 0.00 (0.00-9.04) |
| **US-CDC criteria (2017)** | | | | |
| 1. Any male sex partners in the past six months | 1214 (96.8) | 28 | 1660.12 | 1.69 (1.16-2.44) |
| 2. Not in a monogamous partnership with a recently tested, HIV-negative man | 1190 (94.9) | 28 | 1622.00 | 1.73 (1.19-2.50) |
| 3. Any anal sex without condoms (receptive or insertive) in the past six months | 862 (68.7) | 22 | 1146.50 | 1.92 (1.26-2.91) |
| 4. Any STI diagnosed or reported in the past six months | 116 (9.3) | 3 | 149.16 | 2.01 (0.65-6.24) |
| 5. Is in an ongoing sexual relationship with an HIV-positive male partner | 71 (5.7) | 0 | 78.41 | 0.00 (0.00-4.70) |
| **EACS criteria (2017)** | | | | |
| 1. Inconsistent condom use with casual partners | 517 (41.2) | 16 | 674.86 | 2.37 (1.45-3.87) |
| 2. Recent STI | 116 (9.3) | 3 | 149.16 | 2.01 (0.65-6.24) |
| 3. Use of PEP | 61 (4.9) | 0 | 59.27 | 0.00 (0.00-6.22) |
| 4. Inconsistent condom use with HIV-positive partners who are not receiving treatment | 15 (1.2) | 0 | 12.97 | 0.00 (0.00-28.44) |
| **PNHS criteria (2018)** | | | | |
| 1. Persons who have had condomless sex in the past six months and sexual partners with unknown HIV status | 524 (41.8) | 18 | 652.80 | 2.76 (1.74-4.38) |
| 2. People who engage in sexual intercourse to obtain money, goods, or illicit substances and do not use condoms consistently | 16 (1.3) | 0 | 19.53 | 0.00 (0.00-18.89) |
| 3. Persons who have had condomless sex in the past six months and had an STI diagnosis | 89 (7.1) | 3 | 112.36 | 2.67 (0.86-8.28) |
| 4. Persons who have had condomless sex in the past six months and used PEP for HIV | 25 (2.0) | 0 | 24.62 | 1.65 (1.14-2.39) |
| 5. People whose partner is infected with HIV without medical care or ART or without virologic suppression and do not use condoms consistently | 17 (1.4) | 0 | 15.08 | 0.00 (0.00-24.46) |
| 6. People who refer to the use of psychoactive substances during sexual intercourse | 368 (29.3) | 12 | 481.97 | 2.49 (1.41-4.38) |

ART: antiretroviral therapy; US-CDC: United States, Centers for Disease Control and Prevention; EACS: European AIDS Clinical Society; HIV, human immunodeficiency virus; PEP: postexposure prophylaxis; PNHS: Portuguese National Health Service; STI: sexually transmitted infection; WHO: World Health Organization.

[a] As defined in the guidelines.

**Table 5: Estimates for the expected incidence rate and number needed to treat for one year under different scenarios of relative risk reduction and eligibility defined according to the WHO, CDC, EACS, and PNHS guidelines.**

| Study | ANRS IPERGAY (open-label extension)[27] | | PROUD study[16] and ANRS IPERGAY trial[15] | | Meta-analysis of RCTs among MSM[13] | |
|---|---|---|---|---|---|---|
| **Relative risk reduction** | **0.97** | | **0.86** | | **0.77** | |
| **Guideline used** | **Expected IR per 100 person-years** | **NNT** | **Expected IR per 100 person-years** | **NNT** | **Expected IR per 100 person-years** | **NNT** |
| **WHO (2017)** | 0.057 | 54 | 0.265 | 61 | 0.435 | 69 |
| **US-CDC (2017)** | 0.059 | 53 | 0.274 | 59 | 0.451 | 66 |
| **EACS (2017)** | 0.064 | 48 | 0.299 | 54 | 0.491 | 61 |
| **PNHS (2018)** | 0.074 | 42 | 0.344 | 47 | 0.566 | 53 |

CDC: United States, Centers for Disease Control and Prevention; EACS: European AIDS Clinical Society; IR: incidence rate; MSM, men who have sex with men; NNT: number needed to treat; PNHS: Portuguese National Health Service; RCT: randomized clinical trial; WHO: World Health Organization.

**Supplementary table 1. Association between eligibility for PrEP according to the WHO, US-CDC, and EACS guidelines and HIV incidence (n=2398).**

| | HIV cases | Person-years | IR per 100 person-years (95% CI) | IRR (95% CI) |
|---|---|---|---|---|
| **Overall** | 97 | 5257.75 | 1.84 (1.51-2.25) | |
| **Eligibility for PrEP at baseline** | | | | |
| **WHO (2017)** | | | | |
| Noneligible | 32 | 2326.67 | 1.38 (0.97-1.94) | Reference |
| Eligible | 65 | 2931.08 | 2.22 (1.74-2.83) | 1.61 (1.06-2.46) |
| **US-CDC (2017)** | | | | |
| Noneligible | 22 | 1847.26 | 1.19 (0.78-1.81) | Reference |
| Eligible | 75 | 3410.49 | 2.20 (1.75-2.76) | 1.85 (1.15-2.97) |
| **EACS (2017)** | | | | |
| Noneligible | 49 | 2982.77 | 1.64 (1.24-2.17) | Reference |
| Eligible | 48 | 2274.98 | 2.11 (1.59-2.80) | 1.28 (0.86-1.91) |

US-CDC: United States, Centers for Disease Control and Prevention; CI: confidence interval; EACS: European AIDS Clinical Society; HIV: human immunodeficiency virus; IR: incidence rate; IRR: incidence rate ratio; PrEP: preexposure prophylaxis; WHO: World Health Organization.

**Supplementary table 5: Baseline characteristics of participants with and without follow-up visits among those who with complete information about the eligibility status at baseline.**

| | Participants without follow-up N=2095 | Participants with follow-up N=1254 | p-value |
|---|---|---|---|
| **Age (years)** | | | |
| Mean, SD | 30.6 (9.48) | 30.0 (9.34) | 0.063 [a] |
| Median, 25th-75 percentile | 28.7 (23.5-35.6) | 27.1 (23.0-35.3) | 0.012 [b] |
| Range | 16.2-74.4 | 18.0-69.0 | |
| **Country/region of origin, no., %** | | | 0.001 [c] |
| Portugal | 1500 (71.6%) | 965 (77.0%) | |
| Brazil | 271 (12.9%) | 122 (9.7%) | |
| Other European country | 185 (8.8%) | 111 (8.9%) | |
| African country | 56 (2.7%) | 32 (2.6%) | |
| Other American country | 48 (2.3%) | 16 (1.3%) | |
| Asia/Middle east/Oceania | 34 (1.6%) | 8 (0.6%) | |
| **Educational level, no., %** | | | 0.031 [c] |
| Basic education or less | 119 (5.7%) | 50 (4.0%) | |
| Secondary education | 656 (31.4%) | 428 (34.2%) | |
| Professional training | 51 (2.4%) | 40 (3.2%) | |
| Postsecondary | 26 (1.2%) | 14 (1.1%) | |
| Bachelor | 831 (39.7%) | 452 (36.1%) | |
| Master or doctoral | 409 (19.6%) | 269 (21.5%) | |
| Rather not say | 2 | 1 | |
| **Sexual identity, no., %** | | | 0.557 [c] |
| Gay | 1729 (82.7%) | 1037 (82.8%) | |
| Bisexual | 286 (13.7%) | 177 (14.1%) | |
| Heterosexual | 32 (1.5%) | 12 (1.0%) | |
| Other/does not use a term/does not know | 44 (2.1%) | 27 (2.2%) | |
| Rather not say | 4 | 1 | |
| **Previous HIV testing, no., %** | | | 0.996 [c] |
| No | 493 (23.5%) | 296 (23.6%) | |
| Yes | 1602 (76.5%) | 958 (76.4%) | |
| **Reason for the index test, no., %** | | | 0.215 [c] |
| Reasons related to symptoms [d] | 145 (7.0%) | 76 (6.1%) | |
| Reasons related to risk exposure [e] | 1339 (64.2%) | 835 (67.1%) | |
| Reasons not related to symptoms or risk exposure [f] | 602 (28.9%) | 333 (26.8%) | |
| Missing | 9 | 10 | |
| **Eligible for PrEP, no., %** | | | |
| **WHO** | | | 0.074 [c] |
| Ineligible | 884 (42.2%) | 489 (39%) | |
| Eligible | 1211 (57.8%) | 765 (61.0%) | |
| **US-CDC** | | | 0.645 [c] |
| Ineligible | 679 (32.4%) | 396 (31.6%) | |
| Eligible | 1416 (67.6%) | 858 (68.4%) | |
| **EACS** | | | 0.032 [c] |
| Ineligible | 1154 (55.1%) | 642 (51.2%) | |
| Eligible | 941 (44.9%) | 612 (48.8%) | |
| **PNHS** | | | 0.870 [c] |
| Ineligible | 824 (39.3%) | 495 (39.5%) | |
| Eligible | 1271 (60.7%) | 759 (60.5%) | |

[a] p-value for the t-test for independent samples

[b] p-value for the Mann-Whitney test

[c] p-value for the chi-square test

[d] Participants reported "Symptoms/medical indication."

[e] 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," "Condom failure," "Perception of recent exposure to HIV," or "Perception of exposure to HIV more than 3 months."

[f] 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."

US-CDC: United States, Centers for Disease Control and Prevention; EACS: European AIDS Clinical Society; HIV: human immunodeficiency virus; PNHS: Portuguese National Health Service; PrEP: preexposure prophylaxis; SD: Standard deviation; WHO: World Health Organization.

## 4.5 Transitions between preexposure prophylaxis eligibility states and HIV infection in a Lisbon cohort of HIV-negative Men who have Sex with Men: a multi-state model analysis (Paper V)

Paula Meireles, Carla Moreira, Miguel Rocha, Michael Plankey, Henrique Barros

**Abstract**

**Background:** Eligibility for preexposure prophylaxis (PrEP) is based on self-reported risk behaviors together with clinical data at any one moment. We aimed to describe transitions between PrEP eligibility states and HIV infection among HIV-negative Men who have Sex with Men (MSM).

**Methods:** We used data from 1177 adult MSM enrolled in the Lisbon Cohort of MSM who had at least one follow-up visit and two consecutive measurements of PrEP eligibility from March 2014 to March 2018. A time-homogeneous Markov multi-state model was applied to estimate the frequencies, intensities, and probabilities of transitions between PrEP eligibility states (eligible/ineligible) and from these to HIV infection.

**Results:** The transitions' intensities were similar for ineligible–eligible (I–E) (1.591) and eligible–ineligible (E–I) (1.493) while the transition eligible–HIV infection (E–HIV) was 22.0 times more likely than ineligible–HIV infection (I–HIV) (0.032 vs. 0.001). The transition's probabilities for 90 days were similar for the transition I–E and E–I (0.275 vs. 0.258) while the transition E–HIV was 4.4 times more likely than I–HIV (0.007 vs. 0.002). The transition probabilities increased with time; they were similar between the two eligibility states, but the ratios between the transition's probabilities to HIV infection decreased.

**Conclusions:** The transition probability E-HIV was always higher than from ineligible, but being defined as ineligible was only a short-time indicator of a lower probability of acquiring HIV. Additionally, once an individual moved to eligible, he was at a higher risk of seroconversion. Thus, this demands a timely delivery of PrEP.

**Keywords:** preexposure prophylaxis; HIV; men who have sex with men; eligibility determination; multi-state models

**Background**

Preexposure prophylaxis (PrEP), the use of antiretrovirals to prevent human immunodeficiency virus (HIV) infection, is highly effective when recommended to individuals at high risk, and adherence is high [1-4]. PrEP has been acknowledged as a much-needed additional prevention tool as evidence shows that, among men who have sex with men (MSM), the largest effects on HIV incidence are expected when PrEP is implemented in combination with test-and-treat [5-7].

In 2015, the European Centre for Disease Prevention and Control recommended that European Union Members States should consider integrating PrEP into their existing HIV prevention package for those most at-risk of HIV infection, starting with MSM [8]. Portugal approved the use of tenofovir disoproxil fumarate and emtricitabine as PrEP in 2017, and it has been provided, free of charge, in public hospitals since February 2018. The norm for PrEP use from the Portuguese Ministry of Health was issued in November 2017, and it applies to anyone at increased risk of acquiring HIV infection [9]. Increased risk was defined as 1. having had condomless sexual intercourse in the past 6 months and having had sexual partners with unknown HIV status, or having had a sexually transmitted infection diagnosis, or having used postexposure prophylaxis for HIV; or 2. referring the use of psychoactive substances during sexual intercourse; or 3. having an HIV-positive partner, without medical care or antiretroviral treatment, or without viral suppression and not using condoms consistently; 4. or engaging in sexual intercourse to obtain money or goods or illicit substances and not using condoms consistently; or 5. being in situations of social vulnerability that may expose them to unprotected sex with individuals at high risk of acquiring HIV infection [9].

Ascertainment of eligibility for PrEP is based on the report of any of the above stated behavioral information and clinical information such as the presence of any contraindication. This leads to a dichotomous classification of having or not an indication for PrEP at a given moment. However, it is known that sexual behavior, including condom use, number of partners, sexual practices, as well as life circumstances such as having a steady partner, the HIV status of sexual partners, and their suppressive status change with time [10-12]. This implies that eligibility for PrEP based on the definition of risk behaviors will also change with time. This is also supported by PrEP users' reports of intentions to switch between PrEP regimens indicating that they are aware that their risk of HIV may vary over time and that PrEP use may be adapted accordingly [13].

Considering this, we aimed to describe the transitions between PrEP eligibility states and from these to HIV infection by estimating the intensity and probability of those transitions in a cohort of HIV-negative MSM in Lisbon.

## Methods

We used data from the participants enrolled in the Lisbon Cohort of MSM, an open, noninterval, prospective cohort. Participants were recruited at CheckpointLX – a community-based HIV counseling and testing (CBVCT) center in Lisbon targeted at MSM, and whose entire staff are trained peer community health workers (CHW), MSM themselves. Being a cisgender man, aged 18 or older, reporting sex with men, and presenting a non-reactive HIV test at baseline were criteria to be enrolled in the cohort. A detailed description of the cohort is provided elsewhere [11, 14]. At each visit to CheckpointLX, peer CHWs administer a structured questionnaire and perform an HIV rapid test. Rapid tests for Syphilis, Hepatitis C, and Hepatitis B viruses are also offered according to an individual assessment. Cohort recruitment started in April 2011, but this study only covers the period from March 2014 to March 2018, after a questionnaire revision and considering the ability to assess eligibility for PrEP according to the Portuguese National Health Service (PNHS) guidelines.

All participants provided 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).

*Study instruments and variables*

We defined PrEP eligibility according to the clinical guidelines provided by the PNHS [9]. Each criterion of the guideline was matched with the behavioral information collected at the baseline and follow-up evaluations and was operationally defined as described in Table 1. A more detailed description is available elsewhere [15]. Exposure ascertainment was based on the information regarding the previous 12 months at the baseline visit and, thereafter, based on the period between visits. Participants were defined as eligible when they met any of the PNHS criteria, except for the criterion relating to “persons in situations of social vulnerability that may expose them to unprotected sex with individuals at high risk of acquiring HIV infection” for which there was not enough information collected. A “rather not say” or “do not know” response or missing information associated with a “no” response in all the remaining criteria resulted in exclusion from the analysis.

**Table 6. Operational definition of each eligibility criterion in the PNHS guidelines.**

An HIV third-generation test (Alere Determine HIV-1/2) was performed at each visit, except from October 2016 to October 2017, when a fourth-generation test (Alere Determine, HIV-1/2 Ag/Ab Combo) was used. In case of a reactive test result, a referral was offered to an HIV/infectious diseases clinic of a public hospital of participant’s choice, where a confirmatory test would be

performed. CheckpointLX peer CHWs provided pretest and posttest counseling at every visit in an opt-out strategy.

*Statistical analysis*

We performed a descriptive analysis of the participants' characteristics at baseline and by state at first transition, and compared groups using the t-test for independent variables for the mean age, and the Pearson Chi-Square for the categorical variables. These analyses were performed using SPSS for Windows, version 23.0 (SPSS Inc, Chicago, IL). To describe the transitions between PrEP eligibility states (eligible and ineligible) and from these states to HIV infection, a time-homogeneous Markov multi-state model was implemented. We considered a 3-state model, one of which – the HIV infection, is an absorbing state, as depicted in Figure 1. The four possible transitions are identified by the arrows: 1) 'ineligible' to 'eligible' (I–E), 2) 'eligible'' to 'ineligible'' (E–I), 3) 'ineligible'' to 'HIV infection' (I–HIV), 4) 'eligible'' to 'HIV infection' (E–HIV). We assumed that participants might be in states "ineligible" and "eligible" at time t=0 but can be in the absorbing state only at t=0+u. Since it is impossible to observe participants continuously, the exact times of state-to-state transitions were interval-censored. Under this constraint, standard multi-state methods were adapted. The multi-state models were computed using the 'msm' package in R. [16] Multi-state data can be summarized by counting, for each state s, the number of times an observation from the state r was followed by the state s. These are simply frequencies of pairs of consecutive observed states. The intensities for each possible instantaneous transition was calculated by the maximum likelihood estimation and the corresponding 95% confidence interval (CI) and represents the instantaneous risk of moving between the states. The probabilities of those transitions at multiple window periods were also computed. For a time-homogeneous process, the (r, s) entry of P(t), $P_{rs}(t)$, is the probability of being in state s at a time t+u in the future, given that the state at time u is r. The CI for the transition probabilities were calculated with the bootstrap method. The bootstrap datasets were computed by resampling independent transitions between pairs of states. Then, the CI or standard errors for the corresponding statistic were calculated by summarizing the returned list of the replicated outputs. We have used 500 resamples.

**Figure 1: Model for the transition between PrEP eligibility states (eligible and ineligible) and from these to HIV infection.**

*Participants*

From March 2014 to March 2018, 3565 participants were enrolled in the cohort; among those, 62 were excluded because, at some point, they had used PrEP. Among the remaining, 2203 only

came for the baseline visit, and 1300 came for at least two visits. A comparison between participants with and without follow-up visits is presented in Table 2.

Participants with follow-up visits were slightly younger and more frequently born in Portugal. There were also differences in the educational level and job situation, but no differences in the reported sexual orientation, previous HIV test, reasons for the index test, and eligibility for PrEP at baseline.

**Table 2: Baseline characteristics of participants with and without follow-up visits.**

The final analysis was conducted among those participants with at least two visits and valid information on PrEP eligibility in at least two consecutive visits; therefore, we excluded 123 participants that did not meet the latter. The remaining 1177 had a total of 1655.83 person-years of follow-up and a median of 2 visits.

## Results

Table 3 presents all participants' description and by the state at first transition. Overall, the median age was 27.2 years (25th – 75th percentiles: 23.0-35.5); no differences were found by the state of the first transition. Regarding the country of birth, 77.7% were born in Portugal, followed by those born in Brazil (9.1%) and other European countries (8.9%). The proportions of participants being born in Brazil or European countries besides Portugal were higher among participants at the eligible state in the first transition. 58.1% held a higher education degree (bachelor, master, or doctoral), and 82.3% self-identified as gay. No differences were found between groups for these two characteristics. Regarding the history of a previous HIV test and the reasons for the index test, participants at the eligible state reported more frequently a previous HIV test (77.7% vs. 72.3% among ineligible) and stated more frequently reasons related to risk exposure (73.0% vs. 57.2%).

**Table 3: Baseline characteristics of participants, overall and by state of the first transition.**

There were 335 transitions ineligible to eligible, 412 eligible to ineligible, 5 ineligible to HIV infection, and 22 eligible to HIV infection over 1656 person-years of observation; 1467 transitions were to the same state (668 in the ineligible state and 792 in the eligible state).

Figure 2 shows the intensity and the corresponding 95% CI for each possible transition. The estimated intensities of transitions were 7% higher for I–E (1.591 [95% CI 1.323; 1.913]) than E–I (1.493 [95% CI 1.241; 1.795]) while the transition E–HIV was 22 times more likely than the I–HIV (0.032 [95% CI 0.020; 0.050] vs. 0.001 [95% CI 0.000; 0.982]).

