Oral HIV pre-exposure prophylaxis (PrEP) in Belgium

Understanding PrEP users' behaviours, attitudes, and care needs

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Chapter 1

General introduction

In 2021, an estimated 1.5 million new HIV infections occurred worldwide, more than one million off the 2025 target to end AIDS by 2030. To reduce new infections and reach global targets, there remains a need to better understand how to effectively deploy available and new efficacious HIV prevention strategies. Oral HIV pre-exposure prophylaxis (PrEP) is a relatively recent addition to the HIV prevention toolbox. PrEP entails the use of antiretroviral medication by HIV-negative individuals to reduce their risk of HIV infection. Between 2010 and 2015, various trials demonstrated that, if taken correctly, oral PrEP is highly efficacious in reducing the risk of acquiring HIV. Since then, various demonstration and implementation studies have proven feasibility of and acceptability for its delivery, and countries worldwide started rolling out PrEP. Nevertheless, PrEP uptake remains well short of the UNAIDS global target of ten million people accessing PrEP by 2025. Efforts are needed to better understand approaches for optimising PrEP delivery and scale-up in order to maximise the impact of PrEP.

Since 2017, PrEP has been available in Belgium, making it one of the first countries globally to roll-out PrEP. In this thesis, I will focus on the first five years of PrEP implementation in Belgium from a user perspective. Understanding how end-users engage with PrEP and its delivery is essential to optimise PrEP implementation. As PrEP is recommended by the World Health Organization (WHO) as part of a comprehensive HIV and sexual health strategy, understanding condom use and sexually transmitted infection (STI) prevention among PrEP users will be important. The focus is on men who have sex with men (MSM), as this population is most affected by HIV in Belgium, with 48% of new diagnosis being among MSM in 2021, and they comprise the majority of PrEP users.

1.1 Human immunodeficiency virus

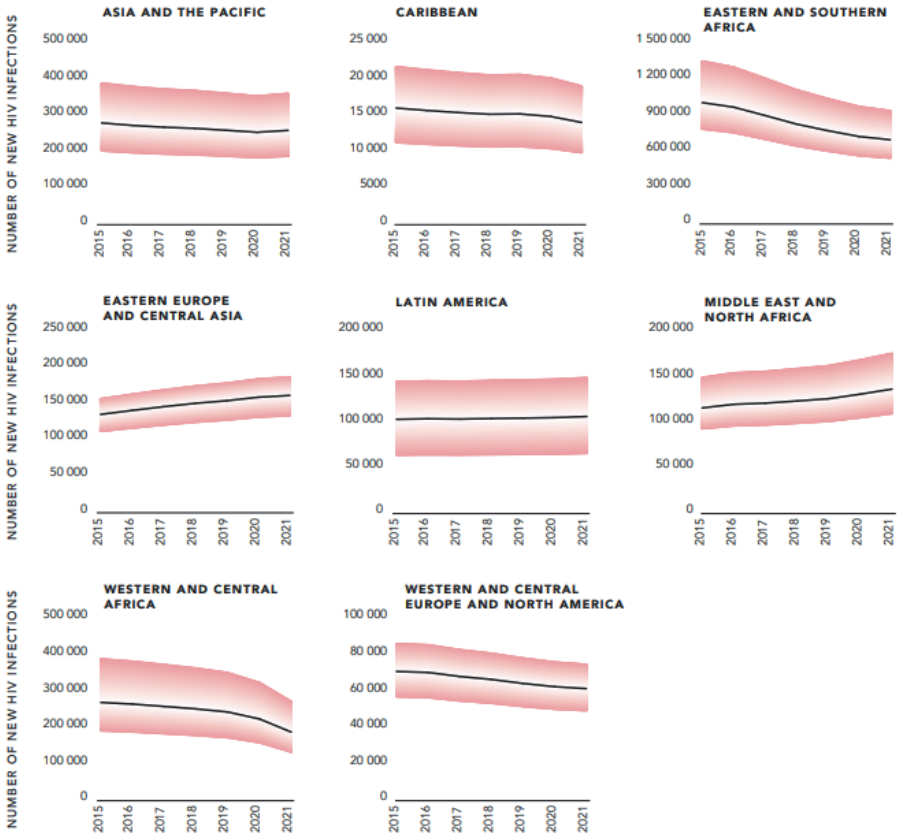
HIV is a retrovirus that targets the immune system, especially the CD4 T-cells.(1) HIV can be transmitted through several routes, including through anal or vaginal sex, vertical transmission, or sharing contaminated injecting equipment.(2–4) If left untreated, an HIV infection evolves to Acquired Immune Deficiency Syndrome (AIDS).(5) To date, there is no vaccine for HIV, nor is there a cure available that is sufficiently effective, safe and can be used on a larger scale.(6) The progression towards

AIDS, and associated morbidity and mortality among people living with HIV (PLHIV) can be prevented since the advent of combination antiretroviral therapy (cART) in 1996. HIV infection has now evolved to become a manageable chronic health condition(1,7), enabling PLHIV, if diagnosed and treated, to lead long and healthy lives.(1,8) Despite progress with HIV prevention and treatment, HIV continues to be a leading cause of death and major health threat to millions worldwide.(9) Understanding how infections can be prevented remains key in addressing the epidemic.

1.1.1 Global epidemiology

In 2021, there were an estimated 38.4 million PLHIV, 1.5 million newly infected people and 650 000 AIDS-related deaths worldwide.(9) The annual number of new HIV infections continues to decline globally, by an estimated 32% compared to 2010. The decline is most likely the result of large-scale expansion of cART and successful strategies such as increasing awareness, and campaigns to increase condom use or HIV testing. Despite the decline in new HIV infections, the reduction in new HIV infections is stalling. In 2021, the reduction in new infections showed the smallest annual decline since 2017, with a reported decrease of only 3.6% compared to 2020.(10) This suggests that it may become even more challenging to achieve the UNAIDS 2025 target for HIV prevention of fewer than 370 000 new infections annually.(10) While the sub-Saharan African region accounted for more than half of newly reported HIV infections in 2021, the share of global new HIV infections in non-African regions has increased.(10) In 2021, 621 000 new HIV infections were reported outside of sub-Saharan African region.(9) (Figure 1) About 107 000 new HIV diagnoses were reported in the WHO European Region in 2021, among which an estimated 17 130 new HIV diagnoses occurred in the West European Region.(11)

Figure 1. New HIV infections, by region, 2015-2021



Source: UNAIDS epidemiological estimates, 2022 (https://aidsinfo.unaids.org/).

1.1.2 HIV and men who have sex with men

In 2021, key populations (including gay men and other men who have sex with men (MSM), people who inject drugs, sex workers and their clients, transgender people and people in prisons) and their sexual partners comprised 70% of new HIV infections globally.(10) Outside of sub-Saharan Africa, key populations account for 94% of new HIV infections.(9) Among MSM, the risk for acquiring HIV is 28 times higher than among adult men in the general population.(10) In the West European Region, sexual transmission between men remains the most common mode of HIV transmission.(11)

Several factors, including biological, sexual behaviour, and socioeconomic factors, explain why MSM are more vulnerable to acquiring HIV.(12) First, the per-act transmission probability of HIV in receptive anal sex is higher compared to vaginal or oral sex.(13) Engaging in penile-anal sex, combined with other sexual behaviours, including multiple sexual partners, condomless sex, and engaging in sexualised drug use, are associated with increased rates of HIV transmission.(14) Secondly, discrimination, stigmatisation and criminalisation affects how MSM access HIV prevention, testing or treatment services.(15)

In this thesis, I will focus on MSM, because of the disproportionate burden of HIV in MSM, and as they currently comprise the majority of PrEP users in high-income countries.

1.2 Advances and challenges in HIV prevention with a focus on men who have sex with men

HIV prevention has evolved since the identification of the first cases of AIDS in 1981(16), the isolation of HIV in 1983(17) and the development of a first commercial diagnostic test in 1985.(18) In the early years of HIV, prevention focused on behaviour change messaging, namely promoting sexual abstinence and reducing the number of sexual partners, and educational campaigns to increase awareness of AIDS and 'safe sex' practices, such as condom use.(19) The first notion of 'safe sex' was developed in this period(20) and countries like Uganda adopted the message 'Abstinence, Be Faithful, and use Condoms', also known as the ABC approach.(21) In the United States, pamphlets were distributed such as 'Play Fair!' and 'How to have sex in an epidemic: one approach', advocating for condom use and self-empowerment.(20)

By the early 1990's, increases in condomless anal sex among MSM were reported.(22,23) As an alternative for condoms, some MSM incorporated HIV testing results in selecting sexual partners and adopted non-condom based risk strategies, such as serosorting (i.e. selecting sexual partners of the same HIV status)(24) and negotiated safety (i.e. an explicit sexual agreement between confirmed seroconcordant negative men in a relationship that established specific boundaries regarding exclusivity and

condom use)(25).(26) These strategies were shown to offer partial risk reduction benefit, although not as effective as consistent condom use.(27)

Between 2007 and 2016, evidence emerged that cART did not only have benefits for PLHIV, but also had potential for HIV prevention, more specifically as 'treatment as prevention' (TasP). In 2012, HPTN 052 trial showed that, among serodiscordant heterosexual couples, early initiation of ART by the HIV-positive partner reduced the risk of sexual transmission to the HIV-negative partner by 96%.(28) Subsequent studies, such as the PARTNER 1(29) and 2(30), and the Opposites Attract(31) studies generated much needed validation that the risk of HIV transmission during condomless anal sex among male couples is effectively zero when HIV viral load is suppressed, equivalent to heterosexual sex. These results provided the scientific basis to the concept 'undetectable equals untransmittable', also known as 'U=U'. This slogan is now used in public health and media campaigns to promote the effectiveness of TasP.(32,33) Based on the 'U=U' principle, HIV-negative individuals reportedly adopted a new risk reduction strategy: viral load sorting, i.e. choosing sexual partners with undetectable HIV viral load. With TasP, the biomedical prevention era started, referring to the use of biomedical agents for primary HIV prevention.

For an HIV negative individual, condoms remained the most effective, self-controlled method available to prevent acquisition of HIV.(34) Consistent condom use during receptive anal intercourse reduces the risk of acquiring HIV by 91%.(35) Despite high efficacy, the effectiveness of condoms is lower due to barriers to their use, including lack of intimacy with the partner and loss of sexual pleasure, increased potential for erectile dysfunction if using condoms, HIV prevention and condom fatigue, alcohol and drug use, perception of low severity of non-HIV STIs, and lack of dialogue or negotiation skills between partners.(36–39) In addition, a perception of low general risk of HIV, often related to the advent of cART (a concept coined as 'treatment optimism'), contributed to decreases in condom use among MSM. In the United States, for example, the percentage of MSM reporting condomless anal sex at least once in the past 12 months increased from 48% in 2005 to 57% in 2011.(40) A lack of a discreet, user-friendly, and highly effective prevention tool, that does not reduce sexual pleasure, enabling MSM to take control of their own protection irrespective of the sexual situation remained a critical gap for HIV prevention.(19)

1.3 Oral pre-exposure prophylaxis for the prevention of HIV

1.3.1 Randomised clinical trials demonstrating efficacy and safety

In 2010, the use of ART was further expanded with evidence of the primary prevention capacities of pre-exposure prophylaxis or PrEP. This relies on the preventive use of antiretroviral agents to reduce new HIV infections among HIV-negative individuals.(41) This method is not to be confused with post-exposure prophylaxis or PEP, which entails the use of a combination of antiretroviral drugs within 72 hours after exposure to HIV to prevent infection after exposure to HIV has taken place.(42)

The first randomised clinical trial (RCT) to show efficacy of once-daily oral co-formulated tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) was the multinational IPrEx trial. The RCT demonstrated that daily oral TDF/FTC provided 44% additional protection from HIV among men and transgender women who have sex with men.(41) Furthermore, the study suggested a correlation between adherence and the efficacy of PrEP on HIV acquisition, with higher protection levels achieved with higher PrEP adherence. Shortly thereafter the FEM-PrEP and VOICE trials did not show efficacy of oral PrEP among heterosexual women.(43,44) In 2015, the PROUD and IPERGAY studies, both among MSM at high risk for HIV, found an efficacy of 86% in reducing HIV risk.(45,46) The PROUD study compared immediate oral daily TDF/FTC to one-year delayed oral daily TDF/FTC.(47) The IPERGAY study was the first study to demonstrate the efficacy of on-demand PrEP use compared to placebo.(46) On-demand PrEP use (also called 'event-driven' or 'intermittent' use) involves the use of two pills of TDF/FTC between 2 and 24 hours before anticipated sexual contact, continuing with one pill every 24 hours until 48 hours after the last sexual contact.

A systematic review of 12 efficacy trials, including the abovementioned studies, concluded that PrEP is effective in reducing the risk for HIV acquisition, having an excellent safety profile and low risk for drug resistance.(48) In 2015, in response to this emerging evidence, WHO recommended to offer PrEP as part of combination HIV prevention for all people at substantial risk of acquiring HIV, including MSM.(49) Combination HIV prevention programmes are defined as 'rights-based, evidence-informed and community-owned programmes that use a mix of biomedical,

behavioural, and structural interventions prioritised to meet the current HIV prevention needs of particular individuals and communities so as to have the greatest sustained impact on reducing new infections'.(10) These programmes operate on different levels, i.e. individual, relationship, community, societal.(50) Substantial risk of HIV infection was provisionally defined as an HIV incidence above 3 per 100 person-years in the absence of PrEP. However, the local context and the individual heterogeneity in risk should also be considered.(51)

1.3.2 Demonstration and implementation projects demonstrating feasibility and acceptability

Since the 2015 WHO recommendation, many open-label, demonstration and oral PrEP implementation projects have been conducted worldwide.(52) Only a minority of these studies focussed on offering daily and on-demand PrEP.(53–59) The 'Be-PrEP-ared' (Belgium) and 'Amsterdam PrEP' (AMPrEP) (the Netherlands) cohort studies were the first demonstration projects globally where participants could choose and switch between daily and on-demand PrEP use during follow-up.(53,54) Results from these studies revealed the feasibility of PrEP delivery and effectiveness of PrEP in real-world settings, with low HIV incidence rates between zero and 0.30 per 100 person-years reported.(53,54) Reported uptake of either daily or on-demand PrEP varied, depending on how both regimens were offered to the patient and the men's risk profiles.(60) Men with a higher risk profile (e.g. more sexual partners) tended to opt for daily PrEP.(61,62) At baseline, uptake of daily PrEP was much higher in Dutch, Belgian and North-American studies, ranging between 73.3% and 78.3%, compared to studies in France or West-Africa (24.4%-50.5%). The most common reasons reported for daily PrEP use were ease of use, as it can be incorporated into daily routines and does not require planning for sex, and the perceived increased protection against HIV. On-demand was mainly appreciated by users who felt the ability to anticipate the risk of HIV, had concerns about side-effects, and had a lower perceived risk of HIV.(61,62) Moreover, these studies showed that the advantages of PrEP use go beyond preventing HIV infection. As such, PrEP use has been associated with reduced anxiety regarding sex and HIV and increases in the quality of sex lives, including increases in sexual satisfaction, pleasure, and well-being.(63,64)

The results of the French ANRS PREVENIR observational cohort study and the abovementioned studies have led WHO to fully endorse on-demand PrEP for cisgender MSM in 2019.(59,60) In 2022, WHO expanded the use of on-demand PrEP to cisgender men, and trans and gender diverse people assigned male at birth who are not taking exogenous estradiol-based hormones.(65) This restriction regarding individuals not taking gender-affirming hormones was included due to the fact that such hormones may reduce the concentrations of TDF and FTC, and thereby may reduce the efficacy of on-demand PrEP.(65)

1.3.3 Real-world PrEP roll-out demonstrating population-level effectiveness and implementation challenges

Since 2016, countries started rolling out PrEP.(66,67) The impact of this roll-out has been demonstrated in a few settings, showing promising reductions in the number of annual new HIV diagnoses among MSM. HIV diagnoses declined by 35% among gay and bisexual men in the United Kingdom between 2014 and 2018.(68) Similar declines have been demonstrated in San Francisco and New South Wales.(69,70) Despite these positive findings, translating the efficacy of PrEP into population-level effectiveness continues to pose implementation challenges.(71) According to the WHO definition, an effective PrEP programme is one in which people at substantial risk of HIV are appropriately identified, offered PrEP and then use PrEP as directed.(72) Achieving this requires addressing all steps of the PrEP cascade, starting from identifying individuals at risk for HIV to continued use during periods of risk.(34,73) In the following paragraphs, I will discuss the current state of PrEP roll-out in terms of uptake, use, and available delivery models, including some of the noted pertinent challenges or gaps.

1.3.3.1 PrEP uptake

By the second quarter of 2022, almost 3.9 million individuals across 90 countries initiated oral PrEP at least once. This is more than ten times the number of PrEP users in 2018 (370 000).(74) Despite this important progress in recent years, PrEP uptake remains well short of the UNAIDS global target of ten million people accessing PrEP by 2025.(75) In addition, inequalities in PrEP uptake have been demonstrated across and within countries. As such, most PrEP users can be found in a fairly small number of

countries, mainly situated in the eastern and southern African, western European and north Americas regions.(10,66) Within western high-income countries, uptake tends to be highest among MSM.(69,76)

1.3.3.2 PrEP use

Maximising the impact of PrEP on the HIV epidemic depends not only on increasing its coverage (i.e. uptake among those benefiting from PrEP), but also on effective use.(77) The latter refers to the appropriate use of PrEP during periods of HIV risk to achieve high levels of protection against HIV acquisition.(65) While effective use messaging for cART for treatment of an HIV infection is simple (i.e. lifelong without interruptions), for PrEP this is less straightforward. Individuals can have variable periods of risks for HIV infection and use other HIV prevention methods.(78) Subsequently, this influences how PrEP could be used. While on-demand oral PrEP has been shown to be highly effective in MSM, the inclusion of this use in international guidelines varies.(60,79) Due to these delays in endorsement, not every PrEP programme worldwide is offering on-demand PrEP use besides daily PrEP. As a result, studies focusing on PrEP use predominantly focus on adherence to daily PrEP. There remains to be a paucity of studies following up users longitudinally who have the option to choose and switch between daily and on-demand regimens.

1.3.3.3 PrEP delivery models

PrEP has commonly been provided through healthcare facilities where PrEP is prescribed by a physician.(80–82) In Europe, these healthcare facilities are mainly centralised and specialised infectious disease facilities.(82) The choice for healthcare facilities as delivery settings is mainly due to the novelty of using antiretrovirals for HIV prevention, the settings used in clinical trials and demonstration projects to investigate efficacy and feasibility, their expertise in dealing with the needs of key populations, and the lack of evidence available for PrEP delivery at scale. However, such delivery models are not always best suited for all PrEP users, who are healthy people seeking preventative care. As a result, this could impede access for individuals who could benefit from PrEP, or discourage continued PrEP use.(83) Additionally, learning from centralised cART delivery experiences, such a centralised model puts pressure on the

facility's capacity as demand grows.(83) Issues around funding and reimbursement, capacity and access such as travel distance, frequency of clinic visits, waiting times or inconvenient operating hours have been reported for PrEP.(84,85) In recent years the offer of different PrEP delivery models is evolving and diversifying to address the range of reported barriers and to accommodate the needs and preferences of its users, and this has accelerated due to the COVID-19 pandemic.(86) Nowadays, community-based services, mobile clinics, peer-supported-, and pharmacy-led PrEP delivery and telehealth approaches are being established to ensure PrEP is reaching those who need it, when they need it, how and where they want it delivered.(81,87,88)

1.3.3.4 Diverging curable bacterial sexually transmitted infection trend

In contrast to the declining HIV epidemic, there is a diverging trend in curable bacterial sexually transmitted infections (STIs) in high-income countries. While the rates of curable STIs decreased rapidly when the HIV epidemic became apparent in the 1980s, reaching their lowest point by mid-1990s, they began to rise again after 1996, with the availability and access to cART.(89) Since 2010, rates of curable STI diagnoses even accelerated, partly due to improved detection after transitioning from culture to nucleic acid amplification testing.(90–93)

Key populations such as MSM, and particularly MSM using PrEP, are disproportionally affected by STIs.(94,95) The reasons for the rise of STIs among MSM are complex. Several interconnected factors acting on different levels contribute to the increasing STI rates, such as changes in sexual behaviour (e.g. increased condomless anal sex), novel partnering strategies (e.g. online sexual or social network applications), dense sexual networks and increased testing.(94,96–103) In contrast to condoms, PrEP only protects against HIV acquisition, and not against other STIs. While the causal connection between PrEP and rising STIs remains inconclusive, PrEP serves as an entry point for reaching people at risk for STIs to access more comprehensive sexual health care. As such, WHO recommends to integrate STI services (e.g. screening and treatment) into PrEP programmes.(104)

1.3.4 User perspective

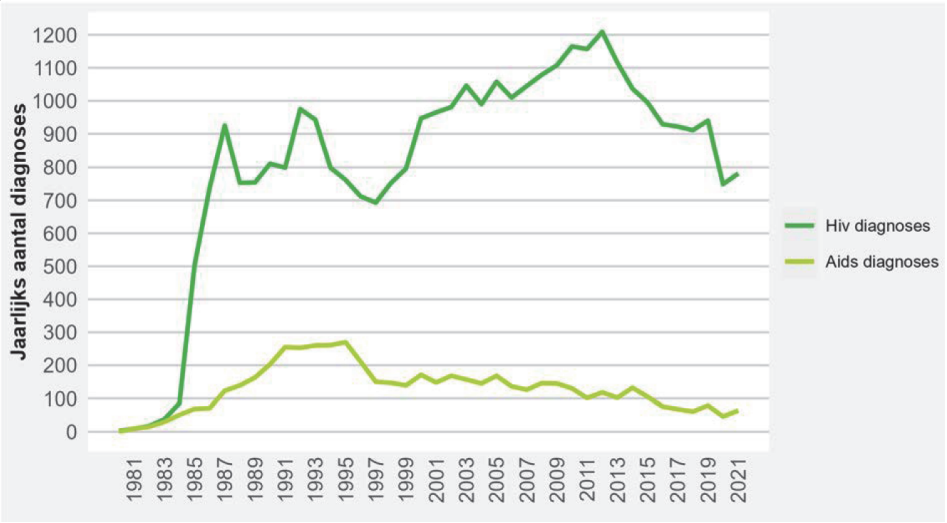
In order to address the abovementioned challenges, efforts are needed to better understand approaches for optimising delivery and scale-up in order to maximise the impact of PrEP. Further understanding of the user perspective will be essential, as successful implementation and mechanisms of impact rely on participant responses to and interactions with an intervention.(105) In order words, whether and how PrEP is being used will have an impact on the decline of new HIV infections.(106) Furthermore, eliciting the experiences and preferences of various population groups that might benefit and are benefitting from PrEP is important for the tailoring of programmes to their unique needs and increasing uptake and the appropriate use of PrEP during periods of HIV risk.(83,107) Hence, in this thesis, I will focus on the users' point of views on PrEP uptake, use and PrEP care as part of combination prevention, embedded in a comprehensive sexual health care approach.

1.4 PrEP in Belgium

1.4.1 HIV epidemic

In 2021, 6.8 new HIV diagnoses were reported per 100 000 population in Belgium, considerably higher than the average for Western Europe (i.e. 3.9/100 000).(11) Of the estimated 19 177 people living with HIV in Belgium in 2021, 17 622 HIV patients were in medical follow-up, and an estimated 1155 individuals were unaware of their HIV status.(108) In 2021, an average of 2.14 new HIV diagnoses were recorded daily. Men accounted for 74% of the new HIV diagnoses. About three out of four new HIV diagnoses were among individuals between 20 and 49 years old.(108) MSM and heterosexual individuals with a migrant background are the two populations hardest hit by the HIV epidemic.(108) A steady decline has been observed in the Belgian HIV epidemic over the last ten years. (Figure 2) Additional efforts and insights are needed on how best to use available and future resources to further reduce the number of new HIV infections to a historical low since the beginning of the epidemic.(109)

Figure 2. Yearly number of new HIV and AIDS diagnoses, Belgium, 1980-2021



Source: Sciensano HIV report, 2022 (https://www.sciensano.be/en/biblio/epidemiologie-van-aids-en-hiv-infectie-belgie-toestand-op-31-december-2021)

1.4.2 STI epidemic

The rates of STIs are steadily increasing in Belgium.(110,111) Chlamydia is the most reported and most widespread STI among the general population. Infection rates increased from 27.2 per 100 000 inhabitants in 2009 to 77.0 per 100 000 inhabitants in 2019. For gonorrhoea, the second most frequently reported STI in Belgium, rates increased from 6.6/100 000 in 2009 to 26.0/100 000 in 2019. The rates for syphilis increased from 5.3/100 000 in 2009 to 21.6/100 000 in 2019.(110,111) It should be noted that testing frequency also increased over time to correctly interpret this increasing trend.(111) Further disaggregated data on national trends among key populations such as MSM are lacking. However, based on sociodemographic and behavioural data additionally collected through a sentinel network of general practitioners, in the period 2017-2019, syphilis, followed by gonorrhoea were mostly reported among men. The share of MSM among the reported syphilis cases is 76.2%, among gonorrhoea 38.5% and for chlamydia 13.5%.(110) Results from the Belgian PrEP demonstration study 'Be-PrEP-ared' showed a high bacterial incidence (i.e. syphilis, gonorrhoea, chlamydia, or

Mycoplasma genitalium) of 75.4 per 100 person-years (95% CI 63.8 to 89.1) among PrEP using men and transgender women who have sex with men and who use PrEP.(54)

1.4.3 PrEP implementation

In 2013, Belgium launched the first national HIV Plan that included the development of a framework for pilot PrEP projects and operational research on PrEP feasibility.(112) In 2015, the PrEP demonstration study, called 'Be-PrEP-ared', was set up to evaluate uptake, acceptability and feasibility of using and adhering to daily and on-demand PrEP.(113) The study enrolled 197 MSM and three transgender women at high risk of HIV. In the 18 months of follow-up, no new HIV infections were diagnosed; the study showed that PrEP is an effective and feasible HIV prevention tool for MSM in Belgium. The results of the 'Be-PrEP-ared' demonstration project contributed to the decision of the Minister of Public Health and Social Affairs of Belgium to offer reimbursed PrEP as prophylactic medication for people who are at increased risk of HIV acquisition via the healthcare system from 1 June 2017 onwards. As such, Belgium was one of the first countries worldwide to roll-out PrEP. In 2019, the research project 'Optimise PrEP to Maximise Impact' (abbreviated as PROMISE), a four-year (2019-2022) research project funded by Research Foundation – Flanders ('Fonds voor Wetenschappelijk Onderzoek', FWO), was set up by the Institute of Tropical Medicine (ITM) in Antwerp. The aim of the project was to learn how PrEP roll-out in Belgium can be optimised in order to achieve maximum impact on HIV and sexual health. Current PhD is part of the PROMISE project.

The Belgian Ministry of Public Health and Social Affairs issued PrEP eligibility criteria for prescription and reimbursement. (Figure 3) These criteria include MSM at high risk to acquire HIV infection, people who inject drugs and share needles, people in sex work or others who may be exposed to greater HIV risk, and partners of HIV-positive individuals without viral load suppression.(114)

Figure 3: PrEP eligibility criteria for prescription and reimbursement in Belgium

PrEP eligibility/reimbursement criteria in Belgium: - **HIV-negative status by testing** - **AND high risk of HIV acquisition, determined by having at least one of the following risk factors:**	
Men having sex with men (MSM) at very high risk of HIV infection :	**High-risk individuals with individual risk :**
- Who have unprotected anal sex with at least two partners in the last six months;	- People who inject drugs (PWID) who share needles ;
- With multiple sexually transmitted infections (STIs) (syphilis, chlamydia, gonorrhoea or a primo infection with hepatitis B or C) during the last year;	- People in sex work who are exposed to unprotected sex;
- Who needed post-exposure prophylaxis (PEP) several times a year;	- People in general exposed to unprotected sex at high risk of HIV infection ;
- Who use psychoactive substances during sexual activity.	- Partner of an HIV-positive patient without viral suppression (newly on treatment or no viral suppression despite adequate treatment)

Source: K.B. 01.02.2018 - IV – 8750000
(https://webappsa.rizivinami.fgov.be/SSPWebApplicationPublic/nl/Public/ProductSearch)

In Belgium, PrEP is delivered through twelve specialised, multidisciplinary HIV clinics, also called HIV reference centres (HRCs). These HRCs are usually embedded in secondary or tertiary health facilities (i.e. university hospitals), located in urban or semi-urban areas. A specialist physician associated within an HRC has the authority to initiate PrEP and to request and renew the yearly reimbursement approval for eligible individuals. PrEP users are partly reimbursed for their PrEP medication; currently, the out-of-pockets expenses are €15 for 90 pills.(114)

A document entitled 'Belgian PrEP guidelines' was drafted by the Belgian PrEP taskforce, a group of clinical and public health researchers, and community representatives. These guidelines have so far not been formally adopted or endorsed by all HRCs, though they were presented and made available by BREACH, i.e. a national consortium of HIV researchers and clinicians. So, therefore, there are no official national PrEP guidelines. The service delivery package generally consists of quarterly follow-up visits at the HRCs, and usually includes: HIV and STI (i.e. syphilis, gonorrhoea, chlamydia and hepatitis C) screening, promotion of adherence and risk reduction strategies, and a repeat prescription for three months (i.e. 90 pills, assuming daily use).

In 2021, 5277 individuals have obtained PrEP at least once through community pharmacies, which is more than a two-fold increase compared to 2018.(108) Almost all of these PrEP users were men and mainly MSM. About one in three were between 30 and 39 years old. A third were first time PrEP users.(108)

THIS THESIS

1.5 Aim and objectives

In the introduction I outlined that, while PrEP is a promising addition to the HIV prevention toolbox, its implementation and scale-up remains inadequate to achieve maximum impact on the global HIV epidemic. PrEP programmes operate within a local context influenced by the local HIV epidemic, health system and target population. This thesis aims to gain insights into Belgian PrEP users' profiles and behaviours, attitudes, and PrEP care needs in order to better understand the Belgian PrEP programme implementation and provide guidance for PrEP care optimisation.

This thesis has three main objectives:

1) To provide insights into the national roll-out of PrEP in the first two years of PrEP implementation.
2) To study PrEP users' HIV prevention behaviour, sexual behaviour, and attitudes towards STIs and condoms.
3) To investigate PrEP users' experiences with, and preferences for PrEP service delivery.

1.6 Outline of this thesis

The findings of this thesis are provided in three subsequent chapters, each covering respectively one of the abovementioned objectives.

In **Chapter 2**, using routinely collected Belgian social health insurance claims data, we identify all users who were dispensed PrEP at least one PrEP description between June 2017 and December 2019. Among these, we describe sociodemographic characteristics

of PrEP users, PrEP dispensing practices, uptake of testing for three bacterial STIs (i.e. gonorrhoea, chlamydia and syphilis) and HIV, and incidence of HIV and STIs.

In **Chapter 3**, we describe PrEP users' HIV prevention behaviour, sexual behaviour, and attitudes towards STIs and condoms. In **Subchapter 3.1**, we assess changes in the sociodemographic and sexual behaviour profile of individuals initiating PrEP at a large HIV reference centre in Belgium over time. We also describe their probabilities of switching between daily and on-demand PrEP, and of interrupting PrEP. Furthermore, we describe dynamics of PrEP follow-up over time. For more nuanced data on PrEP use, we explore the variety of patterns of PrEP use going beyond the daily and on-demand regimens among PrEP users participating in a web-based longitudinal study in **Subchapter 3.2.** We examine factors associated with these patterns and describe PrEP and concurrent condom use by partner type over time. We then explore PrEP users' attitudes towards STIs and condoms and how these attitudes influence their condom use with non-steady partners as a method to prevent STIs in **Subchapter 3.3.** In **Subchapter 3.4**, we assess self-perceived and actual knowledge of effectively starting and stopping oral PrEP. In addition, we identify factors associated with incorrect start-and-stop knowledge.

In **Chapter 4**, we explore experiences of, and preferences for, PrEP care among PrEP users in Belgium. Additionally, we explore PrEP users' willingness to involve family physicians into PrEP care.

In **Chapter 5,** we highlight some of the main findings of this thesis and their implications. Furthermore, we identify future directions for prevention and research in the field of HIV and STI prevention.

1.7 Study design and data sources used in this thesis

To address the aim and objectives of this thesis, we draw on mixed-methods research, using routinely collected data and primary data. An overview of the study topics, data sources and study characteristics included in this thesis is presented per chapter in Table 1. We analysed data of PrEP users from three sources, i.e. national social health insurance claims data, routine healthcare data from the ITM HIV reference centre, and

web-based longitudinal study data as part of the PROMISE project. By combining these three data sources, we analysed data from three different settings, providing complementary views from the PrEP user perspective concerning the implementation of PrEP in Belgium.