**Figure 2: Estimated transition intensities and respective 95% confidence interval of the multi-state model for the transition between PrEP eligibility states and from these to HIV infection.**

Table 4 presents estimated transition probabilities and respective 95% CI at multiple time-points for the PrEP eligibility states and HIV infection. The transition probabilities estimated for 30 days represent the probability of being in a state *s* at time t= 30 (t+*u*) days in the future, given the state at time *u* is *r*. Those were similar for the transition I–E and E–I (0.1151 [95% CI 0.0914; 0.5123] vs. 0.1080 [95% CI 0.0865; 0.4989]), but the transition E–HIV was 9.2 times more likely than the I–HIV (0.0003 [95% CI 0.0001; 0.0017] vs. 0.0025 [95% CI 0.0012; 0.0035]). The estimated transition probabilities increased with time up to a probability of 0.4673 (95% CI 0.4412; 0.4953) to go from eligible to ineligible and 0.4980 (95% CI 0.4724; 0.5191) to go from ineligible to eligible at 1.5 years. Both transitions always showed a similar probability. The transition probabilities of I–HIV and E–HIV also increased up to 0.0284 (95% CI 0.0207; 0.0397) and 0.0380 (95% CI 0.0251; 0.0472), respectively, at 2 years' time. The transition probability to HIV infection was always higher when at the eligible state, but the probabilities' ratio decreased with time (9.20 at 30 days, 4.44 at 90 days, 2.72 at 180 days, 1.76 at 1 year, 1.47 at 1.5 years, and 1.34 at 2 years).

**Table 4: Estimated transition probabilities and respective 95% confidence intervals at multiple time-points.**

## Discussion

The probability of transition to HIV infection is higher at any time-point when coming from the eligible state than when coming from the ineligible state but ratios between these transition's probabilities (I-HIV and E-HIV) decreased with time, indicating that being defined as ineligible is only a short-time indicator of a lower probability of acquiring HIV. The intensity of transitions was, as expected, much higher for E–HIV (0.032) than for I–HIV (0.001). On the other side, the intensities of transitions I–E and E–I were similar (1.591 vs. 1.493).

It is important to note that given the Markov assumption, on which the multi-state models are based, future evolution only depends on the current state. This means that the estimated intensity transitions were independent of any previous states. Having this in mind, it is unequivocal that the risk of transition to an HIV infection state was much higher when it was from the eligible for PrEP state. In practical terms, this means that once an individual meets any of the eligibility criteria for PrEP, he is at 22 times higher risk of becoming infected. The challenge is how to anticipate or detect these changes in a timely manner that allow acting preventively. Transitions between eligibility states were similar, indicating that it is almost as likely for an individual to go from eligible to ineligible as to go from ineligible to eligible. The transition

probabilities results went in the same direction by showing that at any time-point, the probability of transition between these two states was similar.

These results show that having an indication for PrEP based on behavioral information is likely to change over time, and most importantly, they call our attention that those that were, at a given time point, been classified as ineligible need to be reassessed for their eligibility in a short time frame. This has also been discussed previously by Parsons et al. in their proposal of a motivational PrEP cascade, where individuals going in and out of risk would enter the cascade during times when PrEP was indicated [17]. To be able to do so, providers, being health services or community-based services, need to be aware that when a person does not have a behavioral indication for PrEP at a given time point, that is only a short time indicator of their lower risk. Therefore, individuals need to be advised accordingly and be given the tools to be competent to self-identify a potential change in their behavior towards more risk for HIV, to know where to seek for counseling or prevention tools, and be given access to the prevention tools appropriate to their risk management preferences and needs.

Considering the growing evidence that PrEP users are not lifetime users [18-23], these results call attention to the changes in indication for PrEP. Some studies showed that factors associated with PrEP discontinuation included changes in sexual behavior and HIV risk perception, but also associated with side effects, adherence problems, and structural barriers to access PrEP [18-22]. It is, therefore, increasingly important to focus on discussing the appropriate and sustainable preventive health paths to ones' needs, which can include PrEP only at certain times [24].

A major strength of this study is the approach to measure state changes in PrEP eligibility and HIV infection, providing a novel assessment tool for risk prediction considering a longitudinal perspective. However, the limitations of our study need to be discussed. First, the small number of transitions to HIV infection led to imprecise estimates. We cannot exclude that the differences found can be only due to chance. Second, information was collected using a structured questionnaire, not explicitly designed to measure PrEP eligibility. That is why there was 1 criterion impossible to assess, the cohort variables referred to behaviors in the previous 12 months or the time in between evaluations, while the PNHS guidelines ask for a time period of 6 months. Also, we may be missing relevant information to classify participants leading to the overestimation of eligibility. Third, given that this is a cohort recruited at a CBVCT, these results are not generalizable to the entire MSM population. Participants in the cohort were more often self-identified as gay, were more educated, and more aware of HIV risk, as they have been tested for HIV more frequently in the past [14] than observed in previous studies among MSM in

Portugal conducted in different settings [25-28]. Fourth, we may have information bias due to losses to follow-up, and over 50% of participants having only 2 visits. There were small differences in sociodemographic characteristics among those with and without a follow-up visit. However, the proportion of participants eligible for PrEP at baseline and by each criterion was similar, as well as the proportion of a previous HIV test. Additionally, we also conducted sensitivity analyses among those with at least three visits, and the results were in the same direction (data not shown). Finally, social desirability and recall of information may have led to underestimation for eligibility for PrEP. This could have been diminished by the fact that the interviewers are also MSM due to the peer-based approach provided by CheckpointLX, but we cannot exclude it.

In conclusion, among MSM attending a CBVCT in Lisbon, the intensity transitions between being or not eligible for PrEP were similar, but its probability increased with time, up to almost 50%, showing that an indication for PrEP is likely to change over time. Our results also showed that, although being classified as ineligible at a given time point, reassessment is needed. Under these non-experimental conditions, in two years, the probability of transition to HIV infection becomes closer to the one found for those identified as eligible at the same initial point in time. Additionally, once an individual meets any of the eligibility criteria for PrEP, he is at 22 times higher risk of seroconversion. To anticipate and to avoid changes to an eligible state is challenging and demands delivering PrEP sooner than later.

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## Tables and Figures

**Table 1. Operational definition of each eligibility criterion in the PNHS guidelines.**

| PNHS criteria (2018) | Operational definition of eligibility |
|---|---|
| 1. Persons who have had condomless sex in the past 6 months and sexual partners with unknown HIV status, or | Any anal sex with steady or occasional partners without a condom<br>AND<br>having at least 1 sexual partner for whom the HIV status is unknown |
| 2. People who refer the use of psychoactive substances during sexual intercourse, or | Used at least 1 psychoactive substance during sex, including cannabis, heroin, cocaine, ecstasy, amphetamines, poppers, LSD, ketamine, GHB, methadone, substances sold at smart shops, methamphetamines, mephedrone, or other |
| 3. Persons who have had condomless sex in the past 6 months and had an STI diagnosis, or | Any anal sex with steady or occasional partners without a condom<br>AND<br>self-report of syphilis, chlamydia, lymphogranuloma venereum, gonorrhea, trichomoniasis, genital herpes, condyloma or genital warts, or other STI diagnosis |
| 4. Persons who have had condomless sex in the past 6 months and used PEP for HIV, or | Any anal sex with steady or occasional partners without a condom<br>AND<br>use of PEP |
| 5. People whose partner is infected with HIV, without medical care or ART, or without viral suppression and do not use condoms consistently, or | Anal sex with a steady partner<br>AND<br>having at least 1 HIV-positive steady partner<br>AND<br>having at least 1 HIV-positive partner who is not taking treatment or whose HIV status is not known<br>OR<br>having at least 1 HIV-positive partner who had a detectable or unknown viral load<br>AND<br>any anal sex with steady or occasional partners without a condom |
| 6. People who engage in sexual intercourse to obtain money or goods or illicit substances and do not use condoms consistently. | People who report having received money, goods, or drugs in exchange for sex<br>AND<br>any anal sex with steady or occasional partners without a condom |

ART: antiretroviral therapy; GHB: gamma-hydroxybutyric acid; HIV: human immunodeficiency virus; LSD: lysergic acid diethylamide; PEP: postexposure prophylaxis; PNHS: Portuguese National Health Service; STI: sexually transmitted infection.

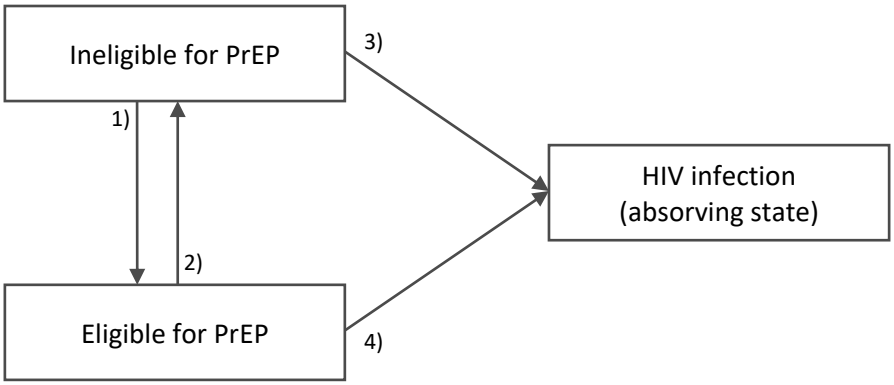


**Figure 1: Model for the transition between PrEP eligibility states (eligible and ineligible) and from these to HIV infection.**
HIV: human immunodeficiency virus; PrEP: preexposure prophylaxis.

**Table 2: Baseline characteristics of participants with and without follow-up visits.**

| Characteristics | Participants without follow-up N=2203 | Participants with follow-up N=1300 | p-value |
|---|---|---|---|
| **Age (years)** | | | |
| Mean (SD) | 30.7 (9.56) | 30.0 (9.34) | 0.030[a] |
| Median (P25-P75) | 28.1 (23.5-35.7) | 27.1 (23.0-35.3) | 0.010[b] |
| min-max | 18.0-77.0 | 18.0-69.1 | |
| **Country/Region of origin, n (%)** | | | 0.001[c] |
| Portugal | 1575 (71.6) | 1002 (77.2) | |
| Brazil | 287 (13.1) | 124 (9.6) | |
| Other European countries | 195 (8.9) | 113 (8.7) | |
| African country | 58 (2.6) | 32 (2.5) | |
| Other American countries | 49 (2.2) | 18 (1.4) | |
| Asia / Middle east / Oceania | 35 (1.6) | 9 (0.7) | |
| Missing | 4 | 2 | |
| **Educational level, n (%)** | | | 0.031[c] |
| Basic education or less | 120 (5.5) | 51 (3.9) | |
| Secondary education | 686 (31.4) | 436 (33.7) | |
| Professional training | 52 (2.4) | 43 (3.3) | |
| Post-secondary | 27 (1.2) | 15 (1.2) | |
| Bachelor | 867 (39.7) | 467 (36.1) | |
| Master or Doctoral | 430 (19.7) | 280 (21.7) | |
| Rather not say/Missing | 21 | 8 | |
| **Job situation, n (%)** | | | 0.025[c] |
| Full-time or self-employed | 1297 (59.5) | 707 (54.8) | |
| Part-time, temporary, student, undeclared and sex work | 262 (12.0) | 156 (12.1) | |
| Unemployed | 149 (6.8) | 108 (8.4) | |
| Others (others, retirees and students) | 471 (21.6) | 320 (24.8) | |
| Rather not say/Missing | 24 | 9 | |
| **Sexual orientation, n (%)** | | | 0.521[c] |
| Gay | 1820 (82.8) | 1071 (82.5) | |
| Bisexual | 296 (13.5) | 186 (14.3) | |
| Heterosexual | 34 (1.5) | 13 (1.0) | |
| Other/Does not use a term/does not know | 48 (2.2) | 28 (2.2) | |
| Rather not say/Missing | 5 | 2 | |
| **Previous HIV testing, n (%)** | | | 0.973[c] |
| No | 518 (23.5) | 306 (23.6) | |
| Yes | 1682 (76.5) | 993 (76.4) | |
| Rather not say/Missing | 3 | 1 | |
| **Reason for the index test, n (%)** | | | 0.126[c] |
| Reasons related to symptoms | 152 (7.0) | 76 (5.9) | |
| Reasons related to risk exposure | 1402 (64.1) | 868 (67.4) | |
| Reasons not related to symptoms or risk exposure | 633 (28.9) | 344 (26.7) | |
| Rather not say/Missing | 16 | 12 | |
| **PNHS criteria, not mutually exclusive, n (%)** | | | |
| 1. Persons who have had condomless sex in the past 6 months and sexual partners with unknown HIV status | 924 (42.5) | 536 (41.6) | 0.619[c] |
| missing | 31 | 12 | |

| | | | |
|---|---|---|---|
| 2. People who refer to the use of psychoactive substances during sexual intercourse | 630 (28.9) | 372 (28.9) | 0.980[c] |
| missing | 20 | 12 | |
| 3. Persons who have had condomless sex in the past 6 months and had an STI diagnosis | 142 (6.5) | 89 (6.9) | 0.730[c] |
| missing | 30 | 10 | |
| 4. Persons who have had condomless sex in the past 6 months and used PEP for HIV | 23 (1.1) | 25 (1.9) | 0.044[c] |
| missing | 14 | 9 | |
| 5. People whose partner is infected with HIV without medical care or ART or without viral suppression and do not use condoms consistently | 22 (1.0) | 17 (1.4) | 0.489[c] |
| missing | 62 | 43 | |
| 6. People who engage in sexual intercourse to obtain money or goods or illicit substances and do not use condoms consistently | 34 (1.6) | 16 (1.2) | 0.548[c] |
| missing | 10 | 8 | |
| **Eligible for PrEP, n (%)** | 1302 (60.7) | 775 (60.7) | 0.976[c] |
| missing | 58 | 23 | |

[a] p-value for the t-test for independent samples

[b] p-value for the Mann-Whitney test

[c] p-value for the chi-square test

ART: antiretroviral therapy; HIV: human immunodeficiency virus; P25: 25$^{th}$ percentile; P75: 75$^{th}$ percentile; PEP: postexposure prophylaxis; PNHS: Portuguese National Health Service; PrEP: preexposure prophylaxis; SD: standard deviation; STI: sexually transmitted infection.

**Table 3: Baseline characteristics of participants, overall and by state of the first transition.**

| Characteristics | Overall N=1177 | Ineligible N= 462 (39.3%) | Eligible N= 715 (60.7%) | p-value |
|---|---|---|---|---|
| **Age (years)** | | | | |
| Mean (SD) | 30.0 (9.33) | 29.6 (9.25) | 30.3 (9.37) | 0.244[a] |
| Median (P25-P75) | 27.2 (23.0 - 35.5) | 26.5 (22.9-34.4) | 27.8 (23.1-35.9) | 0.151[b] |
| min-max | 18.0-69.1 | 18.3-62.3 | 18.0-69.1 | |
| **Country/Region of origin, n (%)** | | | | 0.019[c] |
| Portugal | 913 (77.7) | 379 (82.0) | 534 (74.9) | |
| Brazil | 107 (9.1) | 26 (5.6) | 81 (11.4) | |
| Other European countries | 105 (8.9) | 37 (8.0) | 68 (9.5) | |
| African country | 29 (2.5) | 13 (2.8) | 16 (2.2) | |
| Other American countries | 13 (1.1) | 4 (0.9) | 9 (1.3) | |
| Asia / Middle east / Oceania | 8 (0.7) | 3 (0.6) | 5 (0.7) | |
| Missing | 2 | 0 | 2 | |
| **Educational level, n (%)** | | | | 0.756[c] |
| Basic education or less | 47 (4.0) | 14 (3.0) | 33 (4.6) | |
| Secondary education | 392 (33.5) | 154 (33.5) | 238 (33.5) | |
| Professional training | 41 (3.5) | 17 (3.7) | 24 (3.4) | |
| Post-secondary | 11 (0.9) | 4 (0.9) | 7 (1.0) | |
| Bachelor | 419 (35.8) | 162 (35.2) | 257 (36.1) | |
| Master or Doctoral | 261 (22.3) | 109 (23.7) | 152 (21.4) | |
| Rather not say/Missing | 6 | 2 | 4 | |
| **Sexual identity, n (%)** | | | | 0.747[c] |
| Gay | 969 (82.3) | 386 (83.5) | 583 (81.5) | |
| Bisexual | 172 (14.6) | 64 (13.9) | 108 (15.1) | |
| Heterosexual | 10 (0.8) | 4 (0.9) | 6 (0.8) | |
| Other/Does not use a term/does not know | 26 (2.2) | 8 (1.7) | 18 (2.5) | |
| **Previous HIV testing** | | | | 0.040[c] |
| No | 287 (24.4) | 128 (27.7) | 159 (22.3) | |
| Yes | 889 (75.6) | 334 (72.3) | 555 (77.7) | |
| Rather not say/Missing | 1 | 0 | 1 | |
| **Reason for the index test** | | | | <0.001[c] |
| Reasons related to symptoms | 65 (5.6) | 27 (5.9) | 38 (5.3) | |
| Reasons related to risk exposure | 780 (66.8) | 261 (57.2) | 519 (73.0) | |
| Reasons not related to symptoms or risk exposure | 322 (27.6) | 168 (36.8) | 154 (21.7) | |
| Rather not say/Missing | 10 | 6 | 4 | |

[a] p-value for the t-test for independent samples

[b] p-value for the Mann-Whitney test

[c] p-value for the Fisher exact test

HIV: human immunodeficiency virus; P25: 25$^{th}$ percentile; P75: 75$^{th}$ percentile; SD: standard deviation.

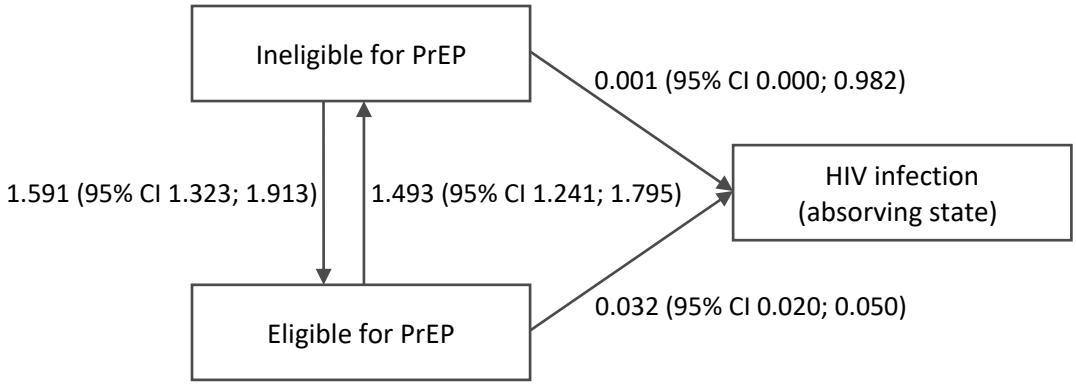


**Figure 2: Estimated transition intensities and respective 95% confidence interval of the multi-state model for the transition between PrEP eligibility states and from these to HIV infection.**
CI: confidence interval; HIV: human immunodeficiency virus; PrEP: preexposure prophylaxis.

**Table 4: Estimated transition probabilities and respective 95% confidence intervals at multiple time-points.**

| | Transitions (current state – state at time-point) | | | |
|---|---|---|---|---|
| | **Ineligible–Eligible** | **Eligible–Ineligible** | **Ineligible–HIV infection** | **Eligible–HIV infection** |
| **Time-point** | p (95% CI) | p (95% CI) | p (95% CI) | p (95% CI) |
| **30 days** | 0.1151 (0.0914; 0.5123) | 0.1080 (0.0865; 0.4989) | 0.0003 (0.0001; 0.0017) | 0.0025 (0.0012; 0.0035) |
| **90 days** | 0.2746 (0.2426; 0.5162) | 0.2577 (0.2247; 0.5007) | 0.0015 (0.0010; 0.0051) | 0.0068 (0.0035; 0.0086) |
| **180 days** | 0.3998 (0.3588; 0.5084) | 0.3751 (0.3357; 0.4953) | 0.0045 (0.0034; 0.0103) | 0.0122 (0.0058; 0.0166) |
| **1 year** | 0.4840 (0.4559; 0.5088) | 0.4541 (0.4205; 0.4960) | 0.0123 (0.0083; 0.0222) | 0.0216 (0.0124; 0.0301) |
| **1.5 years** | 0.4980 (0.4724; 0.5191) | 0.4673 (0.4412; 0.4953) | 0.0205 (0.0150; 0.0325) | 0.0301 (0.0197; 0.0399) |
| **2 years** | 0.4977 (0.4751; 0.5262) | 0.4670 (0.4444; 0.4877) | 0.0284 (0.0207; 0.0397) | 0.0380 (0.0251; 0.0472) |

CI: confidence interval; HIV: human immunodeficiency virus; p: probability.