National claims database

Belgium has detailed records of the services provided within the healthcare sector. All individual data on reimbursed healthcare benefits, so-called claims data, are collected in a uniform way, recorded and stored by the Inter Mutualistic Agency (IMA). IMA, a data-expertise centre, collects these data through the seven Belgian healthcare insurance funds. These claims data are recorded in three databases, i.e. population, healthcare and pharmanet.(115) These databases contain information on demographic and socio-economic characteristics and on reimbursed healthcare expenditures such as medical consultations, dispensed drugs and laboratory tests. IMA compiles these data for analysis and research purposes in order to support the healthcare insurance funds and Belgian policy makers in improving the performance, quality and accessibility of Belgian healthcare and health and disability insurance. IMA operates on its own initiative, but external parties can also request authorisation to work with these pseudonymised data. The fact that these databases have been available since 2002 and that all claims data are linked to unique individuals throughout time enables longitudinal or cohort studies. Additionally, the databases allow to get a nationwide overview of all PrEP users with a social health insurance and how they obtained PrEP and other PrEP care related healthcare expenditures such as HIV/STI testing over time. As social health insurance is mandatory in Belgium, these databases cover the large majority of all users living in Belgium. Moreover, it requires less time and resources for external researchers, since these databases are readily available for secondary analyses and thus do not require primary data collection.

Routine healthcare database from ITM HIV reference centre

The HIV reference centre, part of the Institute of Tropical Medicine in Antwerp, follows the largest cohort of PrEP users in Belgium. Since June 2017, two types of data are being collected for each PrEP user, i.e. clinical records and electronic questionnaire data, both collected during each routine PrEP visit. Clinical records contain all clinically relevant information regarding a patient's health and his/her consultation as part of routine care.

The electronic questionnaire was originally set up to facilitate data collection requested by the National Institute for Health and Disability Insurance (RIZIV-INAMI). PrEP users are invited to fill in this electronic questionnaire at each routine visit either on site on an electronic tablet or online using their own digital media. It includes questions on socio-demographic characteristics, eligibility criteria for PrEP, sexual behaviour and PrEP use regimen of the previous three months. The routine healthcare database thus provides additional, valuable insights into PrEP users, which are missing in the national claims data. Between June 2017 and the end of 2020, the questionnaire was only available in Dutch. During that period consenting participants needed to be 18 years or above and able to read Dutch for completing the questionnaire.

PROMISE Research Project

As mentioned above, 'Optimise PrEP to Maximise Impact' (abbreviated as PROMISE) is a four-year (2019-2022) research project funded by Fonds voor Wetenschappelijk Onderzoek (FWO). The project investigates the PrEP roll-out from different populations' perspectives: (1) potential MSM PrEP users, (2) individuals with a migration background, (3) PrEP users, (4) PrEP providers, and (5) sex workers. As this thesis focusses on PrEP users, data related to this population and generated through the project are discussed hereafter.

As part of this project, a web-based longitudinal study among PrEP users living in Belgium was set up. The aim was to follow-up a cohort of PrEP users for a one-year period during which semi-annually questionnaires were sent. People were recruited irrespective of when they started taking PrEP, but had to have been using PrEP in the six months preceding the baseline questionnaire. PrEP users were recruited through various routes. This allowed to maximise variation regarding types of PrEP users across the country (i.e. independent of the site where they obtained PrEP). The web-based longitudinal study allowed us to study more in-depth socio-demographic characteristics, sexual behaviour and patterns of PrEP use and to investigate needs and preferences. Additionally, qualitative research components were embedded in the project. We conducted in-depth interviews with participants of the web-based longitudinal study, and with PrEP users from the ITM HRC. By triangulating insights from both the quantitative and qualitative study data, we were able to investigate more in-depth particular needs, preferences, attitudes and behaviours of PrEP users, and

provide a more complete picture or explanation of results, thereby enhancing the validity of the findings.(116,117)

We adopted a cohort or longitudinal study design when collecting data from abovementioned three data sources. By using such a study design, which employs continuous or repeated measures to follow particular individuals over prolonged periods of time, we were able to study changes over time, for example trends and patterns in PrEP and condom use and to calculate specific outcomes as HIV or STI infections both at group and individual level.(118) Since these studies are conducted outside of a controlled study setting, such as randomised controlled trials, and often use routine data collection, we were able to better reflect a real-life context. Disadvantages of cohort studies include loss-to-follow-up over time, resulting in missing data, being time-consuming, susceptibility to selection bias and requiring a large sample size.(119)

Table 1. Overview of topics, data sources and study characteristics of studies included in this thesis

Chapter	Topic	Study design	Data source	Period of data collection	Study population
2	PrEP use trajectories and HIV/STI incidence	Quantitative: cohort analysis	National social health insurance claims database	June 2017 – Dec 2019	4559 PrEP users
3.1	PrEP user profiles, dynamics of PrEP use and follow-up	Quantitative: cohort analysis	Routine questionnaire and medical records of ITM HRC	June 2017 – Feb 2020	1347 PrEP users
3.2	Patterns of PrEP and condom use	Quantitative: web-based longitudinal study	PROMISE project	Sep 2020 – Jan 2022	326 PrEP users for baseline assessments, 173 PrEP users for longitudinal assessments
3.3	Attitudes towards STIs and condoms	Mixed-method: Quantitative: web-based longitudinal study Qualitative: in-depth interviews	PROMISE project	Sep 2020 – Jan 2022 (quantitative) Aug 2021 – Jan 2022 (qualitative)	326 PrEP users (quantitative) 22 PrEP users ITM HRC (qualitative)
3.4	Knowledge of starting and stopping PrEP	Quantitative: web-based longitudinal study	PROMISE project	Sep 2020 – Jan 2022	206 PrEP users assigned male at birth
4	PrEP care experiences and preferences	Mixed-method: Quantitative: web-based longitudinal study Qualitative: semi-structured interviews	PROMISE project	Sep 2020 – Jan 2022 (quantitative) Aug 2021 – Dec 2021 (qualitative)	326 PrEP users (quantitative) 21 PrEP users (qualitative)

Abbreviations: HIV = Human Immunodeficiency Virus, HRC = HIV reference centre, ITM = Institute for Tropical Medicine, PrEP = pre-exposure prophylaxis, PROMISE = Optimise PrEP to maximise impact project, STIs = sexually transmitted infections

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Chapter 2

The roll-out of PrEP in Belgium

Chapter 2

Pre-exposure prophylaxis (PrEP) use trajectories and incidence of HIV and other sexually transmitted infections among PrEP users in Belgium: a cohort analysis of insurance claims data from 2017 to 2019

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ABSTRACT

Introduction: Since June 2017, oral pre-exposure prophylaxis (PrEP) has been reimbursed in Belgium for people at substantial risk of HIV. To inform the national PrEP programme, we described sociodemographic characteristics of PrEP users, PrEP dispensing practices, testing for HIV and sexually transmitted infections (STIs; gonorrhoea, chlamydia and syphilis), and incidence of HIV and STIs.

Methods: We analysed routinely collected social health insurance claims data from all individuals who were dispensed at least one PrEP prescription between June 2017 and December 2019. Using logistic regression adjusted for age, we examined associations between sociodemographic characteristics and having been dispensed PrEP only once in the first six months of PrEP use.

Results: Overall, 4559 individuals were dispensed PrEP. Almost all PrEP users were male (99.2%, 4522/4559), with a median age of 37 years (IQR 30-45). A minority were entitled to an increased healthcare allowance (11.4%, 514/4559). Eighteen percent (657/3636) were dispensed PrEP only once in the first six months of PrEP use. PrEP users younger than 25 years, unemployed, entitled to an increased healthcare allowance, and who initiated PrEP between January 2019 and June 2019 were more likely to have had no PrEP dispensing after initiation compared to their counterparts. The testing rate for bacterial STIs was 4.2 tests per person-year (95%CI 4.1-4.2) and for HIV was 3.6 tests per person-year (95%CI 3.5-3.6). We identified 12 individuals who seroconverted during the study period, giving an HIV incidence rate of 0.21/100 person-years (95%CI 0.12-0.36). The incidence of bacterial STIs was 81.2/100 person-years (95%CI 78.7-83.8).

Conclusions: These findings highlight challenges with PrEP persistence and a high incidence of bacterial STIs among individuals who were dispensed PrEP at least once. To optimise PrEP effectiveness, tailored prevention support to individuals with ongoing risk for HIV acquisition is required. Strategic STI testing and prevention interventions, integrated into PrEP care, will be needed to reduce STI acquisition and transmission among PrEP users.

INTRODUCTION

Despite advances in the response to HIV over the past decades, HIV incidence remains high globally, with 1.5 million new infections annually.(1) In Belgium, 781 persons were newly diagnosed with HIV in 2021, an HIV diagnosis rate of 6.8 cases per 100 000 population.(2) Belgian men who have sex with men (MSM) and heterosexual individuals of the sub-Saharan African diaspora community have been disproportionately affected.(3) Like in many high-income countries, Belgium has seen a steady decline in the number of new HIV diagnoses over the past decade, attributable, in large part, to the implementation of combination HIV prevention.(2,3) Since June 2017, individuals defined as having a "substantial risk" of HIV have been eligible to have oral pre-exposure prophylaxis (PrEP) reimbursed through their social health insurance.(4) (Additional file 1) Effective implementation and integration of PrEP into HIV prevention services will be paramount to further curb the epidemic.(5,6)

Real-world PrEP effectiveness studies have shown that PrEP use is associated with a 60% to 74% reduction in the risk of acquiring HIV infection.(7,8) To date, few studies have examined HIV incidence after PrEP initiation in real-world settings using routine data.(9–14) For PrEP to be effective, it should be used appropriately during periods of HIV risk to achieve high levels of protection (i.e. 'prevention effective use'). Moreover, PrEP should be taken consistently over time as long as risk persists (i.e. 'PrEP persistence').(9,15–18) However, insights into PrEP persistence and effective use over time, outside of clinical trials or implementation studies, are relatively scarce.(19–21) Collecting and assessing data on these indicators among PrEP users over time is important to gain insights into the effectiveness of PrEP programmes.

Although PrEP reduces the risk of HIV acquisition, it does not prevent other sexually transmitted infections (STIs). PrEP users, predominantly MSM in many high-income countries, are often at higher risk of other STIs due to sexual behaviours, including multiple sexual partners and condomless anal sex.(22–24) PrEP care is often, as in Belgium, integrated within broader comprehensive sexual health care, offering opportunities for regular STI screening.(25) Reporting on the number of STI tests and

STI diagnoses among PrEP users over time is essential to assess service performance and to follow-up STI trends among this population.

In Belgium, PrEP is delivered through 12 specialised HIV clinics during quarterly scheduled visits. A national PrEP surveillance system has been established, with yearly monitoring reports produced using pharmacy reimbursement data and aggregated data collected via the clinical records of the 12 HIV clinics. In 2021, the pharmacy data registered 5277 PrEP users, 99% of whom were men.(3) Using the aggregated HIV clinic data, we know that the majority of PrEP users were Belgian MSM.(3) These data sources, however, have limitations, as they do not provide an insight into PrEP use and STI diagnoses over time. There is a need to assess more comprehensive individual-level longitudinal data to identify gaps in PrEP roll-out to optimise its outcomes.(26)

The aim of this study was to use routinely collected health insurance claims data to describe sociodemographic characteristics of PrEP users in Belgium, PrEP prescribing and dispensing practices, uptake of STI and HIV testing, and the incidence of HIV and three bacterial STIs (i.e. gonorrhoea, chlamydia, syphilis) among individuals dispensed PrEP. The results will be of particular interest to identify potential areas for optimisation of the Belgian PrEP programme and inform how PrEP programme implementers could use similar data.

METHODS

Study design

We conducted a cohort analysis using routinely collected claims (i.e. social health insurance) data from PrEP users in Belgium from June 2017 through December 2019.

Data source

All individual data on reimbursed healthcare benefits, i.e. claims data, are routinely collected from all seven healthcare insurers by the Inter Mutualistic Agency (IMA; www.ima-aim.be).(27) Social health insurance is mandatory in Belgium, as such the database includes reimbursement data for all legal residents.(28) In addition, this database contains information on sociodemographics (age, sex, area of residence) and

coverage by a special allowance, which entitles individuals, whose annual income is below an established threshold, to request an increased healthcare allowance. This means they pay reduced fees for co-payments on healthcare expenditures. Additionally, the database contains individual data on use of ambulatory and hospital care, including laboratory tests, dispensed drugs and type of prescriber. The database does not contain any direct medical information, such as medical diagnoses or laboratory test results.

Outcomes and explanatory variables

We considered PrEP dispensing as a proxy for PrEP use, and defined PrEP users as individuals who obtained reimbursed PrEP [tenofovir disoproxil fumarate and emtricitabine (TDF-FTC)] at least once between 1 June 2017 and 31 December 2019.

We defined the date of PrEP initiation as the first PrEP dispensing date. Subsequent PrEP dispensing events were considered renewals. The parameters used to establish a PrEP dispensing, and as such a PrEP user, are detailed in additional file 2. Sociodemographic characteristics of PrEP users included sex (male or female), age, region of residence (Flanders, Brussels-Capital, Wallonia, abroad or unknown), occupational status (active or non-active) and coverage by an increased healthcare allowance (no, yes). We calculated age at PrEP initiation by taking the difference between year of PrEP initiation and year of birth, and categorised these as: <25, 25-34, 35-44, 45-54, and ≥55 years. A more detailed description of the Belgian PrEP care delivery system can be found in additional file 3.

We defined a new HIV infection as any combination of HIV antiretrovirals dispensed after the first date of PrEP dispensing, unless regimens were consistent with PrEP and PEP.(29) (Additional file 4)

We defined an STI diagnosis (i.e. gonorrhoea, chlamydia and syphilis) using a combination of 1) a specific STI laboratory test and 2) by a first-line antibiotic treatment for the specific STI, according to Belgian guidelines(30,31), within a 30-day period of the specific laboratory test. (Additional file 5) We considered an individual to have an STI re-infection if a new combination of a specific laboratory test and specific antibiotic treatment was observed in the dataset.

Data analysis

We described sociodemographic characteristics of PrEP users at date of PrEP initiation, including sex, age, region of residence, occupational status and coverage by an increased healthcare allowance.

For each PrEP dispensing, we extracted information on: number of PrEP pills, type of prescriber (general practitioner or specialist physician) and location of dispensing (hospital or community pharmacy). We calculated the mean number (and standard deviation, SD) of PrEP pills dispensed per month per person. Additionally, we calculated the PrEP dispensing rate, overall and by semester of PrEP initiation. (Additional file 6)

Among individuals who initiated PrEP between 1 June 2017 and 30 June 2019, we assessed the number of PrEP dispensing events within the first six months following initiation. We assessed whether age, occupational status, coverage by an increased healthcare allowance, and semester of initiation were associated with having only been dispensed PrEP once, using logistic regression adjusted for age.

We calculated the HIV incidence rate by dividing the number of new HIV diagnoses within 365 days after last PrEP dispensing or before 31 December 2019, whichever was first, by total person-years in follow-up. For each individual who seroconverted, we present their PrEP use trajectory. Each trajectory shows the dates when PEP, PrEP or first ART were dispensed and HIV testing was performed. The number of pills dispensed per PrEP dispensing is also reported. We calculated the testing rates for bacterial STIs and HIV, overall and by semester of PrEP initiation. Finally, bacterial STI incidence rates, overall and by semester of PrEP initiation were calculated together with STI re-infection rate. Additional information on the statistical analysis is provided in additional file 6.

We reported missing values, if any, in a specific category. We used R version 4.0.2 for the analyses.(32)

Ethics

This study received ethical approval by the Institutional review board of the Institute of Tropical Medicine, Antwerp, Belgium (1427/20) and received clearance by the Belgian Information Security Committee. No informed consent was required as the data encompasses claims data, which were routinely collected.

RESULTS

Characteristics of PrEP users at PrEP initiation

Between 1 June 2017 and 31 December 2019, 24 272 PrEP dispensing events were registered of which 4559 (18.8%) were first-time PrEP users and 19 713 (81.2%) were PrEP renewals. Almost all PrEP users were men (99.2%, 4522/4559; Table 1); their median age was 37 years (IQR 30-45). More than half (56.7%, n=2586) were living in Flanders, 27.4% (n=1249) in Brussels, and 14.8% (n=676) in Wallonia. The majority (92.5%, n=4217) were employed and a minority (11.4%, n=514) were entitled to an increased healthcare allowance.

Table 1. Sociodemographic characteristics at PrEP initiation of all PrEP users who initiated PrEP between 1 June 2017 and 31 December 2019 (N=4559), all PrEP users (N=3636) who initiated PrEP between 1 June 2017 and 30 June 2019, and PrEP users who initiated PrEP between 1 June 2017 and 30 June 2019 who were dispensed PrEP only once (N=657) in the first six months of PrEP use, in Belgium.

	All PrEP users between June 2017 and Dec 2019 N=4559	All PrEP users between June 2017 and June 2019 N=3636	PrEP users who initiated between June 2017 and June 2019, who were dispensed PrEP only once in the first six months of PrEP use N=657	OR[†]	Age-adjusted OR[‡]
	n (%)	n (%)	n (%)[£]		
Sex[§]					
Female	36 (0.8)	-	-	-	-
Male	4522 (99.2)	-	-	-	-
Missing	1	-	-	-	-
Age in years					
Median, IQR	37 (30-45)	37 (30-45)	35 (28-43)	-	-
<25	275 (6.1)	212	61 (28.8)	Ref	-
25-34	1573 (34.5)	1237	265 (21.4)	0.64 (0.49 – 0.83)	-
35-44	1496 (32.8)	1206	193 (16.0)	0.47 (0.36 – 0.62)	-
45-54	807 (17.7)	664	85 (12.8)	0.39 (0.29 – 0.52)	-
≥55	404 (8.9)	316	53 (16.8)	0.55 (0.39 – 0.78)	-
Missing	1	1	0	-	-
Residence per region[§]					
Flanders	2586 (56.7)	-	-	-	-
Brussels-Capital	1249 (27.4)	-	-	-	-
Wallonia	676 (14.8)	-	-	-	-
Abroad or unknown	48 (1.1)	-	-	-	-

Occupational status[¶]					
Active	4217 (92.5)	3360	580 (17.3)	Ref	Ref
Non-active	341 (7.5)	275	77 (28.0)	1.86 (1.40 – 2.45)	1.79 (1.33 – 2.39)
Missing	1	1	0	-	-
Covered by an increased healthcare allowance					
No	4006 (88.6)	3204	547 (17.1)	Ref	Ref
Yes	514 (11.4)	396	99 (25.0)	1.62 (1.26 – 2.06)	1.45 (1.13 – 1.86)
Missing	39	36	11		
Semester of initiation					
June 2017	92 (2.0)	92	7 (7.6)	0.49 (0.20 – 1.00)	0.49 (0.20 – 1.02)
July 2017 – Dec 2017	973 (21.3)	973	141 (14.5)	Ref	Ref
Jan 2018 – June 2018	899 (19.7)	899	152 (16.9)	1.20 (0.94 – 1.54)	1.18 (0.92 – 1.52)
July 2018 – Dec 2018	814 (17.9)	814	161 (19.8)	1.45 (1.14 – 1.87)	1.44 (1.12 – 1.85)
Jan 2019 – June 2019	858 (18.8)	858	196 (22.8)	1.75 (1.38 – 2.22)	1.71 (1.34 – 2.17)
July 2019 – Dec 2019	923 (20.2)	-	-	-	-

IQR: interquartile range, OR: odds ratio, PrEP: pre-exposure prophylaxis

[†] using logistic regression, with outcome only one dispensing in the first six months, excluding users who initiated after June 2019 (N=3636), [‡] adjusted for age using logistic regression, [£] percentages are row percentages, [§] due to small cell risk, data were only available for all PrEP users, [¶] occupational status: 'active' includes active worker, active employees, statutory employees in the public sector, active self-employed and 'non-active' includes disabled persons of the general scheme, disabled persons of the self-employed scheme, students 3rd level, spouse-helper of the self-employed, pensioners, widows and widowers and orphans of the public sector and of the general scheme, uninsured persons of the general scheme.

PrEP dispensing practices

The rate of PrEP dispensing was 5.0 (95%CI 5.0-5.1) per person-year; ranging from 4.8 (95%CI 4.7-5.0) between January 2018-June 2018 to 6.9 (95%CI 6.5-7.2) between July 2019-December 2019. (Table 2) The number of PrEP pills dispensed per dispensing event varied, with 30 pills prescribed on 46.2% (11 224/24 272) of dispensing events, 60 pills on 15.0% (n=3645) and 90 pills on 27.7% (n=6728) of dispensing events. Five percent of dispensing events (5.1%, n=1248) comprised 120 pills. (Additional file 7) The mean number of PrEP pills dispensed per dispensing event increased over time, from 50.3 (SD 29.0) between July 2017-December 2017 to 73.4 (SD 38.1) between July 2019-December 2019.

Specialist physicians prescribed 72.2% (17 532/24 272) of all PrEP; 73.7% (3361/4559) of first PrEP dispensing and 71.9% (14 171/19 713) of renewals. (Additional file 8) Overall, 87.3% (21 179/24 272) of all PrEP dispensing occurred at community pharmacies. This percentage was 68.5% (3123/4559) for first PrEP dispensing and 91.6% (18 056/19 713) for renewals. (Additional file 8)

PrEP use over time

Overall, the number of new PrEP users per semester remained relatively consistent over time. (Table 2) The median follow-up time per person was 350 days (IQR 123-625), with a median number of 270 PrEP pills (IQR 123-510) dispensed per person. Few PrEP users (3.9%, 280/4559) obtained a mean <10 pills per month, 22.1% (n=1007) 10 to 19 pills, 26.4% (n=1202) 20 to 29 pills and 47.6% (n=2170) of users obtained 30 or more pills.

In an analysis excluding users who initiated PrEP in the last semester of the study period (n=923), nearly one-fifth (18.1%, 657/3636) of PrEP users were dispensed PrEP only once in the first six months of PrEP use. PrEP users who were ≥25 years were significantly less likely to have had only one PrEP dispensing event compared to those younger than 25 years. (Table 1) PrEP users who were unemployed, who were covered by an increased healthcare allowance, and who initiated PrEP between January 2019 and June 2019, were more likely to have had only one PrEP dispensing event, compared to their counterparts. (Table 1)

Table 2. Rate of PrEP dispensing, overall and by semester of PrEP initiation in Belgium, between 1 June 2017 and 31 December 2019.

	TOTAL	Cohort of PrEP users, by semester of PrEP initiation					
		June 2017	July 2017 - Dec 2017	Jan 2018 – June 2018	July 2018 – Dec 2018	Jan 2019 – June 2019	July 2019 – Dec 2019
New PrEP users‡	N=4559	N=92†	N=973†	N=899†	N=814†	N=858†	N=923†
Number of dispensing events	24 272	1104	8684	6148	4073	2836	1427
Follow-up time (PY)[a]	4826.2	211.9	1793.7	1273.1	807.2	532.7	207.5
Dispensing rate per PY, 95%CI[b]	5.0 (5.0-5.1)	5.2 (4.9-5.5)	4.8 (4.7-4.9)	4.8 (4.7-5.0)	5.0 (4.9-5.2)	5.3 (5.1-5.5)	6.9 (6.5-7.2)

CI: confidence interval, PY: person-years

† N= number of new PrEP users in that period. ‡ New PrEP users were defined as individuals who were dispensed PrEP for the first time in the study period June 2017 – December 2019. a Follow-up time defined as the time between first PrEP dispensing and either the date of last PrEP dispensing plus 90 days, the date of first antiretroviral therapy dispensing (if applicable) or 31 December 2019, whichever was first. b Obtained by dividing the total number of dispensing by the total follow-up time. Confidence intervals are 95% Poisson confidence intervals.

HIV testing rates and seroconversions after PrEP initiation

The testing rate for HIV was 3.6 tests per person-year (95%CI 3.5-3.6) and did not vary substantially by semester of initiation. (Table 3) During the study period, 12 individuals were defined as being diagnosed with HIV after initiating PrEP. Over a total of 5598.7 person-years of follow-up, this resulted in an estimated HIV incidence rate of 0.21 per 100 person-years (95%CI 0.12-0.36). Figure 1 presents the PrEP use trajectories of the individuals who seroconverted. For these 12 individuals, the median time between last PrEP and first ART dispensing date was 208.5 days (IQR 57.8-267.3). Five individuals (A, C, E, I, J) received their first ART within 22 to 113 days after initiating PrEP. For the other individuals, time between last PrEP and first ART dispensing varied between 205 to 335 days. Six individuals (A, C, G, I, K, L) were dispensed PrEP only once, four (B, D, E, J) were dispensed PrEP twice, and two individuals (F, H) were dispensed PrEP four or more times before first being dispensed ART.

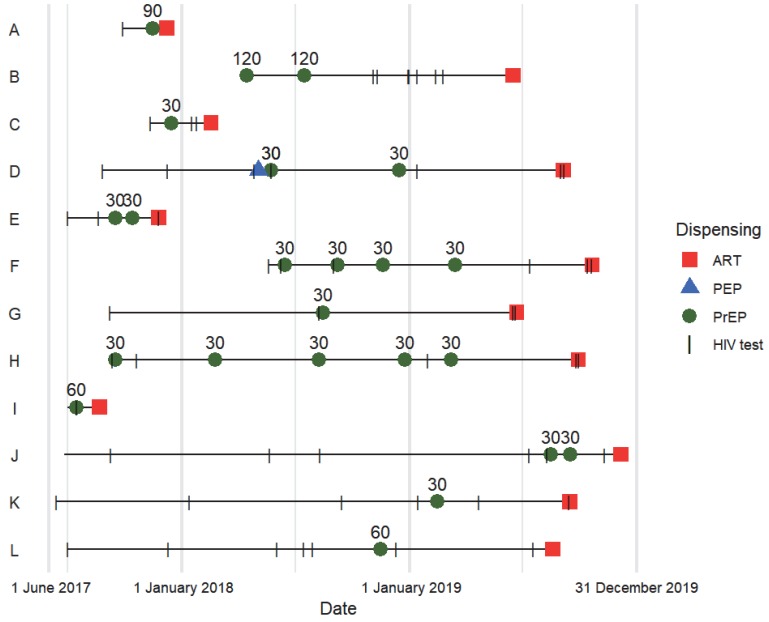

Figure 1: Trajectories of individuals who seroconverted after PrEP initiation, indicated by letter codes (A through L), in Belgium, between 1 June 2017 and 31 December 2019 (N=12)

ART: antiretroviral treatment, PEP: post-exposure prophylaxis, PrEP: pre-exposure prophylaxis. The numbers indicate the number of pills dispensed per PrEP dispensing event.

STI testing rates, incidence and re-infection rate after PrEP initiation

The testing rate for bacterial STIs was 4.2 tests per person-year (95%CI 4.1-4.2). (Table 3) The testing rate for bacterial STIs decreased by semester of PrEP initiation, from 4.6 tests per person-year (95%CI 4.3-4.9) among users who initiated PrEP in June 2017 to 3.7 tests per person-year (95%CI 3.5-4.0) among users who initiated PrEP between July 2019 and December 2019. The incidence of bacterial STIs was 81.2 infections per 100 person-years (95%CI 78.7-83.8). (Table 4) The incidence rate decreased by semester of PrEP initiation, from 95.8 infections per 100 person-years (95%CI 83.2-109.6) to 74.7 infections per 100 person-years (95%CI 63.5-87.1). The incidence rates were 56.6 infections per 100 person-years (95%CI 54.5-58.8) for chlamydia, 14.6 infections per 100 person-years (95%CI 13.6-15.8) for syphilis, and 11.5 infections per 100 person-years for gonorrhoea (95%CI 10.5-12.4). The re-infection rate was highest for chlamydia, with 53.6 (95%CI 50.5-56.8) re-infections per 100 person-years, compared to 27.7 per 100 person-years for gonorrhoea (95%CI 23.1-32.8) and 21.6 per 100 person-years for syphilis (95%CI 18.1-25.5).

Table 3. Rate of testing for any bacterial sexually transmitted infection (gonorrhoea, chlamydia, and syphilis) and HIV, overall and by semester of PrEP initiation in Belgium, between 1 June 2017 and 31 December 2019.

	TOTAL	Cohort of PrEP users, by semester of PrEP initiation					
		June 2017	July 2017 - Dec 2017	Jan 2018 – June 2018	July 2018 – Dec 2018	Jan 2019 – June 2019	July 2019 – Dec 2019
New PrEP users	N=4559	N=92[†]	N=973[†]	N=899[†]	N=814[†]	N=858[†]	N=923[†]
Follow-up time (PY)[a]	4826.2	211.9	1793.7	1273.1	807.2	532.7	207.5
Bacterial STI tests							
Gonorrhoea							
Number of tests	14 812	699	5731	3867	2383	1584	548
Rate per PY, 95%CI [b]	3.1 (3.0-3.1)	3.3 (3.1-3.5)	3.2 (3.1-3.3)	3.0 (2.9-3.1)	3.0 (2.8-3.1)	3.0 (2.8-3.1)	2.6 (2.4-2.9)
Chlamydia							
Number of tests	5940	302	2307	1534	1019	553	225
Rate per PY, 95%CI [b]	1.2 (1.2-1.3)	1.4 (1.3-1.6)	1.3 (1.2-1.3)	1.2 (1.1-1.3)	1.3 (1.2-1.3)	1.0 (1.0-1.1)	1.1 (0.9-1.2)
Syphilis							
Number of tests	17 004	794	6520	4497	2731	1809	653
Rate per PY, 95%CI [b]	3.5 (3.5-3.6)	3.7 (3.5-4.0)	3.6 (3.4-3.6)	3.5 (3.3-3.5)	3.4 (3.3-3.5)	3.4 (3.2-3.6)	3.1 (2.9-3.4)
Any bacterial STI[£]							
Number of tests[§]	20 071	973	7795	5239	3201	2093	770
Rate per PY, 95%CI [b]	4.2 (4.1-4.2)	4.6 (4.3-4.9)	4.3 (4.2-4.4)	4.1 (4.0-4.2)	4.0 (3.8-4.1)	3.9 (3.8-4.1)	3.7 (3.5-4.0)
HIV tests							
Number of tests	17 251	824	6448	4404	2813	1953	809
Rate per PY, 95%CI [b]	3.6 (3.5-3.6)	3.9 (3.6-4.2)	3.6 (3.5-3.7)	3.5 (3.4-3.6)	3.5 (3.4-3.6)	3.7 (3.5-3.8)	3.9 (3.6-4.2)

CI: confidence interval, PY: person-year, STI: sexually transmitted infection. [†] N= number of new PrEP users in that period, £: This includes gonorrhoea, chlamydia and syphilis, §: If several sexually transmitted infection tests were recorded on one day, this was counted as one test. [a] Follow-up time defined as the time between first PrEP dispensing and either the date of last PrEP dispensing plus 90 days, the date of first antiretroviral therapy dispensing (if applicable) or 31 December 2019, whichever was first. [b] Total rate obtained by dividing the total number of tests by the total follow-up time. Confidence intervals are 95% Poisson confidence intervals.

Table 4. Incidence and re-infection rate of bacterial sexually transmitted infections (STI) diagnosed among all PrEP users (N=4559) after PrEP initiation in Belgium, overall and by semester of PrEP initiation in Belgium, between 1 June 2017 and 31 December 2019.

	TOTAL	Cohort of PrEP users, by semester of PrEP initiation					
		June 2017	July 2017 – Dec 2017	Jan 2018 – June 2018	July 2018 – Dec 2018	Jan 2019 – June 2019	July 2019 – Dec 2019
Person-years (PY) at risk	4826.2	211.9	1793.7	1273.1	807.2	532.7	207.5
Gonorrhoea							
Infection events	553	25	237	134	79	60	18
Rate per 100 PY, 95%CI	11.5 (10.5-12.4)	11.8 (7.8-17.0)	13.2 (11.6-15.0)	10.5 (8.8-12.4)	9.8 (7.8-12.1)	11.3 (8.6-14.4)	8.7 (5.3-13.3)
Recurrent infection events	123	11	65	32	10	5	0
PY at risk for recurrent infection	444.7	22.5	209.7	114.4	59.2	31.6	7.4
Re-infection rate per 100 PY, 95%CI	27.7 (23.1-32.8)	49.0 (25.4-83.9)	31.0 (24.1-39.1)	28.0 (19.4-38.8)	16.9 (8.5-29.6)	15.8 (5.7-34.1)	0
Chlamydia							
Infection events	2732	144	1115	715	397	247	114
Rate per 100 PY, 95%CI	56.6 (54.5-58.8)	67.9 (57.4-79.7)	62.2 (58.6-65.9)	56.2 (52.1-60.4)	49.2 (44.5-54.2)	46.4 (40.8-52.4)	54.9 (45.5-65.7)
Recurrent infection events	1126	75	585	301	108	48	9
PY at risk for recurrent infection	2100.4	121.2	829.6	567.0	318.9	184.6	79.2
Re-infection rate per 100 PY, 95%CI	53.6 (50.5-56.8)	61.9 (48.9-77.0)	70.5 (65.0-76.4)	53.1 (47.3-59.3)	33.9 (27.9-40.7)	26.0 (19.3-34.1)	11.4 (5.5-20.5)
Syphilis							
Infection events	707	37	291	195	91	66	27
Rate per 100 PY, 95%CI	14.6 (13.6-15.8)	17.5 (12.4-23.7)	16.2 (14.4-18.2)	15.3 (13.3-17.6)	11.3 (9.1-13.8)	12.4 (9.6-15.6)	13.0 (8.7-18.6)
Recurrent infection events	132	9	72	36	11	4	0
PY at risk for recurrent infection	611.2	36.6	274.8	171.0	71.4	42.0	15.5
Re-infection rate per 100 PY, 95%CI	21.6 (18.1-25.5)	24.6 (11.8-44.4)	26.2 (20.6-32.7)	21.1 (14.9-28.7)	15.4 (8.0-26.4)	9.5 (3.0-22.1)	0
Any bacterial STI[£]							
Infection events	3919	203	1610	1031	557	363	155

Rate per 100 PY, 95%CI	81.2 (78.7-83.8)	95.8 (83.2-109.6)	89.8 (85.4-94.2)	81.0 (76.1-86.0)	69.0 (63.4-74.9)	68.1 (61.4-75.4)	74.7 (63.5-87.1)

Table 4 *(legend) CI: confidence interval, PY: person-year, £ This includes gonorrhoea, chlamydia and syphilis, different infection events diagnosed on same day were counted as one infection event*

Person-years at risk = sum of follow-up time, defined as time between first PrEP dispensing date and 90 days after last PrEP dispensing date, date of first antiretroviral therapy (ART) dispensing, or 31 December 2019, whichever was first. Infection events = total number of infections across all PrEP users, first infection as well as recurrent infections, identified between first PrEP dispensing date and last PrEP dispensing date, extended by 90 days and the maximal treatment delay of 30 days, date of first ART dispensing, or 31 December 2019, whichever was first. Incidence rate per 100 person-years = positive results divided by person-years at risk. Recurrent infection events = number of infection events, minus the first infection. Reinfection rate = number of reinfection events divided by time between first infection and end of follow-up. Confidence intervals are 95% Poisson confidence intervals

DISCUSSION

Between June 2017 and December 2019, 4559 individuals in Belgium initiated oral PrEP according to routinely collected social health insurance claims data. About one-fifth of PrEP users had only one PrEP dispensing event in the first six months of PrEP use, which occurred more often among users who were younger, unemployed, or covered by an increased healthcare allowance. Twelve individuals acquired HIV, giving an estimated incidence rate of 0.21 per 100 person-years among individuals initiating PrEP. Moreover, we found a high incidence of bacterial STIs of 81.2 infections per 100 person-years.

Our data show that the Belgian PrEP programme has reached a majority of men as other West European countries, including France, Germany, and the Netherlands.(19,20,33) Women accounted for less than 1% of PrEP users in our analysis, which suggests that some women more vulnerable to HIV, such as women of the sub-Saharan African diaspora community and sex workers, might be missed.(34) Only about 10% of PrEP users were receiving an increased healthcare allowance, which is only half of the percentage compared to the national, general population (i.e. 19.2%).(35) This might suggest that those who are more socio-economically vulnerable might have potentially more difficulties accessing PrEP services. Correspondingly, about 15% of PrEP users resided in Wallonia, while about 30% of the national general population resided in this region, indicating that there may be some disparities in geographical accessibility.(36) Further research is needed to better understand the PrEP-to-need ratio among affected sub-populations and by geographical area to provide a more granular insight into equitable access to PrEP.(6,37)

We found that the number of new PrEP users per semester did not increase over the study period, whereas one would expect such an increase as the PrEP programme is being rolled out. This calls for further investigation into possible reasons, e.g. lack of awareness among potential beneficiaries or possible capacity constraints at the specialised HIV clinics. In Belgium, PrEP care is exclusively delivered by 12 HIV clinics. A growing population of PrEP users will present a greater burden for these clinics. Consistent with our findings that nearly one in five PrEP users were dispensed PrEP only

once in the first six months of PrEP use, studies have shown high discontinuation rates in the six to 12 months after initiation(38–41), especially among younger(38,42) and/or more socio-economically disadvantaged individuals(43). Discontinuations are often driven by structural issues related to accessibility, acceptability and affordability(44–46), these issues might also be applicable for Belgian PrEP users or to the PrEP care delivery model. To increase PrEP uptake and enhance persistence, adjustments to the Belgian PrEP delivery model might be warranted. Further studies should determine which delivery models are most appropriate. Task-shifting PrEP prescribing to physicians outside specialised HIV clinics, such as family physicians, could address some of these barriers.(20)

The observed HIV incidence of 0.21 per 100 person-years was slightly higher than the incidence of HIV reported in PrEP implementation projects and nationwide cohort studies in high-income countries, with rates between 0.078/100 person-years in Germany and 0.19/100 person-years in France.(13,14,19,47) A national multiyear cohort of PrEP users in the United States found a higher HIV incidence of 0.8/100 person-years.(9) In our study, the five individuals who were first dispensed ART within three to four months after PrEP initiation may have seroconverted prior to or around the time of PrEP initiation. For the other seven individuals, who were first dispensed ART more than seven months after the last PrEP dispensing, seroconversion may be due to ineffective use or suboptimal persistence on PrEP. These seroconversions indicate missed opportunities of the PrEP programme (e.g. loss-to-follow-up in healthcare despite continued risk of HIV). In order to address these missed opportunities, it will be important for additional research (i.e. understand why these seroconversions occurred) and programmatic evaluation that healthcare providers, diagnosing new HIV infections, document previous PrEP use and potential reasons for seroconversion.(48) Moreover, there is a need to develop evidence-based interventions to support PrEP re-initiation among individuals at new or ongoing risk.(42,49) As new PrEP modalities become available, including injectable PrEP, future research is needed to understand how these modalities can reach individuals experiencing difficulties with effective and persistent oral PrEP use.(50)

The observed high incidence of bacterial STIs likely reflects high rates of condomless sex combined with multiple sexual partners, as reported by Belgian MSM who are on

PrEP.(51) These findings indicate that PrEP has been appropriately targeted at individuals at increased risk of HIV acquisition. The incidence of bacterial STIs in our study (81.2/100 person-years) was comparable to that in a cohort study among mainly MSM using PrEP in France (75.8/100 person-years) and higher than in a cohort study among mainly MSM using PrEP in Germany (55.4/100 person-years).(12,19) The latter study was conducted during the COVID-19 pandemic. The social restriction measures to control the epidemic might explain the lower observed incidence.(19) The observed incidence of STIs in our cohort is a public health concern and calls for enhanced STI prevention among PrEP users. Considering the observed STI re-infection rates in this study, indicative of users at higher risk for STI acquisition and transmission, this may suggest the need for a more tailored and targeted STI testing and prevention approach.(52,53)

This study has limitations, mainly related to the data source. First, a recorded date of PrEP dispensing does not necessarily translate into actual PrEP use or use of all PrEP pills. We may therefore have overestimated continued PrEP use in our study population. Second, information on the medical indications for prescriptions and laboratory test results were not available in the dataset. As such, we had to use proxy definitions to determine HIV infections and STIs, which may have caused under-detection or misclassification of infections. For example, we defined an STI based on the combination of a specific laboratory test and specific antibiotic treatment. This may have caused an underestimation, as STIs are often treated based on a syndromic approach or partner notification. We mitigated the risk of HIV seroconversion misclassification by having the HIV drug dispensing reviewed by a clinician specialised in HIV. Third, drug dispensing or healthcare services delivered outside of the reimbursement system are not recorded in the dataset. For example, the restriction on the number of chlamydia tests reimbursed annually underestimates the actual number of chlamydia tests performed. We mitigated this underestimation by considering gonorrhoea tests as chlamydia tests when estimating the number of chlamydia diagnoses. Information on the sexual behaviours or orientation were not available, nor was nationality of PrEP users, impeding further characterizing of the PrEP population in the dataset and an understanding of equitable use. This would require triangulation of different data sources such as claims data with the aggregated data from HIV clinics, to have more detailed information on PrEP use among key-affected populations.

Despite limitations, this study is one of few studies providing a nationwide and longitudinal overview of PrEP dispensing to all PrEP users with social health insurance.(3,54,55) We demonstrate the feasibility and value of analysing routinely collected claims data to inform practice, allowing healthcare providers and policy makers to identify areas to focus efforts on.(26) It also serves as a pilot study for the national health institute to further integrate the use of claims data for national PrEP surveillance. Linking social health insurance data with laboratory databases could optimise estimates of HIV and STI incidence, as proxy definitions can then be validated.

CONCLUSION

Our analysis of Belgian PrEP dispensing data showed a high proportion of early PrEP discontinuation, an HIV incidence of 0.21/100 person-years and a high bacterial STI incidence among individuals who were dispensed PrEP. Strategies to enhance PrEP (re-)initiation for individuals at risk for HIV acquisition together with effective use counselling will be crucial for optimal PrEP programme implementation. Strategic, tailored STI testing and prevention interventions, integrated into PrEP care, will be needed to reduce STI acquisition and transmission among PrEP users.

COMPETING INTERESTS

The institution of M. F. Schim van der Loeff received study funding from Sanofi Pasteur MSD, Janssen Infectious Diseases and Vaccines and GSK; he was a co-investigator in a Merck-funded investigator-initiated study; he was an investigator on a Sanofi Pasteur MSD sponsored trial; he served on advisory boards of GSK and Merck. The institution of TR received fees from GSK/ViiV for attending advisory boards. All other authors declare no competing interests.

AUTHORS CONTRIBUTIONS

Concept and design: AR, BV, TR, CL, MLL, TDZ, DJ
Statistical analysis: TS and AR
Interpretation of the data: AR, TS, BV, BH, MSVDL, DJ, JDB, TDZ, TR, EF, JV
Drafting of the manuscript: AR, TS
Supervision: BV
All authors critically reviewed and approved this manuscript.

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DATA AVAILABILITY STATEMENT

The individual claims data that support the findings of this study are available upon reasonable request to the Intermutualistic Agency (https://metadata.ima-aim.be/nl) and upon approval from the Belgian Information Security Committee, the official national body that preventively investigates compliancy with the principles of the General Data Protection Regulation (GDPR).

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SUPPLEMENTARY MATERIAL

Additional file 1: PrEP eligibility criteria for prescription and reimbursement in Belgium(1)

PrEP eligibility/reimbursement criteria in Belgium: - **HIV-negative status by testing** - **AND high risk of HIV acquisition, determined by having at least one of the following risk factors:**	
Men having sex with men (MSM) at very high risk of HIV infection:	**High-risk individuals with individual risk:**
- Who have unprotected anal sex with at least two partners in the last six months;	- People who inject drugs (PWID) who share needles;
- With multiple sexually transmitted infections (STIs) (syphilis, chlamydia, gonorrhoea or a primo infection with hepatitis B or C) during the last year;	- People in sex work who are exposed to unprotected sex;
- Who needed post-exposure prophylaxis (PEP) several times a year;	- People in general exposed to unprotected sex at high risk of HIV infection;
- Who use psychoactive substances during sexual activity.	- Partner of an HIV-positive patient without viral suppression (newly on treatment or no viral suppression despite adequate treatment).

Additional file 2: Parameters used to establish a PrEP dispensing

We considered the fixed combination of tenofovir disoproxil fumarate and emtricitabine (TDF-FTC) as a PrEP dispensing when: (1) TDF-FTC was not dispensed with any other HIV antiretroviral drugs prescribed within 14 days, and (2) the individual's record did not include data on HIV antiretrovirals considered for treatment of an HIV infection before the first date of PrEP dispensing. In case the latter was observed, and the regimen did not correspond to post-exposure prophylaxis (PEP) (Additional file 4), data were verified by a specialized physician and these individuals (n=51) were excluded from our analysis.

Additional file 3: PrEP care delivery in Belgium

Through social health insurance, PrEP users are partially reimbursed for their PrEP medication; out-of-pocket expenses are currently €15 for 90 pills. Only specialist physicians associated with one of the 12 specialized HIV clinics can request a yearly reimbursement approval.(1) The involvement of primary care providers outside specialised HIV clinics, such as general practitioners, is currently not incentivised by official health authorities (i.e. they cannot provide reimbursed refill prescriptions).(2) PrEP users can opt for daily or on-demand PrEP. In line with the World Health Organization (WHO) recommendations for HIV testing among PrEP users, follow-up visits at the specialized HIV clinics are scheduled on a quarterly basis.(3) Follow-up visits typically include screening for STIs (i.e. gonorrhoea, chlamydia, syphilis and hepatitis C), adherence and risk reduction strategies counselling, and a re-fill prescription for three months (equivalent to 90 pills under the assumption of daily use).

Additional file 4: Post-exposure prophylaxis regimens for adolescents and adults according to Belgian guidelines(4)

PEP after non-occupational exposure
- Emtricitabine + tenofovir disoproxil + (dolutegravir or raltegravir) - Emtricitabine + (tenofovir alafenamide or tenofovir disoproxil) + cobicistat + elvitegravir - Lamivudine + zidovudine + [(lopinavir + ritonavir) or (atazanavir ± ritonavir)]
PEP after occupational exposure
- [(Emtricitabine + tenofovir disoproxil) or (lamivudine + zidovudine)] + [raltegravir or (darunavir + ritonavir) or (lopinavir + ritonavir)] - Emtricitabine + tenofovir disoproxil + dolutegravir

Additional file 5: Proxy definitions for sexually transmitted infections(5,6)

STI	ATC code	Antibiotic treatment and mode of administration	Maximum time between test and start treatment
Gonorrhoea	J01DD04 + J01FA10	Ceftriaxone IM + azithromycin PO	30 days
	J01DD04 + J01AA02	Ceftriaxone IM + doxycycline PO	
	J01DD04	Ceftriaxone IM or IV	
Chlamydia	J01FA10	Azithromycin PO	30 days
	J01AA02	Doxycycline PO	
Syphilis	J01CE08	Benzathine benzylpenicillin IM	30 days
	J01CE01	Benzylpenicillin IV	

ATC: Anatomical Therapeutic Classification, IM: intramuscular, IV: intravenous, PO: per os, STI: sexually transmitted infection

** We considered an individual to have an STI re-infection if a new combination of a specific laboratory test and specific antibiotic treatment was observed in the dataset.*

Additional file 6: detailed information on statistical analysis

We calculated the **PrEP dispensing rate**, overall and by semester of PrEP initiation, by dividing the total number of dispensing events by the total follow-up time defined as time between first PrEP dispensing and either the date of last PrEP dispensing plus 90 days, the date of first antiretroviral therapy (ART) dispensing (if applicable), or 31 December 2019, whichever was first. The 90 days extension was based on the norm of quarterly visits with dispensing for three months. The follow-up time for individuals with only one PrEP dispensing event was defined as 90 days, or time between first PrEP dispensing and the date of first ART dispensing (if applicable), or 31 December 2019, whichever was first.

To calculate the **HIV incidence rate**, we divided the number of new HIV diagnoses within 365 days after last PrEP dispensing or before 31 December 2019, whichever was first, by total person-years in follow-up. We defined follow-up time as the difference between first date of PrEP dispensing and either the date of last PrEP dispensing plus 365 days, date of first ART dispensing or 31 December 2019, whichever was first. The 365 day period is in accordance with WHO and ECDC's monitoring indicator on recent PrEP use among people newly diagnosed with HIV.(7,8)

We calculated the **testing rates for bacterial STIs and HIV**, overall and by semester of PrEP initiation, by dividing the total number of tests between first PrEP dispensing and either the last date of PrEP dispensing plus 90 days, date of first ART dispensing (if applicable), or 31 December 2019, whichever was first, by the total follow-up time as used to calculate the PrEP dispensing rate. When calculating the overall bacterial STI testing rate, we considered different bacterial STI tests performed on the same day as one test. To calculate **bacterial STI incidence rates**, overall and by semester of PrEP initiation, we divided the total number of infections across all PrEP users, first infection as well as recurrent infections, identified between first and either last PrEP dispensing date, extended by 90 days and the maximal treatment delay of 30 days, the date of first ART dispensing, or 31 December 2019, whichever was first, by the total follow-up time as described to calculate the PrEP dispensing rate. Different infection events diagnosed on the same day were considered as one infection event. We calculated **STI re-infection rate** by dividing the number of infection events, minus the first infections, by

time between first infection and end of follow-up as previously described. By extending the observation period by 90 days after last date of PrEP dispensing, we estimated all STI and HIV tests, and STI diagnoses under the assumption of PrEP use.

Additional file 7: Number of PrEP pills dispensed per PrEP dispensing event among total number of PrEP dispensing (N=24 272) in Belgium, between 1 June 2017 and 31 December 2019

	TOTAL	By semester					
Number of PrEP pills dispensed per dispensing event, n (%)		June 2017	July 2017 – Dec 2017	Jan 2018 – June 2018	July 2018 – Dec 2018	Jan 2019 – June 2019	July 2019 – Dec 2019
	N=24 272	N=93	N=2220	N=4144	N=5288	N=6186	N=6341
Mean (SD)	60.4 (35.0)	53.9 (28.1)	50.3 (29.0)	54.8 (32.5)	54.7 (31.8)	59.3 (34.2)	73.4 (38.1)
30	11 224 (46.2)	42 (45.2)	1291 (58.2)	2221 (53.6)	2790 (52.8)	2938 (47.5)	1942 (30.6)
60	3645 (15.0)	13 (14.0)	350 (15.8)	667 (16.1)	913 (17.3)	1033 (16.7)	669 (10.6)
90	6728 (27.7)	25 (26.9)	413 (18.6)	815 (19.7)	1018 (19.3)	1505 (24.3)	2952 (46.6)
120	1248 (5.1)	2 (2.2)	67 (3.0)	230 (5.6)	292 (5.5)	372 (6.0)	285 (4.5)
Other	1427 (5.9)	11 (11.8)	99 (4.5)	211 (5.1)	275 (5.2)	338 (5.5)	493 (7.8)

*N= number of PrEP dispensing events during that semester, * 30 pills equals one box of pre-exposure prophylaxis (PrEP), SD: standard deviation*

Additional file 8: Type of PrEP prescriber and location of all PrEP dispensing (N=24 272), first PrEP dispensing (N=4559), and renewals (N=19 713) in Belgium, between 1 June 2017 and 31 December 2019

	Total N=24 272 n, %	**First PrEP dispensing** N=4559 n, %	**Renewals** N=19 713 n, %
Type of PrEP prescriber			
Specialist physician	17 532 (72.2)	3361 (73.7)	14 171 (71.9)
General practitioner*	6740 (27.8)	1198 (26.3)	5542 (28.1)
Place of PrEP dispensing			
Hospital pharmacy	3093 (12.7)	1436 (31.5)	1657 (8.4)
Community Pharmacy	21 179 (87.3)	3123 (68.5)	18 056 (91.6)

*Percentages are column percentages. * General practitioner includes medical doctor and family physician (general medicine)*

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Chapter 3

PrEP users' HIV prevention and sexual behaviours and attitudes towards condoms and STIs

Chapter 3.1

PrEP user profiles, dynamics of PrEP use and follow-up: a cohort analysis at a Belgian HIV centre (2017-2020)

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ABSTRACT

Introduction: The number of individuals initiating antiretroviral pre-exposure prophylaxis (PrEP) is increasing, but we do not fully understand who is coming forward for PrEP, how they use it, and how they are followed-up. The objective of this study was to examine PrEP user profiles, dynamics in PrEP use and follow-up over time.

Methods: We conducted a cohort analysis of longitudinally collected clinical record and questionnaire data among PrEP users at an HIV centre in Antwerp, Belgium, between June 2017 and March 2020. PrEP follow-up and user profiles were examined using descriptive analyses and bivariate logistic regression. We compared early adopting PrEP users (started before June 2018) with late users. We also calculated the probabilities of switching between daily and on-demand PrEP, and interruption, using a naïve estimator.

Results and discussion: We included 1347 PrEP users in the analysis. After 12 months, retention in care was 72.3%. Median time between PrEP visits was 98 days (IQR 85-119 days). At screening visit, early adopting PrEP users (starting June 2017 – May 2018) were significantly more likely to report one or more sexually transmitted infection in the prior 12 months, having used drugs during sex, a higher number of sexual partners and a history of paid sex and PrEP use prior to initiation, compared with PrEP users who initiated later (starting June 2018 – February 2020). When taking PrEP daily, the probability of staying on daily PrEP at the next visit was 76%, while this was 73% when taking PrEP on-demand. Those using on-demand PrEP had a higher probability (13%) of interrupting PrEP care than daily PrEP users (7%), whereas those returning to PrEP care would mostly re-start with on-demand (35% versus 13% for daily).

Conclusions: The majority of PrEP users in this sample remained in care after 12 months. The probability of remaining on the same PrEP regimen at the subsequent visit was high. Though, we observed a diversity of transitions between regimens and interruptions in between visits. Our findings reaffirm the need to provide tailored PrEP services, counselling PrEP users across their life course.

INTRODUCTION

Pre-exposure prophylaxis (PrEP) is highly efficacious for HIV prevention when used correctly during periods of risk exposure.(1,2) For PrEP to have the greatest impact on the HIV epidemic, it must be taken correctly and persistently by those at substantial risk for HIV. As such, optimising PrEP interventions requires a thorough understanding of who is using PrEP, how they are taking it and how they are followed-up.

Belgium was one of the first countries to offer both daily and on-demand PrEP.(3,4) Since 2017, individuals with an increased risk of acquiring HIV have had access to partially reimbursed PrEP (i.e. currently a PrEP user pays 15 Euros per 90 pills).(5) A Belgian PrEP care trajectory starts with a screening visit in one of 12 specialised HIV centres to assess eligibility for PrEP uptake. When eligible, the individual usually receives a first PrEP prescription at the next visit. Thereafter, PrEP users are expected to visit the HIV centre every three months. During these follow-up visits, PrEP users can receive a new PrEP prescription, adherence and risk-reduction counselling and an HIV and sexually transmitted infection (STI) check-up. This includes testing for syphilis, gonorrhoea, chlamydia and hepatitis C. At the end of 2020, an estimated 4000 PrEP starters were registered in Belgium. These were almost exclusively men (99%).(6)

The objective of this study was to assess PrEP user profiles in a large Belgian HIV centre, the dynamics of their PrEP use and follow-up. These insights will be useful for better understanding PrEP programme implementation and to guide PrEP care optimisation.

METHODS

Study design

This study is a cohort analysis of longitudinal routinely collected data among PrEP users from the only HIV centre in Antwerp, Belgium.

Data sources and extraction

For each PrEP user, we extracted, merged and pseudonymised data from clinical records and electronic questionnaires, both collected during each routine PrEP visit. We

identified PrEP users as any patient with at least two registered PrEP visits at the HIV centre between 1 June 2017 (i.e. approval of reimbursed PrEP in Belgium) and 28 February 2020 (i.e. beginning of the COVID-19 epidemic in Belgium). The questionnaire was only available in Dutch and included socio-demographic characteristics, eligibility criteria for PrEP, sexual behaviour and PrEP use regimen of the previous three months. Participants needed to be 18 years or above and be able to read Dutch to complete the questionnaire.

Definitions, outcomes and statistical analysis

In line with the objectives, we conducted three separate analyses:

PrEP user profiles analysis

We divided the sample of PrEP users with a completed screening visit questionnaire into two cohorts according to the date of their screening visit, that is 'early' and 'late' cohort. PrEP was made available and reimbursed since June 2017. Those who initiated PrEP within the first 12 months after this date were coded as 'early cohort' and those after June 2018 as 'late cohort'.

We conducted bivariate logistic regression analyses to examine the associations between timing of PrEP initiation ('early' vs. 'late' cohort), and sociodemographic and sexual behavioural factors and eligibility criteria for PrEP.

Dynamics of PrEP use analysis

Based on the response options in the questionnaire, we classified PrEP use into three categories: that is 'no PrEP', 'daily' and 'on-demand'. PrEP users were considered as 'interrupted PrEP care' if the time between PrEP visits was longer than six months, or they did not have a visit after August 2019.

We described the probabilities of switching between daily and on-demand PrEP, and interruption, using a naïve estimator that considered all pairs of subsequent visits and the associated status at each visit. PrEP users without two subsequent visits during which a questionnaire was completed, were excluded from the analysis. We did not model missing information on the PrEP regimen variable as we assumed missingness was completely at random.

Dynamics of follow-up analysis

To describe the dynamics of PrEP follow-up, PrEP users were classified in three follow-up categories: 'in follow-up', 'interrupted PrEP care' or 'censored'. 'In follow-up' denotes PrEP users whose subsequent PrEP visits occurred within six months. When there was no visit in the following six months, PrEP users were considered as 'interrupted PrEP care', except when database closure was within six months of the last visit. In that case, they were considered as 'censored'.

All analyses were done using R statistical software version 4.0.2.(7)

Ethical approval

The study received ethical approval from the Institutional Review Board (IRB) of the Institute of Tropical Medicine, Antwerp (IRB 1256-18 and IRB 1352-20) and the ethics committee of the University Hospital of Antwerp (183368). PrEP users consented to complete the questionnaire.

RESULTS AND DISCUSSION

We identified 1347 PrEP users between June 2017 and end of February 2020.

PrEP user profiles

Almost all 1090 PrEP users with a completed screening visit questionnaire were men (99.5%) and men who have sex with men (MSM) (97.2%), with a median age of 37 years (Table 1). Most participants were born in Belgium (83.2%) and highly educated (60.7%). Among self-identified MSM, the most frequently reported MSM-specific PrEP eligibility criterion was unprotected anal sex in the last six months (80.8%).

In the bivariate analysis, early PrEP users were significantly more likely to have had a higher number of sexual partners, paid sex and sex under influence of drugs in the three months before the screening visit or to have used PrEP in the past, when compared with late PrEP users (Table 1). MSM PrEP users belonging to the early cohort were significantly more likely to have had one or more STIs in the 12 months preceding screening visit and to have used drugs during sex, when compared with late MSM PrEP users.

Table 1. PrEP user profiles and bivariate analyses of factors associated with early versus late cohort

	All PrEP users *June 1, 2017 – Feb 28, 2020* N=1090	Early cohort *June 1, 2017 – May 31, 2018* N=431	Late cohort *June 1, 2018 – Feb 28, 2020* N=659	Bivariate analysis[a]	
	n (%)	n (%)	n (%)	OR (95%CI)	p-value
Sociodemographic					
Median age (years) (IQR)	37 (30-46)	37 (30-45)	37 (30-47)	0.99 (0.98-1.00)	0.131
Sex					
Male	1085 (99.5)	431 (100.0)	654 (99.2)	-	-
Female	4 (0.4)	0 (0.0)	4 (0.6)	-	
Missing	1 (0.1)	0 (0.0)	1 (0.2)	-	
Country of birth					
Belgium	907 (83.2)	365 (84.7)	542 (82.2)	Ref	
Other	165 (15.1)	61 (14.2)	104 (15.8)	0.87 (0.61-1.22)	0.43
Missing	18 (1.7)	5 (1.2)	13 (2.0)	-	
Highest degree of education[b]					
Higher education	662 (60.7)	258 (59.9)	404 (61.3)	Ref	
Lower education or no degree	417 (38.3)	170 (39.4)	247 (37.5)	1.08 (0.84-1.38)	0.557
Missing	11 (1.0)	3 (0.7)	8 (1.2)	-	
Steady partner					
No	601 (55.1)	237 (55.0)	364 (55.2)	Ref	
Yes	478 (43.9)	192 (44.5)	286 (43.4)	1.03 (0.81-1.32)	0.807
Missing	11 (1.0)	2 (0.5)	9 (1.4)	-	
Sexual behaviour					
Median number of sexual partners in last 3 months (IQR)	6 (4-12)	8 (4-15)	5 (3-10)	**1.01 (1.01-1.03)**	**<0.001**
Sex of sexual partners in the last 3 months[c,d]					
Male	1071 (98.3)	427 (99.1)	644 (97.7)	1.99 (0.46-13.62)[e]	0.401
Female	36 (3.3)	10 (2.3)	26 (4.0)	0.57 (0.26-1.16)[e]	0.140
Transgender	8 (0.7)	2 (0.5)	6 (0.9)	0.50 (0.07-2.19)[e]	0.401
Paid sex in the last 3 months					
No	1039 (95.3)	402 (93.3)	637 (96.7)	Ref	

Yes	37 (3.4)	24 (5.6)	13 (2.0)	**2.93 (1.50-5.98)**	**0.002**
Missing	14 (1.3)	5 (1.2)	9 (1.4)	-	
Condom during anal sex in the last 3 months[f]					
Always	129 (12.6)	46 (11.1)	83 (13.6)	Ref	
Always, except with steady partner	163 (15.9)	53 (12.8)	110 (18.1)	0.87 (0.53-1.42)	0.573
Most of the time	415 (40.6)	180 (43.6)	235 (38.6)	1.38 (0.92-2.09)	0.121
Sometimes	222 (21.7)	99 (24.0)	123 (20.2)	1.45 (0.93-2.28)	0.102
Never	91 (8.9)	35 (8.5)	56 (9.2)	1.13 (0.65-1.96)	0.671
Missing	2 (0.2)	0 (0.0)	2 (0.3)	-	
Median self-perceived risk to acquire HIV/STIs (IQR) (scale 0 – 10)	5 (3-7)	5 (3-7)	5 (3-7)	1.02 (0.97-1.08)	0.377
Sex under influence of drugs in the last 3 months					
No	530 (48.6)	184 (42.7)	346 (52.5)	Ref	
Yes	529 (48.5)	238 (55.2)	291 (44.2)	**1.54 (1.20-1.97)**	**0.001**
Missing	31 (2.8)	9 (2.1)	22 (3.3)	-	
PrEP use in the past					
No	990 (90.8)	376 (87.2)	614 (93.2)	Ref	
Yes	98 (9.0)	55 (12.8)	43 (6.5)	**2.09 (1.38-3.19)**	**0.001**
Missing	2 (0.2)	0 (0.0)	2 (0.3)	-	
Eligibility criteria for PrEP					
Self-identified risk as general eligibility criterium for PrEP					
MSM	1060 (97.2)	424 (98.4)	636 (96.5)	Ref	
Other than MSM	22 (2.0)	5 (1.2)	17 (2.6)	0.44 (0.14–1.12)	0.110
Missing	8 (0.8)	2 (0.5)	6 (0.9)	-	
MSM specific eligibility criteria for PrEP [c,g]					
Unprotected anal sex with at least 2 partners last 6 months	857 (80.8)	346 (81.6)	511 (80.3)	1.09 (0.79-1.49) [e]	0.610
One or more STIs in the last 12 months	329 (31.0)	162 (38.2)	167 (26.3)	**1.74 (1.33-2.26)** [e]	**<0.001**
Use of PEP in the last 12 months	96 (9.1)	46 (10.9)	50 (7.9)	1.43 (0.93-2.17) [e]	0.098
Use of drugs during sex	328 (30.9)	161 (38.0)	167 (26.3)	**1.72 (1.32-2.24)** [e]	**<0.001**
HIV positive steady partner with detectable viral load	44 (4.2)	21 (5.0)	23 (3.6)	1.39 (0.75-2.55) [e]	0.287

Table 1 *(legend) Note: Values in bold indicate statistically significant results*
Abbreviations: 95% CI: 95% confidence interval; IQR: interquartile range; MSM: men who have sex with men; OR: odds ratio; PEP: post-exposure prophylaxis; STIs: sexually transmitted infection;
a Missing answers were excluded from analysis
b 'Higher education': college or university; 'Lower education or no degree': secondary education or primary education or 'I don't have a degree'
c Number of answers do not equal the number of respondents as respondents could select multiple answers. The resulting percentages can therefore exceed 100%.
d Number of respondents having had sexual partners in last 3 months: N=1079
e Reference group is absence of particular characteristic
f Number of respondents having had anal sex in last 3 months: N=1022
g Number of MSM reporting MSM specific eligibility criteria: N=1060

Dynamics of PrEP use

The probabilities of transitioning between no PrEP, PrEP use categories at each PrEP visit and PrEP care interruption are shown as percentages in Figure 1. A total of 4318 pairs among 907 PrEP users were included. When taking PrEP daily, the probability of continuing with daily PrEP at the following PrEP visit was 76%, while this was 73% when taking PrEP on-demand. Daily PrEP users had a 16% probability to switch to on-demand PrEP use. On-demand users had a 12% probability to switch to daily PrEP use at their following PrEP visit. The probability of reporting no PrEP use was very low. Among those who interrupted PrEP care, the probability to permanently interrupt PrEP care was 49%, whereas this was 35% to re-start with on-demand PrEP and only 13% to daily PrEP use.