## 4.6 Provision of preexposure prophylaxis at the Portuguese National Health Service and the uptake in the Lisbon Cohort of men who have sex with men (Paper VI)

Paula Meireles, Francisco Fernandes, Miguel Rocha, Michael Plankey, Henrique Barros

**Abstract**

**Background**

The Portuguese National Health Service (NHS) provides preexposure prophylaxis (PrEP) for HIV prevention, free of charge, since February 2018. The Lisbon Cohort of men who have sex with men (MSM) is a privileged setting to study the uptake of before and after PrEP implementation in Portugal, in addition to the comparison of characteristics of PrEP users and non-users.

**Methods**

We used data from 6164 participants in the Lisbon Cohort of MSM – an open, prospective cohort of HIV-negative MSM testing at a community-based center in Lisbon, that had either a baseline or follow-up visit between March 2014 and July 2019.

**Results**

From March 2014 to July 2019, 198 (3.2%) participants reported having used PrEP in the previous 12 months or between visits. Approximately one third started after its introduction in the Portuguese NHS. PrEP uptake increased from 0.15% (95% CI 0.02-0.55) in 2014 to 5.36% (95% CI 4.29-6.60) in 2019. Out of the 122 (61.6%) that provided additional information on their first PrEP use, 86 (70.5%) used it daily, 31 (25.4%) on an event-driven scheme, and 5 (4.1%) reported other regimens. How PrEP was obtained varied according to the timing of the initial PrEP experience – prescribed by a physician in Portugal (11.1% before vs. 68.8% after implementation), and online (40.7% before vs. 14.1% after implementation). The presence of eligibility criteria was higher among users than non-users (76.3% vs. 56.4%) and did not change significantly after PrEP implementation (73.8% vs. 78.1%).

**Conclusions**

There was an increase in the uptake of PrEP, particularly after its introduction to the Portuguese NHS. Users seem to have an appropriate self-risk assessment. The proportion of men obtaining PrEP prescribed by a physician increased significantly after it became available at the Portuguese NHS, representing a change to a more equitable and safer way of using PrEP.

**Background**

Preexposure prophylaxis (PrEP) is the use of antiretrovirals (ARVs) to prevent human immunodeficiency virus (HIV) acquisition. It has shown a relative risk reduction in HIV incidence among men who have sex with men (MSM) by at least 86% or higher when adherence is high, both when taken daily or on-demand (1-3). The use of tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) as PrEP, was first approved by the United States Food and Drug Administration in 2012 (4). In 2014, the World Health Organization recommended offering PrEP to MSM as an additional HIV prevention choice (5). This recommendation was expanded to include all population groups at a substantial risk of HIV infection in 2015 (6). In this same year, the European Centre for Disease Prevention and Control recommended that European Union Member States should consider offering PrEP in addition to the existing HIV prevention package for those most at-risk, starting with MSM (7). In 2019, PrEP was being reimbursed within the national health services (NHS) in 16 out of 53 countries in Europe and Central Asia, it was available in healthcare settings, but not fully reimbursed in nine countries, and available through pilot, research or demonstration projects at national or sub-national level in additional five (8). This availability of PrEP excluded the 'informal' access to PrEP online or by other means outside countries' health regulations.

Since February 2018, Portugal delivers PrEP for HIV prevention, free of charge, at the Portuguese NHS hospitals (9, 10). Data from November 2019 showed that there were one thousand PrEP users, mostly highly educated men in their 30s, and at a high-risk situation for HIV (11). Previous to the formal introduction of PrEP in the Portuguese NHS, there were reports of PrEP use by MSM (12-15). Aware of this, CheckpointLX, a community-based center run by and directed to MSM, began offering counseling and follow-up services for PrEP users, reaching 90 appointments by May 2018 (13). Accessing PrEP outside the formal health system was lower among participants from countries where PrEP was available at NHS at the time of the surveys, such France or Belgium than in Portugal or other countries where PrEP was not available at the NHS (14, 15). Data about the regimens of PrEP use in Portugal, and how it has been obtained are scarcer. One study reporting on PrEP use before its formal implementation in Portugal showed that most users obtained PrEP from the internet, from a friend or misused postexposure prophylaxis (PEP) (14).

We aimed to assess the time-trends in the uptake of PrEP, and how it was taken and obtained in the first PrEP experience by comparing the period before and after PrEP implementation in Portugal, taking participants in the Lisbon Cohort of MSM as a sentinel population. We also

aimed to compare PrEP users with non-users and, among users, to compare those who started before and after PrEP implementation.

**Methods**

We used data from the Lisbon Cohort of MSM, which is an open, noninterval, prospective cohort of adult men who report having sex with men, and who have an HIV-negative test result at recruitment (16). Recruitment and data collection takes place at CheckpointLX, a community-based voluntary counseling and testing center (CBVCT) in Lisbon devoted to MSM, whose services are provided by trained peers community-health workers (CHWs) (17). These peer CHWs assess CheckpointLX users for their eligibility to be enrolled in the cohort study and invite them to participate. For those who accept, they administer a structured questionnaire in a baseline or follow-up interview. An HIV test, along with other rapid tests – Syphilis (anti-*Treponema pallidum* antibodies), Hepatitis C (Hepatitis C virus antibodies), and Hepatitis B (Hepatitis B surface antigen) considered appropriate according to the individual risk assessment, are also performed by the peer CHW. CheckpointLX peer CHWs provide pretest and posttest counseling at every visit in an opt-out strategy.

For this study, there were 6444 participants with a baseline or follow-up visit between March 10, 2014, and July 31, 2019, who were asked the question: "did you use PrEP in the last 12 months/since the last visit?". From those, we excluded 184 (2.9%) because they had an HIV-reactive test at baseline, and 96 (1.5%) because they either answered the question with "Rather not say" or did not provide an answer. Therefore, we included in the analysis 6164 participants.

All participants provided written informed consent before inclusion. The ethics committee of São João Hospital Center and Medical School, University of Porto, approved the study protocol (ID 104/12).

*Study instruments and variables*

We used the information regarding PrEP use in the previous 12 months at baseline, or between visits at follow-up (median time between visits=7.8 months: $25^{th}$ percentile-$75^{th}$ percentile=5.2-11.8). Among PrEP users, information about the regimen – how was PrEP taken (daily, event-driven - 2 pills 2 to 24 hours before sex, a third pill 24 hours after the first drug intake and a fourth pill 24 hours later, or other) and source – how was PrEP obtained (prescribed by a medical doctor in Portugal, ordered from an online pharmacy, dispensed in another country, clinical trial/demonstration study, from social networks, or other) corresponds to the first time PrEP was reported, as well as the remaining information about age, educational level, job situation,

and eligibility for PrEP according to the Portuguese NHS guidelines. Participants were defined as eligible for PrEP if they reported one or more of the following criteria: condomless sex in the past 6 months and sexual partners with unknown HIV status, use of psychoactive substances during sexual intercourse, condomless sex in the past 6 months and a sexually transmitted infection (STI) diagnosis, condomless sex in the past 6 months and use of PEP for HIV, an HIV-positive partner without medical care or antiretroviral therapy or without virologic suppression and inconsistent condom use, sexual intercourse to obtain money or goods or illicit substances and inconsistent condom use (18, 19).

For non-users, we considered the information obtained at the most recent visit. Information about the country of birth, sexual orientation, and knowledge about PEP was collected at the baseline for all participants.

An HIV third-generation test (Retrocheck HIV from April 2011 to April 2012, and Alere Determine HIV-1/2 thereafter) was performed at each visit, except from October 2016 to October 2017, when a fourth-generation test (Alere Determine, HIV-1/2 Ag/Ab Combo) was used. In case of a reactive test result, a referral was offered to an HIV/infectious diseases clinic of a public hospital of most convenient to the participant to confirm the HIV infection and enrollment in care.

*Statistical analysis*

We computed the proportion and respective 95% confidence interval (95% CI) based on the binomial distribution of PrEP use at baseline or at follow-up by year. We performed a stratified descriptive analysis of the regimen and source of PrEP by the timing of first use (before vs. after February 2018 when PrEP delivery was implemented in Portugal). We have also described participants' characteristics by the use of PrEP and, among PrEP users, by the timing of first use. For comparisons between groups, we used, for the continuous variables the Student's *t*-test for independent samples and the Mann-Whitney U test and the Pearson Chi-Square or the Fisher exact test for the categorical variables. These analyses were performed using SPSS for Windows, version 23.0 (SPSS Inc, Chicago, IL).

**Results**

Among the 6164 MSM included in the analysis, 198 (3.2%) reported any use of PrEP in the last 12 months or between visits, of whom 143 (72.2%) reported PrEP use in their most recent visit. PrEP use only once was reported by 157 (79.3%) participants; 131 (66.2%) reported to have started using PrEP before February 2018, when it became available in Portugal, 64 (32.3%) started using PrEP after that date, and 3 (1.5%) didn't provide information. The proportion of

PrEP users by year of cohort increased from 0.15% (95% CI 0.02-0.55) in 2014 to 5.36% (95% CI 4.29-6.60) in 2019. (Figure 1). Out of the 122 PrEP users that provided additional information, 86 (70.5%) reported a daily regimen, 31 (25.4%) event-driven, and 5 (4.1%) reported other regimens. Among those reporting other regimens, one took three pills after sex, another took three pills in three consecutive days, another took every other day, another took one week before and after sex, and the other took PEP pills as PrEP. There were no differences in the regimens of PrEP according to the timing of the first PrEP (p=0.594) (Figure 2).

The most-reported mean of obtaining PrEP was a physician prescription in Portugal (41.3%), followed by order online (28.1%), a prescription in a foreign country (16.5%), through friends or sexual partners (8.3%), within a research project (3.3%), and other means were referred by 2.5% of users. The mean of obtaining PrEP varied significantly according to the timing of the first PrEP, as shown in Figure 2 (p<0.001).

Table 1 shows the comparison between those who have not used PrEP and those who have. PrEP users were significantly older than non-users (median age 34.2 vs. 29.4), less frequently born in Portugal (56.1% vs. 72.9%), with higher levels of education (bachelor, master or doctoral: 75.0% vs. 63.8%), more often full-time employed or self-employed (75.5% vs. 65.1%), knowledgeable about PEP at baseline (71.1% vs. 44.5%), and eligible for PrEP (76.3% vs. 56.4%). There were no significant differences in terms of self-reported sexual orientation. Table 1 also shows the comparison of users according to the timing of the first PrEP, and there were no significant differences between the two groups. However, it should be noted that those starting PrEP after February 2018 were slightly younger (median age: 32.5 vs. 35.4) and reported more frequently to have been born in Brazil (23.4% vs. 10.1%) and less frequently in other European countries besides Portugal (9.4% vs. 16.3%).

**Discussion**

Our results provide a first look at PrEP uptake among participants in the Lisbon Cohort of MSM. We found that PrEP was used by 3.2% of all participants, with an increasing trend in the proportion from 2014 to 2019. Our results also showed that those that started PrEP after it has been implemented in the Portuguese NHS reported more frequently a physician prescription in Portugal, and less frequently got it online or in a foreign country. This represented an important change to a more equitable and safer way of using PrEP, with the indicated monitoring.

PrEP uptake among participants in the Lisbon Cohort of MSM was similar to previous reports among MSM in Portugal (14, 15). Non-HIV-positive EMIS 2017 participants in Portugal, reported a 1.5% uptake of PrEP at the time of the survey. Overall the proportion was 3.3%, but the median

was 1% (15, 20). Among a sample recruited via the Hornet gay networking application in 2017, 4.5% of participants in Portugal were using PrEP, while the proportion in the overall sample was 10.1% (14). There was a considerable increase in PrEP uptake in the cohort since 2014, which was more pronounced in 2018 and 2019. However, PrEP use remains low when compared to the estimated global prevalence of self-reported PrEP of 10.7% in 2017 and is expected to rise in the coming years as the odds of reporting PrEP use globally approximately doubled each year (21).

The majority of MSM in this cohort used PrEP daily, and about on quarter used event-driven regimen. This distribution was also found in European demonstration projects in Belgium and the Netherlands (22, 23). The reports of other ways of using PrEP were of concern, reflecting choices for regimens without proven efficacy, or the inability to access safer ways (24). The choice for daily or event-driven PrEP did not change significantly after PrEP implementation in Portugal, even if daily use increased. On the other hand, there was a significant change regarding the means MSM obtained PrEP after it was implemented in the Portuguese NHS. While prescription by a physician in Portugal increased from 11.1% to 68.8%, informal PrEP use (online, friends or sexual partners, or others) decreased from 55.6% to 21.9%. Although no concerns were found about generic TDF/FTC purchased on the internet in terms of drug concentrations (25), and monitoring of renal function and HIV testing has been provided at community-based settings (13), informal use of PrEP poses several challenges: the proper exclusion of acute HIV infection prior to initiation of PrEP, the monitoring of HIV, STIs and renal function while on PrEP, the continuity of PrEP due to drug availability, delay in shipping or affordability of drugs (26). Also, there can be difficulties in ensuring that the proper drugs are being taken, for instance, when taking PEP as PrEP or when using ARVs prescribed to a patient living with HIV (26, 27). Informal use of PrEP also creates inequalities in access since only those knowledgeable and able to afford the costs can access it. Therefore, providing free of charge PrEP at the NHS hospitals may help to overcome many of these problems by making access easier, equitable, and monitoring more adequate. Still, slightly over 20% of PrEP users were obtaining PrEP informally even with PrEP available fully reimbursed at the Portuguese NHS hospitals. Reasons for this should be further investigated; we hypothesize that going to a hospital might feel frightening to some, or it might be seen as a complicated process involving transportation to urban centers, waiting times, and losses from work from people who are healthy and for whom ordering online may seem easier. Alternative places for PrEP delivery besides PrEP referral, such as the primary health care centers, pharmacies, community-based settings, which are closer to potential users, should also receive consideration (27, 28).

In this cohort, PrEP users were older, more frequently born outside Portugal, particularly in other European countries and from American countries besides Brazil, had higher levels of education than non-users, and reported more frequently to know about PEP at baseline. PrEP users also more frequently met the Portuguese NHS criteria for PrEP, which may reflect an appropriate self-perception of risk, as previously shown (14, 29). Also shown by the fact that PrEP users had more visits in the cohort, and therefore more HIV tests. The comparison of PrEP users starting before and after implementation showed some differences – those starting PrEP only after its implementation were slightly younger, more frequently born in Brazil, and less in European countries besides Portugal. Even with caution due to small numbers, this may reflect that the social advantaged profile of very early PrEP users is beginning to change at this initial phase of PrEP implementation and may be seen as a very early sign of more equitable access.

The knowledge provided by this MSM population in Portugal might not reflect the overall reality. However, participants in the Lisbon Cohort of MSM can be seen as a sentinel population given that, even if sampling is not probabilistic, CheckpointLX offers a non-judgmental and inclusive HIV testing service aligned with MSM preferences; therefore, able to capture a relevant target group, and its promotion strategies remained similar over time contributing to the stability of sampling (30-34). It should be noted that the Lisbon Cohort of MSM is not a PrEP users' cohort, and visits do not occur at regular intervals. Therefore, PrEP use among participants is likely underestimated since those on PrEP may be enrolled in hospital care and not need the service CheckpointLX provides. Yet, the proportion of participants with a follow-up visit was higher among PrEP users. Additionally, we lack information about the PrEP use regimen and source for 38% of PrEP users, who were also the earliest PrEP starters since the question was added only in July 2017. This most likely underestimates informal PrEP use before PrEP implementation in Portugal. Limitations related to social desirability and recall bias in reporting behavioral information used to compute eligibility for PrEP are also expected (19).

In conclusion, the uptake of PrEP has been increasing but remains lower than what is observed globally. It was higher among those with behavioral indication, showing an appropriate self-risk assessment. The regimens of PrEP use were similar to other European settings and did not change much with PrEP policy implementation in the Portuguese NHS, while the sources of PrEP varied. A physician prescription in Portugal became the most frequent way of obtaining PrEP, contributing to a safer and more equitable access to a highly effective HIV prevention tool.