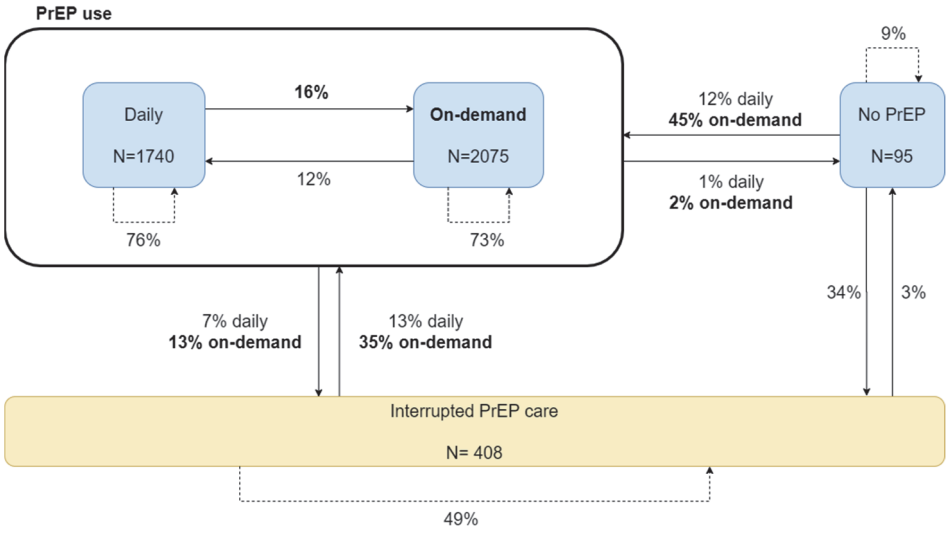

Figure 1: Schematic representation of probabilities to transition between no PrEP, PrEP use categories and interrupted PrEP care.

N= total number of pairs of subsequent visits. Interrupted PrEP care includes both temporarily and final interruptions. Percentages may not add up to 100% due to rounding.

Dynamics of follow-up

Of the 1347 PrEP users, 1021 (75.8%) were in follow-up and 326 (24.2%) had interrupted PrEP care at the end of February 2020. Retention rate at 12 and 24 months after the initial visit was 60.0% (95% CI 56.7% - 63.2%) and 53.6% (95% CI 48.3% - 58.9%),

respectively. Retention at 12 and 24 months changed to 72.3% (95% CI 69.2% - 75.2%) and 64.5% (95% CI 59.3% - 69.4%), respectively, when including those PrEP users who temporarily interrupted PrEP care at 12 or 24 months, but who returned afterwards.

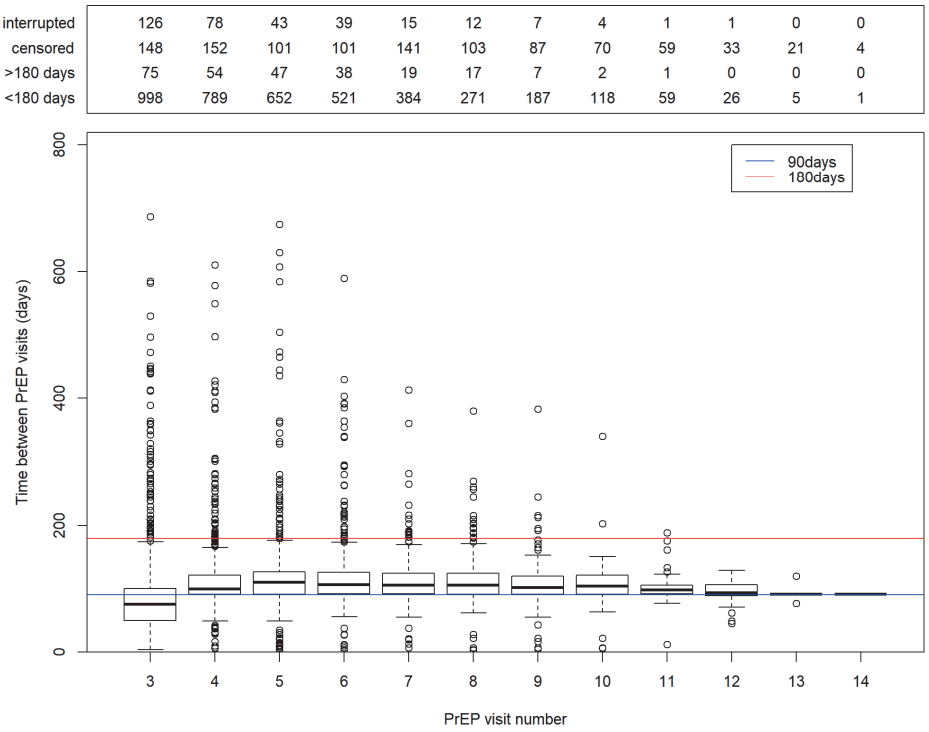

Figure 2: Time between PrEP visits per PrEP user

'Interrupted': PrEP user who did not have a PrEP visit after August 2019, 'censored': PrEP user not long enough in care to decide whether PrEP user is in follow-up or had interrupted PrEP care at this point in time, but was in follow-up at the previous point in time, '>180days': time between visits exceeds 180 days, PrEP user who interrupted PrEP care, but who did return at one point '<180days': PrEP user in follow-up, time between PrEP visits within 180days.

On average there were 4.1 and 6.6 visits since the screening visit after 12 and 24 months, respectively. The median time between follow-up PrEP visits was 98 days (IQR 85-119 days). About 21% of the PrEP users in follow-up at the end of the analysis (n=214) had at least one time period longer than six months between two PrEP visits (Figure 2).

The PrEP users in this study were all considered high risk for HIV infection, as is required for PrEP reimbursement. Though, we found that early adopters reported more HIV risk behaviour as compared with PrEP users starting one year or later after PrEP was introduced in Belgium. The eligibility criteria for PrEP did not change during this period. We have not found other studies reporting changes over time in risk profiles of PrEP initiators. The median number of sexual partners of PrEP demonstration and open-label study participants before enrolment is higher compared with the median number found among early adopting PrEP users in our study.(8–10) Early adopting PrEP users in our study were more likely to have more sexual partners compared with late PrEP users. This might suggest an evolution towards inclusion of lower risk profile PrEP users as the roll-out of PrEP continues. Such a trend is in line with the theory of diffusion of innovations, whereby characteristics and needs of users of a new innovation might shift as implementation proceeds and becomes more common.(11,12) However, reaching a broader public with lower HIV risk could have certain implications towards cost-effectiveness of PrEP interventions.(13–17) Further research is needed to examine whether similar trends in PrEP user profiles emerge in other settings and to explore the impact of variation in HIV risk and uptake on cost-effectiveness.(13)

In Belgium, people with a migrant background such as heterosexuals originating from sub-Saharan African countries and non-European MSM, may also be at high risk of acquiring HIV. However, we found very few of these individuals in our PrEP cohort.(6) Further efforts are needed to ensure every person who could benefit from PrEP has access to it.

We found that the reported PrEP regimen remained relatively steady over time, with a probability of approximately 75% to either stay with daily or on-demand PrEP use at a subsequent visit. Nevertheless, switches between PrEP regimens and (temporarily) interruptions in follow-up and PrEP use occurred. This is consistent with results from other studies, where 17-30% of the PrEP users switched at least once during the study period and 13-69% temporarily interrupted use of PrEP.(18–20) To further enhance prevention-effective PrEP adherence, healthcare providers could offer PrEP as a dynamic intervention over time, such as allowing for switching between PrEP regimens and temporarily interrupting PrEP intake. This should include adequate support in guiding PrEP users in safely starting and stopping PrEP.(21)

In line with the Belgian and World Health Organization PrEP guidelines, we found a median time of three months between PrEP visits.(22) For half of the visits, the period in between visits ranged between 85 and 119 days. However, for a quarter of the visits this time interval exceeded four months. Such irregular intervals between PrEP visits are in line with previous studies.(23–26) Further research is needed to define the optimal time and modality of follow-up according to PrEP users' needs and risk profiles. This may include assessing who could benefit from telemedicine follow up.

An important limitation is that not all questionnaires were completed. In addition, the questionnaire was only available in Dutch. We cannot exclude that there was a self-reporting bias in how the questionnaires were completed. This bias was, however, mitigated by using a digital tool for completing the questionnaire.(27) Responses to the questionnaires were not used by the providers to guide individual patient care. For the analysis, we only included those patients meeting our definition of a PrEP user, that is patients with at least two PrEP visits. This limits the generalizability of our findings. Secondly, we assumed that PrEP initiation coincided with a second PrEP visit since the clinical records did not contain detailed information about this event. Due to the cut-off of our dataset period, we could have erroneously interpreted the follow-up status of the PrEP users in our study. For example, PrEP users who received the status 'interrupted PrEP care', could have scheduled a new PrEP visit after our cut-off date.

CONCLUSIONS

Whilst the self-reported risks of late PrEP users still placed them at an elevated risk for HIV acquisition, this risk was lower compared with early PrEP users in our cohort. The majority of PrEP users remained in care and had a high probability of remaining on the same PrEP dosing regimen at subsequent visits. However, we observed a diverse pattern of switches between PrEP regimens and interruptions of PrEP use or care. Our findings reaffirm the need to offer PrEP services in a tailored manner, counselling PrEP users across their life course.

COMPETING INTERESTS

No conflicts of interest to declare.

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DATA AVAILABILITY STATEMENT

The datasets generated during and/or analysed during the current study are not publicly available, but are available upon reasonable request and if approved by the Institutional Review Board of the Institute of Tropical Medicine (Antwerp).

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Chapter 3.2

Patterns of PrEP and condom use among PrEP users in Belgium: a web-based longitudinal study

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ABSTRACT

Background: Tailoring pre-exposure prophylaxis (PrEP) service delivery is key to scaling-up PrEP uptake. Optimal implementation of tailored services requires, among other things, insights into patterns of PrEP use, sexual behaviours and condom use over time.

Methods: Between September 2020 and January 2022, we conducted a web-based, longitudinal study among PrEP users in Belgium. In three questionnaire rounds every six-months, we assessed PrEP and condom use, and sex with steady, casual and anonymous partners in the preceding three months. Based on the patterns of PrEP use in the preceding three months, we identified distinct PrEP use categories. We investigated differences in baseline socio-demographics and sexual behaviours by PrEP use category using Fisher's exact and one-way ANOVA tests. Patterns in PrEP and condom use over time were examined using descriptive analyses and visualised in alluvial diagrams.

Results: In total, 326 participants completed the baseline questionnaire, and 173 completed all three questionnaires. We identified five distinct PrEP use categories: daily (≥90 pills), almost daily (75-89 pills), long period (>7 consecutive days and <75 pills) with or without additional short period use, short period (1-7 consecutive days and <75 pills) and no PrEP use (0 pills). During the study, percentages of individuals in each PrEP use category varied, but did not change significantly over time. At baseline, daily and almost daily users were more likely to report five or more casual sex partners, ten or more anonymous sex partners and anal sex on a weekly basis with casual or anonymous partners compared to those using PrEP for long or short periods. Up to 12.6% (n=16/127) of participants reporting anal sex with casual or anonymous partners, indicated always using condoms and PrEP with these partners. One in three (n=23/69) participants who reported anal sex with steady partners had condomless anal sex and did not use PrEP with these partners; with casual or anonymous partners less than 3% reported this.

Conclusions: Our findings show that there is little variation in PrEP use over time and that PrEP use was associated with sexual behaviours, which could be taken into account when designing tailored PrEP care.

INTRODUCTION

To achieve the UNAIDS target of fewer than 370 000 annual new HIV infections globally by 2025, efficacious HIV prevention tools, including oral pre-exposure prophylaxis (PrEP), need to be scaled up (1,2). Achieving equitable scale-up requires innovative delivery approaches that are differentiated, tailored, and adopt a person-centred focus (3). Enabling tailored care, which is adapted to the needs and preferences of its users, requires in addition to other information, insights into patterns of PrEP use.

PrEP demonstration projects and cohort studies have shown that PrEP users can safely switch between daily and on-demand regimens or temporarily discontinue PrEP (4–6). In response to these findings, the World Health Organization (WHO) recommends that cisgender men, and trans and gender diverse people assigned male at birth, who are not taking exogenous estradiol-based hormones, are eligible for either daily or on-demand PrEP (3). In practice, PrEP users often adapt their PrEP use according to changes in sexual behaviours and perceived prevention needs (7). As such, distinguishing between daily and on-demand use may be less straightforward. Exploring patterns of PrEP use and associated factors may help inform how PrEP services can be adapted for different types of users with differing needs.

Various PrEP implementation and open-label studies have demonstrated increased number of sexual partners (4,5), reduced condom use (4,5,8), and increased sexual well-being (9,10) among PrEP users. Although some studies have shown that PrEP users continue to use condoms, either consistently or in certain settings or with certain types of sexual partners, as a viable option to prevent HIV and other sexually transmitted infections (STIs) (7,11), there may be an evolving shift in PrEP users' social norms regarding condom use and thus in the notion of 'safe sex' (11–13). With the expansion of HIV prevention options, 'safe sex' no longer only implies condom use. (13) Ineffective PrEP use combined with reduced condom use poses an HIV acquisition risk for MSM (14). Therefore, to fully understand the implications of PrEP use patterns on potential HIV risk, it is important to assess sexual behaviour, in particular condom use and how PrEP and condoms are combined over time (15). This will help to design appropriate counselling strategies and prevention interventions.

MSM are a priority population for PrEP in Europe, including Belgium (16), where almost 5300 individuals have started PrEP since its roll-out in 2017 (17). Despite evidence that 58% of individuals starting PrEP opted for on-demand PrEP in 2021 (17), there are few insights into actual patterns of PrEP and condom use over time among PrEP users in Belgium (6). The objectives of this study were to describe patterns of PrEP use over time, to examine socio-demographic and sexual behaviour factors associated with PrEP use, and to describe PrEP and concurrent condom use by partner type over time among PrEP users in Belgium in order to inform PrEP programmes.

METHODS

Study design

Between September 2020 and January 2022, we conducted a web-based, longitudinal study consisting of three rounds of questionnaires among PrEP users in Belgium.

Data collection

We recruited participants through the social media platforms of MSM community organisations, HIV/STI clinics and through social and sexual networking apps. Eligibility criteria were being 16 years or older, having a self-reported HIV negative or unknown HIV serostatus, living in Belgium and having used PrEP in the six months prior to the baseline questionnaire. In Belgium, the minimum age to be eligible for PrEP and to be entitled for reimbursement is 16. The minimum age at which an individual is legally considered old enough to consent to participation in sexual activities is also 16 years. With regard to participating in online research, the minimum age of consent for processing personal data is 13. After the baseline questionnaire, participants were invited, via email, to complete two follow-up questionnaires (FU1 and FU2) at six-month intervals. Up to two reminders were sent in case of non-response. Questionnaires were available in Dutch, French and English.

Measures and definitions

The baseline questionnaire included modules on: socio-demographics (age, nationality, education, occupational and financial status, social health insurance, sex assigned at birth) and sexuality. We measured sexual health based on the WHO framework of

sexual health indicators, including sexual satisfaction, safety and autonomy(18) with a scale of four items measuring sexual satisfaction, sexual safety and sexual autonomy (e.g. 'I'm happy with my sex life'; 'the sex I have is always as safe as I want it to be'). These four items were derived from a previous study, using four 5-point Likert items ranging from 'strongly disagree' (1) to 'strongly agree' (5) (9). (Additional file 1) The mean of these four items was used to estimate the sexual health score; higher means indicate better sexual health. Furthermore, we assessed the propensity to attain optimal levels of sexual excitement and to engage in novel sexual experiences using the 10-item sexual sensation-seeking scale (SSSS) ranging from 'not at all like me' (1) to 'very much like me' (4). (Additional file 2) The mean of the ten items was the sexual sensation score; higher mean values indicates scoring higher on the sexual sensation-seeking scale (19).

At baseline, we assessed time since PrEP start (options provided: <6 months, 6-12 months, 12-24 months, >24 months ago) and PrEP use in the preceding three months by asking about type of PrEP regimen chosen (options provided: daily, non-daily, no PrEP). For more nuanced data on PrEP use, we adapted the PrEP use question in the questionnaires for FU1 and FU2. Here, we asked about the number of PrEP pills taken in the preceding three months (options provided: 0, 1-7, 8-29, 30-74, 75-90). Participants who indicated daily PrEP use at baseline or to have taken between 75 and 90 PrEP pills at FU1 or FU2, completed a follow-up question on the number of days when they did not use PrEP in the preceding three months. Participants who indicated non-daily PrEP use at baseline or to have taken between one and 74 PrEP pills in FU1 or FU2, completed follow-up questions on length and frequencies of periods of use, i.e. whether PrEP was used for more than seven consecutive days or for a maximum of seven consecutive days.

Based on participants' responses, we constructed the following five mutually exclusive PrEP use categories per three months: (1) daily (at least 90 pills taken), (2) almost daily (75-89 pills taken), (3) long period (more than 7 consecutive days of use and <75 pills taken overall) with or without additional short period use, (4) short periods only (1 to 7 consecutive days of use and <75 pills taken overall), and (5) no PrEP use (zero pill intake). Inconsistent answers were coded as missing.

In all three questionnaires, we asked about sexual behaviours with steady, casual and anonymous sex partners in the preceding three months. Having a steady partner was defined as "not being single and considering yourself to have a serious relationship with someone (e.g. husband, wife), whereby length of the relationship did not matter". A casual sex partner was described as a person with whom "you have regular sex but not a steady relationship, but who is not anonymous". An anonymous sex partner was defined as a person who "you do not know or you just got to know". For each type of partner we asked about the number of partners (we provided predefined options per partner type), frequency of anal sex (daily, weekly, monthly, less than monthly), frequency of condom use (never, sometimes, always) and PrEP use (never, sometimes, always) during anal sex. At each study round, participants were asked whether they had been diagnosed with an STI in the preceding six months (options provided: yes, no).

For each questionnaire and each partner type, we combined the responses on frequency of condom use and PrEP use during anal sex into nine condom and PrEP use categories. For example, participants reporting never using condoms, but always using PrEP, during anal sex with casual partners, were combined into a variable of 'never using condoms, always using PrEP' with casual partners.

Data analysis

We compared baseline socio-demographics and sexual behaviours between three types of PrEP users: (1) daily users, which combines daily and almost daily users, (2) long period users with or without additional short period use, referred to as long period users, (3) short period users only, using Fisher's exact and one-way ANOVA tests.

We restricted subsequent analyses to participants who completed all three questionnaires rounds. To explore potential attrition bias, we compared baseline characteristics of participants who completed all three study rounds to those who did not, using Pearson's Chi-square, Fisher's exact and Wilcoxon rank sum tests, as appropriate. We examined patterns of PrEP use at each study round using the five defined PrEP use categories and visualised patterns of PrEP use over the study period in alluvial diagrams using the 'ggalluvial' R package (20). Across the three study rounds, we assessed whether the percentage of individuals in each PrEP use category changed over time when compared to all other PrEP use categories combined, using a Chi-

square test with Rao and Scott adjustment for repeated measures (21). Similarly, we examined patterns in condom and PrEP use combinations per partner type at each study round and visualised these patterns using alluvial diagrams. For this analysis, we excluded participants who either never reported having a particular partner or never having had anal sex with such a partner in all the three rounds. We assessed whether the percentage of individuals in each condom and PrEP use combination category changed over time when compared to all other condom and PrEP use combination categories combined, using a Chi-square test with Rao and Scott adjustment for the repeated measures (21). We used R statistical software version 4.0.2 for all analyses(22).

Ethics approval

Potential participants provided consent by agreeing to participate, after having been informed about the study and its procedures. The study received ethical approval through the Institutional Review Board of the Institute of Tropical Medicine, Antwerp (IRB 1380/20 and IRB 1352/20).

RESULTS

Study population

Among the 326 participants who completed the baseline questionnaire, 208 (63.8%) completed the FU1, and 186 (57.1%) FU2. About one in five (21.5%, n=70) baseline participants did not consent or did not provide their contact details for follow-up. Approximately half (53.1%, n=173) of the baseline participants completed all three study rounds. Among baseline participants, almost all were male (99.1%, n=323) and sexually attracted to men (98.8%, n=322). Their median age was 42 years (IQR 34-50; Table 1). Most were born in Belgium (85.6%, n=279), had a higher education (81.6%, n=266) and were employed (82.6%, n=269). Almost half reported to be "living comfortably" on their current income (47.2%, n=154) and that they had initiated PrEP more than 24 months ago (46.0%, n=150). About one in three (30.1%, n=98) reported an STI diagnosis in the preceding six months.

Compared to participants who did not complete all study rounds, participants who completed all three rounds were more likely to be older (median age 44 years vs. 38 years) ($p<0.001$), to use PrEP more for short periods only (31.2% vs. 19.0%) ($p=0.032$) and to report consistent PrEP use for anal sex with casual (95.1% vs. 85.6%) ($p=0.013$) and anonymous sex partners (97.6% vs. 83.5%) ($p<0.001$). Participants who completed the three study rounds had more casual sex partners, but there was no evidence that this difference was statistically significant. (Table 1)

Table 1. Sociodemographic and sexual behaviour characteristics, reported sexually transmitted infections and PrEP use at baseline of all participants at baseline (N=326), participants completing all study rounds (N=173) and those who did not (N=153); study on PrEP users' patterns of PrEP use, Belgium, 2020-2022

	All participants at baseline N=326	Participants who completed all study rounds N=173	Participants who did not complete all study rounds N=153	
	n (%)	n (%)	n (%)	p-value[£]
Sociodemographic characteristics				
Age in years, median [IQR]	42 [34-50]	44 [36-52]	38 [32-48]	**<0.001**
Born in Belgium	279 (85.6)	151 (87.3)	128 (83.7)	0.440
Higher education[1]	266 (81.6)	136 (78.6)	130 (85.0)	0.182
Occupational status[2]				0.779
Employed	269 (82.5)	142 (82.1)	127 (83.0)	
Unemployed	52 (16.0)	29 (16.8)	23 (15.0)	
Other	5 (1.5)	2 (1.1)	3 (2.0)	
Financial status				0.208
Living really comfortably on present income	65 (19.9)	31 (17.9)	34 (22.2)	
Living comfortably on present income	154 (47.2)	84 (48.6)	70 (45.8)	
Neither comfortable nor struggling on present income	75 (23.0)	45 (26.0)	30 (19.6)	
Struggling or really struggling on present income	26 (8.0)	12 (6.9)	14 (9.2)	
Preferred not to say	6 (1.8)	1 (0.6)	5 (3.3)	
Having social health insurance	320 (98.2)	169 (97.7)	151 (98.7)	0.688
Sex and sexuality				
Male sex at birth	323 (99.1)	171 (98.8)	152 (99.3)	1
Sexually attracted to men	322 (98.8)	171 (98.8)	151 (98.7)	1
Sexual health score, median [IQR]	3.7 [3.3-4.3]	3.8 [3.3-4.3]	3.8 [3.3-4.3]	0.539
Sexual sensation seeking scale score, median [IQR]	2.9 [2.5-3.2]	2.9 [2.5-3.2]	2.8 [2.5-3.2]	0.895
PrEP use				
First started taking PrEP				0.125
Less than 6 months ago	21 (6.4)	6 (3.5)	15 (9.8)	

6 – 12 months ago	49 (15.0)	25 (14.4)	24 (15.7)	
12 – 24 months ago	106 (32.5)	58 (33.5)	48 (31.4)	
More than 24 months ago	150 (46.0)	84 (48.6)	66 (43.1)	
PrEP use in the preceding 3 months				**0.032**
Daily/almost daily	142 (43.6)	77 (44.5)	65 (42.5)	
Long period use with or without additional short period use	64 (19.6)	26 (15.0)	38 (24.8)	
Short period use only	83 (25.5)	54 (31.2)	29 (19.0)	
No PrEP	13 (4.0)	5 (2.9)	8 (5.2)	
Missing	24 (7.4)	11 (6.4)	13 (8.5)	
Sexually transmitted infections				
Reported having had an STI in the preceding 6 months	98 (30.1)	50 (28.9)	48 (31.4)	0.716
Sexual behaviour in the preceding 3 months				
STEADY PARTNERS				
Number of steady partners				0.906
0	162 (49.7)	87 (50.3)	75 (49.0)	
1 or more	164 (50.3)	86 (49.7)	78 (51.0)	
Anal sex with steady partners*				0.735
No	43 (26.2)	24 (27.9)	19 (24.4)	
Yes	121 (73.8)	62 (72.1))	59 (75.6)	
Condom use during anal sex with steady partners**				0.692
Always	4 (3.3)	3 (4.8)	1 (1.7)	
Sometimes	11 (9.1)	5 (8.1)	6 (10.2)	
Never	106 (87.6)	54 (87.1)	52 (88.1)	
PrEP use during anal sex with steady partners**				0.691
Always	66 (54.5)	35 (56.5)	31 (52.5)	
Sometimes	12 (9.9)	7 (11.3)	5 (8.5)	
Never	43 (35.5)	20 (32.3)	23 (39.0)	
CASUAL SEX PARTNERS				
Number of casual partners				0.076
0	38 (11.7)	16 (9.2)	22 (14.4)	
1	24 (7.4)	17 (9.8)	7 (4.6)	
2-4	101 (31.0)	48 (27.7)	53 (34.6)	
5 or more	163 (50.0)	92 (53.2)	71 (46.4)	
Frequency of anal sex with casual partners*				0.292

No anal sex	27 (9.4)	14 (8.9)	13 (9.9)	
Less than monthly	46 (16.0)	29 (18.5)	17 (13.0)	
Monthly	111 (38.5)	58 (36.9)	53 (40.5)	
Weekly	101 (35.1)	56 (35.7)	45 (34.4)	
Daily	3 (1.0)	0 (0.0)	3 (2.3)	
Condom use during anal sex with casual partners**				0.203
Always	27 (10.3)	12 (8.4)	15 (12.7)	
Sometimes	113 (43.3)	58 (40.6)	55 (46.6)	
Never	121 (46.4)	73 (51.0)	48 (46.8)	
PrEP use during anal sex with casual partners**				**0.013**
Always	237 (90.8)	136 (95.1)	101 (85.6)	
Sometimes	20 (7.7)	5 (3.5)	15 (12.7)	
Never	4 (1.5)	2 (1.4)	2 (1.7)	
ANONYMOUS SEX PARTNERS				
Number of anonymous partners				0.612
0	75 (23.0)	34 (19.7)	41 (26.8)	
1	23 (7.1)	14 (8.1)	9 (5.9)	
2-5	122 (37.4)	66 (38.2)	56 (36.6)	
6-9	25 (7.7)	14 (8.1)	11 (7.2)	
10 or more	81 (24.8)	45 (26.0)	36 (23.5)	
Frequency of anal sex with anonymous partners*				0.135
No anal sex	27 (10.8)	11 (8.0)	15 (13.4)	
Less than monthly	56 (22.3)	35 (25.4)	21 (18.7)	
Monthly	92 (36.7)	55 (39.9)	37 (32.0)	
Weekly	74 (29.5)	37 (26.8)	37 (33.0)	
Daily	2 (0.8)	0 (0.0)	2 (1.8)	
Condom use during anal sex with anonymous partners**				0.176
Always	36 (16.1)	16 (12.6)	20 (20.6)	
Sometimes	90 (40.2)	50 (39.4)	40 (41.2)	
Never	98 (43.8)	61 (48.0)	37 (38.1)	
PrEP use during anal sex with anonymous partners**				**<0.001**
Always	205 (91.5)	124 (97.6)	81 (83.5)	
Sometimes	15 (6.7)	3 (2.4)	12 (12.4)	
Never	4 (1.8)	0 (0.0)	4 (4.1)	

Table 1 *(legend) IQR: interquartile range, PrEP: Pre-Exposure Prophylaxis, STIs: sexually transmitted infections, £: using Pearson's Chi-square, Fisher's exact or Wilcoxon rank sum tests. 1: higher education means college or university and includes higher education long type (i.e. more than 3 years) and short type (i.e. 3 years or less), 2: occupational status: 'unemployed' includes long-term sick/leave/medically retired, technical unemployed, retired, student, and unemployed. 'employed' includes employed full-time, employed part-time and self-employed. Values in bold indicate significant p-values < 0.05. * Among those with respectively steady, casual or anonymous sex partners; ** Among those who report anal sex with respectively steady, casual or anonymous sex partner*

Associations between PrEP use categories at baseline and socio-demographics and sexual behaviours

At baseline, 142 (43.6%) participants reported taking PrEP daily or almost daily, 64 (19.6%) reported using PrEP for long periods and 83 (25.5%) used PrEP for short periods only. (Table 2) Thirteen participants reported no PrEP use in the preceding three months and the responses of 24 participants were inconsistent. Daily PrEP users were more likely to score higher on the sexual health scale (mean=3.9) than long (mean=3.6) and short period users (mean 3.7) (p=0.002).

About half of daily (51.4%, n=73) and short period users (44.6%, n=37) had started taking PrEP more than two years ago, versus 31.3% (n=20) of long period users (p=0.046). Daily users were more likely to report five or more casual sex partners (69.0%, n=98 vs. 45.3%, n=29; 28.9% n=24, respectively), and a higher frequency of anal sex with casual partners compared to long and short period users in the preceding three months (p<0.001). Short period users were less likely to report anonymous sex partners and frequent anal sex with anonymous partners compared to daily or long period users (p<0.001). Although less likely to report anonymous partners, short period users were more likely to report never using condoms during anal sex with anonymous sex partners (52.2%, n=24) compared to daily (43.1%, n=50) or long period users (37.0%, n=17) (p<0.001).

Table 2. Sociodemographics, reported sexually transmitted infections and sexual behaviours by PrEP use category in the preceding three months (i.e. daily (N=142), long period (N=64), and short period (N=83) use) at baseline and associations between these factors and PrEP use category; study on PrEP users' patterns of PrEP use, Belgium, 2020-2022.

	Daily/almost daily N=142	Long period use with or without additional short period use N=64	Short period use only N=83	
	n (%)	n (%)	n (%)	p-value[£]
Sociodemographic baseline characteristics				
Age in years, mean (SD)	41.4 (9.4)	41.0 (9.4)	43.8 (10.7)	0.143
Born in Belgium	117 (82.4)	56 (87.5)	75 (90.4)	0.247
Higher education[1]	111 (78.2)	52 (81.3)	70 (84.3)	0.531
Occupational status[2]				0.365
Employed	122 (85.9)	54 (84.4)	66 (79.5)	
Unemployed	19 (13.4)	10 (15.6)	14 (16.9)	
Other	1 (0.7)	0 (0.0)	3 (3.6)	
Financial status				0.072
Living really comfortably on present income	30 (21.1)	14 (21.9)	12 (14.5)	
Living comfortably on present income	68 (47.9)	29 (45.3)	39 (47.0)	
Neither comfortable nor struggling on present income	25 (17.6)	18 (28.1)	26 (31.3)	
Struggling or really struggling on present income	18 (12.7)	2 (3.1)	4 (4.8)	
I prefer not to say	1 (0.7)	1 (1.6)	2 (2.4)	
Having social health insurance	139 (97.9)	62 (96.9)	83 (100.0)	0.304
Sex and sexuality				
Male sex at birth	141 (99.3)	63 (98.4)	83 (100.0)	0.461
Sexually attracted to men	141 (99.3)	62 (96.9)	83 (100.0)	0.204
Sexual health score (scale 1-5), mean (SD)	3.9 (0.7)	3.6 (0.6)	3.7 (0.7)	**0.002**
Sexual sensation seeking scale score (scale 1-4), mean (SD)	2.9 (0.5)	2.8 (0.4)	2.8 (0.5)	0.174
Time since PrEP start				
First started taking PrEP				**0.046**
Less than 6 months ago	13 (9.2)	3 (4.7)	5 (6.0)	
6 – 12 months ago	19 (13.4)	9 (14.1)	14 (16.9)	

12 – 24 months ago	37 (26.1)	32 (50.0)	27 (32.5)	
More than 24 months ago	73 (51.4)	20 (31.3)	37 (44.6)	
Sexually transmitted infections				
Reported having had an STI in the preceding 6 months	50 (35.2)	20 (31.3)	19 (22.9)	0.157
Sexual behaviour in the preceding 3 months				
STEADY PARTNER				
Number of steady partners				0.879
0	72 (50.7)	30 (46.9)	40 (48.2)	
1 or more	70 (49.3)	34 (53.1)	43 (51.8)	
Anal sex with steady partners*				0.162
No	15 (21.4)	15 (44.1)	9 (20.9)	
Yes	55 (78.6)	19 (55.9)	34 (79.1)	
Condom use during anal sex with steady partners**				0.234
Always	2 (3.6)	0 (0.0)	1 (2.9)	
Sometimes	4 (7.3)	4 (21.1)	3 (8.8)	
Never	49 (89.1)	15 (78.9)	30 (88.2)	
PrEP use during anal sex with steady partners**				**<0.001**
Always	47 (85.5)	4 (21.1)	9 (26.5)	
Sometimes	2 (3.6)	5 (26.3)	4 (11.8)	
Never	6 (10.9)	10 (52.6)	21 (61.8)	
CASUAL SEX PARTNER				
Number of casual partners				**<0.001**
0	6 (4.2)	7 (10.9)	11 (13.3)	
1	7 (4.9)	5 (7.8)	11 (13.3)	
2-4	31 (21.8)	23 (35.9)	37 (44.6)	
5 or more	98 (69.0)	29 (45.3)	24 (28.9)	
Frequency of anal sex with casual partners*				**<0.001**
No anal sex	10 (7.4)	7 (10.9)	7 (9.7)	
Less than monthly	14 (10.3)	5 (8.8)	21 (29.2)	
Monthly	42 (30.9)	30 (52.6)	31 (43.1)	
Weekly	68 (50.0)	15 (26.3)	13 (18.1)	
Daily	2 (1.5)	0 (0.0)	0 (0.0)	
Condom use during anal sex with casual partners**				0.160
Always	12 (9.5)	4 (8.0)	8 (12.3)	

Sometimes	58 (46.0)	25 (50.0)	22 (33.8)	
Never	56 (44.4)	21 (42.0)	35 (53.8)	
PrEP use during anal sex with casual partners**				**0.005**
Always	121 (96.0)	45 (90.0)	55 (84.6)	
Sometimes	3 (2.4)	5 (10.0)	10 (15.4)	
Never	2 (1.6)	0 (0.0)	0 (0.0)	
ANONYMOUS SEX PARTNER				
Number of anonymous partners				**<0.001**
0	16 (11.3)	11 (17.2)	33 (39.8)	
1	7 (4.9)	3 (4.7)	10 (12.0)	
2-5	51 (35.9)	30 (46.9)	28 (33.7)	
6-9	13 (9.2)	7 (10.9)	4 (4.8)	
10 or more	55 (38.7)	13 (20.3)	8 (9.6)	
Frequency of anal sex with anonymous partners*				**<0.001**
No anal sex	10 (7.9)	7 (13.2)	4 (8.0)	
Less than monthly	23 (18.3)	9 (17.0)	18 (36.0)	
Monthly	38 (30.2)	28 (52.8)	22 (44.0)	
Weekly	54 (42.9)	9 (17.0)	6 (12.0)	
Daily	1 (0.8)	0 (0.0)	0 (0.0)	
Condom use during anal sex with anonymous partners**				**<0.001**
Always	15 (12.9)	7 (15.2)	10 (21.7)	
Sometimes	51 (44.0)	22 (47.8)	12 (26.1)	
Never	50 (43.1)	17 (37.0)	24 (52.2)	
PrEP use during anal sex with anonymous partner**				**<0.001**
Always	112 (96.6)	39 (84.8)	40 (87.0)	
Sometimes	3 (2.6)	6 (13.0)	5 (10.9)	
Never	1 (0.9)	1 (2.2)	1 (2.2)	

SD: standard deviation, PrEP: Pre-Exposure Prophylaxis, STIs: sexually transmitted infections, £ using Fisher's exact or one-way ANOVA tests. 1: higher education means college or university and includes higher education long type (i.e. more than 3 years) and short type (i.e. 3 years or less), 2: occupational status: 'unemployed' includes long-term sick/leave/medically retired, technical unemployed, retired, student, and unemployed. 'employed' includes employed full-time, employed part-time and self-employed., values in bold indicate significant p-values < 0.05.

** Among those with respectively steady, casual or anonymous sex partners / ** Among those who report anal sex with respectively steady, casual or anonymous sex partners*

Patterns of PrEP use over time

Figure 1 shows participants' transitions between PrEP use categories over the study period. At baseline, 42 (24.3%) participants reported using PrEP daily, 35 (20.2%) almost daily, 26 (15.0%) for long periods (with or without additional short period use) and 54 (31.2%) for short periods only. These percentages did not change significantly over time. Among those who switched PrEP categories, transitions most often occurred to an adjacent category. For example, between FU1 and FU2, eight of the 19 participants who transitioned from long period use did so to short period use. The number of participants reporting no PrEP use in the preceding three months changed significantly over time from, from five at baseline to 18 at FU1 to 14 at FU2 (p=0.007). Participants who reported no PrEP use in the preceding three months mainly reported short period use in previous rounds (Baseline: n=7, FU1: n=4).

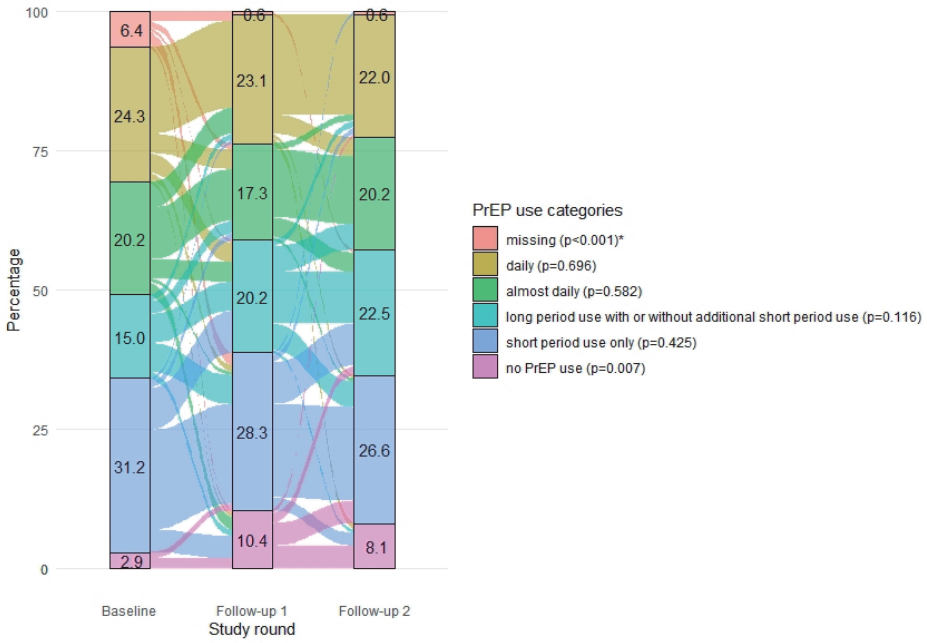

Figure 1. Alluvial diagram of PrEP use over time, N=173

PrEP use in the preceding three months: daily: ≥ 90 pills; almost daily: 75 - 89 pills; long period use with or without additional short period use: using PrEP in episodes of more than 7 days in a row and less than 75 pills in total, with or without additional short period use; short period use only: taking PrEP in episodes of 1 up to 7 consecutive days and less than 75 pills; None: zero pills.

** The p-value between brackets represents the p-value of the Chi-squared test with Rao and Scott adjustment. This test assessed whether the proportion of each PrEP use category differed significantly over time when compared to all other PrEP use categories combined.*

Condom and PrEP use by partner type over time

Figure 2 shows participants' transitions between combined condom and PrEP use categories by partner type across the study. Among all participants who completed the three questionnaires, 85 (49.1%) reported anal sex with a steady partner in the preceding three months in one or more questionnaires. Among the 62 participants who reported anal sex with a steady partner at baseline half (48.4%, n=30/62) reported never using condoms and always using PrEP, almost one-third (29.0%, n=18/62) reported never using condoms or PrEP and 9.7% (n=6/62) reported never using condoms and sometimes using PrEP. While these percentages remained relatively consistent over time, the percentage of participants reporting no steady partner decreased from 22.4% (n=19) to 5.9% (n=5) between baseline and FU2 (p=0.003).

During the study period, 154 (89.0%) participants reported anal sex with a casual partner in one or more questionnaires. Between half and almost two-thirds of these individuals reported never using condoms and always using PrEP (Baseline: 49.0%, n=70/143; FU1: 62.3%, n=71/114; FU2: 56.3%, n=63/112), with between one-fifth and one-third reporting sometimes using condoms and always using PrEP (Baseline: 38.5%, n=55/143; FU1: 22.8%, n=26/114; FU2: 33.0%, n=37/112). Over the study period, the percentage of participants reporting no casual sex partner increased significantly from 3.9% (n=6/154) at baseline to 22.1% (n=34/154) at FU1 and FU2 (p<0.001). Moreover, the percentage of individuals reporting sometimes using condoms and always using PrEP during anal sex with a casual partner decreased significantly from baseline (38.5%, n=55/143) to FU2 (33.0%, n=37/112) (p<0.001). Furthermore, the percentage of participants always using condoms and PrEP decreased significantly from baseline (7.7%, n=11/143) to FU2 (2.7%, n=3/112) (p=0.028).

During the study, 162 (93.6%) participants indicated having had anal sex with anonymous partners in one or more questionnaires. At baseline, 48.0% (n=61/127) of participants who reported anal sex with anonymous partners indicated never using condoms and always using PrEP compared to 43.0% (n=58/135) at FU2; 37.0% (n=47/127) to 43.7% (n=59/135) sometimes using condoms and always using PrEP, respectively, and 12.6% (n=16/127) to 8.1% (n=11/135) always using condoms and PrEP, respectively.

Over the study period, the percentage of participants protected neither by PrEP nor by condoms during anal sex ranged between 29.0% (n=18/62) and 33.3% (n=23/69) with steady partners, between 0% (n=0/114) and 2.7% (n=3/112) with casual sex partners, and between 0% (n=0/127) and 0.7% (n=1/135) with anonymous sex partners.

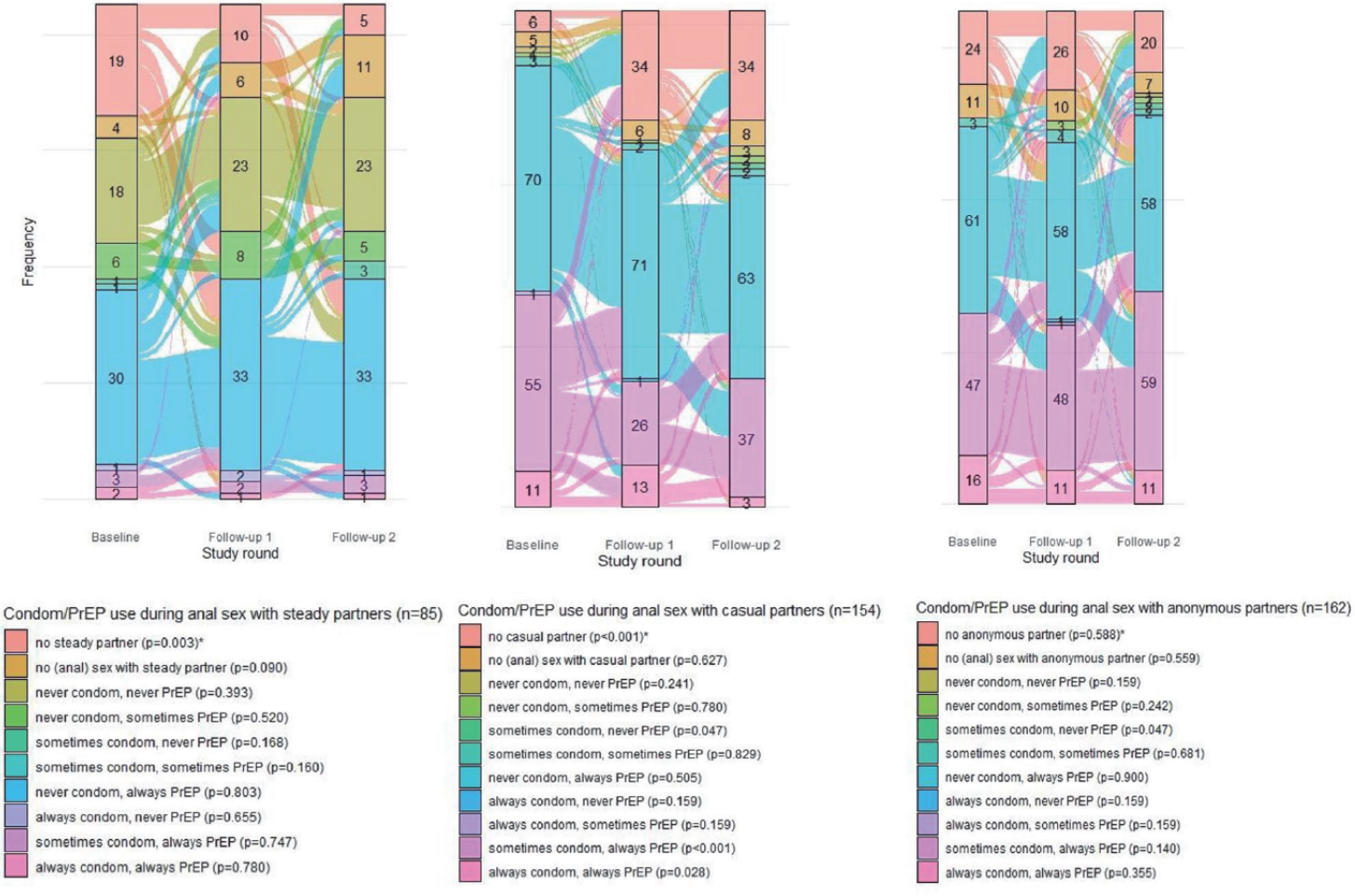

Figure 2. Alluvial diagrams of condom and PrEP use during anal sex with steady (n=85)[£], casual (n=154)[£], and anonymous partners (n=162)[£] over time

Figure 2 *(legend) * The p-value between brackets represents the p-value of the chi-square test with Rao and Scott adjustment. This test assessed whether the proportion of each condom and PrEP use combination category differed significantly over time when compared to all other condom and PrEP use combination categories combined*
£ 173 participants completed all three study rounds. For the analysis of PrEP and condom use with one particular partner type we excluded participants who either never reported having such partner or reported never having had anal sex with such a partner during the three study rounds. Therefore numbers vary by partner type. None of the participants reported always using condoms and sometimes using PrEP during anal sex with steady partners, therefore, this category is not reported in the alluvial diagram about condom and PrEP use during anal sex with steady partners.

DISCUSSION

This study among PrEP users, who were mainly MSM, in Belgium shows that in practice, distinct categories of PrEP use exist, going beyond the daily and on-demand distinction. We found associations between PrEP use categories and type and number of sexual partners. PrEP users were likely to remain in the same PrEP use category, though switches between these categories were also observed. Sexual acts not protected by condoms nor PrEP with casual or anonymous sex partners were rarely reported, but was more frequent with steady partners. Overall, condom use was relatively low and almost one-third of participants reported being diagnosed with any STI 6-months prior to the baseline questionnaire. These findings demonstrate that PrEP users have different patterns of PrEP and condom use and that these are associated with sexual behaviours with different partners.

To our knowledge, this is one of the first studies investigating patterns of PrEP use over time. A group-based trajectory modelling study among MSM and transgender women in the Netherlands and Belgium between 2015 and 2020 identified four trajectories based on the reported number of PrEP pills taken per week, ranging from low frequency use to daily use (23). Similar to our findings, high proportions of users reported using PrEP in a consistent manner over time. Nevertheless, we also observed transitions to other categories of use, mainly adjacent categories, which is in line with previous studies on PrEP regimen use (6,24,25). Our study reaffirms the association between sexual behaviour and how PrEP is used, with daily users reporting more casual and anonymous sex partners and a higher frequency of anal sex with these partners compared to long and short period users (8,24,26,27). This finding suggests that PrEP users know how to adapt their PrEP use to meet their needs.

This study provides additional evidence that most PrEP users report never or occasionally using condoms when taking PrEP during anal sex with casual or anonymous partners and thus are at risk for acquiring STIs other than HIV (8,9,28,29). A minority of participants reported always using condoms and PrEP concurrently with casual or anonymous partners. As shown in a systematic review, PrEP users experience PrEP as a facilitator to physical closeness and sexual pleasure and thus choose not to

use condoms (30). Mixed-methods and qualitative studies among MSM demonstrate that the decision to use condoms is driven by a trade-off between additional protection against HIV/STIs and increased sexual pleasure (11,28,31). Although PrEP use in isolation often seems to be the preferred HIV prevention option among PrEP users, condoms remain one of the most effective and widely available STI prevention tools (32). With increasing incidence of STIs among MSM, control and prevention of STIs are a public health priority (29). Therefore, the promotion of condoms among MSM who use PrEP remains important to reduce the rate of STIs. These findings on PrEP and condom use could help guide who to target for tailored PrEP care. For example, a group that could be targeted are those PrEP users who never use condoms, but always use PrEP with anonymous sex partners. For these individuals, condom promotion and offering STI testing services can be of added value to their PrEP care. Further investments and research are also needed to explore and develop STI prevention strategies that allow for physical closeness and sexual pleasure.

The low percentage of participants reporting never using condoms and PrEP for anal sex acts with casual and anonymous partners highlights that only a minority of PrEP users in this study are not effectively protected against HIV acquisition during anal sex with these partners. A mixed-methods study on condom use among PrEP users in the Netherlands similarly showed that 1.4% of sex acts with known casual partners and 1.2% of sex acts with unknown casual partners were without use of condoms or PrEP (28). By contrast, a French cohort study found that about 13% of on-demand PrEP users reported no PrEP or condom use at their most recent sexual act in the preceding three months, whereas this was 3% among participants using daily PrEP (26). The latter study did not specify the type of sexual acts and type of partners. If we are to maximise the potential of PrEP, we recommend enhanced approaches to differentiate these PrEP users likely to have anal condomless sex without PrEP with casual or anonymous partners, and provide tailored follow-up such as PrEP adherence support.

About one in three participants in our study reported never using condoms or PrEP during anal sex with a steady partner. These findings are in line with a Dutch study on condom use among PrEP users (28), which showed that 25% of sex acts with steady partners were without condoms or PrEP. The open-label extension phase of the ANRS IPERGAY trial found similar patterns, with 85% of sexual acts with main sexual partners

without condoms or PrEP (33). Our findings confirm that PrEP users take into account the type of partner during HIV prevention decision-making (11,28,33). Applying such HIV risk management strategy is not without risks. Modelling studies estimated that between 32% and 68% of HIV infections among MSM stem from sexual intercourses within main relationships (34,35), in particular because of non-exclusive sex (36), and the high prevalence of HIV among MSM (2). Hence, it is essential to consider the relationship context to tailor prevention recommendations as HIV serostatus and PrEP status of the dyad and their sexual agreement influence their HIV acquisition risk (36,37). Couples-based HIV prevention interventions, such as couples HIV testing and counselling and establishing and adhering to sexual agreements, have proven to be effective in reducing HIV risk (38–40) and should be integrated in PrEP programmes.

A first limitation of this study is that, inherent to online surveys, we cannot exclude self-selection bias. Individuals associated with LGBTQI or sexual health organisations were more likely to be recruited due to the chosen recruitment strategies (e.g. social media platforms of MSM community). Therefore, it is unlikely that our study population is a random and representative sample of all PrEP users in Belgium. Second, many participants did not complete all three study rounds, and were thus excluded from the longitudinal analyses. This likely created a selection bias, particularly as, participants completing all study rounds were older and reported more consistent PrEP use during anal sex with casual or anonymous partners at baseline compared to those who did not complete all rounds. This could have led to an overestimation of the percentage of sex acts covered by PrEP and condoms. Third, due to the limited sample size, we were not able to examine associations between sociodemographic and sexual behaviour characteristics, and patterns of PrEP use over time. Fourth, the 6-monthly intervals did not allow us to verify effective PrEP use (i.e. the appropriate use of PrEP during periods of HIV risk to achieve high levels of protection against HIV acquisition), which requires more detailed data such as timing of sexual acts and PrEP intake. Fifth, we lacked information on participants' knowledge of the HIV status and use of antiretroviral therapy of their sexual partners, information which in all likelihood would have influenced their PrEP and condom use. Finally, this study started during the COVID-19 pandemic, and its related restrictions. These restrictions could have impacted sexual behaviour(27), and therefore PrEP and condom use, which might have affected our results and their generalizability to other PrEP users.

Nevertheless, our study was able to recruit 8.2% (326/3986) of registered PrEP users in Belgium in 2020, irrespective of the clinic where they were prescribed PrEP.(41) The percentage of men (99.1% vs 99.2%) and daily or almost daily users (43.6% vs 38.7%) in our sample was comparable to the national PrEP users' population in 2020.(41) Giving the paucity of longitudinal studies with different oral PrEP regimen options outside the scope of clinical trials, our study provides valuable insights into the variability of PrEP and condom use by sexual partner type over time. Such insights are important to better understand how PrEP care can be tailored to such patterns.

CONCLUSIONS

We identified five distinct patterns in PrEP use ranging from daily use, to episodes of seven or fewer consecutive days of use, to no PrEP use. Most PrEP users remained in the same PrEP use category throughout the study and PrEP use was associated with sexual behaviours. We advocate for moving away from the regimen dichotomy of daily and on-demand use, and to provide tailored care for different types of PrEP users to enhance the effectiveness of PrEP programmes and to support adherence to PrEP based on users' needs and preferences. While overall condom use was relatively low, condomless sex without PrEP with casual or anonymous partners were rare, but more frequent during sex with steady partners. This suggests room for targeted counselling, such as couples-based HIV prevention interventions, considering the potentially high risk of acquiring HIV in a steady relationship. Further research is needed to investigate how PrEP care could be tailored according to different PrEP and condom use patterns.

LIST OF ABBREVIATIONS

IQR interquartile range
IRB institutional review board
FU follow-up questionnaire
MSM men who have sex with men
PrEP pre-exposure prophylaxis
SD standard deviation
STI sexually transmitted infections

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DATA AVAILABILITY

The datasets generated during and/or analysed during the current study are not publicly available, but are available upon reasonable request to the corresponding author and if approved by the Institutional Review Board of the Institute of Tropical Medicine (Antwerp).

DECLARATIONS

COMPETING INTERESTS

The authors have no competing interests to declare that are relevant to the content of this article.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The research was conducted in accordance with the Declaration of Helsinki. The study received ethical approval through the Institutional Review Board of the Institute of Tropical Medicine, Antwerp (IRB 1380/20 and IRB 1352/20). Eligible participants

provided informed consent by agreeing to participate, after having been informed about the study and its procedures.

CONSENT FOR PUBLICATION

Not applicable

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SUPPLEMENTARY MATERIAL

Additional file 1. Sexual health scale[1]

To what extent do you disagree or agree with the following statements?

1. I am happy with my sex life.
   (1) Strongly disagree – (2) disagree – (3) neutral or uncertain – (4) agree – (5) strongly agree

2. The sex I have is always as safe as I want it to be.
   (1) Strongly disagree – (2) disagree – (3) neutral or uncertain – (4) agree – (5) strongly agree

3. I find it easy to say no to sex I don't want.
   (1) Strongly disagree – (2) disagree – (3) neutral or uncertain – (4) agree – (5) strongly agree

4. I am sexually as confident as I would like to be.
   (1) Strongly disagree – (2) disagree – (3) neutral or uncertain – (4) agree – (5) strongly agree

Scoring involved summing the items and taking the mean response (sum of items/4).

Additional file 2. Sexual sensation seeking scale[2]

A number of statements that some people have used to describe themselves are given below. Read each statement and then select the number to show how well you believe the statement describes you.

1. I like wild 'unhibited' sexual encounters.
   (1) Not at all like me – (2) slightly like me – (3) mainly like me – (4) very much like me
2. The physical sensations are the most important thing about having sex.
   (1) Not at all like me – (2) slightly like me – (3) mainly like me – (4) very much like me
3. My sexual partners probably think that I take many risks in general.

(1) Not at all like me – (2) slightly like me – (3) mainly like me – (4) very much like me

4. When it comes to sex, physical attraction is more important to me than how well I know the person.

(1) Not at all like me – (2) slightly like me – (3) mainly like me – (4) very much like me

5. I enjoy the company of sensual people.

(1) Not at all like me – (2) slightly like me – (3) mainly like me – (4) very much like me

6. I enjoy watching porn movies.

(1) Not at all like me – (2) slightly like me – (3) mainly like me – (4) very much like me

7. I am interested in trying out new sexual experiences.

(1) Not at all like me – (2) slightly like me – (3) mainly like me – (4) very much like me

8. I feel like exploring my sexuality.

(1) Not at all like me – (2) slightly like me – (3) mainly like me – (4) very much like me

9. I like to have new and exciting sexual experiences and sensations.

(1) Not at all like me – (2) slightly like me – (3) mainly like me – (4) very much like me

10. I enjoy the sensations of intercourse without a condom.

(1) Not at all like me – (2) slightly like me – (3) mainly like me – (4) very much like me

Scoring involved summing the items and taking the mean response (sum of items/10).

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Chapter 3.3

Pre-Exposure Prophylaxis users' attitudes about sexually transmitted infections and its influence on condom use: a mixed-method study in Belgium

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ABSTRACT

Incidence rates of sexually transmitted infections (STIs) are rising among men who have sex with men (MSM). Since the roll-out of HIV Pre-Exposure Prophylaxis (PrEP), promoting condom use to prevent the spread of STIs has become more challenging. Using a mixed-method design, we explored MSM PrEP users' attitudes towards STIs, condoms and condom use with nonsteady partners to prevent STIs. We triangulated data from 22 in-depth interviews conducted at a large HIV/STI clinic between August 2021 and January 2022 and an online survey among 326 PrEP users between September 2020 and January 2022. Interviews were analysed iteratively using a thematic analysis approach. We used bivariate and multi-variate ordered logistic regression to analyse the online survey data. Themes identified in the qualitative data influencing condom use decisions to prevent STIs were: (1) awareness (i.e. perceived severity of and susceptibility to STIs, condom counselling), (2) motivation (i.e. concerns about STIs, sexual pleasure and protection of own health), and (3) perceived social norms and practices (e.g. reduced condom use at community level). Overall, 10.7% of survey respondents consistently used condoms with nonsteady partners. Survey respondents who reported high or moderate levels of willingness to use condoms to prevent acquiring STIs were significantly more likely to use condoms for anal sex with nonsteady partners; those who initiated PrEP 6-12 months ago were less likely to use condoms. We found a wide variation in attitudes toward condom use for the prevention of STIs among MSM using PrEP. We recommend client-centred approaches, taking into account PrEP users' values and priorities towards STI prevention to help reduce the spread of STIs.

INTRODUCTION

Oral HIV Pre-Exposure Prophylaxis (PrEP) is highly effective to prevent HIV, and has contributed to the declining trend of new HIV diagnoses among men who have sex with men (MSM) in Europe.(1) However, PrEP does not protect against other sexually transmitted infections (STIs), such as gonorrhoea, chlamydia or syphilis. Rising rates of these STIs among MSM are posing a public health concern in many countries.(2–5)

Condoms remain one of the most effective tools to prevent STIs.(6) However, promoting consistent condom use to prevent STI acquisition has become more challenging in the era of 'treatment as prevention' and the roll-out of PrEP.(7–9) It was recommended that PrEP should be provided as part of a combination prevention strategy, that is complementary and not as a replacement to condoms.(10) However, various PrEP implementation studies among MSM have demonstrated reduced condom use for anal sex with nonsteady partners among their participants.(11–13) An Australian study also demonstrated a community-level decrease in consistent condom use among MSM, alongside an increase in PrEP use.(13) Hence, it remains unclear to what extent PrEP users are willing to combine condoms with PrEP for the prevention of STIs other than HIV and how they take these decisions.

Several studies assessed the knowledge of MSM concerning STIs.(14,15) However, few studies explored their attitudes towards such STIs. HIV is generally considered the most severe STI.(16) Recent qualitative research demonstrated that MSM also have concerns towards hepatitis C and antibiotic resistant STIs.(17,18) However, another study reported that many PrEP users have become indifferent towards STIs.(19) A latent class analysis study among gay and bisexual men using PrEP indicated that a high proportion of PrEP users being highly concerned and at higher risk considered STIs to be a serious health issue.(20) As condom use among PrEP users is likely to be influenced by how they perceive STIs(20,21), it is important to better understand these heterogenous perceptions towards STIs.

In this complex prevention context, our objective was to explore their attitudes towards STIs and condoms and how these attitudes influence their condom use with nonsteady

sexual partners as a method to prevent STIs. These insights may help to improve and tailor STI prevention counselling for PrEP users.

METHODS

Study design

We adopted a convergent, parallel mixed-method study design.(22) The qualitative strand included in-depth interviews among PrEP users of a large Belgian HIV/STI clinic between August 2021 and January 2022. For the quantitative strand, we collected data through an online longitudinal survey among PrEP users living in Belgium between September 2020 and January 2022. We simultaneously developed the baseline questionnaire and interview topic guide, ensuring that they addressed the same concepts. Insights from one strand led to new or refined questions in the other strand in subsequent data collections, and vice versa. We combined both data sources for a complete understanding of the research question, and jointly interpreted the results to compare and contrast the findings.(22)

Data collection

Qualitative data collection

We conducted 22 in-depth interviews with PrEP users. We purposively selected potential interviewees based on their answers in a routine follow-up questionnaire for PrEP users at the HIV/STI clinic. To maximise variation in perceptions and experiences we purposively selected them based on self-reported PrEP use (i.e. daily, intermittent for long periods, intermittent for events, interrupted use), and condom use with nonsteady partners (i.e. never, sometimes, always). The topic guide included questions on PrEP and condom use, sexual behaviour, STI prevention strategies, and attitudes towards condoms and STIs. Upon verbal consent, interviews were either conducted online, or in-person by researchers (AR or TR) trained in qualitative research. All interviews were audio-recorded and transcribed verbatim, except one interview as the interviewee refused audio-recording.

Quantitative data collection

We recruited participants for the online longitudinal survey through social media channels of MSM community organisations, HIV/STI clinics and social and sexual

networking apps such as Grindr. Participants had to be 16 years or older, have a self-reported HIV negative or unknown serostatus, live in Belgium and have used PrEP in the six months prior to filling in the baseline questionnaire. Eligible participants were instructed to complete the questionnaire using questionnaire logics. We invited those who consented to be contacted to complete two online follow-up questionnaires at six-month intervals. Questionnaires were available in Dutch, French and English.

We collected sociodemographic information on: age (year of birth), sex assigned at birth (male, female), nationality (born in Belgium), education (none, primary, secondary, higher (< 3 or more than 3 years)), relationship status (having a steady partner) and sexual attraction (men, women, trans men, trans women, none of these, or other). For this analysis, we only assessed baseline data regarding condom use in the preceding three months (never, sometimes, always) during anal sex with anonymous and casual partners, STI acquisition in the preceding six months (yes/no), PrEP regimen in the preceding three months (daily, on-demand, none), and PrEP start (less than 6 months, 6-12 months, 12-24 months, more than 24 months ago). An anonymous sex partner was defined as a person who "you do not know or you just got to know". A casual sex partner was described as a person with whom "you have regular sex but not a steady relationship, but who is not anonymous". We further refer to both partner types as nonsteady partners. In the baseline questionnaire, five 11-point Likert items assessed participants' attitudes towards condoms and STIs. The second follow-up questionnaire included one 11-point Likert item to rate concerns about acquiring resistant STIs. (Appendix 1) Furthermore, we assessed their strategies for avoiding STIs in the first follow-up questionnaire. Research on PrEP and sexual health guided the composition of the questions and the Likert items.(11,23) The questionnaires were pilot tested within the research team and volunteering MSM community representatives.

Data analysis

Qualitative data analysis

Qualitative data were collected and analysed iteratively using a thematic analysis approach(24) and Nvivo12.(25) We inductively developed an initial coding scheme. Subsequently, we re-analysed all interviews with the focus on finding patterns for using condoms with nonsteady partners to avoid STI acquisition. In correspondence with the online survey, we divided interviewees into three groups based on their reported

condom use with nonsteady partners, respectively 'never', 'sometimes' and 'always'. We re-read all interviews to identify factors influencing these condom use patterns. Next, these factors were refined, and themes were combined into an explanatory framework through discussion with members of the research team. We compared the qualitative results with the findings from the quantitative data analysis to seek similarities or contradictions.

Quantitative data analysis

We included 326 fully completed baseline questionnaires in the analysis. Respectively 208 and 187 respondents completed the first and second follow-up questionnaire. We recoded the 11-point Likert items exploring attitudes towards condoms and STIs at baseline as follows so that 0 to 3 denotes 'no/low'; 4 to 6 'medium/neutral'; and 7 to 10 'high'. We recoded baseline condom use with anonymous partners and condom use with casual partners as condom use with nonsteady partners into three categories, i.e. 'never', 'sometimes' or 'always'. We examined associations between condom use for anal sex with nonsteady sex partners (i.e. outcome), STI acquisition, PrEP regimen, PrEP start and attitudes towards STIs and condoms assessed at baseline, using bivariate and multivariate ordered logistic regression analyses. The reference category in the analysis was never using a condom. We used R statistical software version 4.0.2.(26)

Ethics approval

The study received ethical approval through the Institutional Review Board of the Institute of Tropical Medicine, Antwerp (IRB 1380/20 and IRB 1352/20).

RESULTS

Sociodemographic profiles and reported condom use

Interviewees and survey respondents were comparable in terms of sociodemographic factors. (Table 1) At the time of interview, 12 interviewees were taking PrEP on-demand and ten daily. At baseline, about half of the survey respondents (50.6%) had used on-demand PrEP in the preceding three months. Less than half of the respondents (45.6%)

had started taking PrEP more than two years ago. In the preceding six months, 30.1% (n=98) reported having had an STI. (Appendix 2)

Most interviewees reported less condom use with steady partners than with nonsteady partners. Nine interviewees reported to have completely abandoned condom use. Two always combined PrEP with condoms for sex with nonsteady partners and 11 reported to occasionally use condoms and PrEP concurrently. The proportion of survey respondents at baseline indicating never having used a condom during anal sex in the preceding three months varied from 87.6% with steady partners, to 46.4% for casual partners and 43.6% for anonymous partners.