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## Tables and Figures

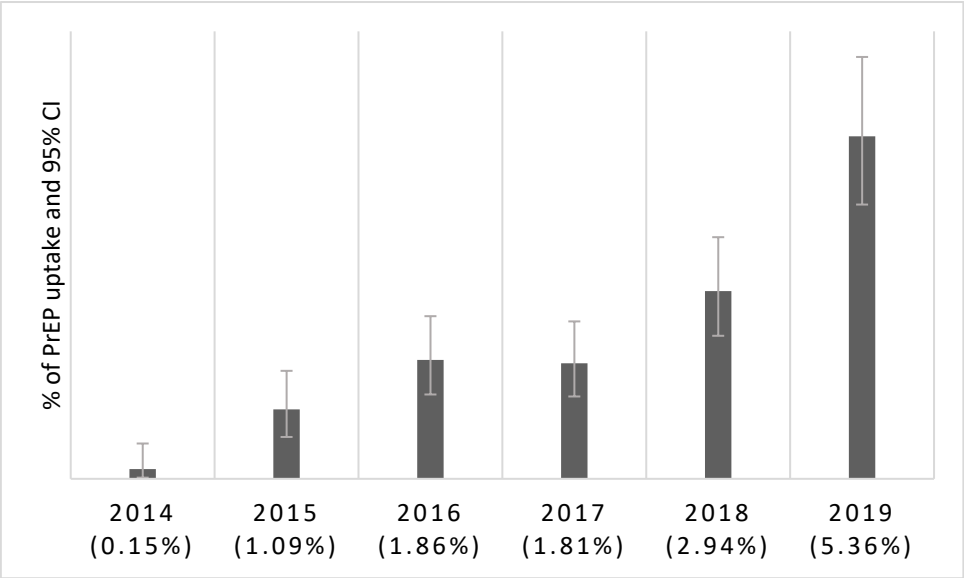


**Figure 1: PrEP uptake by cohort year, % and 95% confidence interval**

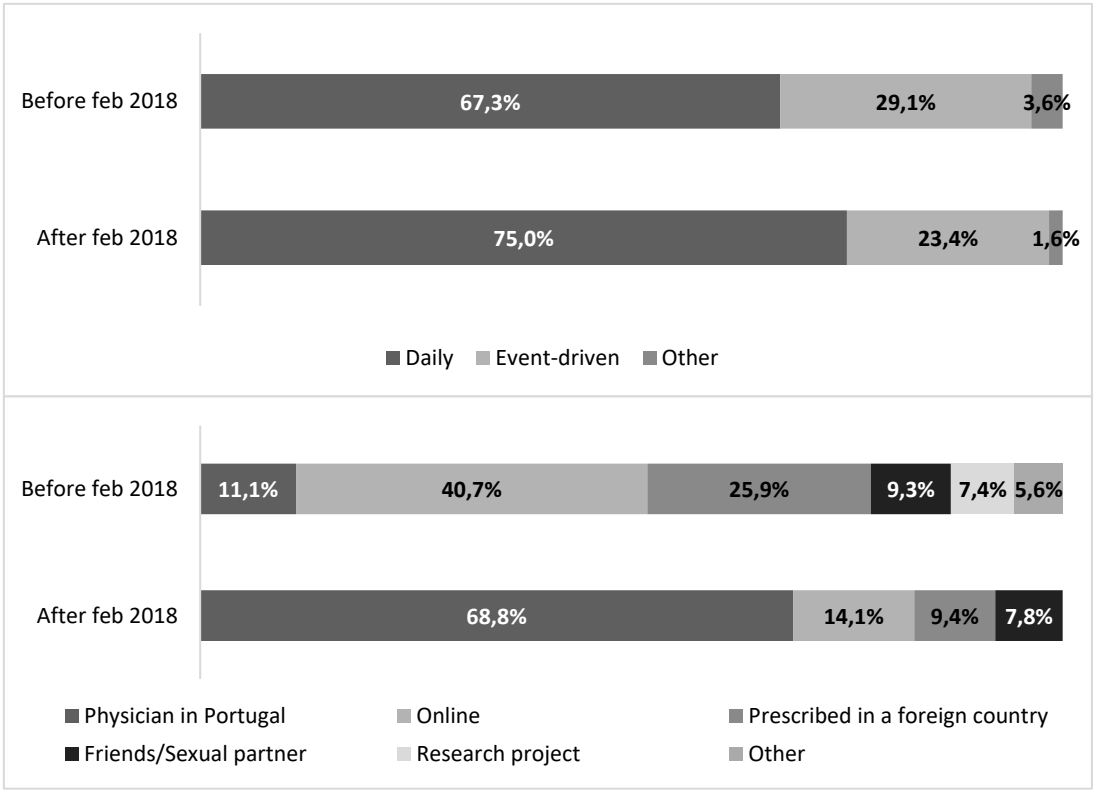


**Figure 2. Distribution of PrEP users according to the regimen and source of the first reported PrEP.**

**Table 1: Comparison of participants' characteristics by PrEP use and timing of first PrEP.**

| | PrEP use | | | Timing of first PrEP | | |
|---|---|---|---|---|---|---|
| **Characteristics** | **No PrEP use** | **PrEP use** | **p-value** | **Before Feb 2018** | **After Feb 2018** | **p-value** |
| | **5966** | **198** | | **131** | **64** | |
| **Age (years)** | | | | | | |
| Mean (SD) | 31.9 (9.51) | 35.6 (9.09) | <0.001[a] | 35.9 (9.28) | 34.6 (8.35) | 0.359[a] |
| Median (P25-P75) | 29.4 (24.7-37.4) | 34.2 (28.7-41.5) | <0.001[b] | 35.4 (29.0-41.6) | 32.5 (28.5-40.8) | 0.351[b] |
| min-max | 18.0-77.8 | 19.1-58.2 | | 19.1-58.0 | 21.5-56.5 | |
| **Country/Region of origin, n (%)** | | | <0.001[c] | | | 0.181[d] |
| Portugal | 4319 (72.9) | 110 (56.1) | | 73 (56.6) | 36 (56.3) | |
| Brazil | 745 (12.6) | 28 (14.3) | | 13 (10.1) | 15 (23.4) | |
| Other European countries | 517 (8.7) | 28 (14.3) | | 21 (16.3) | 6 (9.4) | |
| African country | 151 (2.5) | 6 (3.1) | | 5 (3.9) | 1 (1.6) | |
| Other American countries | 125 (2.1) | 16 (8.2) | | 12 (9.3) | 4 (6.3) | |
| Asia / Middle east / Oceania | 69 (1.2) | 8 (4.1) | | 5 (3.9) | 2 (3.1) | |
| Rather not say/missing | 40 | 2 | | 2 | 0 | |
| **Educational level, n (%)** | | | 0.002[c] | | | 0.390[d] |
| Basic education or less | 255 (4.3) | 3 (1.6) | | 1 (0.8) | 2 (3.3) | |
| Secondary education | 1659 (27.9) | 39 (20.3) | | 25 (19.5) | 13 (21.3) | |
| Professional training | 156 (2.6) | 1 (0.5) | | 1 (0.8) | 0 (0.0) | |
| Post-secondary | 88 (1.5) | 5 (2.6) | | 3 (2.3) | 2 (3.3) | |
| Bachelor | 2384 (40.1) | 81 (42.2) | | 51 (39.8) | 29 (47.5) | |
| Master or Doctoral | 1410 (23.7) | 63 (32.8) | | 47 (36.7) | 15 (24.6) | |
| Other, Rather not say/Missing | 14 | 6 | | 3 | 3 | |
| **Job situation, n (%)** | | | 0.021[c] | | | 0.087[c] |
| Full-time employed or self-employed | 3714 (65.1) | 145 (75.5) | | 96 (75.0) | 46 (75.4) | |
| Part-time, temporary, student, undeclared and sex work | 717 (12.6) | 20 (10.4) | | 10 (7.8) | 10 (16.4) | |
| Unemployed | 364 (6.4) | 9 (4.7) | | 6 (4.7) | 3 (4.9) | |
| Others (others, retirees and students) | 911 (16.0) | 18 (9.4) | | 16 (12.5) | 2 (3.3) | |
| Rather not say/Missing | 260 | 6 | | 3 | 3 | |
| **Sexual orientation, n (%)** | | | 0.325[d] | | | 0.856[d] |
| Gay | 4574 (83.9) | 158 (87.3) | | 106 (87.6) | 49 (86.0) | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Bisexual | 715 (13.1) | 17 (9.4) | | 11 (9.1) | 6 (10.5) | |
| Heterosexual | 63 (1.2) | 1 (0.6) | | 1 (0.8) | 0 (0.0) | |
| Other/Does not use a term/does not know | 101 (1.9) | 5 (2.8) | | 3 (2.5) | 2 (3.5) | |
| Rather not say/missing | 513 | 17 | | 10 | 7 | |
| **Knowledge about PEP at baseline, n (%)** | | | <0.001[c] | | | 0.338[c] |
| Doesn't know | 2986 (55.5) | 50 (28.9) | | 30 (26.1) | 19 (34.5) | |
| Knows | 2393 (44.5) | 123 (71.1) | | 85 (73.9) | 36 (65.5) | |
| Rather not say/missing | 587 | 25 | | 16 | 9 | |
| **Portuguese NHS eligibility for PrEP, n (%)** | | | <0.001[c] | | | 0.294[c] |
| not eligible | 2421 (43.6) | 45 (23.7) | | 33 (26.2) | 11 (17.2) | |
| eligible | 3137 (56.4) | 145 (76.3) | | 93 (73.8) | 50 (78.1) | |
| missing | 408 | 8 | | 5 | 3 | |
| **Number of visits** | | | | | | |
| mean (SD) | 2.6 (2.65) | 5.6 (4.68) | <0.001[a] | 5.7 (4.75) | 5.4 (4.59) | 0.634[a] |
| median (P25-P75) | 2 (1-3) | 5 (2-8) | <0.001[b] | 5 (2-8) | 4 (2-8) | 0.523[b] |
| min-max | 1-65 | 1-27 | | 1 a 27 | 1 a 21 | |

[a] p-value for the t-test for independent samples
[b] p-value for the Mann-Whitney U test
[c] p-value for the chi-square test
[d] p-value for the Fisher exact test
Unless stated otherwise information refers to the most recent visit, in case of non-users, or at the first PrEP report in case of PrEP-users
CI: Confidence interval, HIV: human immunodeficiency virus; NHS: National Health Service; P25: 25th percentile; P75: 75th percentile; PEP: postexposure prophylaxis; PrEP: preexposure prophylaxis; SD: standard deviation

## 5. OVERALL DISCUSSION

This research was based on the participants of the Lisbon Cohort of MSM, which we have described in its characteristics and processes (Paper I). We defined as objectives to respond to issues regarding the eligibility for HIV PrEP – the quantification of the eligible population (Paper III), the association of eligibility with HIV seroconversion (Paper IV), and the transitions between states of eligibility and HIV infection (Paper V); and the uptake of PrEP among cohort participants comparing the period before and after policy implementation in Portugal (Paper VI). The quantification of the eligible population and the ability of the guidelines' criteria to predict HIV were assessed using four different guidelines (Paper III and IV), while the eligible states transitions were defined only with the Portuguese NHS clinical guidelines (Paper V). We have also used cohort data to advocate for the need of PrEP-related data, and for its implementation in Portugal (Paper II).

The establishment of the Lisbon Cohort of MSM was an important step towards a deeper understanding of the HIV epidemic among this key population in Portugal. In 2011, when the cohort started recruiting, an increasing trend in the HIV cases among MSM was evident and alarming (116, 142-144). These increases were of particular concern for several reasons: it happened concurrently with an overall declining trend in the HIV cases (142, 145), it occurred despite high coverage of ART (125), and it affected the younger MSM (115, 143). The need for alternative approaches to prevention was urgent, as well as the need for inclusive and non-judgmental HIV testing services aiming to increase testing coverage and to promote early detection and immediate linkage to care (128, 146). The decision to run CheckpointLX and their vision of bringing together science, training, advocacy, and high-quality services was a unique opportunity to establish a prospective study within the service and a major step forward in the co-production of knowledge.

MSM cohort studies are almost as old as the epidemic and have been crucial to our understanding of HIV transmission and pathogenesis by characterizing risk factors associated with disease acquisition and progression, and the effects of therapy (147-149). Prospective cohort studies are also the best designs to accurately estimate incidence and an opportunity to monitor trends in prevention, treatment, and disease outcomes in well-defined populations (150).

The Lisbon Cohort of MSM was so far able to provide the first estimates of HIV incidence and its predictors (57). It showed a high HIV incidence, from inception in April 2011 to February 2014, of 2.80/100 person-years (95% CI: 1.89-4.14), which was likely to be driven by short-term

contextual and behavioral changes during follow-up (57). We have also provided an extensive description of cohort participants regarding sociodemographic characteristics, the uptake of primary prevention, such as condom use and PEP, HIV testing, and the frequency of HIV risk factors such as psychoactive substance use associated with sex, STI diagnosis, sex work, or exposure to violence (not reported yet). Looking at these indicators throughout the five papers presented in this thesis based on primary data describing three different time-periods, we found similar sociodemographic characteristics such as age, the proportion of those born in Portugal, with high education, and self-identified as gay (Papers I, and III to VI). However, the proportion of those with a previous HIV test at baseline slightly decreased as papers were reporting more recent data (Papers I, and III to IV), probably reflecting the effect of the structure in the concerned community or changes in the population base from which participants come from. The proportion of those who have used PEP and who have a previous diagnosis of an STI was also similar (Paper I and III). This favors no substantial change of selection bias over time, apart from the fact that we may be increasingly capturing first testers, which was expected given CheckpointLX promotion strategies remained similar over time (Paper I) and may have attracted first those already familiar with testing. Nevertheless, a formal test of the time trends of baseline characteristics of those recruited to the cohort would be desirable, particularly since we aim to monitor trends in behavior and infection.

*Table 7: Summary of participants' characteristics included in the research papers.*

| | **Paper I** | **Paper III** | **Paper IV** | **Paper V** | **Paper VI** |
|---|---|---|---|---|---|
| **Period analyzed** | Apr/11-Feb/14 | Mar/14-Mar/18 | Mar/14-Mar/18 | Mar/14-Mar/18 | Apr/11-Jul/19 |
| **Number of participants included (baseline; follow-up; refusals)** | 2183; 804; 923 | 3392 | 1245[1] | 2203; 1177 | 5966; 198[2] |
| **% HIV-reactive at baseline** | 195 (5.9) | 148 (4.0) | 148 (4.0) | n.a. | 184 (2.9) |
| **Person-years of observation** | 893 | n.a. | 1724 | 1656 | 8041; 596 |
| **Study design** | Cross-sectional | Cross-sectional | Longitudinal | Longitudinal | Longitudinal |
| **Age (median; P25-P75)** | 29 (23-36) | 27 (23-35) | 27 (23-35) | 27 (23-35); 27 (23-35) | 29 (25-37); 34 (29-41) |
| **% Born in Portugal** | 75.7 | 73.4 | 77.0 | 77.2; 77.7 | 72.9; 56.1 |
| **% High education** | 58.1 | 58.7 | 57.5 | 57.8; 58.1 | 63.8; 75.0 |
| **% Full-time employed** | n.a. | n.a. | n.a. | 54.8 | 65.1; 75.5 |
| **% Self-identified as gay** | 83.9 | 82.6 | 82.7 | 82.5; 82.3 | 83.9; 87.3 |
| **% Previous HIV testing** | 82.3 | 76.6 | 76.4 | 76.4; 75.6 | |

| | | | | | |
|---|---|---|---|---|---|
| **% Sexual intercourse with an HIV-positive men** | 12.0 | 5.1[3] | n.a. | n.a. | n.a. |
| **% Being paid for sex** | 3.3 | 1.4[4] | n.a. | 1.2[2] | n.a. |
| **% Use of alcohol or drugs before or during sex** | 59.5 | 29.7[5] | n.a. | 28.9[3] | n.a. |
| **% Use of PEP** | 2.7 | 2.1 | n.a. | n.a. | n.a. |
| **% Previous diagnosis of a STI** | 9.9 | 8.5 | n.a. | n.a. | n.a. |

[1] Only follow-up.
[2] Non-PrEP-users; PrEP-users.
[3] Steady partner HIV positive.
[4] And condomless sex.
[5] Excluding alcohol.
HIV: human immunodeficiency virus; n.a.: not applicable; P25: 25$^{th}$ percentile; P75: 75$^{th}$ percentile; PEP: postexposure prophylaxis; STI: sexually transmitted infections.

It is important to remember when discussing selection bias that, by design, we did not expect or aimed at reaching representativeness. It is difficult, not to say impossible, to define a sampling frame for populations such as MSM, often hidden and stigmatized, and for which a probabilistic sampling strategy is inefficient (151-154). Therefore, the extent to which any MSM sample is representative of the overall MSM population is, most likely, impossible to assess, and absolute generalizability regarding the whole MSM population is not expected. However, the comparison with previous studies is helpful in assessing the extent of possible selection bias, that in fact, we could just consider an instance of representation for particular sub-groups, for example, urban young adults, etc. Cohort participants were more self-identified as gay and perhaps more aware of HIV risk since the uptake of HIV testing was higher than in previous studies with MSM samples (122, 155) (Paper I). More recently, a comparison of MSM testing at CheckpointLX with MSM testing at other CBVCT in Portugal found that the former were younger, more frequently born in Portugal, and less in Brazil or African countries, had higher levels of education, self-identified more frequently as gay, and reported more frequently symptoms or other reason related to risk exposure as the motive for testing (156). Any condomless sex in the previous 12 months was more frequently reported by MSM testing at other CBVCT, as well as injected drug use and sex work. Knowledge and use of PEP and PrEP prophylaxis were more frequently reported by CheckpointLX testers. However, HIV prevalence was similar for both groups; Syphilis prevalence was higher among CheckpointLX testers, while Hepatitis C prevalence was lower (156).

From a public health practice perspective, the differences found among MSM testing at CBVCTs suggest that a single HIV testing approach to reach a key population such as MSM is not enough, and diverse responses have the potential to reach different groups of the same key population (156).

From a public health and epidemiological research perspective, all this taken together suggest that cohort participants may represent a younger and highly-educated subset of the overall MSM population, who self-identify as gay and are engaged with the MSM community, at least with the channels CheckpointLX uses to publicize and make its activities known, and who might be on average more aware of prevention options, even the most innovative, and more aware of their risk and the benefits of early detection of HIV infection.

For the above-stated reasons, this cohort stood as a privileged setting to study in Portugal the introduction of a new prevention tool such as PrEP. Our findings suggest that having a strict risk-based approach to the indication for PrEP is likely to preclude some people at risk from receiving PrEP. We showed that the differences in the quantification of the eligible population could be as big as 20 percentage points across guidelines and that as much as 39% of seroconversions occurred among participants defined as ineligible at baseline. Additionally, we have shown that the probability of transition between eligible and ineligible states was almost 50% at 1.5 years. This is indicative that behavioral indication for PrEP is likely to change over time. We have also concluded that MSM defined as ineligible for PrEP, need to be reassessed shortly since that was only a short-term indicator of a lower probability of acquiring HIV and, that once defined as eligible, the risk of transition to HIV infection was much higher than from ineligible. Anticipating or timely detecting changes to an eligible state is challenging and requires discussing appropriate and sustainable preventive options that may include being given access to PrEP even when not indicated by a risk assessment. Empowering individuals to a safe start and stop of PrEP, according to their needs, fits within these findings. Lastly, by having been able to follow this cohort of MSM, we were able to capture very early uptake of PrEP in the pre and post-implementation era in Portugal. Although very significant changes were observed in the means participants used to obtain PrEP before and after implementation of the program, towards a safer use, it still did not reach a more diverse and less advantaged group of MSM.

In spite of the previously mentioned strengths of cohort studies, maintaining contact with cohort participants is of major importance to ensure the validity of results in prospective studies, particularly if subjects lost to follow-up are lost for reasons related to both the exposure and the outcome (157). Given this is a noninterval cohort, the ability to measure attrition is limited, once participants can appear for a follow-up evaluation whenever they find appropriate despite a scheduled time is proposed, though loosely. Additionally, given the characteristics of service provision at CheckpointLX, we are maintaining an anonymous cohort. Participants are identified with only an alphanumeric code, which can be subject to errors at least at two stages: 1. the participant may misinterpret the instructions given and not provide the correct code, and 2. the

peer community healthcare worker may understand or digit the code wrongly. It is possible that the same participant has two different codes, therefore, his visits will not be linked. We have tried to minimize these problems by having the contacts and visits confirmed prior to the administration of the questionnaire and have already corrected some codes.

Despite these challenges, we have previously defined as lost-to-follow-up those that had chosen to participate but appeared for testing only once, excluding those who have been recruited for the cohort within less than a year (57). Attrition was estimated at 52% (57), and later we have updated this estimate to 41.5% among those recruited until July 31, 2019 (data not shown). Efforts have been made to minimize losses to follow-up, such as sending active reminders for follow-up visits. Nevertheless, missing information regarding possible HIV occurrence for slightly more than 40% of the sample is an important limitation. On the bright side, baseline information regarding known predictors of HIV seroconversion, namely sexual intercourse with HIV-positive men, having an HIV-positive steady partner, and condom use with a steady partner or an occasional partner in the previous 12 months were not found to significantly differ between those with and without a follow-up visit (57). As well, the overall proportion of participants eligible for PrEP according to the Portuguese NHS guidelines and by each criterion, and the previous HIV testing were similar between these groups (Paper IV). Even if small differences in sociodemographic characteristics were found (Paper IV), we hypothesize that HIV occurrence among dropouts might be similar or even lower to the one observed among cohort participants. The reasons to hypothesize that HIV incidence may be higher among cohort participants are related to the fact that participation in the cohort depends on the frequency of the HIV testing at CheckpointLX, which is itself influenced by risk uptake. However, we have also found that the major decrease in the survival function was observed at the first two years of follow-up (1 to 0.96), with a slower decrease as the duration of follow-up increased (158). Besides, the possible effect at the community level of treatment as prevention, the differential losses-to follow-up and the effect of risk reduction counseling and participation in a cohort study, known as the Hawthorne effect, can also be playing a role in decreasing the risk of HIV throughout follow-up (158, 159).

It is also important to acknowledge the limitations of the data collection process. Data are self-reported during an interview with a peer community healthcare worker using a structured questionnaire, which includes sensitive issues related to sexual practices or drug use. We hypothesize that the peer-based approach and the anonymity of the process may reduce social desirability bias, and positively influence the completeness of reporting and disclosure of risk. Nevertheless, it is possible that underreporting of perceived less socially accepted behaviors

occurs. Another potential source of bias is the recall of information, particularly when the time between visits is long. Lastly, questionnaires are long (mean duration of follow-up questionnaire is approximately 20 minutes) and repetitive. There are cases of participants not wishing to provide information to the majority of behavioral questions during a follow-up visit due to being tired; therefore, only the participant's code and the test results are recorded. To overcome these difficulties the shift to a self-administered questionnaire is being considered; a non-inferiority randomized trial is underway to inform this decision.

There are also limitations related to the measurement of disease outcomes. CheckpointLX used point-of-care tests for HIV assessment, these tests are not diagnostic tests, and therefore, the HIV infection needs to be confirmed in another setting. CheckpointLX provides a referral to a hospital at the NHS, where the confirmation of HIV infection occurs. Since 2014, no data is communicated back to CheckpointLX or to the cohort despite several attempts to operationalize it. This would be very important, to work with confirmed seroconversions instead of reactive tests, to evaluate the process of linkage to care and the ability to detect recent infections. Other European community-based centers similar to CheckpointLX have shown to have high efficiency in HIV detection and linkage to care (160, 161), it would be good to assess whether the same is occurring in our setting. To overcome this limitation, CheckpointLX has, since August 2019, the opportunity to confirm HIV reactive tests with a molecular qualitative ribonucleic acid HIV test (Xpert® HIV-1 qual, Cepheid), which is also used if an acute-HIV infection is suspected and open new opportunities in the near future.