Table 1. Baseline characteristics of in-depth interview and online survey participants, study on pre-exposure prophylaxis users' attitudes about sexually transmitted infections and condoms, Belgium, 2020-2022.

	In-depth interviews N=22 n (%)	Online longitudinal survey N=326 n (%)
Age in years, median [IQR]	43 [39-49]	42 [34-50]
Male	22 (100.0%)	323 (99.1%)
Born in Belgium	15 (83.3%)	279 (85.6%)
Higher education[b]	15 (83.3%)	266 (81.6%)
Having a steady partner	11 (50.0%)	164 (50.3%)
Sexually attracted to men	22 (100.0%)	322 (98.8%)

Data missing in born in Belgium (n=4) and education (n=4)
[a]Higher education includes higher education long type (i.e. more than 3 years) and short type (i.e. 3 years or less)
IQR, interquartile range

Qualitative results

We identified three themes of factors influencing condom use to prevent STI acquisition, presented as an explanatory framework (Figure 1): (1) awareness, (2) motivation, and (3) perceived social norms and practices. Where appropriate, we refer to the quantitative findings for comparison.

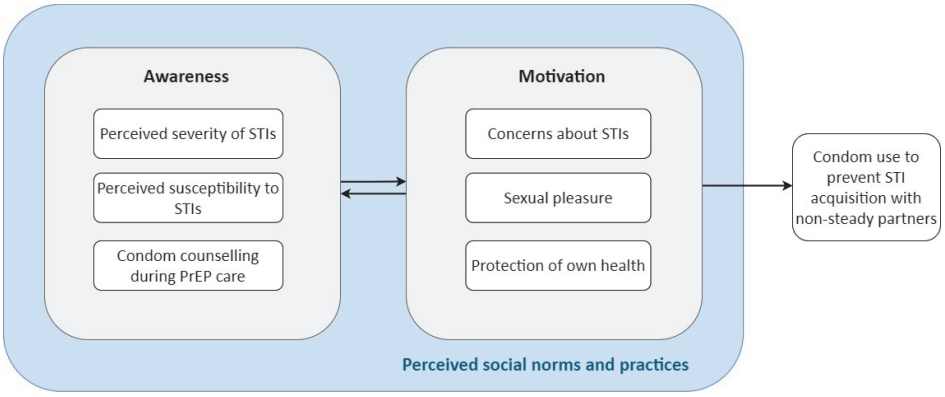

Figure 1. Explanatory framework: factors influencing condom use behaviour with nonsteady partners to prevent sexually transmitted infection acquisition among PrEP users.
PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection.

Awareness

Perceived severity of STI

Interviewees perceived STIs, particularly asymptomatic STIs, as causing little to no discomfort or harm, and thus as less severe. A few interviewees explained that they found STIs less severe for men, compared to women as they could become infertile when infected. All interviewees made a major distinction between HIV and the 'other STIs', since HIV can cause irreversible harm and is not curable. Some interviewees were primarily concerned about HIV and therefore considered condoms as a redundant prevention option when using PrEP, making condoms superfluous.

A number of interviewees considered hepatitis C the most serious compared to other STIs, because they perceived it to be a chronic disease more difficult and expensive to treat. Some interviewees also reported concerns regarding the emergence of resistant, nontreatable STIs such as gonorrhoea, which was corroborated by the quantitative findings. ***(See below: quantitative finding A)*** However, they did not perceive this resistance as an immediate threat.

"With the resistant gonorrhoea that is coming, I also have […] the idea: 'Yes, we may have to start doing it a bit more carefully again', with what we do and condom use'. But is that something that keeps me awake? No, not so much. Certainly not compared to HIV in the past."

(never uses condom)

Perceived susceptibility to STIs

In general, interviewees believed that their susceptibility to STIs had increased since PrEP due to the overall reduced use of condoms. ***(See below: quantitative finding B)***

Reported strategies for reducing susceptibility

Interviewees who used condoms sometimes explained that their use depended on the situation: for example if the setting did not allow discussing HIV or PrEP status (e.g., in saunas or sex clubs), they would opt for condoms. Likewise, they used condoms more often with anonymous sex partners due to a lack of trust. ***(See below: quantitative finding C)***

"That [condom use] is so dependent on trust, the sex partner on that front. Even though that is just a ridiculous, utopian reasoning, but yes, if I don't feel 100% confident about it I'm going to ask [to use a condom]."
(sometimes uses condom)

Interviewees reported various strategies for deciding to use a condom, such as self-defined criteria (e.g., physical appearance of a person or their anticipated sexual behaviour), visually checking for clues that may indicate the presence of STIs, and asking about PrEP use. For example, they considered PrEP users to be safer due to regular HIV and STI testing.

"But I do want to know a little bit who that person is. And you can immediately, if you are a bit smart, figure out what kind of person that is. And also of course ask, 'Are you taking PrEP?' And then if we're both on it [.....] I also know that the person knows roughly what STIs they might contract or have. So they get screened. Then I dare to say: 'Okay, we'll do it without [condoms]'."
(sometimes uses condom)

Some interviewees, irrespective of their condom use, avoided certain sexual activities (e.g., no oral or anal sex when they did not trust their partner) or settings (e.g., sex clubs, saunas) or type of partners (e.g., only having sex with casual partners and not with anonymous partners) as they associated these practices with increased STI risk.

"I'm pretty picky anyway. I'm really not going to have sex with anyone and everyone. That might be much easier, but then I think the chances would be much higher for acquiring STIs."
(sometimes uses condom)

Non-use of condoms for oral sex increases susceptibility

Although oral sex was recognised as an STI transmission mode, none of the interviewees, except for one, used condoms during oral sex. They reported that condom use for oral sex was not practiced among MSM. Interviewees who never or only sometimes used condoms explained that because STIs can also be transmitted via oral sex, they were less eager to also use them for anal sex.

"Yes, it [a condom] will save a lot, but it doesn't stop everything. People also need to know that if they use a condom, they shouldn't think of it as: 'No problem, because I used a condom.' That's definitely not the case. I think that's in most people's mind: 'Condom, no problem.' But then they don't use it for oral sex, for example. I think they really assume, only condom for penetration and then they're protected for other STIs, they're going to be very deceived."
(sometimes uses condom)

Perceived susceptibility based on STI diagnoses
While some interviewees reported regular STI diagnoses, others reported having never or rarely been diagnosed despite never using condoms. They alluded this to being lucky, or considered the risk to acquire an STI to be low. Interviewees never using condoms and regularly diagnosed with an STI considered themselves highly susceptible, but it did not motivate them to change their condom prevention behaviour permanently.

"Yes, then [after STI diagnosis] you notice that there is a dip in sexual activities. But at some point, that first date takes place again and then that is all forgotten rather quickly. People forget rather quickly."
(never uses condom)

Counselling on condom use as part of PrEP follow-up
Interviewees reported different experiences with counselling on condom use during their PrEP visits, ranging from no counselling to discussing its frequency for reinforcing that PrEP should be combined with condoms. Although some interviewees personally did not feel the necessity to receive such counselling, the majority agreed that it remained important to create awareness of the presence and risks of STIs and how condoms can prevent them. However in general, interviewees agreed that regular condom counselling would not change their own condom use. Some suggested that counselling should be targeted to the younger generation, should only be given at PrEP initiation or to individuals with a higher sexual risk behaviour or STI history.

"Does that [condom counselling] have to be said? Yes, I do think that people who are often the receptive sexual partner […] can get a lot of virus or infections. They have a higher risk. They might think to themselves: 'Sorry, I don't feel like overloading the

system, making myself resistant to that one antibiotic […]' So then I think you have to do it [condom counselling]. But it depends: 'What does your history look like?'"
(sometimes uses condom)

Motivation

Concerns towards STIs

Overall, interviewees generally perceived STIs as unpleasant and undesirable. The degree of concern regarding acquiring an STI varied among the interviewees, which was corroborated by the quantitative findings, but in general they were not worried about it. ***(See below: quantitative finding D)***

"Just to avoid confusion: I absolutely do not like having an STI. It is a hassle and a very painful hassle sometimes. […] Do I worry about that? Yes and no."
(sometimes uses condom)

Sexual pleasure

Interviewees considered condoms as useful, providing safety, and effective to protect against STIs and valued their existence in that regard. However, they also considered using condoms to be a hassle and impractical. ***(See below: quantitative finding E)*** All interviewees experienced sex without a condom as more pleasurable. Many saw putting on a condom as a barrier for intimacy between sexual partners. Moreover, for some, condom use resulted in losing an erection. Another frequently reported disadvantage of condoms was the potential of condom failure (e.g., breaking or sliding), while PrEP offered reassurance in such situations. Those never or sometimes using condoms while being on PrEP felt that the risks of acquiring STIs did not outweigh the sexual pleasure and convenience of condomless sex.

"A condom is still the best tool to prevent STI. I am convinced of that, but it is an inconvenient means. It is a means that is not pleasant to use, so if possible I don't use it."
(never uses condom)

Protection of own health

While all interviewees were aware that PrEP does only protect against HIV, only interviewees highly motivated to avoid STI acquisition always used a condom combined with PrEP. ***(See below: quantitative finding F)***

"Continuing with a condom. PrEP still doesn't protect against STIs.[…] I think [condom use] is still 100% part of the sex life […] also with PrEP."
(always uses condom)

Interviewees often mentioned the responsibility to decide for themselves how safely their sex should be. Some interviewees stated that taking PrEP and putting on a condom ensures that they are independently protected from STIs.

"But since I take PrEP and always use a condom, I don't need to have any confidence in the other one. So in that sense, maybe the comfort is there. That you shouldn't trust anyone blindly when that person says: 'I'm okay.'."
(always uses condom)

In contrast, several interviewees never or sometimes using a condom, perceived STIs as part of their sexual lifestyle, which included dating multiple partners or having condomless sex, thus leading to a decreased motivation to use condoms.

"That [STIs] is simply an effect of life. Those STIs are out there. You can contract them and then you try to factor that into your condom use. But then in the end you don't."
(never uses condom)

Perceived social norms and practices

Interviewees reported that they knew many MSM who had abandoned condom use. Moreover, they explained that discussing safe sex among sexual partners no longer entailed asking about condom use, but had now shifted to asking about PrEP use. If someone uses PrEP, it is often automatically assumed that sex will be condomless. Many interviewees explained that this implicit norm also decreased the likelihood of using condoms.

"And the thing is, the perception is there: if you use PrEP, you don't have to use a condom anymore." (never uses condom)

This trend did not influence interviewees who always used a condom. One of them talked about even refusing to have sex with a partner who rejected to use a condom. In contrast, if a sex partner requested a condom, interviewees in general would agree on using one.

Quantitative results

In accordance with the qualitative data concerns towards STIs and self-perceived risk of acquiring STIs varied also among survey respondents. Nearly half of them reported to be highly concerned (n=157, 48.2%) to acquire an STI, whereas 18.7% were not or slightly concerned. (See above: qualitative finding D) During the third survey, 78 respondents (41.7%) reported to be highly concerned to acquire a resistant STI. (See above: qualitative finding A) At baseline, half of the survey respondents (n=162, 49.7%) perceived themselves at high risk to acquire an STI. (See above: qualitative finding B) Condoms were considered as highly burdensome among 60.7% (n=198) of the respondents. (See above: qualitative finding E) While 212 (65.0%) respondents found it highly important to protect themselves against STIs, 14 (4.3%) indicated they did not find this important. Respectively 39.9% (n=130) and 34.0% (n=111) reported high to medium degrees of willingness to use a condom to limit the risks of getting an STI. (See above: qualitative finding F) (Figure 2)

The main reported strategies to avoid STIs in the first follow-up questionnaire (n=208) were either asking their sex partner when they were last tested for STIs (n=89, 42.8%) and whether they had an STI (n=77, 37.0%). Almost 23% (n=47) used a condom to prevent STIs during anal sex and 26.0% (n=54) used a condom with sex partners of whose STI status they were not sure. One-third of the first follow-up survey respondents indicated they were not consciously avoiding an STI (n=69, 33.2%). (See above: qualitative finding C)

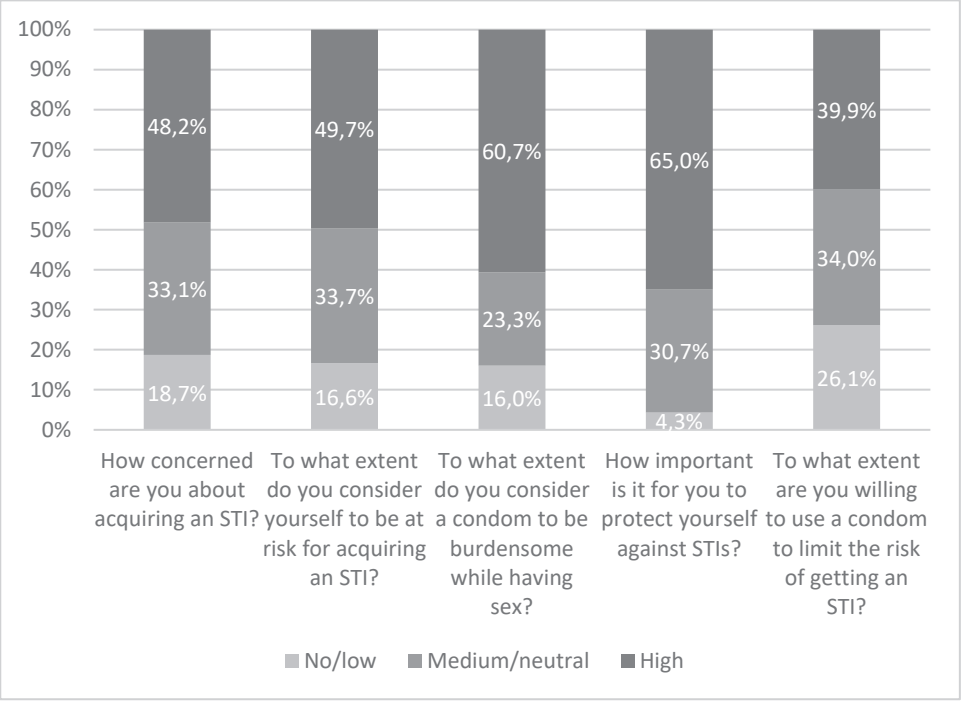

Figure 2. Attitudes towards sexually transmitted infections (STIs) and condoms among baseline online survey respondents (n=326), study on PrEP users' attitudes about STIs and condoms, Belgium, 2020-2022.

At baseline, 272 (83.4%) survey respondents reported they had anal sex with nonsteady partners in the preceding three months. Among these, 113 (41.5%) reported never using a condom, 130 (47.8%) sometimes, and 29 (10.7%) always. In the multivariate ordered logistic regression analysis, those who reported high [aOR=10.85, 95%CI (4.73-25.94), p <0.001] or moderate [aOR=3.21, 95%CI (4.73-6.56), p = 0.001] levels of willingness to use a condom to prevent acquiring STIs were significantly more likely to use condoms for anal sex with nonsteady partners compared with their counterparts. Those who initiated PrEP 6-12 months ago [aOR=0.29, 95%CI (0.09-0.94), p <0.05] were less likely to use a condom compared with those who initiated PrEP <6 months ago, when holding constant all other variables. (Appendix 2)

DISCUSSION

The PrEP users in our study varied in their concern towards STIs, motivation and willingness to use a condom to prevent them. Most study participants perceived the need for condoms to be lower due to PrEP use, resulting in no or casual condom use for anal sex with nonsteady partners. This low perceived need resulted from balancing perceived severity of, susceptibility to and concerns towards STIs against sexual pleasure of condomless sex, protective benefits of condoms and perceived social norms and practices. Condoms were considered an important strategy to avoid STIs during anal sex with nonsteady partners among participants who were highly motivated to prevent STIs other than HIV, when a sexual partner or venue was associated with a higher HIV or STI risk or when a sexual partner insisted to use a condom. Educational condom counselling was perceived as having minimal impact on own condom use, yet considered necessary for some people and sexual practices.

Concerns to acquire STIs varied both among online survey participants and interviewees. This is in contrast to a study among male couples living in the United States, which reported general indifference towards STIs.(19) Our findings are in line with previous studies among MSM PrEP users and nonusers where concerns towards STIs were nuanced.(16–18,20,27) For example, some less concerned participants were nevertheless worried about particular STIs such as hepatitis C or resistant gonorrhoea. The qualitative data showed that while interviewees were somewhat concerned about STIs, they were balancing their decision to use a condom against sexual pleasure of condomless sex, seeing HIV as the primary STI to be protected against, the low harm caused by STIs and the transmission risk during condomless oral sex. This is consistent with literature on the impact of PrEP on sexual behaviour.(21,28,29) Caution should be raised regarding the fact that many interviewees perceived all STIs as causing little harm. Research showed that ambivalence towards STIs is often based on the knowledge individuals have about STIs' health effects, while correct knowledge was often lacking.(16) Integrating opportunities to share such information in risk reduction discussions could enable PrEP users to better understand the benefits of adopting risk reduction strategies.

Among the online survey respondents, 10.7% always used a condom during anal sex with nonsteady partners. This is in line with a cross-sectional study among German MSM, where 8.2% of the PrEP users had sex with a condom in the preceding six months.(30) A Dutch PrEP demonstration project showed that 18.3% of the anal sex acts with nonsteady partners were covered by concomitant PrEP and condom use.(29) A longitudinal exposure-matched study in the Netherlands showed that, two years after PrEP-initiation, PrEP initiators had a higher number of casual partners, and a higher proportion reported condomless anal sex with casual partners and had more diagnosed anal STIs compared with matched controls who did not initiate PrEP.(31) Despite the low consistent condom use found in our study, participants acknowledged condoms as an effective STI protection tool. However, two main factors affected their decision to not use a condom: a perceived reduced condom use in their social/sexual networks, and a perceived reduced susceptibility due to other reported STI prevention strategies (e.g., avoiding certain sexual activities). These findings suggest and reaffirm the evolving shift in PrEP users' social norms regarding the notion of 'safe sex'.(32,33) Subsequently, these changing norms and practices challenge the combination prevention recommendations which underline PrEP as an additional prevention option.

Interviewees in our study felt that the condom counselling they had received minimally impacted on their condom use. As such, our study findings have important implications for STI prevention counselling among PrEP users. While PrEP care offers many opportunities to discuss sexual health protection strategies beyond PrEP(34), we conclude that the focus should not solely be on consistent and concurrent condom use. Instead, providers should explore and understand an individual's STI prevention practices, STI risk perceptions, and values. Such a client-centred approach would allow to consider individual, interpersonal and situational factors, which have been demonstrated to influence STI prevention behaviour. This would allow PrEP users to make informed choices and feel supported in those choices. Such patient-centred discussions about sexual health protection(35), and motivational preventive HIV/STI counselling on condom use(36) appeared to be feasible to be integrated into clinical care visits.

One of the limitations of our study is that the study populations of the qualitative and quantitative strand were recruited differently. For pragmatic reasons, we could not

sample interviewees among the online survey participants. However, both study populations had comparable sociodemographic characteristics. As interviewees were recruited through and interviewed in an HIV/STI clinic, we cannot exclude a social desirability bias, for example, overreporting of safe sexual behaviour. We mitigated this bias by using interviewers who were not involved in interviewees' PrEP care. Inherent to online surveys, a self-selection bias could have occurred, which may limit the generalizability of our findings. Finally, a randomised clinical trial regarding resistant STIs was ongoing at the HIV/STI clinic at the time of our interviews which could have made our interviewees more aware and knowledgeable about the topic compared to Belgian PrEP users in general. This study started during the COVID-19 pandemic, and its related restrictions. These restrictions could have impacted our study population's sexual behaviour, which might have affected our results.

In conclusion, perceptions about STIs and condoms among PrEP users in this study varied, influencing their condom use behaviour for STI prevention. A minority consistently used condoms and PrEP concurrently; for others, condoms remained a valuable additional STI prevention option in certain situations and settings. PrEP presents both opportunities and challenges for STI prevention. Taking into account PrEP users' values and priorities regarding STI prevention will be essential to reduce the spread of STIs.

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AVAILABILITY OF DATA AND MATERIAL

The datasets generated and/or analysed during the current study are not publicly available, but are available upon reasonable request and if approved by the Institutional Review Board of the Institute of Tropical Medicine (Antwerp).

AUTHOR DISCLORUSE STATEMENT

MSVDL participated in Advisory Boards of MSD. All other authors have no competing interests, which are relevant to the content of this article, to declare.

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SUPPLEMENTARY MATERIAL

Appendix 1. 11-point Likert items used in the online survey to assess attitudes towards sexually transmitted infections and condoms

Baseline questionnaire (n=326)
To what extent do you consider yourself to be at risk for acquiring a sexually transmitted infection (STI, such as syphilis or chlamydia)? Very low risk 0 1 2 3 4 5 6 7 8 9 10 very high risk
How unconcerned or concerned are you about acquiring a sexually transmitted infection? Very unconcerned 0 1 2 3 4 5 6 7 8 9 10 very concerned
How unimportant or important is it for you to protect yourself against STIs? Very unimportant 0 1 2 3 4 5 6 7 8 9 10 very important
To what extent do you consider a condom to be burdensome while having sex? Not burdensome at all 0 1 2 3 4 5 6 7 8 9 10 very burdensome
To what extent are you willing to use a condom to limit the risk of getting an STI? Not willing at all 0 1 2 3 4 5 6 7 8 9 10 very willing
Second follow-up questionnaire (n=187)
How concerned are you about acquiring a resistant sexually transmitted infection, such as gonorrhoea? With a resistant STI we mean an STI that is more difficult or no longer treatable with antibiotics. Not concerned at all 0 1 2 3 4 5 6 7 8 9 10 very concerned

STI, sexually transmitted infection.

Appendix 2. Bivariate and multivariate ordered logistic regression analyses assessing associations between frequency of condom use during anal sex with nonsteady partners (outcome) and attitudes towards condoms and STIs, having acquired an STI, PrEP use regimen and recency of PrEP start, study on PrEP users' attitudes about STIs and condoms, Belgium 2020-2022.

		Condom use during anal sex with nonsteady partners			Bivariate analysis		Multivariate analysis	
	Total sample N=272 n (%)	Never N=113 n (%)	Sometimes N=130 n (%)	Always N=29 n (%)	OR (95% CI)	p-value	aOR (95% CI)	p-value
Attitudes towards STIs and condoms								
Concerned about STI acquisition								
No/low	54 (19.9)	32 (28.3)	17 (13.1)	5 (17.2)	Ref		Ref	
Medium/neutral	92 (33.8)	40 (35.4)	46 (35.4)	6 (20.7)	1.67 (0.86-3.28)	0.133	1.50 (0.67-3.39)	0.325
High	126 (46.3)	41 (36.3)	67 (51.5)	18 (62.1)	**2.83 (1.50-5.44)**	**0.002**	1.57 (0.71-3.51)	0.267
Being at risk for STI acquisition								
No/low	36 (13.2)	12 (10.6)	16 (12.3)	8 (27.6)	Ref		Ref	
Medium/neutral	94 (34.6)	37 (32.7)	49 (37.7)	8 (27.6)	0.59 (0.27-1.25)	0.167	0.73 (0.31-1.70)	0.460
High	142 (52.2)	64 (56.6)	65 (50.0)	13 (44.8)	0.49 (0.24-1.01)	0.067	0.69 (0.29-1.62)	0.392
Consider condom burdensome								
No/low	44 (16.2)	9 (8.0)	26 (20.0)	9 (31.0)	Ref		Ref	
Medium/neutral	61 (22.4)	15 (13.3)	36 (27.7)	10 (34.5)	0.78 (0.36-1.67)	0.522	1.29 (0.55-3.05)	0.564
High	167 (61.4)	89 (78.8)	68 (52.3)	10 (34.5)	**0.23 (0.12-0.45)**	**<0.001**	0.70 (0.31-1.57)	0.382
Importance to protect against STIs								
No/low	12 (4.4)	9 (8.0)	3 (2.3)	0 (0.0)	Ref		Ref	
Medium/neutral	89 (32.7)	52 (46.0)	34 (26.2)	3 (10.3)	2.14 (0.60-10.10)	0.271	0.95 (0.23-5.08)	0.947
High	171 (62.9)	52 (46.0)	93 (71.5)	26 (89.7)	**7.29 (2.12-33.64)**	**0.004**	1.83 (0.44-9.79)	0.433
Willingness to use a condom to limit risk of STI acquisition								
No/low	75 (27.6)	56 (49.6)	18 (13.8)	1 (3.4)	Ref		Ref	
Medium/neutral	98 (36.0)	42 (37.2)	52 (40.0)	4 (13.8)	**3.79 (2.01-7.37)**	**<0.001**	**3.21 (4.73-6.56)**	**0.001**
High	99 (36.4)	15 (13.3)	60 (46.2)	24 (82.8)	**18.79 (9.30-39.81)**	**<0.001**	**10.85 (4.73-25.94)**	**<0.001**
Acquired an STI in the preceding 6 months								
No	179 (65.8)	71 (62.8)	89 (68.5)	19 (65.5)	Ref		Ref	

Yes	93 (34.2)	42 (37.2)	41 (31.5)	10 (34.5)	0.84 (0.52-1.35)	0.468	1.06 (0.60-1.85)	0.849
PrEP regimen in the preceding 3 months[a]								
Daily	140 (51.5)	57 (50.4)	68 (52.3)	15 (51.7)	Ref		Ref	
On-demand	130 (47.8)	55 (48.7)	61 (46.9)	14 (48.3)	0.95 (0.60-1.50)	0.827	0.72 (0.42-1.22)	0.227
PrEP start								
< 6 months ago	19 (7.0)	3 (2.7)	9 (6.9)	7 (24.1)	Ref		Ref	
6-12 months ago	39 (14.3)	17 (15.0)	19 (14.6)	3 (10.3)	**0.18 (0.06-0.54)**	**0.002**	**0.29 (0.09-0.94)**	**0.039**
12-24 months ago	90 (33.1)	34 (30.1)	49 (37.7)	7 (24.1)	**0.22 (0.08-0.59)**	**0.003**	0.36 (0.12-1.03)	0.055
> 24 months ago	124 (45.6)	59 (52.2)	53 (40.8)	12 (41.4)	**0.16 (0.06-0.44)**	**<0.001**	0.37 (0.13-1.02)	0.054

Values in bold indicate statistically significant results, at p<0.05.
[a]Two PrEP-users reported no PrEP use in preceding three months, results are not in the table
aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection.

Chapter 3.4

Putting 2-1-1 into practice: PrEP users' knowledge of effectively starting and stopping oral PrEP use

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ABSTRACT

Starting and stopping oral HIV pre-exposure prophylaxis (PrEP) in a way that compromises its effectiveness should be avoided. Between September 2020 and June 2021, we assessed self-perceived and actual knowledge of effectively starting and stopping oral PrEP through an online survey among 206 PrEP users assigned male at birth in Belgium. We examined associations between incorrect start-and-stop knowledge and socio-demographics, sexual behaviour and PrEP use, using bi- and multivariable logistic regression. The majority of men (84.9%) perceived their start-and-stop knowledge as 'very good', but only 62.1% of all men correctly indicated how to effectively start and stop with PrEP. Using PrEP daily [adjusted OR= 2.12, 95%CI 1.06-4.28, p=0.034 was significantly associated with incorrect start-and-stop knowledge. To enable PrEP users to effectively use PrEP, they need to be better informed about how to start and stop use, irrespective of the dosing regimen.

INTRODUCTION

Oral pre-exposure prophylaxis (PrEP) is highly efficacious in preventing HIV infection among men who have sex with men (MSM), when taken daily,(1) or on-demand.(2) As sexual behaviours can vary over time, so does HIV risk.(3) A prevention-effective approach to PrEP adherence requires that PrEP is used during periods of exposure to HIV.(3)

In 2015, the IPERGAY study demonstrated the efficacy of a 2-1-1 approach to PrEP use among MSM through its event-driven regimen: i.e. taking two pills before having sex, followed by one pill every 24 hours until 48 hours after the last sex act.(2) The Be-PrEP-ared (Belgium) and AMPrEP (The Netherlands) studies demonstrated the feasibility of providing daily and on-demand PrEP to MSM.(4,5) In these studies, participants chose and switched between these two PrEP regimens according to their needs and preferences.(6) However, in real-life, users may not distinguish between these proposed regimens and rather use PrEP when they feel the need to. For example, it is demonstrated that the main reason for not returning for follow-up is a perceived lower risk for HIV, resulting in stopping with PrEP.(7) The World Health Organization (WHO) now suggests that cisgender men and trans and gender diverse people assigned male at birth who are not taking exogenous estradiol-based hormones are eligible for on-demand PrEP. Whether they intend to use oral daily PrEP or on-demand PrEP, they can start and stop PrEP using the 2-1-1 approach. (8) Cycling on and off PrEP requires planning and a well-informed understanding of when adherence to PrEP is critical.(9,10) However, we do not know to what extent PrEP users know how to effectively start and stop and can apply these guidelines in practice.

In 2020, an average of two new HIV infections per day were diagnosed in Belgium.(11) Almost half of these newly registered HIV infections were among MSM.(11) In 2020, 3983 individuals were using PrEP in Belgium, almost all exclusively male.(11) Of the PrEP starters in 2020 (n=1354), the majority were Belgian (75%) and almost all were MSM (96%).(11) In Belgium, PrEP is reimbursed by social health insurance for people at risk of acquiring HIV yet requires users to make an obligatory co-payment (e.g. approximately €15 for 90 pills).(12) MSM in Belgium have the option to use daily or on-

demand PrEP. In 2020, 61% (n=1063) of individuals with a first PrEP consultation opted for non-daily (i.e. on-demand) PrEP.(11) The objective of this study was to assess PrEP users' self-perceived and actual knowledge of how to effectively start and stop oral PrEP use. A secondary objective was to identify characteristics associated with incorrect knowledge of starting and stopping PrEP. Such insights are crucial to support and empower PrEP users in effectively adapting their PrEP use according to their needs.

METHODS

Between September 2020 and June 2021, we collected data through online surveys among PrEP users in Belgium. Three rounds of surveys took place, i.e. one baseline and two follow-up. Participants were recruited through social media of MSM community organisations, eight PrEP-delivery HIV reference centres in Belgium and through social and sexual networking apps such as Grindr. Potential participants provided consent by agreeing to participate, after having been informed about the study and its procedures. Subsequently, the following inclusion criteria were verified: (1) aged 16 years or older, (2) self-reported HIV negative or have an unknown serostatus, (3) living in Belgium and (4) having used PrEP in the six months before the baseline survey. Eligible participants were instructed to start the questionnaire. In this analysis, we mostly made use of the results of the first follow-up questionnaire, which was distributed in June 2021 via email to consenting participants.

Questionnaires were available in Dutch, French and English. We piloted each questionnaire for feasibility and user-friendliness within the research team and among volunteering MSM community representatives. All questionnaires included questions on sexual behaviour and PrEP use. The baseline questionnaire also included socio-demographics (age, nationality, education, information on sex assigned at birth, and sexual attraction). Only the first follow-up questionnaire assessed knowledge on effectively starting and stopping PrEP and asked how participants were informed about effectively starting and stopping PrEP.

For this analysis, we only included data from participants assigned male at birth who completed the baseline and first follow-up questionnaire. For sexual behaviours and

PrEP use data, we only included the data from the first follow-up questionnaire, as this is when participants were asked about effectively starting and stopping PrEP.

We used the question: "How do you assess your own knowledge on starting and stopping PrEP safely?" to measure self-perceived knowledge, and coded the response 'I know very well how to start and stop PrEP' as 'high self-perceived knowledge'. All other answers were coded as 'lower self-perceived knowledge:', i.e. 'I know in general how to start and stop, but not exactly' and 'I am not sure how to start and stop PrEP' and 'I don't know how to start and stop PrEP at all'.

'Actual knowledge' was measured using two questions, each with a case scenario instructing participants to indicate how to effectively start or stop PrEP. (Additional file 1) Both timing of intake and number of pills were assessed based on WHO's 2019 technical brief on 2-1-1.(13) Accordingly, effectively starting and stopping involves taking two pills 2-24 hours before sexual exposure, and continuing taking a daily pill for two sex-free days after the last sex act.(13) The first question was about effectively starting PrEP; a multiple choice question with four answer options of which two were correct. Participants could select more than one response. If at least one of the correct answers was ticked, and the incorrect answers were unticked, we considered this as correctly answering this question. Any other combination of answers was denoted as incorrect. The second question asked about effectively stopping PrEP and had only one correct response and three incorrect responses. Participants who correctly answered both effective-start-and-stop questions were considered to have 'correct knowledge'. All other participants were categorised as having 'incorrect knowledge'.