Even with all the shortcomings of real-world constraints and lack of sustained funding, the cohort is a tremendous joint effort of academic and community partners. At CheckpointLX, participants are invited, and data are collected every day following the highest standards of research in human subjects. And information generated from the cohort has been often used to improve and tailor practice at service provision, and to advocate for PrEP implementation and delivery (Paper II) together with other causes. Additionally, the research priorities are proposed, discussed, and outputs presented by both the community and academic partner, as with all remaining aspects as data collection tools, funding, or equipment.

More research can and need to be continued; new research topics are already being pursued. So far, and particularly regarding the present work, the cohort provided important information to understand critical issues regarding the eligibility criteria and the early uptake of PrEP, which we believe are useful to inform and improve PrEP delivery in Portugal.

## 6. CONCLUSIONS

The implementation and follow-up of the Lisbon Cohort of MSM is a valuable tool to monitor HIV incidence and trends in primary and secondary prevention among HIV-negative MSM testing at a CBVCT center in Lisbon. It is also a privileged setting to study the introduction of a new prevention tool such as the PrEP in Portugal. Data, though describing a well-defined population, seems to have a relevant external validity.

The present study showed differences in the proportion of men belonging to the same population, which would be defined as eligible for PrEP according to four guidelines. It ranged from 46.5% to 67.7%, though all guidelines included the same well-known predictors of HIV seroconversion. The number of HIV infections identified among participants defined as ineligible at baseline also varied according to the guideline used, as well as the magnitude of the risk of HIV seroconversion. These results highlighted the potential for missing people who would benefit from PrEP when a strict risk-based approach is used to determine who is eligible to receive PrEP.

Regarding the measurement of eligibility throughout the follow-up and the transitions to different states, we observed that the intensity of transitions between being or not eligible for PrEP was similar, but its probability increased with time, up to almost 50%. The probability of transition eligible-HIV infection was always higher than from ineligible but being defined as ineligible was only a short-time indicator of a lower probability of acquiring HIV. Additionally, once an individual meets any of the eligibility criteria for PrEP, he is at a much higher risk of seroconversion. These results showed that the indication for PrEP is likely to change over time and that the anticipation or timely detection of changes to an eligible state demands a well-timed delivery of PrEP.

Finally, we detected an increase in PrEP uptake, particularly after its introduction to the Portuguese NHS. However, uptake is still lower than what is observed globally; the reason for it was not directly studied, but the identification of structural and individual barriers is urgently needed. The regimens of PrEP use did not change much after PrEP policy implementation in the Portuguese NHS, while the sources of PrEP changed significantly. A physician prescription in Portugal became the most frequent way of obtaining PrEP, contributing to safer and more equitable access to a highly effective HIV prevention tool.

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**ANNEXES**

**Annex 1. Short screening form.**

REDE DE RASTREIO

# GUIA DE TRIAGEM
Versão 2019/07

ID Rastreio [ ]
ID Participante [ ]

## IDENTIDADE SEXUAL

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| P0.1 | Sexo atribuído à nascença | Masculino [ ] | Feminino [ ] | Outros [ ] | | | |
| P0.2 | Identidade de género | Masculino [ ] | Feminino [ ] | Outros [ ] | | | |
| P0.3 | Tem sexo com | Homens [ ] | Mulheres [ ] | Ambos [ ] | | | |
| P0.4 | Quantos anos tens? [ ] | < 12 [Não admitir para rastreio] | ≥ 12 [Triar para rastreio] | | | | |
| P0.5 | Em que país nasceste? | [ ] | | | | | |

## VIH (deteção precoce aos 30 dias | fim de período janela aos 90 dias)

| | | | |
|---|---|---|---|
| P1. | Alguma vez foste diagnosticado com VIH? | Sim [P5] | Ñ/NS [P1.1] |
| P1.1 | Fizeste o teste para VIH nos últimos 12 meses? | Sim [Rastrear] | Nunca fez/Ñ/NS [Rastrear] |

## SÍFILIS (deteção precoce aos 30 dias | fim de período janela aos 90 dias)

| | | | |
|---|---|---|---|
| P2 | Alguma vez foste diagnosticado com sífilis? | Sim [Ligar a consulta de IST] | Ñ/NS [P2.1] |
| P2.1 | Fizeste o teste para sífilis nos últimos 12 meses? | Sim [Rastrear] | Nunca fez/Ñ/NS [Rastrear] |

## VHB (deteção precoce aos 30 dias | fim de período janela aos 60 dias)

| | | | | | |
|---|---|---|---|---|---|
| P3. | Alguma vez foste diagnosticad@ com hepatite B? | Sim [P5] | | Não/Não sei [P3.1] | |
| P3.1 | Tens 3 doses de vacina contra a hepatite B? | Sim [Não rastrear] | Ainda não [P3.2] | Não/Não sei [P3.3 se PT; P3.4 se outro] | |
| P3.2 | Tomaste alguma dose da vacina nas últimas 2 semanas? | Sim/não sei [Adiar rastreio] | | Não [Rastrear] | |
| P3.3 | Nasceu em Portugal: em que ano? [ ] | < 1990 [Test] | ≥1990 | [Não rastrear, confirmar vacinas na app MySNS carteira] | |
| P3.4 | Nasceu noutro país: endémico para hepatite B? | Sim [Se P0.5 = P3.5 rastrear, alta prioridade] | | Não [rastrear – baixa prioridade] | |

P3.5 Países endémicos para VHB: África do Sul; Albânia; Angola; Arábia Saudita; Argélia; Azerbaijão; Bangladeche; Belize; Benim; Bielorrússia; Brunei; Bulgária; Burquina Faso; Burundi; Butão; Cabo Verde; Camboja; Cazaquistão; China; Chipre; Colômbia; Congo; Coreia do Sul; Costa do Marfim; Djibuti; Equador; Eritreia; Estado Federado da Micronésia; Etiópia; Fiji; Filipinas; Gabão; Gâmbia; Geórgia; Guiné Bissau; Guiné; Guiné Equatorial; Haiti; Iémen; Ilhas Marshall; Ilhas Salomão; Itália; Jamaica; Kiribati; Kosovo; Laos; Libéria; Líbia; Madagáscar; Maláui; Mali; Mauritânia; Mianmar; Moçambique; Moldávia; Mongólia; Namíbia; Nauru; Níger; Nigéria; Niue; Nova Zelândia; Omã; Palau; Papua Nova Guiné; Paquistão; Perú; Quénia; Quirguistão; Republica Central Africana; Republica Democrática do Congo; Republica Dominicana; Roménia; Ruanda; Rússia; Samoa; Senegal; Serra Leoa; Singapura; Síria; Somália; Sri Lanka; Sudão; Sudão do Sul; Suazilândia; Suriname; Tailândia; Taiti; Tajiquistão; Togo; Tonga; Tunísia; Turquia; Tuvalu; Uganda; Uzbequistão; Vanuatu; Vietnam; Zâmbia; Zimbabué.

## VHC (deteção precoce aos 90 dias | fim de período janela aos 180 dias)

| | | | |
|---|---|---|---|
| P4. | Alguma vez foste diagnosticado com VHC? | Sim [P5] | Não [P4.1] |
| P4.1 | Fizeste o teste para VHC nos últimos 12 meses? | Sim/Ñ/NS [P4.4] | Nunca fez teste [P4.2] |
| P4.2 | Nascimento noutro país: endémico para VHC? | Sim [Se P0.5 = P4.3, rastrear] | Não [P4.4] |

P4.3 Países endémicos para VHC: Azerbaijão, Benim, Camarões, Camboja, Cazaquistão, Congo (República Democrática do), Costa do Marfim, Egito, Gabão, Gâmbia, Geórgia, Iémen, Iraque, Itália, Letónia, Lituânia, Moldova (República da), Mongólia, Nigéria, Paquistão, Porto Rico, Quirguistão, Roménia, Rússia (Federação da), Tailândia, Taiwan, Tajiquistão, Turquemenistão, Ucrânia e Uzbequistão

| | | | |
|---|---|---|---|
| P4.4 | Aconteceu alguma destas situações na vida/desde o último rastreio? | Sim [Rastrear] | Não [Não rastrear] |

*Leia todas as situações à pessoa, peça para que diga sim no final, caso tenha acontecido alguma das situações na vida/desde o último rastreio:*

Ter sexo anal sem uso de preservativo
Ter sexo em grupo sem preservativo durante a penetração (vaginal ou anal) ou não ter usado um preservativo novo na mudança de parceiro
Ter práticas de *fisting* (inserção da mão além do nó dos dedos no ânus ou vagina) sem luva ou não ter usado luva nova na mudança de parceiro
Ter partilhado o boião de lubrificante durante práticas de *fisting* em grupo
Ter partilhado material para lavagem retal interna (*douching*, enema ou chuca)
Ter partilhado material para snifar drogas (inclui a garrafa de *poppers* se encostada à asa do nariz)
Ter partilhado material no consumo de substâncias por via injetada (inclui frasco de esteroides)
Ter partilhado material para fumar drogas que possam queimar os lábios (inclui cachimbos)
Ter feito piercings, tatuagens, manicure ou pedicure onde houve partilha de material (ex. casa, rua, prisão ou tropa)
Ter recebido transfusão de sangue ou órgãos ou ter sido submetido a cirurgias antes de 1992
Estar a fazer hemodiálise de longa duração
Ter contacto de sangue com sangue em contexto de trabalho

## REFERENCIAÇÃO HOSPITALAR

| | | | |
|---|---|---|---|
| P5. | Procuras acesso à confirmação e/ou tratamento para a infeção? | Sim [P5.1] | Não [Não rastrear] |
| P5.1 | Trazes identificação e prova da infeção com o teu nome? | Sim [Não rastrear] | Não [Rastrear] |

## RESULTADOS

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **VIH** | Não reativo | Reativo | [Aceita/Recusa ligação ao SNS] | **SIFLIS** | Não reativo | Reativo | [Aceita/Recusa ligação ao SNS] |
| **HEP B** | Não reativo | Reativo | [Aceita/Recusa ligação ao SNS] | **HEP C** | Não reativo | Reativo | [Aceita/Recusa ligação ao SNS] |

**Annex 2. English translation of the current version of the questionnaire**

## IDENTIFICATION

COHORT QUESTIONNAIRE

### 1. IDQuest

Please write your answer here:

|__|__|__|__|__|__|__|__|__|__|

### 2. Type of questionnaire*

Please select only one of the following options:

- Baseline
- Follow-up
- Refusal

### 3. Peer counselor

Please write your answer here:

### 4. How did you hear about CheckpointLX? (Answer this question only if the following conditions are true: the answer is 'Baseline' or 'Refusal' in question 2)

Enter comments only when choosing an answer

Please select all that apply and provide a comment:

- Through friends
- Promotional material
- Internet
- Media
- I passed the location/street
- Health services
- CheckpointLX screening in outreach (saunas, etc.)
- Other

5. Cohort code (Answer this question only if the following conditions are true: the answer is 'Baseline' or 'Follow-up' in question 2)

Please write your answer here:

Birthdate (YYMMDD) – First name and last name (two first letters in capital format), E.g., 540712JOPE

6. Age (Answer this question only if the following conditions are true: the answer is 'Baseline' or 'Refusal' in question 2)

The answer must be between 18 and 99

Only an integer value can be entered in this field.

Please write your answer here:

7. Gender

Please select only one of the following options:

- Male
- Transgender

## HIV TEST

8. Have you ever been tested for HIV and had access to the result? (Answer this question only if the following conditions are true: the answer is 'Baseline' or 'Refusal' in question 2)

Please select only one of the following options:

- Yes
- No
- I prefer not to answer

9. What were the reasons for not being tested before/not collecting the result? (Answer this question only if the following conditions are true: the answer is 'Baseline' in question 2 and 'No' in question 8)

Please select all that apply:

- I took the test, but I did not get the result
- I had not started my sex life at the time
- I had situations of risk but did not want to know the result
- Fear that the result was not anonymous or confidential
- The test was expensive
- I did not feel bad

- I had not been in at-risk situations
- I was afraid of the result
- I did not think it was important to take the test
- I did not know where to take the test.
- I was too busy
- Other [specify]:

10. How many times were you tested previously/since the last test at CheckpointLX? (Answer this question only if one of the following conditions are true: the answer is 'Yes' in question 8 OR the answer is 'No' in question 8 and 'I did the test, but I did not get the result' response in question 9)

Your response should be at least 1

Only an integer value can be entered in this field.

Please write your answer here:

1. in case the participant does not want to respond, register 777
2. in case the participant does not know, register an estimate

11. Where did you take your last test? (Answer this question only if the following conditions are true: the answer is 'Baseline' in question 2 and 'Yes' in question 8 OR the answer is 'Baseline' in question 2 and 'No' in question 8 and 'I did the test, but I did not get the result' response in question 9 OR the answer is 'Follow-up' in question 2)

Please select only one of the following options:

- In this center (CheckpointLX)
- In another community center
- With a Family doctor (National Health Service)
- At a Public hospital (National Health Service)
- At a Private hospital or clinic
- At a private laboratory
- At an occupational medicine center
- At a public network of voluntary counseling and testing center (CAD)
- At Integrated Response Centers (CRI)/ Drug Treatment teams (ET) (CAT)
- Abroad
- While donating blood
- In a mobile unit
- At home (with a self-test kit)
- At a bar, pub, sauna, nightclub
- I prefer not to answer
- Other [specify]:

12. Date of the last test (Answer this question only if the following conditions are true: the answer is 'Yes' in question 8 OR the answer is 'No' in question 8 and 'I did the test but I did not get the result' in question 9 OR the answer is 'Follow-up' in question 2)

Please write your answer here:

1. In case the participant does not know, register estimate for the year and month

2. In case the participant does not know the month, register the year and the estimate for the month

3. In case the participant does not want to respond, register 7777 77

13. Result (Answer this question only if the following condition is true: the answer is 'Yes' in question 8)

Please select only one of the following options:

- Negative
- Undetermined
- Positive
- I don't know
- I prefer not to answer

14. Why do you want to get tested? (Please select the appropriate position for each item)

| | Yes | No | I prefer not to answer |
|---|---|---|---|
| My partner asked me to take the test | ○ | ○ | ○ |
| Before I stop using condom with my partner | ○ | ○ | ○ |
| I am in the beginning of a new relationship | ○ | ○ | ○ |
| I am at the end of the relationship with my usual partner | ○ | ○ | ○ |
| My partner was diagnosed with HIV / told me that they are HIV+ | ○ | ○ | ○ |
| Window period in the previous test | ○ | ○ | ○ |
| Symptomatology / medical indication | ○ | ○ | ○ |
| To know my health status / Routine test | ○ | ○ | ○ |
| There was an accident while using a condom (broke/stayed in) | ○ | ○ | ○ |
| Perception of HIV exposure (More than 3 months ago) | ○ | ○ | ○ |
| Perception of HIV exposure (less than three months ago) | ○ | ○ | ○ |
| I received the reminder from my participation in the cohort (Answer this question only if the following conditions are true: the answer is 'Follow-up' in question 2) | ○ | ○ | ○ |
| Other [specify] | ○ | ○ | ○ |

15. Other [specify] (Answer this question only if the following condition is true: the answer is 'Other' in question 14)

16. Have you ever taken the HIV test at CheckpointLX? (Answer this question only if one of the following conditions are true: the answer is 'Baseline' in question 2 AND 'any of the options excluding "In

this center (CheckpointLX)"' in question 11 OR the answer is 'Refusal' in question 2 and 'Yes' response in question 8)

Please select only one of the following options:

- Yes
- No
- I don't know
- I prefer not to answer

17. Date of the last test at CheckpointLX (Answer this question only if the following condition is true: the answer is 'Baseline' in question 2 AND the answer is 'Yes' in question 16)

Please write your answer here:

1. In case the participant does not know, register an estimate for the year and month

2. In case the participant does not know the month, register the year and the estimate for the month

3. In case the participant does not want to respond, register 7777 77

18. How many tests did you do at CheckpointLX? (Answer this question only if the following conditions is true: the answer is 'Yes' in question 16 OR the answer is 'Baseline' in question 2 and the answer is 'In this center (CheckpointLX)' in question 11)

Your response should be at least 1

Only an integer value can be entered in this field.

Please write your answer here:

1. In case the participant does not want to respond, register 777

2. In case the participant does not know, register an estimate

19. Since your last visit, did you receive a reminder from CheckpointLX (email, SMS, call)? (Answer this question only if the following condition is true: the answer is 'Follow-up' in question 2)

Please select only one of the following options:

- Yes, last week
- Yes, last month
- Yes, over a month ago
- No
- I did not consent to the reminder system

If you have received more than one reminder, report the last one.

## SEX LIFE

20. How would you define your sexual orientation? (Answer this question only if the following condition is true: the answer is 'Baseline' or 'Refusal' in question 2)

Please select only one of the following options:

- Homosexual/Gay
- Bisexual
- Heterosexual (who has sex with men)
- Other
- I do not usually use a term
- I prefer not to answer

21. Have you ever been a victim of verbal or physical abuse because of your sexual orientation or gender identity? (Answer this question only if the following condition is true: the answer is 'Baseline' in question 2)

Please select only one of the following options:

- Yes
- No
- I prefer not to answer

22. In the past 12 months (since the last test at CheckpointLX), have you been a victim of verbal or physical abuse because of your sexual orientation or gender identity? (Answer this question only if the following conditions are true: the answer is 'Baseline' in question 2 OR the answer is 'Follow-up' in question 2)

Please select only one of the following options:

- Yes
- No
- I prefer not to answer

23. In the past 12 months (since the last test at CheckpointLX), in which context have you been a victim of verbal or physical abuse because of your sexual orientation or gender identity? (Answer this question only if the following condition is true: the answer is 'Yes' in question 22)

Please select the appropriate position for each item:

| | Yes | No | I prefer not to answer |
|---|---|---|---|
| At the workplace/school | ○ | ○ | ○ |
| In the street/neighborhood | ○ | ○ | ○ |
| Within my family | ○ | ○ | ○ |
| In relationships with sexual partners | ○ | ○ | ○ |
| On social networks | ○ | ○ | ○ |
| Other [specify] | ○ | ○ | ○ |

24. Other [specify] (Answer this question only if the following condition is true: the answer is 'Other' in question 23)

Please write your answer here:

25. Have you ever had (since the last test at CheckpointLX) anal intercourse (insertive or receptive) with a man? (Answer this question only if the following conditions are true: the answer is 'Baseline' in question 2 OR the answer is 'Follow-up' in question 2)

Please select only one of the following options:

- Yes
- No
- I prefer not to answer

26. How old were you when you first had anal sex with a man for the first time? (Answer this question only if the following conditions are true: the answer is 'Baseline' in question 2 AND the answer is 'Yes' in question 25)

Only an integer value can be entered in this field.