We conducted bivariable and multivariable logistic regression analyses to examine associations between incorrect knowledge of effectively starting and stopping PrEP (i.e. the outcome) and socio-demographic, sexual behaviour characteristics and PrEP use in the previous three or six months. All independent variables were included in the multivariable logistic regression model. We treated all variables as categorical. We used Cohen's Kappa to assess agreement between self-perceived (i.e. high and lower self-perceived knowledge) and actual knowledge (i.e. correct knowledge and incorrect knowledge). We used the Landis and Koch (1977) scoring system to interpret the strength of agreement.(14) We used R for all analyses.(15)

RESULTS

The analysis included responses from 206 participants. The majority felt sexually attracted to men (99.5%, n=205), were Belgian (87.4%, n=180) and highly educated (78.6%, n=162). About half of the participants had a steady partner (56.8%, n=117) and used PrEP non-daily (48.1%, n=99) in the three months before the follow-up questionnaire. (Table 1) The most frequently reported sources of information about effectively starting and stopping PrEP were healthcare providers in an HIV reference centre (96.1%, n=198) or social media (38.3%, n=79).

Table 1. Bivariable and multivariable analyses of associations between incorrect knowledge and socio-demographics, sexual behaviour, PrEP use and self-perceived knowledge.

	Total sample N=206	Correct knowledge[a]	Incorrect knowledge[a]	Crude OR		Adjusted OR[I]	
	n (Column %)	N=128 n (Column %)	N=78 n (Column %)	OR (95% CI)	p-value	aOR (95% CI)	p-value
Socio-demographic factors[A]							
Sexually attracted to men[H]	205 (99.5)	128 (100.0)	77 (98.7)	-	-	-	-
Age							
18-35	47 (22.8)	31 (24.2)	16 (20.5)	Ref		Ref	
36-55	130 (63.1)	79 (61.7)	51 (65.4)	1.25 (0.63-2.56)	0.530	1.74 (0.82-3.84)	0.159
56+	29 (14.1)	18 (14.1)	11 (14.1)	1.18 (0.45-3.10)	0.731	1.86 (0.59-5.9)	0.288
Belgian nationality	180 (87.4)	116 (90.6)	64 (82.1)	0.47 (0.20-1.08)	0.077	0.52 (0.02-1.28)	0.150
Education							
Higher education[G]	162 (78.6)	102 (79.7)	60 (76.9)	0.85 (0.43-1.70)	0.639	0.77 (0.37-1.63)	0.486
Sexual behaviour in the last 6 months[B]							
Sex with anonymous partner	154 (74.8)	97 (75.8)	57 (73.1)	0.87 (0.46-1.67)	0.665	0.85 (0.35-2.14)	0.722
Sex with casual partner	143 (69.4)	91 (71.1)	52 (66.7)	0.81 (0.44-1.50)	0.504	0.73 (0.34-1.58)	0.419
Sex with steady partner							
No steady partner	89 (43.2)	60 (46.9)	29 (37.2)	Ref		Ref	
Steady partner but no sex	23 (11.2)	13 (10.2)	10 (12.8)	1.59 (0.61-4.06)	0.331	1.81 (0.63-5.14)	0.263
Steady partner and sex	94 (45.6)	55 (43.0)	39 (50.0)	1.47 (0.80-2.70)	0.214	1.64 (0.85-3.23)	0.143
Group sex	103 (50.0)	61 (47.7)	42 (53.8)	1.28 (0.73-2.26)	0.389	2.17 (0.99-4.91)	0.055
Chemsex[C]							
No drug user	119 (57.8)	70 (54.7)	49 (62.8)	Ref		Ref	
Drug user, but no chemsex	9 (4.4)	6 (4.7)	3 (3.8)	0.71 (0.15-2.85)	0.645	0.65 (0.12-2.80)	0.570
Drug user and chemsex	78 (37.9)	52 (40.6)	26 (33.3)	0.71 (0.39-1.29)	0.268	0.60 (0.29-1.25)	0.177
Alcohol use	185 (89.8)	116 (90.6)	69 (88.5)	0.79 (0.31-2.03)	0.619	0.81 (0.29-2.36)	0.698
PrEP use in the last 3 months[B]							
Non-daily PrEP use[D]	99 (48.1)	71 (55.5)	28 (35.9)	Ref		Ref	

Daily PrEP use[E]	81 (39.3)	44 (34.4)	37 (47.4)	**2.13 (1.15-3.99)**	**0.016**	**2.12 (1.06-4.28)**	**0.034**
None	26 (12.6)	13 (10.2)	13 (16.7)	**2.54 (1.04-6.20)**	**0.039**	2.49 (0.78-8.18)	0.125
Self-perceived knowledge[B]							
High	175 (85.0)	114 (89.1)	61 (78.2)	Ref		Ref	
Lower[F]	31 (15.0)	14 (10.9)	17 (21.8)	**2.27 (1.05-4.98)**	**0.038**	2.06 (0.87-4.96)	0.103

Values in bold indicate statistically significant results.
MSM Men who have sex with men; PrEP pre-exposure prophylaxis; OR odds ratio; CI confidence interval; aOR adjusted odds ratio
[A]Self-reported at baseline questionnaire
[B]Self-reported at first follow-up questionnaire
[C]Sex under the influence of any recreational drug
[D]Non-daily PrEP use equals the self-reported use of one to 74 pills in the last 3 months before follow-up questionnaire completion
[E]Daily PrEP use equals the self-reported use of 75 to 90 pills in the last 3 months before follow-up questionnaire completion
[F]Lower perceived knowledge is a combination of those who self-reported to know in general, who were not sure and who did not know how to safely start and stop PrEP
[G]Higher education included higher education long type (i.e. more than 3years) and short type (i.e. 3 years or less)
[H]We found no variability in this outcome so we could not assess its association with the outcome
[I]Adjusting for the effect of all other variables in the model

[a] Effectively starting and stopping involves taking two pills two to 24 hours before sexual exposure, and stopping with a single daily pill for two days after the last sex act.(13)

Self-perceived and actual knowledge

The majority of participants (n=175, 84.9%) reported to know very well how to effectively start and stop PrEP. About 14% (n=29) indicated they knew in general how to start and stop and only two participants were not sure how to start and stop. None of the participants indicated not knowing how to effectively start and stop using PrEP. Overall, 128 (62.1%) participants correctly answered both questions on effectively starting and stopping PrEP. (Table 2) With regard to effectively starting with PrEP, 82.0% (n=169) of the participants answered at least one of the two correct answers, and 46.1% (n=95) selected both correct answers, without ticking any incorrect answer options. With regard to effectively stopping, 75.2% (n=151) of the participants indicated the correct answer (i.e. Tuesday, two days after last sex act); (Table 3) 31 and 15 participants indicated Monday (i.e. one day after) and Wednesday (i.e. three days after), respectively. The result of Cohen's Kappa test of agreement between self-perceived and actual knowledge was 0.12 [95% CI (0.00-0.24), $p < 0.05$], which is considered slight agreement.

Table 2. Self-perceived and actual knowledge on effectively starting and stopping PrEP (N=206)

Self-perceived knowledge	Actual knowledge	
	Correct knowledge[a] (n=128)	Incorrect knowledge[a] (n=78)
I know very well how to start and stop PrEP (n=175, 100%)	114 (65.1%)	61 (34.8%)
I know in general how to start and stop, but not exactly (n=29, 100%)	14 (48.3%)	15 (51.7%)
I am not sure how to start and stop PrEP (n=2, 100%)	0 (0.0%)	2 (100.0%)
I don't know how to start and stop PrEP at all (n=0)	0	0

[a] *effectively starting and stopping involves taking two pills two to 24 hours before sexual exposure, and stopping with a single daily pill for two days after the last sex act.(13)*

Table 3. Actual knowledge of 2-1-1 approach (N=206)

Start scenario	Stop scenario		Total
	Correct	Incorrect	
2/2 answers correct, and no incorrect answers	79	16	95 (46.1%)
1/2 answers correct, and no incorrect answers	49	25	74 (35.9%)
All other answer combinations	23	14	37 (18.0%)
Total	151 (75.2%)	55 (26.7%)	206 (100.0%)

Start scenario: a multiple choice question with four answer options of which two were correct; Stop scenario: a single choice question with four answer options of which only one was correct and three incorrect

Factors associated with incorrect knowledge to effectively start and stop

In the bivariable analysis, daily PrEP users were more likely not to know how to effectively start and stop with PrEP use relative to non-daily users [aOR= 2.06, 95% CI (1.15-43.99), p <0.05]; similarly, individuals who interrupted PrEP use were more likely not to know how to effectively start and stop with PrEP use relative to non-daily users [aOR= 2.54, 95% CI (1.04-6.20), p <0.05].. Those with incorrect knowledge of starting and stopping PrEP were also more likely to indicate in advance that they were unsure or only knew in general how to start and stop with PrEP [aOR= 2.27, 95% CI (1.06-4.98), p <0.05]. (Table 1)

In the multivariable analysis, only being a daily PrEP user [aOR= 2.12, 95% CI (1.05-4.28), p <0.05] remained associated with incorrect knowledge. (Table 1)

DISCUSSION

More than four-fifths of participants perceived their start-and-stop knowledge as 'very good', but only 62.1% correctly indicated how to effectively start and stop PrEP use.

Actual knowledge in our study is much higher compared with findings from an Australian survey among PrEP-experienced gay and bisexual men.(16) In the Australian study, only 12.5% of the participants knew the correct details of the 2-1-1 approach, though different questions were asked.(16) The Australian study directly asked about details of the 2-1-1 method (e.g. number of pills to be taken before sex), whereas we used scenarios to test the application of such knowledge. Recalling the correct details of the method could be likely more difficult than answering the scenarios, which may

account for the different study outcomes. The difference between both studies results could also be partially explained by the different implementation of on-demand PrEP, a PrEP dosing regimen that follows the 2-1-1 approach. In Belgium, on-demand PrEP has been implemented alongside daily PrEP since the roll-out started in 2017.(17) In Australia, daily PrEP is the only regimen approved by the Australian Therapeutic Goods Administration, although the Australian PrEP clinical guidelines endorsed on-demand PrEP in 2019.(18,19) This indicates that knowledge about starting and stopping PrEP is probably lower in countries that started with daily PrEP only. As such, increased efforts are needed to educate PrEP users on effectively starting and stopping PrEP.

The finding that daily users are less likely to indicate the correct way of starting and stopping PrEP is perhaps unsurprising. Daily PrEP users are unlikely to need to put these guidelines into practice compared to non-daily users, who need to be aware of and are likely using the 2-1-1 approach. However, it has been shown that many MSM tend to cycle on and off PrEP or switch between regimens, according to their varying perceived risk for acquiring HIV.(20) Therefore, we strongly recommend that all PrEP users, irrespective of their PrEP regimen, are well-counselled and supported to correctly apply such guidelines on how to effectively start and stop PrEP use. Our study suggests that there is a need to increase healthcare providers' knowledge and confidence regarding the 2-1-1 approach(21,22) as well as improving their counselling and communication skills to deliver tailored instructions to increase knowledge and self-efficacy of PrEP users. Moreover, promoting the use of mobile apps, featuring information on effectively starting and stopping, could support PrEP users to align adherence with their evolving needs.(23,24)

This study identified a group of PrEP users with low self-perceived and actual knowledge. Among them, much could already be achieved by discussing starting and stopping as a potential strategy, and assessing existing information needs. The use of self-assessment tools to screen for incorrect knowledge could support healthcare providers in this. Furthermore, targeted social media campaigns addressing the issue of effectively starting and stopping could increase awareness and knowledge among PrEP users and may also lower barriers for non-users. For example, reaching MSM through social media of MSM community organisations.(25)

Incorrectly following the guidelines for starting and stopping PrEP does not necessarily mean ineffective use. For example, if users stop using PrEP three days (instead of two) after the last sex event, they will most likely remain protected against HIV. Moreover, we found varying guidelines in Belgium and internationally on how to stop PrEP using the 2-1-1, which further complicates determining what is correct or incorrect knowledge. For example, in the case of multiple consecutive episodes of sexual intercourse, recommendations are either to stop after two post-exposure pills (i.e. IPERGAY guidelines) (2,26), or to take one pill per day until 48 hours after the last sexual event(27), or to stop with a single daily pill for each of two days after the last sex act(13). The original guidelines used in the IPERGAY study are therefore less strict on the post-sex period, and do not require two sex-free days with PrEP. To avoid confusion, such guidelines should be uniform and widely distributed. We additionally recommend that such differences in guidelines could be avoided by clearly applying them in multiple real-life scenarios.

Correct knowledge on starting and stopping PrEP may not be the only determinant of putting a 2-1-1 strategy into practice. Besides the need for partner-, provider- and social-support for PrEP use, PrEP users need to be able to continually estimate their actual HIV risk.(28–30) Oral PrEP provides individuals with some autonomy over their PrEP use without consulting a healthcare provider.(31) Although this can empower individuals, research shows that judging one's own HIV risk can be a challenge.(32,33) Therefore, it is important to support PrEP users early on in objectively evaluating their HIV risk and to inform them about other risk-reduction strategies when stopping with PrEP.

As a limitation, a self-selection bias may be present as we collected data through an online survey; individuals associated with the LGBTQI community or sexual health organisations could be more likely to be recruited and the PrEP users in our sample were more likely to be highly educated (78.6%) compared with a cohort analysis among PrEP users at a Belgian HIV centre, in which 60.7% were highly educated.(34) This also limits the generalizability of the findings. Furthermore, this study only focussed on knowledge. We recognise this is an important, but not the only prerequisite to optimal adherence to PrEP.

CONCLUSION

Although self-perceived knowledge was high, more than one-third of study participants failed to correctly answer questions on effectively starting and stopping PrEP. We recommend that all PrEP users, irrespective of the PrEP regimen, are better informed about how to start and stop PrEP, for example through targeted social media campaigns or the use of mobile apps featuring relevant information. Moreover, uniform guidelines should be widely distributed in this regard (e.g. with real-life scenarios as examples).

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DATA AVAILABILITY

The datasets generated during and/or analysed during the current study are not publicly available, but are available upon reasonable request and if approved by the Institutional Review Board of the Institute of Tropical Medicine (Antwerp).

CODE AVAILABILITY

Not applicable

DECLARATIONS

CONFLICT OF INTEREST

The authors have no conflict of interests to declare that are relevant to the content of this article.

ETHICAL APPROVAL

This study was performed in line with the principles of the Declaration of Helsinki. Ethical approval was granted by the Institutional Review Board of the Institute of Tropical Medicine, Antwerp (IRB 1380/20).

CONSENT TO PARTICIPATE

Eligible participants provided consent by agreeing to participate, after having been informed about the study and its procedures.

CONSENT FOR PUBLICATION

Not applicable

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SUPPLEMENTARY MATERIAL

Additional file 1. Questions regarding actual knowledge on effectively starting and stopping PrEP

Questions about starting and stopping PrEP

Below, we present some scenarios to find out what you know about 'starting and stopping with PrEP'. These scenarios are about Bruno. Bruno was born as a man, and also has a male gender. He does NOT use PrEP on a daily basis (event-driven). Below we show scenarios where a smiley face represents the day he had anal sex.

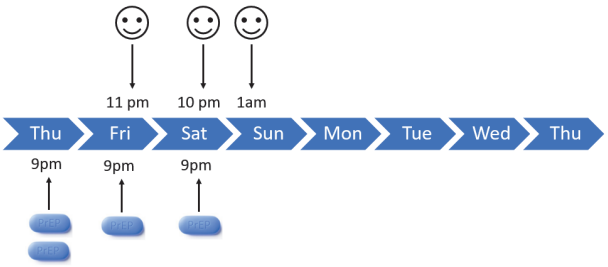
Scenario 1: Bruno has one-time anal sex with another man on Friday at 11 pm and has not taken PrEP for more than a month in the preceding days. In which of the following circumstances did Bruno start well to build up sufficient protection before sex?
Note, in this scenario we only ask about safe starting; the following scenarios are about safe stopping. Multiple answers possible.

- ∆ He takes two pills on Friday at 7pm.
- ∆ He takes one pill on Friday at 1 pm.
- ∆ He takes two pills on Friday at 10 pm.
- ∆ He takes one pill on Thursday 11pm.
- ∆ He takes two pills on Friday at 7am.
- ∆ I don't know

The correct answer is: Bruno has to take 2 PrEP pills 2 to 24 hours before the scheduled sex to be protected before this sex, so this is between Thursday 11 pm and Friday 9 pm.

The questions below are about safe stopping, both are necessary to be fully protected by PrEP for this activity.

Scenario 2: Bruno started with 2 pills on Thursday at 9pm. Then he had anal sex with different men on 3 consecutive days (Friday, Saturday and Sunday). He took a pill each time at 9pm on Friday and Saturday. The last time he had sex was on Sunday at 1 am. In order to remain sufficiently protected against HIV when he stops taking PrEP, Bruno has to take his last pill on :



- Sunday (last "sex day"), at 9pm.
- Monday (1 day after the last "sex day"), at 9 pm.
- Tuesday (2 days after the last "sex day"), at 9 pm.
- Wednesday (3 days after the last "sex day"), at 9 pm.

The correct answer is: Tuesday. Bruno should take 1 PrEP pill every 24 hours up to 2 days after the last day of sex. So taking PrEP for at least 2 consecutive days and not having unprotected contact during these last two days.

Chapter 4

PrEP users' perception on PrEP care

Chapter 4

HIV pre-exposure prophylaxis (PrEP) care in Belgium: a mixed-methods study on PrEP users' experiences and service delivery preferences.

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ABSTRACT

In Belgium, HIV pre-exposure prophylaxis (PrEP) services are mainly provided through specialised HIV clinics. To optimise PrEP uptake and retention in care, we require insights into users' perspectives on PrEP care. We aimed to elicit experiences with, and preferences for, PrEP service delivery among PrEP users in Belgium, including willingness to involve their family physicians (FP) in PrEP care. We adopted a sequential mixed-methods design. We used a web-based longitudinal study among 326 PrEP users that consisted of two questionnaires at six-month intervals, and complemented this with 21 semi-structured interviews, between September 2020 and January 2022. We conducted descriptive analyses and logistic regression to examine factors associated with willingness to involve their FP in PrEP care. Interviews were analysed using thematic analysis. Survey respondents reported high satisfaction with care received in HIV clinics [median score 9 (IQR 8-10), 10='very satisfied']. Interviews revealed the importance of regular HIV/STI screening, and the expertise and stigma-free environment of HIV clinics. Yet, they also contextualised service delivery barriers reported in the questionnaire, most notably the burden of cost and challenges integrating PrEP visits into their private and professional lives. Although 63.8% (n=208/326) of baseline respondents preferred attending an HIV clinic for PrEP follow-up, 51.9% (n=108/208) of participants in the follow-up questionnaire reported to be willing to have their FP involved in PrEP care. Participants reporting trust in FPs' PrEP and sexual health expertise, or who didn't feel judged by their FP, were more likely to be willing to involve them in PrEP care. Based on our results, we recommend a more differentiated PrEP service delivery approach, including involving FPs, to make PrEP care more client-centred.

INTRODUCTION

Reducing HIV incidence remains a global public health priority, and requires continued investments in primary prevention [1]. Oral HIV pre-exposure prophylaxis (PrEP), when taken correctly, is highly efficacious in reducing the risk of HIV acquisition [2]. As such, many countries have begun to roll-out PrEP programmes [3]. However, the uptake of PrEP has been slow, and retention in PrEP care remains sub-optimal to maximise its impact on HIV prevention [4–7]. Previous studies have identified several implementation barriers related to PrEP service delivery, including on the supply side (e.g. lack of provider knowledge, skills or interest in PrEP care) and demand side (e.g. limited awareness and low self-perceived HIV risk) [8–14]. Understanding how these barriers can be addressed is critical to further optimise the roll-out of PrEP and maximise its impact on the epidemic.

Differentiated service delivery (DSD) is a client-centred approach originating from HIV care, that can help make services more acceptable and accessible for PrEP users [15,16]. It is grounded in the notion that the needs and preferences of a diverse population of PrEP users are more likely to be met if service delivery options are diversified. As such, DSD does not put forward one preferred model of care, but aims to tailor the setting ('where'), type of provider ('who'), frequency of follow-up ('when') and the package of care ('what') to the needs of service users [17]. The underlying assumption of DSD is that such a responsive care model will result in a more efficient use of resources, better access for underserved populations and improved quality of care and life [17]. The shift towards DSD for PrEP care has recently been accelerated by the constraints placed on health systems by the COVID-19 pandemic, and has already led to simplified PrEP follow-up options (e.g. offering online visits) [18].

To understand how PrEP services can be better tailored to the needs of a diverse group of users, we require more insights into their current experiences and preferences [19,20]. Research on PrEP service delivery from a user perspective has mainly focused on barriers to PrEP care among actual or potential PrEP users [21–23]. These studies provided useful suggestions for reducing some of the identified barriers. However, insights into PrEP users' preferences for alternative service delivery options are

insufficiently investigated. The few studies that did investigate PrEP service delivery preferences were mainly conducted in sub-Sahara Africa or among individuals who could benefit from PrEP but who were not (yet) using it [24–28]. These studies predominantly focused on (hypothetical) preferences for providers and settings to receive PrEP care from, and suggest that individuals would mainly prefer to access PrEP from convenient locations and/or familiar providers already accessed for other services (e.g. antenatal care or family planning clinics for women, and out-patient or primary care settings). However, we require more context-specific insights into service delivery preferences among individuals who experienced first-hand some of the advantages and challenges of receiving PrEP care under the real-world conditions of health systems.

In Belgium, the HIV epidemic primarily affects men how have sex with men (MSM) and individuals of the sub-Saharan African diaspora community [29]. In 2017, Belgium was among the first countries in Europe to make publicly funded oral PrEP available via 12 specialised HIV clinics, and according to government-issued reimbursement regulations [30]. These regulations require quarterly follow-up visits at specialised HIV clinics, including HIV testing and screening for other sexually transmitted infections (STIs). Other care activities include adherence and risk reduction counselling, and a re-fill prescription for three months (i.e. equivalent of 90 pills if daily use). PrEP users with health insurance usually co-pay 15 Euro for 90 pills, in addition to out-of-pocket costs for consultation fees and laboratory testing. In 2021, 5,277 unique individuals obtained reimbursed PrEP at least once from these clinics, constituting an increase of 126% compared to 2018 [29]. Notably, almost all (98%) PrEP starters in 2021 identified as MSM. The Belgian health system currently does not allow for the provision of reimbursed PrEP through non-specialist providers, such as family physicians (FP) [30]. However, their engagement may be crucial to scale-up PrEP services by reducing the burden on specialised services, and to avoid inequities in access [31].

The objective of this study was to explore experiences with, and preferences for, PrEP care among PrEP users in Belgium. Additionally, we explored PrEP users' willingness to involve their FP into PrEP care. These findings will inform the development of more differentiated PrEP service delivery in Belgium, and in other countries with similar target populations and service delivery characteristics.

METHODS

Study design

We adopted an explanatory, sequential, mixed-methods design (QUAN + qual), using a web-based longitudinal study among PrEP users in Belgium, complemented by 21 semi-structured interviews with a sub-sample of participants who completed the baseline survey. The purpose of these interviews was to contextualise quantitative findings and explore some particular topics more in-depth (e.g. the importance attached to some care aspects and the extent to which barriers impacted on PrEP users' lives) [32]. This is a sub-study of a larger study primarily designed to longitudinally assess patterns of PrEP use among current PrEP users through three rounds of web-based questionnaires, at 6-month intervals, between September 2020 and January 2022 [33,34]. We conducted semi-structured interviews between August 2021 and December 2021.

Study population and recruitment

We recruited survey participants through social media platforms of relevant community organisations, advertisements in HIV/STI clinics, and via social and sexual networking apps [33]. Eligibility criteria were: being 16 years or older, having a self-reported HIV negative or unknown HIV serostatus, living in Belgium and having used PrEP in the six months prior to the baseline questionnaire. After the baseline questionnaire, we invited participants who consented to complete the two follow-up questionnaires (FU1 and FU2). Interviewees were purposively selected based on their responses to the baseline questionnaire (see 'data collection' below).

Data collection

Web-based longitudinal study

Only data from the first two questionnaire rounds were used for this study, as these included questions on service delivery experiences and preferences. Questionnaires were available in Dutch, French and English. The baseline questionnaire collected sociodemographic information (e.g. age, sex assigned at birth, educational attainment). Participants were asked about their PrEP use in the preceding three months, settings visited for PrEP care, frequency of follow-up visits, whether they

experienced six particular barriers to PrEP care (e.g. cost, clinic location and visit duration) (with answer options "no barrier", "minor barrier" and "major barrier") and their satisfaction with PrEP care (assessed on an 11-point Likert scale). Through eight questions, we explored which care aspects participants would prefer to have included. For example, we asked "What care aspects need to be part of a minimum care package during a PrEP follow-up consultation?" (with response options: "HIV testing"; "STI testing"; "counselling on: PrEP side effects, adherence, risk reduction counselling, mental wellbeing, chemsex use and condom use"). We also asked which settings they would prefer to attend for PrEP follow-up care (with response options: "HIV clinic"; "family physician"; "community health centre"; "HIV/STI testing centre" or "other"). We asked about the preferred frequency of follow-up visits, with response options being every 3, 6 or 12 months or 'other'.

The first follow-up questionnaire included questions on experiences with receiving PrEP and sexual healthcare from PrEP providers (i.e. clinicians working at HIV clinics and/or FPs). Three statements inquired about their opinions towards their current PrEP care (i.e. control, decision-making and tailoring) using 4-point scales without "middle point" to disallow neutrality. Four statements asked about the extent of being able to ask providers questions about sex or sexuality, or whether they felt judged in current PrEP care or by their FP, using 5-point Likert scales ([definitely] agree, not agree nor disagree, [definitely] disagree). Willingness to involve their FP in PrEP care (i.e. "To what extent would you be willing to have your family physician involved in your PrEP follow-up?") was assessed on a 5-point Likert scale (definitely agree, agree, not agree nor disagree, disagree, definitely disagree).

Semi-structured interviews

We conducted semi-structured interviews with 21 individuals. To capture variation in utilisation and experiences with PrEP care, we purposively selected questionnaire participants according to the types of facilities they had visited for PrEP care (e.g. HIV clinic and FP), and their reported levels of satisfaction with care. We considered interviewees with high and low satisfaction with PrEP care to be potentially information-rich cases, i.e. cases from which one can learn a great deal with regard to the central issue being investigated [35]. Topics included participants' experiences with PrEP care and their preferences for PrEP and sexual health services, including for

involving their FP in PrEP care. Three researchers (AR, JV and TV) with training in qualitative research conducted the interviews in Dutch, French or English, depending on interviewees' preferences. Interviews took place in a private place or online via a secured platform, respecting General Data Protection Regulations. We only invited participants who indicated in the baseline questionnaire that they could be contacted for future studies via email. Participants were asked to provide informed consent verbally prior to the interviews, which were audio-recorded upon agreement.

Data analysis

Quantitative data analysis

We analysed sociodemographics, PrEP utilisation and experiences and preferences for PrEP care using descriptive statistics. As not all participants completed both web-based questionnaires, we explored potential attrition bias by comparing sociodemographic characteristics, PrEP use and PrEP care utilisation of participants who completed only the baseline questionnaire to those who completed the baseline and FU1 questionnaire, using Chi-square, Fisher's exact or Mann Whitney U tests, as appropriate. We dichotomised "barriers to PrEP care" so that response categories included "no barriers" and "major or minor barriers", and examined factors associated with experiencing major or minor barriers using Chi-square or Fisher's exact test. Additionally, given the very high overall scores for "satisfaction with PrEP care" (scale 0-10; 10=very satisfied), this variable was dichotomised at seven (1-7 and 8-10), to allow investigating meaningful associations with barriers to care.

We explored the association between willingness to involve their FP in PrEP care and explanatory variables of interest (e.g. socio-demographics) using logistic regression. We dichotomised the variable "willingness to involve their FP in PrEP care", so that "definitely agree" and "agree" denoted a willingness to involve their FP in PrEP care, and "definitely not agree", "not agree" and "not agree, nor disagree" denoted not being willing. For dependent variables, we dichotomised statements with 4-point Likert scales and re-coded those with 5-point Likert scales into three categories ([definitely] agree, not agree nor disagree, [definitely] disagree). All models were adjusted for age *a priori*. To estimate independent associations between different variables and the outcome "willingness to include their FP in PrEP care", and to avoid over-adjusting for covariates that may act as mediators, we only adjusted for factors hypothesised to be

on the causal pathway between the variable and outcome. All statistical analysis were performed in R version 4.0.2 [36].

Qualitative data analysis

All interviews were transcribed verbatim, pseudonymised, and analysed in Nvivo 12 [37]. In a first step, we familiarised ourselves with the data by reading the transcripts. Secondly, we used an inductive coding process following a thematic analysis approach and developed an initial coding scheme [38]. These codes were then combined to relevant themes in accordance with the quantitative analyses on PrEP care experiences, barriers, and preferences. Subsequently, we re-analysed all interviews with the focus on finding agreements and disagreements with the quantitative results and to further contextualise particular quantitative findings.

RESULTS

Description of the study population and PrEP care utilization at baseline

Overall, 326 participants completed the baseline questionnaire and 208 (63.8%) completed FU1 questionnaire (Table 1). Those who did not complete the FU1 questionnaire (n=118) were younger (median age 39; IQR [33-48] vs. median age 44; IQR [36-52]; p=0.007) and less likely to have visited their FP for PrEP care (3.4%; n=4 vs. 8.7%; n=18; p=0.022) compared to those who completed both the baseline and FU1 questionnaire (n=208) (Table 1). At baseline, the majority of participants were men (99.1%; 323/326), sexually attracted to men (98.8%; n=322), with a median age of 42 years (IQR 34-50) and born in Belgium (85.6%; n=279) (Table 1). Characteristics of the 21 interviewed questionnaire participants are available in Supplementary File 1.

Half of all participants reported having used PrEP on a non-daily regimen in the past three months (50.6%; n=165), and most exclusively attended an HIV clinic (84.4%; n=275) for their PrEP follow-up visits. Just over half of participants had discussed PrEP use with their FP (54.6%; n=178).

Table 1. Baseline characteristics of web-based longitudinal study (N=326) participants, and comparison of participants who completed both baseline and FU1 questionnaire (N=208) and participants who only completed the baseline questionnaires (N=118).

	Web-based study participants who completed baseline questionnaire N=326	Web-based study participants who completed baseline and FU1 questionnaire N=208	Web-based study participants who only completed baseline questionnaire N=118	
	n (%)	n (%)	n (%)	p-value[a]
Age in years, median [IQR]	42 [34-50]	44 [36-52]	39 [33-48]	**0.007**
Male sex at birth	323 (99.1)	206 (99.0)	116 (98.3)	1.000
Born in Belgium	279 (85.6)	182 (87.5)	97 (82.2)	0.191
Educational attainment[b]				0.089
Secondary or lower	60 (18.4)	44 (21.2)	16 (13.6)	
Higher education	266 (81.6)	164 (78.8)	102 (86.4)	
Occupational status[c]				0.526
Employed	269 (82.5)	172 (82.7)	97 (82.2)	
Unemployed	52 (16.0)	34 (16.3)	18 (15.3)	
Other	5 (1.5)	2 (1.0)	3 (2.5)	
Perceived financial status				0.420
Living really comfortably on present income	65 (19.9)	38 (18.3)	27 (22.9)	
Living comfortably on present income	154 (47.2)	100 (48.1)	54 (45.8)	
Neither comfortably nor struggling on present income	75 (23.0)	51 (24.5)	24 (20.3)	
Struggling or really struggling on present income	26 (8.0)	17 (8.2)	9 (7.6)	
Prefer not to say	6 (1.8)	2 (1.0)	4 (3.4)	
Sexually attracted to men	322 (98.8)	206 (99.0)	116 (98.3)	1.000
PrEP use – regimen over the past 3 months				0.398
Daily use	154 (47.2)	96 (46.2)	58 (49.2)	
Non-daily use	165 (50.6)	107 (51.4)	58 (49.2)	
No use	7 (2.2)	5 (2.4)	2 (1.7)	

Satisfaction with PrEP care[d], median [IQR]	9 [8-10]	9 [8-10]	8 [8-10]	0.129
Settings visited for PrEP follow-up since start PrEP use				**0.022**
HIV clinic-only	275 (84.4)	177 (85.1)	98 (83.1)	
HIV clinic and FP	22 (6.7)	18 (8.7)	4 (3.4)	
Other[e]	29 (8.9)	13 (6.3)	16 (13.6)	
Frequency of PrEP follow-up visits since start PrEP use				0.081
At least 3 monthly	221 (67.8)	147 (70.7)	74 (62.7)	
4-6 monthly	78 (23.9)	49 (23.6)	29 (24.6)	
Less than 6 monthly	8 (2.5)	5 (2.4)	3 (2.5)	
Other	19 (5.8)	7 (3.4)	12 (10.2)	
FP informed about PrEP use				0.070
I discussed with my FP that I'm taking PrEP	178 (54.6)	117 (56.3)	61 (51.7)	
My FP is aware of my PrEP use, but we did not discuss it	44 (13.5)	29 (13.9)	15 (12.7)	
I don't know/I'm not aware that my FP knows I'm taking PrEP	40 (12.3)	28 (13.5)	12 (10.2)	
My FP doesn't know that I'm taking PrEP	34 (10.4)	14 (6.7)	20 (16.9)	
Does not have an FP	30 (9.2)	20 (9.6)	10 (8.5)	

FP: family physician, FU1: follow-up 1, IQR: interquartile range, PrEP: pre-exposure prophylaxis

[a] P-value of comparing those who completed baseline and FU1 questionnaire with those who only completed the baseline questionnaire. Values significant at 0.05 threshold are displayed in bold.