Please write your answer here:

1. In case the participant does not want to respond, register 777

2. In case the participant does not know, register an estimate

27. Which is your position during anal sex? (Answer this question only if the following conditions are true: the answer is 'Baseline' in question 2 AND the answer is 'Yes' in question 25)

Please select only one of the following options:

- Exclusively insertive
- Exclusively receptive
- Both
- I do not usually have anal sex with men
- I prefer not to answer

28. Did you have sexual intercourse in the last 12 months (since the last test at CheckpointLX)? (Answer this question only if the following conditions are true: the answer is 'Baseline' in question 2 OR the answer is 'Follow-up' in question 2)

Please select only one of the following options:

- Yes
- No
- I prefer not to answer

29. In the last 12 months (since the last test at CheckpointLX) did you have sexual intercourse with (Answer this question only if the following condition is true: the answer is 'Yes' in question 28):

| | Yes | No | I prefer not to answer |
|---|---|---|---|
| Men | ○ | ○ | ○ |
| Women | ○ | ○ | ○ |
| Transgender/Transsexual | ○ | ○ | ○ |

30. In the last 12 months (since the last test at CheckpointLX), did you have penetrative sex (vaginal and/or anal insertive or receptive sex) and without condom, with partners that you know that they are (Answer this question only if the following condition is true: the answer is 'Yes' in question 28):

Please select the appropriate position for each item:

| | Yes | No | Does not know | I prefer not to answer |
|---|---|---|---|---|
| Male | ○ | ○ | ○ | ○ |
| Transgender/ Transsexual | ○ | ○ | ○ | ○ |
| Sex workers (even if you have not paid) | ○ | ○ | ○ | ○ |
| Men with HIV | ○ | ○ | ○ | ○ |
| Injected substance users (excluding for medical reasons) | ○ | ○ | ○ | ○ |
| Female | ○ | ○ | ○ | ○ |
| Threesomes/Group sex | ○ | ○ | ○ | ○ |

31. In your opinion, when was the last time you were at risk of getting infected by HIV? (Answer this question only if the following condition is true: the answer is 'Baseline' in question 2)

Please select only one of the following options:

- In the last 24 hours
- Last week
- In the last month
- In the last 6 months
- In the last 12 months
- More than 12 months ago
- I have never been at risk of contracting HIV

32. In your opinion, when have you been at risk for HIV infection for the last time? (Answer this question only if the following condition is true: the answer is 'Follow-up' in question 2)

Please select only one of the following options:

- In the last 24 hours
- Last week
- In the last month
- In the last 6 months
- Since the last test at CheckpointLX

- I have not had any risky situations since the last test in CheckpointLX

## STEADY PARTNER

33. In the last 12 months (since the last test at CheckpointLX), did you have a steady partner?

Please select only one of the following options:

- Yes
- No
- I prefer not to answer

- Including current steady partner
- Someone with whom you have an emotional attachment and with whom you have sex regularly, not necessarily monogamous

34. Do you currently have a steady partner? (Answer this question only if the following condition is true: the answer is 'Yes' in question 33)

Please select only one of the following options:

- Yes
- No
- I prefer not to answer

- Someone with whom you have an emotional attachment and with whom you have sex regularly, not necessarily monogamous

35. How many steady partners did you have in the last 12 months (since the last test at CheckpointLX)? (Answer this question only if the following condition is true: the answer is 'Yes' in question 33)

Only numbers can be entered in this field. Your response should be at least 1

Please write your answer here:

1. In case the participant does not want to respond, register 777

2. In case the participant does not know, register an estimate

36. When did you start the relationship with your steady partner 1? (Answer this question only if the following condition is true: the answer is 'equal or superior to 1' in question 35)

Please write your answer here:

1. Consider the steady partner 1 as the main or the last
2. In case the participant does not know, register an estimate for the year and month
3. In case the participant does not know the month, register the year and an estimate for the month

4. In case the participant does not want to answer, register 7777 77

37. What is the gender of your steady partner 1? (Answer this question only if the following condition is true: the answer is 'equal or superior to 1' in question 35)

Please select only one of the following options:

- Male
- Female
- Transgender
- I prefer not to answer

38. When did you start the relationship with your steady partner 2? (Answer this question only if the following condition is true: the answer is 'equal or superior to 2' in question 35)

Please write your answer here:

1. In case the participant does not know, register an estimate for the year and month
2. In case the participant does not know the month, register the year and an estimate for the month
3. In case the participant does not want to answer, register 7777 77

39. What is the gender of your steady partner 2? (Answer this question only if the following condition is true: the answer is 'equal or superior to 2' in question 35)

Please select only one of the following options:

- Male
- Female
- Transgender
- I prefer not to answer

40. When did you start the relationship with your steady partner 3? (Answer this question only if the following condition is true: the answer is 'equal or superior to 3' in question 35)

Please write your answer here:

1. In case the participant does not know, register an estimate for the year and month
2. In case the participant does not know the month, register the year and an estimate for the month
3. In case the participant does not want to answer, register 7777 77

41. What is the gender of your steady partner 3? (Answer this question only if the following condition is true: the answer is 'equal or superior to 3' in question 35)

Please select only one of the following options:

- Male

- Female
- Transgender
- I prefer not to answer

42. When did you start the relationship with your steady partner 4? (Answer this question only if the following condition is true: the answer is 'equal or superior to 4' in question 35)

Please write your answer here:

1. In case the participant does not know, register an estimate for the year and month
2. In case the participant does not know the month, register the year and an estimate for the month
3. In case the participant does not want to answer, register 7777 77

43. What is the gender of your steady partner 4? (Answer this question only if the following condition is true: the answer is 'equal or superior to 4' in question 35)

Please select only one of the following options:

- Men
- Women
- Transgender
- I prefer not to answer

44. When did you start the relationship with your steady partner 5? (Answer this question only if the following condition is true: the answer is 'equal or superior to 5' in question 35)

Please write your answer here:

1. In case the participant does not know, register an estimate for the year and month
2. In case the participant does not know the month, register the year and an estimate for the month
3. In case the participant does not want to respond, register 7777 77

45. What is the gender of your steady partner 5? (Answer this question only if the following condition is true: the answer is 'equal or superior to 5' in question 35)

Please select only one of the following options:

- Male
- Female
- Transgender
- I prefer not to answer

46. In the last 12 months (since the last test at CheckpointLX), did you have any of the following sexual practices with your steady partner? (Answer this question only if the following conditions are true: the answer is 'Yes' in question 34 OR the answer is 'Yes' in question 33)

Please select the appropriate position for each item:

| | Yes | No | I prefer not to answer |
|---|---|---|---|
| Oral sex with ejaculation in your partner's mouth | ○ | ○ | ○ |
| Oral sex with ejaculation in your mouth | ○ | ○ | ○ |
| Fisting (insertive or receptive) | ○ | ○ | ○ |
| Anal penetration | ○ | ○ | ○ |
| Vaginal penetration | ○ | ○ | ○ |

47. In the last 12 months (since the last test at CheckpointLX), how often did you use condoms for anal penetration (insertive or receptive) with a steady partner? (Answer this question only if the following conditions are true: the answer is 'Yes' in question 46 AND the answer is 'Yes' in question 33)

Please select only one of the following options:

- Always
- Often
- Occasionally
- Rarely
- Never
- I prefer not to answer

48. During your last anal penetration (insertive or receptive) with a steady partner, did you use a condom? (Answer this question only if the following conditions are true: the answer is 'Yes' in question 46 AND the answer is 'Yes' in question 33)

Please select only one of the following options:

- Yes
- No
- I prefer not to answer

49. Which of the following is your steady partner 1? (Answer this question only if the following condition is true: the answer is 'equal or superior to 1' in question 35)

Please select only one of the following options:

- HIV-negative
- HIV-positive
- I don't know
- I prefer not to answer

50. Your steady partner 1 last viral load was? (Answer this question only if the following condition is true: the answer is 'HIV-positive' in question 49)

Please select only one of the following options:

- Detectable

- Undetectable
- I don’t know
- I prefer not to answer

52. Is your steady partner 1 currently on antiretroviral treatment? (Answer this question only if the following condition is true: the answer is 'HIV-positive' in question 49)

Please select only one of the following options:

- Yes
- No
- I don’t know
- I prefer not to answer

53. Your steady partner 2 is? (Answer this question only if the following condition is true: the answer is 'equal or superior to 2' in question 35)

Please select only one of the following options:

- HIV-negative
- HIV-positive
- I don’t know
- I prefer not to answer

54. Your steady partner’s 2 last viral load was? (Answer this question only if the following condition is true: the answer is 'HIV-positive' in question 53)

Please select only one of the following options:

- Detectable
- Undetectable
- I don’t know
- I prefer not to answer

56. Is your steady partner 2 currently on antiretroviral treatment? (Answer this question only if the following condition is true: the answer is 'HIV-positive' in question 53)

Please select only one of the following options:

- Yes
- No
- I don’t know
- I prefer not to answer

57. Your steady partner 3 is? (Answer this question only if the following condition is true: the answer is 'equal or superior to 3' in question 35)

Please select only one of the following options:

- HIV-negative
- HIV-positive
- I don’t know
- I prefer not to answer

58. What was your steady partner’s 3 last viral load? (Answer this question only if the following condition is true: the answer is 'HIV-positive' in question 57)

Please select only one of the following options:

- Detectable
- Undetectable
- I don’t know
- I prefer not to answer

60. Is your steady partner 3 currently on antiretroviral treatment? (Answer this question only if the following condition is true: the answer is 'HIV-positive' in question 57)

Please select only one of the following options:

- Yes
- No
- I don’t know
- I prefer not to answer

61. Your steady partner 4 is? (Answer this question only if the following condition is true: the answer is 'equal or superior to 4' in question 35)

Please select only one of the following options:

- HIV-negative
- HIV-positive
- I don’t know
- I prefer not to answer

62. What was your steady partner’s 4 last viral load? (Answer this question only if the following condition is true: the answer is 'HIV-positive' in question 61)

Please select only one of the following options:

- Detectable
- Undetectable
- I don’t know
- I prefer not to answer

64. Is your steady partner 4 currently on antiretroviral treatment? (Answer this question only if the following condition is true: the answer is 'HIV-positive' in question 61)

Please select only one of the following options:

- Yes
- No
- I don’t know
- I prefer not to answer

65. Which of the following is your steady partner 5? (Answer this question only if the following condition is true: the answer is 'equal or superior to 5' in question 35)

Please select only one of the following options:

- HIV-negative
- HIV-positive
- I don’t know
- I prefer not to answer

66. What was your steady partner’s 5 last viral load? (Answer this question only if the following condition is true: the answer is 'HIV-positive' in question 65)

Please select only one of the following options:

- Detectable
- Undetectable
- I don’t know
- I prefer not to answer

68. Is your steady partner 5 currently on antiretroviral treatment? (Answer this question only if the following condition is true: the answer is 'HIV-positive' in question 65)

Please select only one of the following options:

- Yes
- No
- I don’t know
- I prefer not to answer

69. Are any of your steady partners a CheckpointLX user? (Answer this question only if the following condition is true: the answer is 'Yes' in question 33)

Please select only one of the following options:

- Yes
- No
- I don’t know
- I prefer not to answer

70. How many of your steady partners are CheckpointLX users? (Answer this question only if the following conditions are true: the answer is 'higher than 1' in question 35 AND the answer is 'Yes' in question 69)

Your response should be at least 1

Only numbers can be entered in this field.

Please write your answer here:

1. In case the participant does not want to respond, register 777

2. In the event that the participant does not know, register an estimate

## OCCASIONAL PARTNER

71. In the last 12 months (since the last test at CheckpointLX), did you have sex (oral, anal, vaginal) for the purpose of getting money, goods, or drugs?

Please select only one of the following options:

- Yes
- No
- I prefer not to answer

72. In the last 12 months (since the last test at CheckpointLX), did you have sex (oral, anal, vaginal) and/or other sexual practices with occasional partners?

Please select only one of the following options:

- Yes
- No
- I prefer not to answer

73. In the last 12 months (since the last test at CheckpointLX), did you have anal sex (penetration) with how many occasional partners? (Answer this question only if the following condition is true: the answer is 'Yes' in question 72)

Please write your answer here:

74. In the last 12 months (since the last test at CheckpointLX), did you have any of the following sexual practices with an occasional partner? (Answer this question only if the following condition is true: the answer is 'Yes' in question 72)

Please select the appropriate position for each item:

| | Yes | No | I don't know |
|---|---|---|---|
| Oral sex with ejaculation in your partners' mouth | ○ | ○ | ○ |
| Oral sex with ejaculation in your mouth | ○ | ○ | ○ |
| Fisting (insertive or receptive) | ○ | ○ | ○ |
| Anal penetration | ○ | ○ | ○ |
| Vaginal penetration | ○ | ○ | ○ |

75. In the last 12 months (since the last test at CheckpointLX), how often did you use condoms for anal penetration (insertive or receptive) with occasional partners? (Answer this question only if the following conditions are true: the answer is 'Yes' in question 72 AND the answer is 'Yes' in question 74)

Please select only one of the following options:

- Always
- Often
- Occasionally
- Rarely
- Never
- I prefer not to answer

76. At your last anal penetration (insertive or receptive) with an occasional partner, did you use a condom? (Answer this question only if the following conditions are true: the answer is 'Yes' in question 72 AND the answer is 'Yes' in question 74)

Please select only one of the following options:

- Yes
- No
- I prefer not to answer

77. Are any of the occasional partners you have had in the last 12 months (since the last test at CheckpointLX) HIV positive? (Answer this question only if the following condition is true: the answer is 'Yes' in question 72)

Please select only one of the following options:

- Yes
- No
- I don't know
- I prefer not to answer

78. The viral load of your HIV-positive occasional partner(s) is? (Answer this question only if the following conditions are true: the answer is 'Yes' in question 72 AND the answer is 'Yes' in question 77):

Please select the appropriate position for each item:

| | Yes | No | I don’t know |
|---|---|---|---|
| Undetectable | ○ | ○ | ○ |
| Detectable | ○ | ○ | ○ |
| I don´t know his(their) viral load | ○ | ○ | ○ |

79. Are any of the occasional partners you´ve had in the last 12 months (since the last test at CheckpointLX), a CheckpointLX user? (Answer this question only if the following condition is true: the answer is 'Yes' in question 72)

Please select only one of the following options:

- Yes
- No
- I don’t know
- I prefer not to answer

80. How many of your occasional partners are CheckpointLX users? (Answer this question only if the following condition is true: the answer is 'Yes' in question 79)

Your response should be at least 1

In this field, only an integer value can be entered

Please write your answer here:

1. In case the participant does not want to respond, register 777

2. In the event that the participant does not know, register an estimate

81. Where do you usually meet your occasional partners? (Answer this question only if the following conditions are true: the answer is 'Baseline' in question 2 AND the answer is 'Yes' in question 72)

| | Yes | No | I don’t know |
|---|---|---|---|
| Discos and gay bars | ○ | ○ | ○ |
| Saunas | ○ | ○ | ○ |
| “Dark rooms” (including sex-shops) | ○ | ○ | ○ |
| Sex clubs | ○ | ○ | ○ |
| Internet | ○ | ○ | ○ |
| Mobile applications | ○ | ○ | ○ |
| Cruising sites (WCs, parks, parking lots, etc.) | ○ | ○ | ○ |
| Street (casually) | ○ | ○ | ○ |
| Gym | ○ | ○ | ○ |
| Friends | ○ | ○ | ○ |
| Newspaper ads | ○ | ○ | ○ |
| Other [specify] | ○ | ○ | ○ |

82. Other [specify] (Answer this question only if the following condition is true: the answer is 'Other' in question 81)

## CONDOM

84. In the last 12 months (since the last test at CheckpointLX), why did you have anal sex without using condoms? (Answer this question only if the following conditions are true: the answer is 'Yes' in question 25 AND the answer is 'Yes' in question 46 AND the answer wasn't 'Always' in question 47 AND the answer is 'Yes' in question 33 **OR** the answer is 'Yes' in question 25 AND the answer is 'Yes' in question 34 AND the answer is 'Yes' in question 46 AND the answer wasn't 'Always' in question 47 **OR** the answer is 'Yes' in question 25 AND the answer is 'Yes' in question 74 AND the answer wasn't 'Always' in question 75):

Please select the appropriate position for each item:

| | Yes | No | I don't know |
|---|---|---|---|
| I had a steady partner | ○ | ○ | ○ |
| I trusted the sexual partner | ○ | ○ | ○ |
| I don't use condoms with my steady partner since we both tested for HIV and were negative | ○ | ○ | ○ |
| My partner said he is HIV-negative | ○ | ○ | ○ |
| My partner said he has an undetectable viral load | ○ | ○ | ○ |
| My partner said he does not want to use condoms | ○ | ○ | ○ |
| I have used alcohol or drugs | ○ | ○ | ○ |
| I was too aroused | ○ | ○ | ○ |
| It would reduce pleasure / I don't like to use | ○ | ○ | ○ |
| I am allergic to latex | ○ | ○ | ○ |
| It was going to make me lose my erection | ○ | ○ | ○ |
| It would interrupt sexual intercourse | ○ | ○ | ○ |
| I didn't have condoms with me | ○ | ○ | ○ |
| Condoms are expensive | ○ | ○ | ○ |
| I'm taking pre-exposure prophylaxis | ○ | ○ | ○ |
| Other [specify] | ○ | ○ | ○ |

85. Other [specify] (Answer this question only if the following condition is true: the answer is 'Other' in question 84)

86. Do you use lubricants during anal sex? (Answer this question only if the following conditions are true: the answer is 'Yes' in question 2 AND the answer is 'Yes' in question 25)

Please select only one of the following options:

- Always

- Often
- Occasionally
- Rarely
- Never
- I prefer not to answer

87. What kind of lubricants do you use for anal sex? (Answer this question only if the following conditions are true: the answer is 'Yes' in question 2 AND the answer is 'Always' OR 'Often' OR 'Occasionally' OR 'Rarely' in question 86)

Please select all that apply:

- Water-based
- Silicone-based
- Oil-based (vaseline, creams)
- Saliva
- Other [specify]

88. Other [specify] (Answer this question only if the following condition is true: the answer is 'Other' in question 87)

## ALCOHOL AND DRUGS

89. In the last 12 months (since the last test at CheckpointLX), did you use alcohol or drugs?

Please select only one of the following options:

- Yes
- No
- I prefer not to answer

90. In the last 12 months (since the last test at CheckpointLX), when was the last time you consumed alcohol or drugs? (Answer this question only if the following condition is true: the answer is 'Yes' in question 89)

Please select the appropriate position for each item:

| | In the last 24 hours | In the last 7 days | In the last 4 weeks | In the last 6 months | In the previous 12 months / since the last test | Never | I prefer not to answer |
|---|---|---|---|---|---|---|---|
| Alcohol | | | | | | | |
| Cannabis | | | | | | | |
| Smart shop substances (including online) | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Cocaine | | | | | | | |
| Ecstasy (MDMA) | | | | | | | |
| Poppers | | | | | | | |
| Viagra/ Cialis /similar | | | | | | | |
| Amphetamines (speed) | | | | | | | |
| LSD | | | | | | | |
| GHB | | | | | | | |
| Ketamine | | | | | | | |
| Heroin | | | | | | | |
| Methadone | | | | | | | |
| Mephedrone (meow meow) | | | | | | | |
| Methamphetamines (crystal) | | | | | | | |
| Others | | | | | | | |

91. Others [specify] (Answer this question only if the following condition is true: the answer is 'In the last 24 hours' OR 'In the last 7 days' OR 'In the last 4 weeks' OR 'In the last 6 months' in question 90)

92. Did you have sex under the influence of alcohol? (Answer this question only if the following condition is true: the answer is 'In the last 24 hours' OR 'In the last 7 days' OR 'In the last 4 weeks' OR 'In the last 6 months' in question 90)

Please select only one of the following options:

- Yes
- No
- I prefer not to answer

93. Did you have sex under the influence of cannabis? (Answer this question only if the following condition is true: the answer is 'In the last 24 hours' OR 'In the last 7 days' OR 'In the last 4 weeks' OR 'In the last 6 months' in question 90)

Please select only one of the following options:

- Yes
- No
- I prefer not to answer

94. Did you have sex under the influence of smart shop substances (including online)? (Answer this question only if the following condition is true: the answer is 'In the last 24 hours' OR 'In the last 7 days' OR 'In the last 4 weeks' OR 'In the last 6 months' in question 90)

Please select only one of the following options:

- Yes

- No
- I prefer not to answer

95. Did you have sex under the influence of cocaine? (Answer this question only if the following condition is true: the answer is 'In the last 24 hours' OR 'In the last 7 days' OR 'In the last 4 weeks' OR 'In the last 6 months' in question 90)

Please select only one of the following options:

- Yes
- No
- I prefer not to answer

96. Did you have sex under the influence of ecstasy (MDMA)? (Answer this question only if the following condition is true: the answer is 'In the last 24 hours' OR 'In the last 7 days' OR 'In the last 4 weeks' OR 'In the last 6 months' in question 90)

Please select only one of the following options:

- Yes
- No
- I prefer not to answer

97. Did you have sex under the influence of poppers? (Answer this question only if the following condition is true: the answer is 'In the last 24 hours' OR 'In the last 7 days' OR 'In the last 4 weeks' OR 'In the last 6 months' in question 90)

Please select only one of the following options:

- Yes
- No
- I prefer not to answer

98. Did you have sex under the influence of Viagra/ Cialis /similar? (Answer this question only if the following condition is true: the answer is 'In the last 24 hours' OR 'In the last 7 days' OR 'In the last 4 weeks' OR 'In the last 6 months' in question 90)

Please select only one of the following options:

- Yes
- No
- I prefer not to answer

99. Did you have sex under the influence of Amphetamines (speed)? (Answer this question only if the following condition is true: the answer is 'In the last 24 hours' OR 'In the last 7 days' OR 'In the last 4 weeks' OR 'In the last 6 months' in question 90)

Please select only one of the following options:

- Yes
- No
- I prefer not to answer

100. Did you have sex under the influence of LSD? (Answer this question only if the following condition is true: the answer is 'In the last 24 hours' OR 'In the last 7 days' OR 'In the last 4 weeks' OR 'In the last 6 months' in question 90)

Please select only one of the following options:

- Yes
- No
- I prefer not to answer

101. Did you have sex under the influence of GHB? (Answer this question only if the following condition is true: the answer is 'In the last 24 hours' OR 'In the last 7 days' OR 'In the last 4 weeks' OR 'In the last 6 months' in question 90)

Please select only one of the following options:

- Yes
- No
- I prefer not to answer

102. Did you have sex under the influence of Ketamine? (Answer this question only if the following condition is true: the answer is 'In the last 24 hours' OR 'In the last 7 days' OR 'In the last 4 weeks' OR 'In the last 6 months' in question 90)

Please select only one of the following options:

- Yes
- No
- I prefer not to answer

103. Did you have sex under the influence of Heroin? (Answer this question only if the following condition is true: the answer is 'In the last 24 hours' OR 'In the last 7 days' OR 'In the last 4 weeks' OR 'In the last 6 months' in question 90)

Please select only one of the following options:

- Yes
- No
- I prefer not to answer

104. Did you have sex under the influence of Methadone? (Answer this question only if the following condition is true: the answer is 'In the last 24 hours' OR 'In the last 7 days' OR 'In the last 4 weeks' OR 'In the last 6 months' in question 90)

Please select only one of the following options:

- Yes
- No
- I prefer not to answer

105. Did you have sex under the influence of Mephedrone (meow meow)? (Answer this question only if the following condition is true: the answer is 'In the last 24 hours' OR 'In the last 7 days' OR 'In the last 4 weeks' OR 'In the last 6 months' in question 90)

Please select only one of the following options:

- Yes
- No
- I prefer not to answer

106. Did you have sex under the influence of Methamphetamines (crystal meth)? (Answer this question only if the following condition is true: the answer is 'In the last 24 hours' OR 'In the last 7 days' OR 'In the last 4 weeks' OR 'In the last 6 months' in question 90)

Please select only one of the following options:

- Yes
- No
- I prefer not to answer

107. Did you have sex under the influence of any “other substance”? (Answer this question only if the following condition is true: the answer is 'In the last 24 hours' OR 'In the last 7 days' OR 'In the last 4 weeks' OR 'In the last 6 months' in question 90)

Please select only one of the following options:

- Yes
- No
- I prefer not to answer

108. In which city(ies) did you have sex with GHB, mephedrone (meow meow), and/or methamphetamines (crystal)? (Answer this question only if the following conditions are true: the answer is 'Yes' in question 101 OR the answer is 'Yes' in question 105 OR the answer is 'Yes' in question 106)

Please write here your answer(s):

City

City

City

City

City

City

City

City

City

City

City

109. Did you ever inject any substance (excluding for medical reasons)? (Answer this question only if the following condition is true: the answer is 'Yes' in question 89)

Please select only one of the following options:

- Yes
- No
- I prefer not to answer

110. The injection of that substance was (Answer this question only if the following condition is true: the answer is 'Yes' in question 109):

Please select the appropriate position for each item:

| | Yes | No | I don't know |
|---|---|---|---|
| Related to sexual intercourse | ○ | ○ | ○ |
| Not related to sexual intercourse | ○ | ○ | ○ |

111. When was the last time you injected any substance (excluding for medical reasons)? (Answer this question only if the following condition is true: the answer is 'Yes' in question 109)

Please write your answer here:

1. In case the participant does not know, register an estimate for the year and month

2. In case the participant does not know the month, register the year and an estimate for the month

3. In case the participant does not want to respond, register 7777 77

## POST-EXPOSURE PROPHYLAXIS (PEP)

112. Do you know about post-exposure prophylaxis? (Answer this question only if the following condition are true: the answer is 'Baseline' OR 'Refusal' in question 2)

Please select only one of the following options:

- Yes
- No
- I prefer not to answer

113. Tell us what PEP is? Register if the participant referred each of the following statements: (Answer this question only if the following condition is true: the answer is 'Yes' in question 112)

Please select the appropriate position for each item:

| | Yes | No |
|---|---|---|
| PPE is a treatment to prevent HIV infection | ○ | ○ |
| It must be started as soon as possible after exposure | ○ | ○ |
| It is accessible at the public hospital emergency services | ○ | ○ |

114. Have you ever used PEP? (Answer this question only if the following condition is true: the answer is 'Yes' in question 112)

Please select only one of the following options:

- Yes
- No
- I prefer not to answer

115. Did you use PEP in the last 12 months (since the last test at CheckpointLX)? (Answer this question only if the following condition are true: the answer is 'Baseline' OR 'Refusal' in question 2 AND the answer is 'Yes' in question 114 OR the answer is 'Follow-up' in question 2)

Please select only one of the following options:

- Yes
- No
- I prefer not to answer

116. Did you complete the 28 days / 4 weeks of medication? (Answer this question only if the following conditions are true: the answer is 'Yes' in question 114 OR the answer is 'Yes' in question 115)

Please select only one of the following options:

- Yes
- No
- I prefer not to answer

117. Have you ever (since the last test at CheckpointLX) been denied PPE? (Answer this question only if the following conditions are true: the answer is 'Follow-up' in question 2 OR the answer is 'Yes' in question 112)

Please select only one of the following options:

- Yes
- No
- I prefer not to answer

118. In which hospitals have you been denied PPE? (Answer this question only if the following condition is true: the answer is 'Yes' in question 117)

Please select all that apply:

- São José Hospital
- São Francisco Xavier Hospital
- Santa Maria Hospital
- Hospitals of the University of Coimbra
- Beatriz Ângelo Hospital
- Braga Hospital
- Caldas da Rainha Hospital
- Cândido de Figueiredo Hospital
- Conde de Bertiandos Hospital
- Famalicão Hospital
- Santa Luzia Hospital
- Distrital de Chaves Hospital
- Distrital de Lamego Hospital
- Distrital de Torres Vedras Hospital
- Distrital do Montijo Hospital
- Distrital Vila Nova de Gaia Hospital
- Eduardo Santos Silva Hospital
- Espírito Santo Hospital
- Faro Hospital
- Fernando Fonseca Hospital
- Garcia de Orta Hospital
- Geral Covões Hospital
- Geral Santo António Hospital
- Infante D. Pedro Hospital
- José Joaquim Fernandes Hospital
- Lagos Hospital
- Nossa Senhora do Rosário Hospital
- Padre Américo Hospital
- Pedro Hispano Hospital
- Pêro da Covilhã Hospital
- Portimão Hospital
- Santarém Hospital
- Santo Tirso Hospital
- São Bernardo Hospital

- São Gonçalo-Amarante Hospital
- São João Hospital
- São Pedro de Vila Real Hospital
- São Pedro Gonçalves Telmo Hospital
- São Teotónio Hospital
- Other: [ ]

## PRE-EXPOSURE PROPHYLAXIS (PrEP)

119. Do you know about pre-exposure prophylaxis? (Answer this question only if the following condition is true: the answer is 'Baseline' in question 2)

Please select only one of the following options:

- Yes
- No
- I prefer not to answer

120. Tell us what PrEP is? Register if the participant referred each of the following statements: (Answer this question only if the following condition is true: the answer is 'Yes' in question 119)

Please, choose the appropriate position for each item:

| | Yes | No |
|---|---|---|
| PrEP is a treatment to prevent HIV infection | ○ | ○ |
| It has to be taken before a possible exposure | ○ | ○ |

121. Have you ever used pre-exposure prophylaxis? (Answer this question only if the following condition is true: the answer is 'Yes' in question 119)

Please select only one of the following options:

- Yes
- No
- I prefer not to answer

122. In the last 12 months (since the last CheckpointLX test), did you use pre-exposure prophylaxis? (Answer this question only if the following condition are true: the answer is 'Baseline' in question 2 AND the answer is 'Yes' in question 121 OR the answer is 'Follow-up' in question 2)

Please select only one of the following options:

- Yes
- No
- I prefer not to answer

123. In the last 12 months (since the last CheckpointLX test), how did you use pre-exposure prophylaxis? (Answer this question only if the following condition is true: the answer is 'Yes' in question 122)

Please, choose the appropriate position for each item:

| | Yes | No | I don't know |
|---|---|---|---|
| Taken according to sexual practices (Two pills 2 to 24 hours before sex, one pill 24 hours after, and one pill 48 hours after) | ○ | ○ | ○ |
| Taken daily (One pill taken once every day) | ○ | ○ | ○ |
| Other | ○ | ○ | ○ |

124. Other [specify] (Answer this question only if the following condition is true: the answer is 'Yes' in question 123)

Please write down your answer:

125. When did you start intermittent PrEP? (Answer this question only if the following condition is true: the answer is 'Yes' in option 'Taken according to sexual practices (Two pills 2 to 24 hours before sex, one pill 24 hours after, and one pill 48 hours after)' in question 123)

Please write down your answer:

DD MM YYYY

1. If the participant does not know, register estimate for the year, month, and day.
2. If the participant does not wish to answer, write down 77 77 7777

126. When did you finish intermittent PrEP? (Answer this question only if the following condition is true: the answer is 'Yes' in option 'Taken according to sexual practices (Two pills 2 to 24 hours before sex, one pill 24 hours after, and one pill 48 hours after)' in question 123)

Please write down your answer:

DD MM YYYY

1. If the participant does not know, register estimate for the year, month, and day.
2. If the participant does not wish to answer, write down 77 77 7777

127. How many cycles of PrEP did you do, taken intermittently? (Answer this question only if the following condition is true: the answer is 'Yes' in option 'Taken according to sexual practices (Two pills 2 to 24 hours before sex, one pill 24 hours after, and one pill 48 hours after)' in question 123)

Please write down your answer:

128. When did you start daily PrEP? (Answer this question only if the following condition is true: the answer is 'Yes' in option 'Taken daily (One pill taken once every day)', question 123)

Please write down your answer:

DD MM YYYY

1. If the participant does not know, register estimate for the year, month, and day.
2. If the participant does not wish to answer, write down 77 77 7777

129. When did you finish daily PrEP? (Answer this question only if the following condition is true: the answer is 'Yes' in option 'Taken daily (One pill taken once every day)', question 123)

Please write down your answer:

DD MM YYYY

1. If the participant does not know, register estimate for the year, month, and day.
2. If the participant does not wish to answer, write down 77 77 7777

130. How did you obtain the medication in the last time you had PrEP? (Answer this question only if the following condition is true: the answer is 'Yes' in question 122)

Please select the appropriate position for each item:

| | Yes | No | I don't know |
|---|---|---|---|
| Prescribed by a medical doctor in Portugal | ○ | ○ | ○ |
| Ordered from an online pharmacy | ○ | ○ | ○ |
| Dispensing in another country | ○ | ○ | ○ |
| Clinical trial / Demonstration study | ○ | ○ | ○ |
| From social networks | ○ | ○ | ○ |
| Other | ○ | ○ | ○ |

131. Other [specify] (Answer this question only if the following condition is true: the answer is 'Other' in question 130)

Please write down your answer:

132. Would you consider using pre-exposure prophylaxis for HIV prevention?

Please select only one of the following options

- Yes
- Maybe

- No
- I don’t know
- I prefer not to answer

133. Which are the places of your preference for dispensing PrEP? (Answer this question only if the following conditions are true: the answer is 'Yes' OR 'Maybe' in question 132)

Please rank your answers and choose no more than 3 items

- Hospital
- Public network of voluntary counseling and testing center (CAD)
- Drug Treatment Teams
- Pharmacy
- Primary healthcare center
- Community-based organizations
- CheckpointLX
- Other

134. Other [specify] (Answer this question only if the following condition is true: the answer is 'Other' in question 133)

Please write down your answer

135. What are the main reasons you are not interested in using PrEP? (Answer this question only if the following condition is true: the answer is 'No' in question 132)

Please rank your answers and choose no more than 3 items

- I need more information about PrEP and its effects
- I have heard/read negative things about PrEP as a means of prevention
- I have to think more about it
- I do not wish to take medication
- I am afraid that others will think that I have HIV for having PrEP
- I am afraid that others will think that I have sex with many people for having PrEP
- I do not trust in PrEP’s efficacy
- I am satisfied with my current prevention practices
- Other

136. Other [specify] (Answer this question only if the following condition is true: the answer is 'Other' in question 135)

Please write down your answer

## SEXUALLY TRANSMITTED INFECTIONS AND HEPATITIS

137. Have you ever had one of the following symptoms? (Answer this question only if the following condition is true: the answer is 'Baseline' in question 2)

Please select the appropriate position for each item.

| | Yes | No | I prefer not to answer |
|---|---|---|---|
| Burning sensation when you urinate | ○ | ○ | ○ |
| Discharge | ○ | ○ | ○ |
| Lesions | ○ | ○ | ○ |
| Warts | ○ | ○ | ○ |
| Other symptoms | ○ | ○ | ○ |

138. Other [specify] (Answer this question only if the following condition is true: the answer is 'Yes' in question 137)

Please write down your answer

139. In the last 12 months (Since the last CheckpointLX test), did you have the following? (Answer this question only if the following conditions are true: the answer is 'Baseline' in question 2 AND the answer is 'Yes' in option 'Burning sensation when you urinate', in question 137 OR the answer is 'Follow-up' in question 2)

| | Yes | No | Does not respond |
|---|---|---|---|
| Burning sensation when you urinate | ○ | ○ | ○ |

140. In the last 12 months (Since the last CheckpointLX test), did you have the following symptom? (Answer this question only if the following conditions are true: the answer is 'Baseline' in question 2 AND the answer is 'Yes' in option 'discharge', in question 137 OR the answer is 'Follow-up' in question 2)

| | Yes | No | Does not respond |
|---|---|---|---|
| Discharge | ○ | ○ | ○ |

141. In the last 12 months (Since the last CheckpointLX test), did you have the following symptom? (Answer this question only if the following conditions are true: the answer is 'Baseline' in question 2 AND the answer is 'Yes' in option 'Lesions', in question 137 OR the answer is 'Follow-up' in question 2)

| | Yes | No | Does not respond |
|---|---|---|---|
| Lesions | ○ | ○ | ○ |

142. In the last 12 months (Since the last CheckpointLX test), did you have the following symptom? (Answer this question only if the following conditions are true: the answer is 'Baseline' in question 2 AND the answer is 'Yes' in option 'Warts', in question 137 OR the answer is 'Follow-up' in question 2)

| | Yes | No | Does not respond |
|---|---|---|---|
| Warts | ○ | ○ | ○ |

143. In the last 12 months (Since the last CheckpointLX test), did you the following symptom? (Answer this question only if the following conditions are true: the answer is 'Baseline' in question 2 AND the answer is 'Yes' in option 'Other symptoms', question 137 OR the answer is 'Follow-up' in question 2)

| | Yes | No | Does not respond |
|---|---|---|---|
| Other symptoms | ○ | ○ | ○ |

144. Have you ever had an STI? (Answer this question only if the following conditions are true: the answer is 'Baseline' in question 2)

Please, select the appropriate position for each item:

| | Yes | No | I prefer not to answer |
|---|---|---|---|
| Syphilis | ○ | ○ | ○ |
| Chlamydia | ○ | ○ | ○ |
| Genital Herpes | ○ | ○ | ○ |
| Gonorrhea | ○ | ○ | ○ |
| Condylomas or Genital Warts | ○ | ○ | ○ |
| Trichomonas | ○ | ○ | ○ |
| Lymphogranuloma venereum (LGV) | ○ | ○ | ○ |
| Human papillomavirus (HPV) | ○ | ○ | ○ |
| Other (including HAV/HBV/HCV) | ○ | ○ | ○ |

145. Specify other STI (Answer this question only if the following condition is true: the answer is 'Other' in question 144)

Please, write down your answer

146. In the last 12 months (Since the last CheckpointLX test), did you have the following STI? (Answer this question only if the following conditions are true: the answer is 'Baseline' in question 2 AND the answer is 'Yes' in option 'Syphilis', in question 144 OR the answer is 'Follow-up' in question 2)

| | Yes | No | I prefer not to answer |
|---|---|---|---|

| | | | |
|---|---|---|---|
| Syphilis | ○ | ○ | ○ |

147. In the last 12 months (Since the last CheckpointLX test), did you have the following STI? (Answer this question only if the following conditions are true: the answer is 'Baseline' in question 2 AND the answer is 'Yes' in option ‘Chlamydia, in question 144 OR the answer is 'Follow-up' in question 2)

| | Yes | No | I prefer not to answer |
|---|---|---|---|
| Chlamydia | ○ | ○ | ○ |

148. In the last 12 months (Since the last CheckpointLX test), did you have the following STI? (Answer this question only if the following conditions are true: the answer is 'Baseline' in question 2 AND the answer is 'Yes' in option ‘Genital Herpes’, in question 144 OR the answer is 'Follow-up' in question 2)

| | Yes | No | I prefer not to answer |
|---|---|---|---|
| Genital Herpes | ○ | ○ | ○ |

149. In the last 12 months (Since the last CheckpointLX test), did you have the following STI? (Answer this question only if the following conditions are true: the answer is 'Baseline' in question 2 AND the answer is 'Yes' in option ‘Gonorrhea’, in question 144 OR the answer is 'Follow-up' in question 2)

| | Yes | No | I prefer not to answer |
|---|---|---|---|
| Gonorrhea | ○ | ○ | ○ |

150. In the last 12 months (Since the last CheckpointLX test), did you have the following STI? (Answer this question only if the following conditions are true: the answer is 'Baseline' in question 2 AND the answer is 'Yes' in option ‘Condylomas or Genital Warts’, in question 144 OR the answer is 'Follow-up' in question 2)

| | Yes | No | I prefer not to answer |
|---|---|---|---|
| Condylomas or Genital Warts | ○ | ○ | ○ |

151. In the last 12 months (Since the last CheckpointLX test), did you have the following STI? (Answer this question only if the following conditions are true: the answer is 'Baseline' in question 2 AND the answer is 'Yes' in option ‘Trichomonas’, in question 144 OR the answer is 'Follow-up' in question 2)

| | Yes | No | I prefer not to answer |
|---|---|---|---|
| Trichomonas | ○ | ○ | ○ |

152. In the last 12 months (Since the last CheckpointLX test), did you have the following STI? (Answer this question only if the following conditions are true: the answer is 'Baseline' in question 2 AND the answer is 'Yes' in option ‘Lymphogranuloma venereum (LGV)’, in question 144 OR the answer is 'Follow-up' in question 2)

| | Yes | No | I prefer not to answer |
|---|---|---|---|

| | | | |
|---|---|---|---|
| Lymphogranuloma venereum (LGV) | ○ | ○ | ○ |

153. In the last 12 months (Since the last CheckpointLX test), did you have the following STI? (Answer this question only if the following conditions are true: the answer is 'Baseline' in question 2 AND the answer is 'Yes' in option 'Human papillomavirus (HPV)', in question 144 OR the answer is 'Follow-up' in question 2)

| | Yes | No | I prefer not to answer |
|---|---|---|---|
| Human papillomavirus (HPV) | ○ | ○ | ○ |

154. In the last 12 months (Since the last CheckpointLX test), did you have the following STI? (Answer this question only if the following conditions are true: the answer is 'Baseline' in question 2 AND the answer is 'Yes' in option 'Other (including HAV/HBV/HCV)', in question 144 OR the answer is 'Follow-up' in question 2)

| | Yes | No | I prefer not to answer |
|---|---|---|---|
| Other (including HAV/HBV/HCV) | ○ | ○ | ○ |

155. Have you ever been tested for STIs or hepatitis? (Answer this question only if the following condition is true: the answer is 'Baseline' in question 2)

Please select only one of the following options

- Yes
- No
- I prefer not to answer

156. In the last 12 months (Since the last CheckpointLX test), have you been tested for STIs or hepatitis? (Answer this question only if the following conditions are true: the answer is 'Baseline' in question 2 AND the answer is 'Yes' in question 155 OR the answer is 'Follow-up' in question 2)

Please select only one of the following options

- Yes
- No
- I prefer not to answer

157. Do you consider that you are routinely screened for STIs or hepatitis (Answer this question only if the following conditions are true: the answer is 'Baseline' in question 2 AND the answer is 'Yes' in question 155)

Please select the appropriate position for each item:

| | Yes | No | Does not respond |
|---|---|---|---|

| | | | |
|---|---|---|---|
| Regularly (once every two years, annually, once every 6 months) | ○ | ○ | ○ |
| Included as part of routine checkup | ○ | ○ | ○ |
| When I feel that I had been at risk | ○ | ○ | ○ |
| When I have symptoms | ○ | ○ | ○ |
| When I have a new steady partner | ○ | ○ | ○ |
| When the opportunity arises (e.g. screening outreach) | ○ | ○ | ○ |
| Other | ○ | ○ | ○ |

158. Other [specify] (Answer this question only if the following condition is true: the answer is 'Yes' in question 157)

Please, write down your answer.

159. Do you know of any current health problems frequently discussed among MSM?

Please select only one of the following options

- Yes
- No
- I prefer not to answer

160. Specify (Answer this question only if the following condition is true: the answer is 'Yes' in question 159)

Please, write down your answer.

## SOCIODEMOGRAPHIC CHARACTERIZATION

### 161. In which country do you currently live?

Please, select only one of the following options:

- Afghanistan
- Albania
- Algeria
- Andorra
- Angola
- Anguilla
- Antigua & Barbuda
- Argentina
- Armenia
- Australia
- Austria
- Azerbaijan
- Bahamas
- Bahrain
- Bangladesh
- Barbados
- Belarus
- Belgium
- Belize
- Benin
- Bermuda
- Bhutan
- Bolivia
- Bosnia & Herzegovina
- Botswana
- Brazil
- Brunei Darussalam
- Bulgaria
- Burkina Faso
- Burundi
- Cambodia
- Cameroon
- Canada
- Cape Verde
- Cayman Islands
- Central African Republic
- Chad
- Chile
- China
- China - Hong Kong / Macau
- Colombia
- Comoros

- Congo
- Congo, Democratic Republic of (DRC)
- Costa Rica
- Croatia
- Cuba
- Cyprus
- Czech Republic
- Denmark
- Djibouti
- Dominica
- Dominican Republic
- Ecuador
- Egypt
- El Salvador
- Equatorial Guinea
- Eritrea
- Estonia
- Ethiopia
- Fiji
- Finland
- France
- French Guiana
- Gabon
- Gambia
- Georgia
- Germany
- Ghana
- Great Britain
- Greece
- Grenada
- Guadeloupe
- Guatemala
- Guinea
- Guinea-Bissau
- Guyana
- Haiti
- Honduras
- Hungary
- Iceland
- India
- Indonesia
- Iran
- Iraq
- Israel and the Occupied Territories
- Italy
- Ivory Coast (Cote d'Ivoire)
- Jamaica
- Japan

- Jordan
- Kazakhstan
- Kenya
- Korea, Democratic Republic of (North Korea)
- Korea, Republic of (South Korea)
- Kosovo
- Kuwait
- Kyrgyz Republic (Kyrgyzstan)
- Laos
- Latvia
- Lebanon
- Lesotho
- Liberia
- Libya
- Liechtenstein
- Lithuania
- Luxembourg
- Macedonia, Republic of
- Madagascar
- Malawi
- Malaysia
- Maldives
- Mali
- Malta
- Martinique
- Mauritania
- Mauritius
- Mayotte
- Mexico
- Moldova, Republic of
- Monaco
- Mongolia
- Montenegro
- Montserrat
- Morocco
- Mozambique
- Myanmar/Burma
- Namibia
- Nepal
- New Zealand
- Nicaragua
- Niger
- Nigeria
- Norway
- Oman
- Pacific Islands
- Pakistan
- Panama

- Papua New Guinea
- Paraguay
- Peru
- Philippines
- Poland
- Portugal
- Puerto Rico
- Qatar
- Reunion
- Romania
- Russian Federation
- Rwanda
- Saint Kitts and Nevis
- Saint Lucia
- Saint Vincent and the Grenadines
- Samoa
- Sao Tome and Principe
- Saudi Arabia
- Senegal
- Serbia
- Seychelles
- Sierra Leone
- Singapore
- Slovak Republic (Slovakia)
- Slovenia
- Solomon Islands
- Somalia
- South Africa
- South Sudan
- Spain
- Sri Lanka
- Sudan
- Suriname
- Swaziland
- Sweden
- Switzerland
- Syria
- Tajikistan
- Tanzania
- Thailand
- Netherlands
- Timor Leste
- Togo
- Trinidad & Tobago
- Tunisia
- Turkey
- Turkmenistan
- Turks & Caicos Islands

- Uganda
- Ukraine
- United Arab Emirates
- United States of America (USA)
- Uruguay
- Uzbekistan
- Venezuela
- Vietnam
- Virgin Islands (UK)
- Virgin Islands (US)
- Yemen
- Zambia
- Zimbabwe

### 162. In which country were you born? (Answer this question only if the following condition is true: the answer is 'Refusal' OR 'Baseline' in question 2)

Please, select only one of the following options

- Afghanistan
- Albania
- Algeria
- Andorra
- Angola
- Anguilla
- Antigua & Barbuda
- Argentina
- Armenia
- Australia
- Austria
- Azerbaijan
- Bahamas
- Bahrain
- Bangladesh
- Barbados
- Belarus
- Belgium
- Belize
- Benin
- Bermuda
- Bhutan
- Bolivia
- Bosnia & Herzegovina
- Botswana
- Brazil
- Brunei Darussalam
- Bulgaria
- Burkina Faso

- Burundi
- Cambodia
- Cameroon
- Canada
- Cape Verde
- Cayman Islands
- Central African Republic
- Chad
- Chile
- China
- China - Hong Kong / Macau
- Colombia
- Comoros
- Congo
- Congo, Democratic Republic of (DRC)
- Costa Rica
- Croatia
- Cuba
- Cyprus
- Czech Republic
- Denmark
- Djibouti
- Dominica
- Dominican Republic
- Ecuador
- Egypt
- El Salvador
- Equatorial Guinea
- Eritrea
- Estonia
- Ethiopia
- Fiji
- Finland
- France
- French Guiana
- Gabon
- Gambia
- Georgia
- Germany
- Ghana
- Great Britain
- Greece
- Grenada
- Guadeloupe
- Guatemala
- Guinea
- Guinea-Bissau
- Guyana

- Haiti
- Honduras
- Hungary
- Iceland
- India
- Indonesia
- Iran
- Iraq
- Israel and the Occupied Territories
- Italy
- Ivory Coast (Cote d'Ivoire)
- Jamaica
- Japan
- Jordan
- Kazakhstan
- Kenya
- Korea, Democratic Republic of (North Korea)
- Korea, Republic of (South Korea)
- Kosovo
- Kuwait
- Kyrgyz Republic (Kyrgyzstan)
- Laos
- Latvia
- Lebanon
- Lesotho
- Liberia
- Libya
- Liechtenstein
- Lithuania
- Luxembourg
- Macedonia, Republic of
- Madagascar
- Malawi
- Malaysia
- Maldives
- Mali
- Malta
- Martinique
- Mauritania
- Mauritius
- Mayotte
- Mexico
- Moldova, Republic of
- Monaco
- Mongolia
- Montenegro
- Montserrat
- Morocco

- Mozambique
- Myanmar/Burma
- Namibia
- Nepal
- New Zealand
- Nicaragua
- Niger
- Nigeria
- Norway
- Oman
- Pacific Islands
- Pakistan
- Panama
- Papua New Guinea
- Paraguay
- Peru
- Philippines
- Poland
- Portugal
- Puerto Rico
- Qatar
- Reunion
- Romania
- Russian Federation
- Rwanda
- Saint Kitts and Nevis
- Saint Lucia
- Saint Vincent and the Grenadines
- Samoa
- Sao Tome and Principe
- Saudi Arabia
- Senegal
- Serbia
- Seychelles
- Sierra Leone
- Singapore
- Slovak Republic (Slovakia)
- Slovenia
- Solomon Islands
- Somalia
- South Africa
- South Sudan
- Spain
- Sri Lanka
- Sudan
- Suriname
- Swaziland
- Sweden

- Switzerland
- Syria
- Tajikistan
- Tanzania
- Thailand
- Netherlands
- Timor Leste
- Togo
- Trinidad & Tobago
- Tunisia
- Turkey
- Turkmenistan
- Turks & Caicos Islands
- Uganda
- Ukraine
- United Arab Emirates
- United States of America (USA)
- Uruguay
- Uzbekistan
- Venezuela
- Vietnam
- Virgin Islands (UK)
- Virgin Islands (US)
- Yemen
- Zambia
- Zimbabwe

163. What year did you arrive in [country of residence]? (for the first time) (Answer this question only if the following condition is true: the answer is 'Baseline' in question 2 AND 'Other than Portugal' in question 161)

Please write your answer here:

If you do not want to respond, register 7777

164. What is the highest level of schooling that you completed?

Please, select only one of the following options

- 2nd cycle of basic education or less (6th grade or less)
- 3rd cycle of basic education (9th or less)
- Secondary education, via continuing studies (12th grade)
- Secondary education with professional training (12th grade professional)
- Post-secondary non-higher education (CET – technological specialization course)
- Bachelor's degree
- Master's degree or PhD
- I prefer not to answer
- Other (specify):

Always consider the previous academic degree in the case of non-completion

### 165. What is your employment situation?

Please, select only one of the following options

- Full-time employee
- Part-time employee
- Temporary worker
- Unemployed (with or without social subsidy)
- Independent worker
- Sex worker
- Student/worker
- Student
- Retired
- Undeclared work
- I prefer not to answer
- Other (specify):

## SYPHILIS SCREENING

166. Was the participant tested for syphilis?

Please, select only one of the following options:

- Yes
- No

167. Why was the syphilis test not performed? (Answer this question only if the following condition is true: the answer is 'No' in question 166)

Please, select only one of the following options:

- Not eligible
- Test not available
- Refused

168. Syphilis test result (Answer this question only if the following condition is true: the answer is 'Yes' in question 166)

Please, select only one of the following options:

- Reactive
- Non-reactive

169. Syphilis test brand (Answer this question only if the following condition is true: the answer is 'Yes' in question 166)

Please, select only one of the following options:

- Alere Determine™ Syphilis
- Other

170. Syphilis test lot (Answer this question only if the following condition is true: the answer is 'Yes' in question 166)

Please, write down your answer:

171. Syphilis test expiration date (Answer this question only if the following condition is true: the answer is 'Yes' in question 166)

Please enter a date:

Response must be greater than or equal to [current date]

172. Was the referral accepted? (Answer this question only if the following condition is true: the answer is 'Reactive' in question 168)

Please, select only one of the following options:

- Yes
- No

173. Place of referral (Answer this question only if the following condition is true: the answer is 'Yes' in question 172)

Please, select only one of the following options:

- Checklist
- Other

174. Observations (Answer this question only if the following condition is true: the answer is 'Reactive' in question 168):

Please, write down your answer.

Enter "XXXX" if there is nothing to register.

## HCV SCREENING

175. Was the participant tested for HCV?

Please, select only one of the following options:

- Yes
- No

176. Why was the HCV test not performed? (Answer this question only if the following condition is true: the answer is 'No' in question 175)

Please, select only one of the following options:

- Not eligible
- Test not available
- Refused

177. HCV test result (Answer this question only if the following condition is true: the answer is 'Yes' in question 175)

Please, select only one of the following options:

- Reactive
- Non-reactive

178. HCV test brand (Answer this question only if the following condition is true: the answer is 'Yes' in question 175)

Please, select only one of the following options:

- Info Anti-HCV Rapid Test (Turklab)
- Other

179. HCV test lot (Answer this question only if the following condition is true: the answer is 'Yes' in question 175)

Please, write down your answer:

180. HCV test expiration date (Answer this question only if the following condition is true: the answer is 'Yes' in question 175)

Please enter a date:

Response must be greater than or equal to [current date]

181. Was the referral accepted? (Answer this question only if the following condition is true: the answer is 'Reactive' in question 177)

Please, select only one of the following options:

- Yes
- No

182. Place of referral (Answer this question only if the following condition is true: the answer is 'Yes' in question 181)

Please, select only one of the following options:

- Pulido Valente Hospital
- Santo António dos Capuchos Hospital
- Santa Maria Hospital
- Egas Moniz Hospital
- São José Hospital
- Curry Cabral Hospital
- Other

183. Observations (Answer this question only if the following condition is true: the answer is 'Reactive' in question 177):

Please, write down your answer.

Enter "XXXX" if there is nothing to register.

## HBsAg SCREENING

### 184. Was the participant tested for HBsAg?

Please, select only one of the following options:

- Yes
- No

### 185. Why wasn't the HBsAg test performed? (Answer this question only if the following condition is true: the answer is 'No' in question 184)

Please, select only one of the following options:

- Not eligible
- Test not available
- Refused

### 186. HBsAg test result (Answer this question only if the following condition is true: the answer is 'Yes' in question 184)

Please, select only one of the following options:

- Reactive
- Non-reactive

### 187. HBsAg test brand (Answer this question only if the following condition is true: the answer is 'Yes' in question 184)

Please, select only one of the following options:

- Vikia HBsAG
- Other

### 188. HBsAg test lot (Answer this question only if the following condition is true: the answer is 'Yes' in question 184)

Please, write down your answer:

### 189. HBsAg test expiration date (Answer this question only if the following condition is true: the answer is 'Yes' in question 184)

Please enter a date:

Response must be greater than or equal to [current date]

190. Was the referral accepted? (Answer this question only if the following condition is true: the answer is 'Reactive' in question 186)

Please, select only one of the following options:

- Yes
- No

191. Place of referral (Answer this question only if the following condition is true: the answer is 'Yes' in question 190)

Please, select only one of the following options:

- Pulido Valente Hospital
- Santo António dos Capuchos Hospital
- Santa Maria Hospital
- Egas Moniz Hospital
- São José Hospital
- Curry Cabral Hospital
- Other

192. Observations (Answer this question only if the following condition is true: the answer is 'Reactive' in question 186):

Please, write down your answer.

Enter "XXXX" if there is nothing to register.

## HIV SCREENING

193. Was the participant tested for HIV?

Please, select only one of the following options:

- Yes
- No

194. Why was the HIV test not performed? (Answer this question only if the following condition is true: the answer is 'No' in question 193)

Please, select only one of the following options:

- Not eligible

- Test not available
- Refused

195. HIV test result (Answer this question only if the following condition is true: the answer is 'Yes' in question 193)

Please, select only one of the following options:

- Reactive
- Non-reactive

196. HIV test brand (Answer this question only if the following condition is true: the answer is 'Yes' in question 193)

Please, select only one of the following options:

- INSTI HIV-1 / HIV-2 Antibody Test
- Alere Determine HIV-1/2 Antibodies (3rd generation)
- Alere Determine HIV-1/2 Ag/Ab (4th generation)
- Other

197. HIV test lot (Answer this question only if the following condition is true: the answer is 'Yes' in question 193)

Please, write down your answer:

198. HIV test expiration date (Answer this question only if the following condition is true: the answer is 'Yes' in question 193)

Please enter a date:

Response must be greater than or equal to [current date]

199. Was the referral accepted? (Answer this question only if the following condition is true: the answer is 'Reactive' in question 195)

Please, select only one of the following options:

- Yes
- No

200. Place of referral (Answer this question only if the following condition is true: the answer is 'Yes' in question 199)

Please, select only one of the following options:

- Pulido Valente Hospital

- Santo António dos Capuchos Hospital
- Santa Maria Hospital
- Egas Moniz Hospital
- São José Hospital
- Curry Cabral Hospital
- Other

201. Observations (Answer this question only if the following condition is true: the answer is 'Reactive' in question 195):

Please, write down your answer.

Enter "XXXX" if there is nothing to register.

## COHORT PARTICIPATION

202. Will you (Will you continue to) participate in the cohort? (Answer this question only if the following conditions are true: the answer is 'Baseline' OR 'Follow-up' in question 2)

Please select only one of the following options:

- Yes
- No

203. Why? (Answer this question only if the following condition is true: the answer is 'No' in question 202)

Please select only one of the following options:

- Not eligible
- Does not give consent

204. What is the reason for not giving consent for cohort participation? (Answer this question only if the following condition is true: the answer is 'Does not consent' in question 203)

Please select only one of the following options:

- Is not interested in the study
- Does not have time to participate
- Does not live in Portugal
- Linguistic barriers to understand the study and the questions
- Other reason: _____

205. What is the reason for not participating in the cohort? (Answer this question only if the following condition is true: the answer is 'Refusal' in question 2)

Please select only one of the following options:

- Is not interested in the study
- Does not have time to participate
- Does not want to provide personal identifiable information
- Linguistic barriers to comprehend the study and understand the questions
- Other: _____

## OBSERVATIONS

### 206. Did the participant accept counseling?

Please select only one of the following options:

- Yes
- No

### 207. Observations

Please, write down your answer:

Enter "XXXX" if there is nothing to register.

Thank you for your participation!

Submit your survey.

Thank you for completing this survey.

## Annex 3. Current version of the informed consent

Doc. 104/12 - V.5

ID [redacted] C

# DECLARAÇÃO DE CONSENTIMENTO

Conforme a "Declaração de Helsínquia" da Associação Médica Mundial (Helsínquia 1964; Tóquio 1975; Veneza 1983, Hong Kong 1989, Somerset West 1996, Edimburgo 2000, Washington 2002, Tóquio 2004, Seul 2008, Fortaleza 2013)

**DESIGNAÇÃO DO ESTUDO: LISBON COHORT OF MEN WHO HAVE SEX WITH MEN (MSM)**

A Lisbon MSM Cohort tem como objetivo promover o conhecimento sobre a infeção VIH e os comportamentos que lhe estão associados nos homens que têm sexo com homens (HSH) em Portugal. Este estudo integra a COBA-cohorts – uma rede Europeia de coortes dirigidas a HSH e com o mesmo objetivo (https://www.cobatest.org/). Esta investigação é promovida em Portugal pelo GAT, pela Faculdade de Medicina e pelo Instituto de Saúde Pública da Universidade do Porto.

Para a concretização deste estudo, pedimos a sua colaboração através de:

a) registo dos resultados dos rastreios e análises ao VIH e outras Infeções Sexualmente Transmissíveis (IST) realizados no CheckpointLX;
b) resposta a um questionário sobre conhecimentos, atitudes e comportamentos associados ao VIH e outras IST.

Estes dados relativos à sua participação na Lisbon MSM Cohort serão armazenados na Universidade do Porto e disponíveis apenas aos investigadores autorizados pela Comissão Executiva do estudo.

Adicionalmente queremos pedir a sua autorização para recolha e armazenamento dos seus contactos, que serão utilizados para:

| | Autoriza: | |
|---|---|---|
| 1. Envio de lembrete para repetir o teste de VIH e responder ao questionário de seguimento, no âmbito da minha participação no estudo | Sim | Não |
| 2. Divulgação de resultados do estudo na forma de artigos científicos, comunicações orais, posters e outros | Sim | Não |
| 3. Divulgação e convite à participação em outros estudos | Sim | Não |

Os seus dados de contacto serão armazenados no CheckpointLX e apenas disponíveis aos inquiridores autorizados pela Comissão Executiva do estudo. Em nenhum momento os seus contactos serão acessíveis aos investigadores.

Compreendi a explicação que me foi fornecida acerca do estudo que se vai realizar. Foi-me dada a oportunidade de fazer as perguntas que julguei necessárias, tendo obtido resposta satisfatória. A informação ou explicação que me foi prestada versou os objetivos, os métodos, os benefícios previstos e o eventual desconforto decorrente da minha participação. Foi-me assegurada a confidencialidade da minha identidade, bem como dos dados que entender fornecer, nos termos que a lei exige. Explicaram-me, ainda, que poderei deixar de participar em qualquer momento, sem que daí advenham quaisquer desvantagens, nomeadamente nos cuidados de saúde prestados. Por isso, aceito participar no estudo Lisbon MSM Cohort.

Este documento é feito em duplicado tendo ficado uma cópia para quem pede consentimento e outra para quem consente.

**CÓDIGO DE COORTE** [redacted]

**OBSERVAÇÕES:**

**RÚBRICA / ASSINATURA DO TÉCNICO**

**RÚBRICA / ASSINATURA DO PARTICIPANTE**

Comissão Executiva da Lisbon MSM Cohort
ce.lisboncohort@ispup.up.pt
Investigador Principal: Henrique Barros