[b] 'Higher education' means college or university and includes higher education long type (i.e. more than 3 years) and short type (i.e. 3 years or less).

[c] 'unemployed' includes long-term sick leave and medically retired, technically unemployed, retired, student, and unemployed. 'employed' includes employed full-time, employed part-time and self-employed.

[d] Scale 0-10, 10=very satisfied

[e] 'Other' includes combinations involving a community health centre and/or sourcing PrEP either informally (e.g. online) or through services across national borders (e.g. through public health services in the Netherlands).

Experiences with PrEP care

Overall satisfaction with PrEP care

Overall, satisfaction with PrEP care was high at baseline (median 9/10; IQR 8-10) (Table 1). Among interviewees, satisfaction with PrEP care was related to feeling comfortable being able to regularly access testing and treatment for STIs, including HIV. The perceived safety of being followed up for potential side-effects, and feeling reassured not putting sexual partners at risk for STIs, were considered important benefits of PrEP care.

"The peace of mind of knowing your HIV status every time and also knowing the status of all the other STIs, knowing that I can't put anyone at risk or are putting anyone at risk. So that is one of the positive things. That is also why I keep doing it [continuing PrEP care]."
[ID253; age category: 35-44 years old]

Several interviewees valued the expertise in PrEP and sexual health available at the HIV clinic. The majority of interviewees did not feel judged, nor did they experience difficulties in asking questions or discussing certain (sexual) health issues in the HIV clinic.

Experienced barriers to PrEP care

The most frequently reported barriers for PrEP care among survey participants were difficulties taking time off from work (45.4%; 143/326) and the direct out-of-pocket costs for follow-up care (36.2%; n=114) (Figure 1). Experiencing any barrier was significantly associated with lower PrEP care satisfaction scores (i.e. score 7/10 or lower) (Supplementary File 2). Younger age (i.e. <25 years old) was significantly associated with experiencing cost, difficulty taking time off from work and clinic location as a barrier. Participants experiencing financial hardship were more likely to experience cost as a barrier, and those with an educational attainment higher than secondary school were less likely to experience visit duration as a barrier (Supplementary File 2).

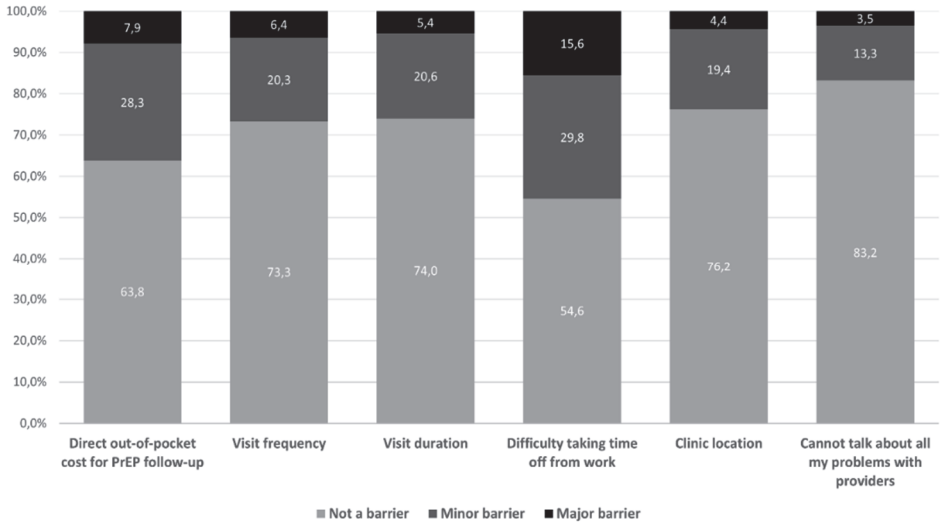

Figure 1. Reported experienced barriers to PrEP care among PrEP users (% of total). Data based on baseline questionnaire (N=326)

Interviews further contextualised these barriers, and we identified three main themes regarding negative PrEP care experiences: (1) limited provider-client interaction, (2) burden related to cost and challenges navigating the insurance system, and (3) difficulties incorporating follow-up visits in private and professional life.

Limited provider-client interaction: Feeling at ease to openly discuss intimate sexual practices or mental health problems was considered important. Yet interviewees reported various factors limiting optimal client-provider interaction, such as frequently changing providers limiting good rapport building and continuity of care, feeling treated "as a number", or that the consultation was too rushed or routinised for the investment they had to make from their part. This led some interviewees questioning the need of having to attend specialised services for PrEP:

"It felt like a very routine job. And then I was like: 'Do we really have to come here and sit in the waiting room for 2 hours just to have blood drawn?' So then I was like: 'Can't we just do that at the family doctor's?' Surely he can also ask 'Are you OK?' and send your blood. So it felt like a lot of trouble for a routine job."

[ID253; age category: 35-44 years old]

Burden of cost and challenges navigating the insurance system: Interviewees reported the costs of testing and consultations as most burdensome, compared to costs for PrEP pills. All interviewees found that without reimbursement, PrEP care would not be affordable. Concurrently, many interviewees considered that the current reimbursement system with co-payments is already not financially feasible for everyone.

> *"I'm okay with it [the cost]. But I'm like the moment I would fall without a job, for example, I would have a problem. It's just getting so expensive, for something that should be available to everyone. And right now that's not the case." (ID228)*
> [ID228; age category: 25-34 years old]

Two interviewees did not have a Belgian health insurance when initiating PrEP and perceived the administration and reimbursement system too complex to navigate. The lack of guidance on the reimbursement process had led to one interviewee paying the full price for PrEP pills and PrEP-related healthcare expenditures (e.g. STI testing, consultation) when starting with PrEP.

Challenges incorporating follow-up visits in private and professional life: this related to PrEP visits only offered during office hours, the frequency of the visits (i.e. too many), and the time lost to PrEP visits (e.g. having also to take into account travel time to the clinic). Some interviewees had trouble making sense of how these difficulties related to the limited gains they got out of three-monthly visits, especially when inconsistent with their PrEP use or sexual behaviour:

> *"I cannot do anything there [at the HIV clinic], because I did not do anything. So there is no reason for testing or for me to go and get examined or to go and get more prescriptions, because to put it flat my sex life was just at a standstill."*
> [ID183; age category: 35-44 years old]

Abovementioned perceived barriers did not keep interviewees from staying in care, as these did not outweigh the benefits of using PrEP (i.e. feeling protected for HIV), for which they needed to access specialised services. However, several interviewees

reported that they searched for alternative settings for PrEP care, such as their FP or another HIV clinic, to overcome some of the barriers they experienced.

Preferences for PrEP service delivery

Setting and providers

In the baseline questionnaire, 63.8% (208/326) of participants preferred only attending the HIV clinic to receive PrEP care. The remainder (36.2%; n=118) preferred having different options available (e.g. FP and community-based organisation). Interviewees stressed the importance of being able to receive PrEP care in a non-judgmental setting with sufficient expertise in PrEP and STI care, and having a regular, fixed, contact person with whom they could connect and build a trusting relationship. For some interviewees it did not really matter whether this person was a specialist physician, FP or nurse.

> *"You build a relationship of trust. After all, you tell these people a lot from your private life. So I think it is important that they are often the same people. If it were always someone else, you would have to start telling your story all over again. OK, they can go through your medical file. But it's not the same."*
>
> [ID174: age category: 45-54 years old]

In-person contact versus remote follow-up

Participants valued in-person visits for PrEP care, with 79.8% (260/326) preferring fully in-person visits and 20.2% (n=66) a format that included a remote option (e.g. tele-visits combined with in-person visits). The preference for in-person or remote follow-up had much to do with the degree of human contact interviewees desired. In-person visits would allow physical examination and more open conversations, while online or teleconsultations would be more practical for some interviewees (e.g. time saving).

Frequency of visits

The majority (63.8%; 208/326) preferred quarterly PrEP follow-up visits. A main motivator among interviewees to opt for quarterly visits was the opportunity to receive regular STI and HIV testing. Others, mainly those who had been using PrEP for a long time and/or were not taking PrEP daily, suggested to reduce visit frequency. A few

interviewees suggested that follow-up visits should be scheduled based on shared decision-making between provider and PrEP user.

"The [visit]frequency, I think, has to be discussed depending also on the risks that have occurred, there is no good answer for everybody […]. I think that for some people once every three months is good, and for others perhaps less regularly but there is no good answer I think."

[ID43; age category: 25-34 years old]

Content of care

Most participants mentioned HIV testing, STI testing and counselling on PrEP side effects and adherence as essential elements of the care package (Figure 2). In addition, the majority indicated that other aspects of counselling, i.e. on sexual risk reduction (76.1%; 248/326), mental wellbeing (66.0%; n=215) and 'chemsex' (62.0%; n=202), should be provided during follow-up. Interviewees emphasised the need for STI and HIV testing. For some, this was the only requirement for a follow-up visit. Other interviewees mentioned they would like a proactive offer for support by a sexologist or psychologist for mental health related issues they experienced:

"It would be helpful to at least have a psychologist to say: 'How are you within your life? How much are you using [drug use]? How much is it affecting you stress-wise? […] it could be helpful to have a more specialized person on the mental impact of it, rather than just a doctor who will just do the quick blood test results and stuff and be done."

[ID49; age category: 25-34 years old]

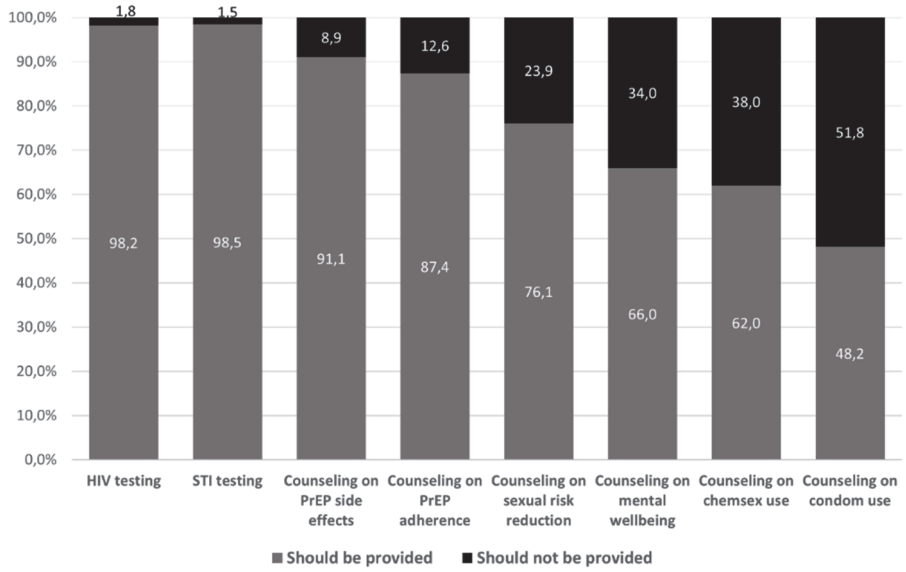

Figure 2. Preferred care components to be included in a minimum package for PrEP follow-up visits among PrEP users (% of total). Data based on baseline questionnaire (N=326)

Willingness to involve their family physician in PrEP care

Among the 208 participants who completed the FU1 questionnaire, 108 (51.9%) were willing to have their FP involved in PrEP care, either by having all follow-up visits there, or alternating PrEP follow-up visits between their FP and the HIV clinic (Table 2). Willingness to engage FPs in follow-up care was higher among participants with higher educational attainment (i.e. higher than secondary school) (adjusted odds ratio [aOR]=2.19; 95% confidence interval [CI] 1.10-4.49) and among those who had previously visited their FP for PrEP care (aOR=3.63; 95%CI 1.18-13.79), compared to their counterparts. Alternatively, willingness to engage FPs in PrEP care was lower among those reporting feeling unsure (aOR=0.34; 95%CI 0.14-0.78) or unable (aOR=0.13; 95%CI 0.06-0.27) to go to their FP for questions on PrEP, sexual health or sexuality, compared to their counterparts. Those who felt judged on their sexual behaviour by their FP (aOR=0.23; 95%CI 0.11-0.47) or who neither agreed nor disagreed with feeling judged by their FP (aOR=0.34; 95%CI 0.15-0.76) were also less willing to engage their FP in PrEP care than those who reported not feeling judged on their sexual behaviour by their FP (Table 2).

Table 2. Willingness to involve their family physician into PrEP care, and associated factors, among follow-up 1 questionnaire participants (N=208).

	All FU1 web-based participants N=208 (100%) n (%)	Willing to have their FP involved in PrEP follow-up N=108 (51.9%) n (row %)	Age-adjusted OR (95% CI)[a]	Adjusted OR (95% CI)[b]
Age group in years				
18-24	6 (2.9)	4 (66.7)	2.13 (0.39 -16.09)	2.13 (0.39-16.09)
25-34	37 (17.8)	19 (51.4)	1.06 (0.47 -2.40)	1.06 (0.47-2.40)
35-44	68 (32.7)	34 (50.0)	Ref	Ref
45-54	62 (29.8)	37 (59.7)	1.57 (0.78 - 3.19)	1.57 (0.78-3.19)
≥55	35 (16.8)	14 (40.0)	0.71 (0.30 - 1.62)	0.71 (0.30-1.62)
Born in Belgium				
Yes	182 (87.5)	93 (51.1)	Ref	Ref
No	26 (12.5)	15 (57.7)	1.40 (0.59 - 3.42)	1.40 (0.59-3.42)
Educational attainment[c]				
Secondary education or lower	44 (21.2)	16 (36.4)	Ref	Ref
Higher education	164 (78.8)	92 (56.1)	**2.19 (1.10-4.49)**	**2.19 (1.10-4.49)**
Occupational status				
Employed	172 (82.7)	90 (52.3)	Ref	Ref
Unemployed	34 (16.3)	16 (47.1)	0.90 (0.40 - 2.01)[d]	0.95 (0.42-2.16)[d]
Other	2 (1.0)	2 (100)		
Perceived financial status				
Living really comfortably on present income	38 (18.3)	18 (47.4)	Ref	Ref
Living comfortably on present income	100 (48.1)	52 (52.0)	1.16 (0.53 -2.54)	1.19 (0.54-2.63)
Neither comfortably nor struggling on present income	51 (24.5)	28 (54.9)	1.27 (0.53 - 3.07)	1.43 (0.59-3.52)
Struggling or really struggling on present income	17 (8.2)	9 (52.9)	1.12 (0.33 -3.82)	1.40 (0.40-5.00)
Prefer not to say	2 (1.0)	1 (50.0)	0.80 (0.02 -24.03)	0.67 (0.02-0.44)
Current PrEP use				
Daily use	96 (46.2)	52 (54.2)	Ref	Ref
Non-daily or no use	112 (53.8)	56 (50.0)	0.87 (0.49 - 1.54)	0.82 (0.46-1.46)

Settings visited for PrEP follow-up since start PrEP use				
HIV clinic-only	177 (85.1)	89 (50.3)	Ref	Ref
HIV clinic and FP	18 (8.7)	14 (77.8)	**3.44 (1.14 -12.81)**	**3.63 (1.18-13.79)**
Other	13 (6.2)	5 (38.5)	0.60 (0.17 - 1.91)	0.57 (0.16-1.82)
"I trust that my PrEP providers decide whatever is best for my PrEP FU" [fo]				
Totally agree or agree	182 (88.3)	93 (51.1)	Ref	Ref
Strongly disagree or disagree	24 (11.7)	13 (54.2)	1.30 (0.54 - 3.21)	1.20 (0.49-3.03)
"I would like to be more in control over my PrEP FU" [e]				
Totally agree or agree	85 (41.5)	42 (49.4)	Ref	Ref
Strongly disagree or disagree	120 (58.5)	63 (52.5)	1.06 (0.60 - 1.87)	1.09 (0.61-1.95)
"I have the impression that the care I receive is adapted to my personal situation" [ef]				
Totally agree or agree	138 (67.0)	72 (52.2)	Ref	Ref
Strongly disagree or disagree	68 (33.0)	34 (50.0)	0.90 (0.49 - 1.66)	0.92 (0.49-1.72)
"I feel able to go to my PrEP provider for questions on PrEP, sexual health and sexuality" [g]				
Agree or definitely agree	171 (82.2)	89 (52.0)	Ref	Ref
Not agree nor disagree	21 (10.1)	11 (52.4)	1.08 (0.42 -2.80)	1.36 (0.51-3.68)
Disagree or definitely disagree	16 (7.7)	8 (50.0)	0.94 (0.32 -2.71)	1.13 (0.38-3.38)
"I feel able to go to my FP for questions on PrEP, sexual health and sexuality" [g]				
Agree or definitely agree	83 (39.9)	62 (74.7)	Ref	Ref
Not agree nor disagree	44 (21.2)	22 (50.0)	**0.36 (0.16 - 0.79)**	**0.34 (0.14 - 0.78)**
Disagree or definitely disagree	81 (38.9)	24 (29.6)	**0.14 (0.07 0.28)**	**0.13 (0.06 - 0.27)**
"I feel judged on my sexual behaviour by my PrEP providers" [g]				
Agree or definitely agree	35 (16.8)	18 (51.4)	0.83 (0.39 – 1.78)	0.95 (0.44 – 2.08)
Not agree nor disagree	17 (8.2)	5 (29.4)	0.35 (0.39 – 1.78)	0.38 (0.11 -1.15)
Disagree or definitely disagree	156 (75.0)	85 (54.5)	Ref	Ref
"I feel judged on my sexual behaviour by my FP" [g]				
Agree or definitely agree	55 (26.4)	19 (34.5)	**0.27 (0.14 – 0.54)**	**0.23 (0.11 – 0.47)**
Not agree nor disagree	36 (17.3)	13 (36.1)	**0.33 (0.15 – 0.72)**	**0.34 (0.15 – 0.76)**
Disagree or definitely disagree	117 (56.3)	76 (65.0)	Ref	Ref
"My FP is aware of my PrEP use" [gh]				

Yes	146 (71.2)	87 (59.6)	Ref	Ref
No or unsure	39 (19.0)	13 (33.3)	**0.30 (0.14 - 0.62)**	**0.31 (0.14 - 0.66)**
I don't have an FP	20 (9.8)	8 (40.0)	0.46 (0.16 - 1.22)	0.44 (0.15 - 1.22)

CI = confidence interval; FP = family physician; FU1 = follow-up questionnaire 1; OR = odds ratio; PrEP = pre-exposure prophylaxis.
Values in bold indicate significant p-values <0.05.
[a] *Odds ratios of which the confidence interval does not include 1.00 are highlighted in bold. All odds ratios in this column are adjusted for age only.*
[b] *Odds ratios of which the confidence interval does not include 1.00 are highlighted in bold. Odds ratios of 'sex at birth', 'born in Belgium' and 'education status' were adjusted for age; odds ratios of 'occupational status', 'financial status', 'current PrEP use' and 'settings previously visited for PrEP' were adjusted for age and 'education level'; odds ratios of all eight statements of attitudes, experiences and perceptions related to PrEP care were adjusted for age, 'education level' and 'settings previously visited for PrEP'. The eight statements of attitudes, experiences and perceptions related to PrEP care were not adjusted for each statement separately.*
[c] *'Higher education' means college or university and includes higher education long type (i.e. more than 3 years) and short type (i.e. 3 years or less).*
[d] *Categories 'unemployed' and 'other' merged to calculate odds ratio and p-value due to small cell value.*
[e] *Statement on a 4-point Likert scale with original categories 'Definitely agree', 'Agree', 'Disagree', 'Strongly disagree' was dichotomised into '[definitely] agree' and [strongly] disagree.*
[f] *Missing data for 2 individuals (no PrEP use and/or report currently not being followed-up for PrEP use).*
[g] *Statement on a 5-point Likert scale with original categories 'Definitely Agree', 'Agree', 'Not agree nor disagree', 'Disagree' 'Definitely disagree' was re-coded into three categories: '[definitely] agree', 'Not agree nor disagree' and '[definitely] disagree.*
[h] *Missing data for 3 individuals (no PrEP use and/or report currently not being followed-up for PrEP use).*

Interviewees confirmed the importance of their FP knowing about their PrEP use in order to provide better care, for example in case of medication interactions or side effects. Interviewees who had a good rapport with their FP considered the involvement of their FP as an advantage as it enhanced openness, trust and PrEP follow-up continuity. For some, involving FPs in care would mean more accessible and low-threshold care due to reduced consultation costs, enhanced proximity, or more flexible consultation hours.

Interviewees who were not willing to disclose their PrEP use to their FP and/or to have their FP involved in PrEP care explained they felt not at ease to discuss their sexual health with their FP. Reasons for this varied from a perceived lack of knowledge among FPs about PrEP care protocols and STI management among gay men, the FP being too close to other family members, and anticipating negative reactions and judgment (e.g. due to lack of understanding of the gay community):

> *"I can't do that [discussing sexual life openly] with my FP, or I don't dare to. Then I think: 'she [FP] doesn't need to know, because if I already see how she reacts in certain ways, I'm not going to do that'. […] I noticed when I did give a little hint of that [same-sex attraction] to my FP, that for her it was something she was not familiar with."*
>
> [ID317; age category: >55 years old]

Some interviewees indicated that this discomfort could be overcome by properly training FPs to conduct PrEP care consultations.

DISCUSSION

This mixed-methods study provides contextualised insights into PrEP users' care experiences, including barriers to PrEP care, and preferences for PrEP service delivery in Belgium. Our study shows that most study participants were satisfied with the PrEP care they received in specialised HIV clinics. Yet, their care experiences were also influenced by service delivery barriers, including planning for PrEP visits and out-of-pocket costs. We found that PrEP users strongly value having access to regular (e.g. quarterly) HIV/STI testing, but that there are differences in the preferred formats (i.e. in-person or remote visits), providers or settings to receive such PrEP care aspects.

Difficulties planning for follow-up visits (e.g. during office hours) and out-of-pocket costs were found to be the most important barriers to PrEP care among survey participants, especially for younger PrEP users. This was corroborated by qualitative findings, indicating that being 'on PrEP' requires considerable direct and indirect personal investments in terms of cost and time (e.g. finding time during office hours, navigating the healthcare system). However, interviewees explained that, for them, such barriers did not outweigh the benefits, in particular the opportunity to receive regular STI and HIV testing. Yet, individuals who may benefit from PrEP and experience more difficulties prioritising preventive strategies amidst other needs and commitments (e.g. experiencing financial hardship, not able to afford time off from work) may be less likely to start or continue PrEP use [39,40]. Notably, costs and challenges navigating complex insurance schemes have previously been reported to result in inequitable access to PrEP among socio-economically disadvantaged communities at increased risk of HIV in the USA [41,42]. In Europe, PrEP and associated services (e.g. STI screening and laboratory costs) are often not fully free-of-charge, requiring co-payments that may discourage people who are less able to pay for such services to seek care, despite being at risk of acquiring HIV [43]. A recent study among migrant MSM in Belgium revealed that, in addition to cost, accessing PrEP care through specialised HIV clinics presented particular barriers related to language and stigma attached to HIV [44]. We therefore recommend that rolling-out PrEP programmes should be accompanied by adequate investments in safeguarding financial accessibility for all potential PrEP users, particularly for socio-economically vulnerable populations. Expanding PrEP care to peer-led and/or community-based delivery settings may be a strategy to ensure broad acceptability among people experiencing difficulties accessing specialised clinical settings [45].

Our results highlight that user preferences for PrEP care are a result of an individual balancing exercise between practical considerations (e.g. cost, distance to clinic, ability to take off from work), perceived PrEP need (e.g. associated with sexual risk behaviour) and the level of importance people attach to feeling cared for in a non-judgmental and trusted environment with appropriate expertise. Previous work has shown that, for MSM, making up this balance often results in separating sexual healthcare from attending other forms of healthcare [46,47]. Such decisions were often found to be

grounded in their previous experiences and interactions with the health system, such as having been exposed to judgment, stigma or discrimination by certain providers [47]. Consistent with this literature, we found that the existence of an already established comfortable and trusted relationship with a specific provider, or the anticipated potential of building one, was deemed particularly important by participants in deciding on their provider of choice in PrEP care. The explicit purpose of HIV and/or STI clinics to deliver discrete services in the sexual health domain might be a particularly attractive option for (potential) PrEP users without any other regular or fixed provider, such as young people, or those who prefer not to go to their FP [48,49]. Moreover, despite the data being collected during and right after the COVID-19 pandemic, almost 80% of participants preferred fully in-person visits for PrEP care. This finding suggests that, while remote care options (e.g. tele-visits) are increasingly investigated and may improve access for some, conventional, facility-based, PrEP care will remain the preferred modality for a sub-group of PrEP users in Belgium [50–53].

Interestingly, our study demonstrates that at least half of the PrEP users would prefer, or be willing to, involve their FP in PrEP care, and that this was indeed contingent on their previous experiences (e.g. being able to talk openly to their FP about sexuality) and perceptions of their FP (e.g. feeling unable to go with questions on PrEP and sexual health). These results are in line with previous studies on willingness to involve FPs in STI-related care in the UK and Australia, showing that 62% and 41% of clients, respectively, would accept appointments with their FP for sexual health care aspects [54,55]. We previously showed in a large online focus group study that Belgian FPs are increasingly being confronted with PrEP in their practices [56]. Moreover, they showed to be willing to be more involved in aspects of PrEP care follow-up, provided that they can count on the support of experienced PrEP care providers [56]. Hence, we observe a convergence in attitudes from both providers and users towards supporting the idea of better engaging FPs in PrEP care. This could help to decrease practical barriers to care for some and thus make PrEP care more client-centred and affordable. Future research needs to focus on how collaborative care models can be effectively implemented to efficiently leverage and share the valuable PrEP expertise built in specialised HIV clinics with motivated primary care providers who currently lack experience. For example, collaborative care models have been found to be cost-efficient for a range of health conditions and associated with higher patient and provider satisfaction in the field of

mental health and chronic care [57,58]. Policy and practice must ensure that the appropriate conditions are installed to maximise the success of such care models, including implementing low-threshold communication and referral mechanisms between primary care and specialised services, and foresee an efficient coordination structure to ensure care continuity [59].

Lastly, our study also points towards a need to better tailor the offered PrEP care package to individual user needs. For instance, our results show that over half of PrEP users prefer counselling on mental well-being and "chemsex" to be part of PrEP follow-up. Yet, interviewees pointed towards a lack of provider-initiated discussions on these topics as a barrier to comprehensively address their needs. Investigating how PrEP care can be better integrated with related services (e.g. mental health and substance use services) is, therefore, needed. For example, studying the implementation of rapid needs assessment tools with referral options to specialised care, and investing in the development of tailored clinical care pathways, could help fill this gap [60]. Interestingly, about 75% of PrEP users in our study preferred receiving counselling on sexual risk reduction during PrEP care follow-up, but considerably fewer participants (i.e. about 50%) reported counselling in condom use should be part of this. This may partially be explained by their consideration that counselling on condom use does not impact their condom use that much, as we found in previous research among this study population[33]. While we did not explore this discrepancy between risk reduction and condom use counselling preference in-depth, this may suggest a need for a more comprehensive approach to discussing sexual health and STI prevention with PrEP users, going beyond condom use only, tailored to individuals' personal situations, values, motivations and existing STI prevention practices [33,61].

A limitation of this study is that we cannot exclude a self-selection bias, inherently linked to the use of web-based questionnaires and the chosen recruitment strategies. Therefore, our sample is not representative of all PrEP users in Belgium. However, on several socio-demographic characteristics (i.e. gender and sexual identity, age and nationality) our sample largely matches that of PrEP users reported in the national routine surveillance system [29]. Moreover, as we recruited only individuals already having access to PrEP care, we cannot generalise their needs and preferences towards other potential PrEP users. This could have led to overestimating satisfaction scores

and underreporting of barriers to care, as individuals for whom such barriers were too high to access or stay on PrEP at the time of the study likely did not participate. As this study was promoted by an institution also involved in the delivery of PrEP care, participants may have been more likely to report being satisfied with PrEP care, being a potentially more socially desired answer. During interviews, we mitigated this by having trained interviewers, who were not involved in respondents' PrEP care. Findings of this study will need to be complemented with insights from a provider perspective (e.g. on perceived required clinical practice norms for PrEP) to better understand how PrEP users' service delivery preferences can be met without jeopardising good quality of care, unwillingly contributing to negative health outcomes.

CONCLUSION

This mixed-methods study among PrEP users in Belgium found high satisfaction with care, explained by the ability to access regular HIV and STI testing, and the expertise and stigma-free environment of specialised HIV clinics. However, we also identified health system barriers that hinder the delivery of personalised and client-centred PrEP care, which may jeopardise access and care continuity. Furthermore, study participants also preferred, or were willing to, receive PrEP care through settings, formats or at frequencies other than the "standard" quarterly in-person visits in HIV clinics. These findings support the need for a more differentiated PrEP service delivery approach to better accommodate differing user needs and preferences while preserving essential care values for users. Feasible strategies for this may include fostering collaborations between specialised providers and primary care practitioners, such as FPs. More flexibility and choice for individual PrEP users, especially regarding clinic opening hours, might facilitate access to PrEP services and support sustained motivation of healthy individuals to keep (re-)engaging with this primary prevention service as long as their HIV risk continues.

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STATEMENTS AND DECLARATIONS

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CONFLICT OF INTEREST

MFSVDL served on advisory boards of GSK and Merck; fees were paid to his institution. TR served on advisory boards of GSK/ViiV; fees were paid to his institution. All other authors have no competing interests to declare that are relevant to the content of this article.

ETHICS APPROVAL

The research was conducted in accordance with the Declaration of Helsinki. The study received ethical approval through the Institutional Review Board of the Institute of Tropical Medicine, Antwerp (IRB 1380/20).

CONSENT TO PARTICIPATE

Eligible participants provided consent by agreeing to participate, after having been informed about the study and its procedures.

CONSENT FOR PUBLICATION

Not applicable

AVAILABILITY OF DATA AND MATERIALS

The datasets generated during and/or analysed during the current study are not publicly available, but are available upon reasonable request to the corresponding

author and if approved by the Institutional Review Board of the Institute of Tropical Medicine (Antwerp).

COMPLIANCE WITH ETHICAL STANDARDS

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Institutional Review Board of the Institute of Tropical Medicine, Antwerp (IRB 1380/20). Eligible participants provided informed consent by agreeing to participate, after having been informed about the study and its procedures.

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SUPPLEMENTARY MATERIAL

Supplementary table 1. Sociodemographic and PrEP care utilisation characteristics of interview participants (N=21); study on PrEP users' PrEP care experiences and preferences, Belgium, 2020-2022.

	Semi-structured interviews N=21
	n
Age in years, median [IQR]	46 [41-53]
Male sex at birth	21
Born in Belgium	18
Educational attainment°	
Secondary education or lower	2
Higher education	19
Occupational status°	
Employed	16
Unemployed	5
Other	0
Perceived financial status	
Living really comfortably on present income	2
Living comfortably on present income	8
Neither comfortably nor struggling on present income	8
Struggling or really struggling on present income	3
Prefer not to say	0
Sexually attracted to men	21
PrEP use – regimen over the past 3 months	
Daily use	10
Non-daily use	11
No use	0
Satisfaction with PrEP care*, median [IQR]	9 [8-9.5]
Settings visited for PrEP follow-up since start PrEP use	
HIV clinic-only	15
HIV clinic and FP	3
Other°	3
Frequency of PrEP follow-up visits since start PrEP use	
At least 3 monthly	8
4-6 monthly	8
Less than 6 monthly	2
Other	3
FP informed about PrEP use	
I discussed with my FP that I'm taking PrEP	12
My FP is aware of my PrEP use, but we did not discuss it	2
I don't know/I'm not aware that my FP knows I'm taking PrEP	4
My FP doesn't know that I'm taking PrEP	1
I do not have an FP	2

FP: family physician, FU1: follow-up 1, IQR: interquartile range, PrEP: pre-exposure prophylaxis

° *'Higher education' means college or university and includes higher education long type (i.e. more than 3 years) and short type (i.e. 3 years or less).*

$ *'unemployed' includes long-term sick/leave/medically retired, technical unemployed, retired, student, and unemployed. 'employed' includes employed full-time, employed part-time and self-employed.*

* *Scale 0-10, 10=very satisfied*

§ *'Other' includes combinations involving a community health centre and/or sourcing PrEP either informally (e.g. online) or through services across national borders (e.g. through public health services in the Netherlands).*

Supplementary table 2. Experienced barriers towards receiving PrEP care and associations of socio-demographics, PrEP use, PrEP care utilisation and satisfaction with experienced barriers; study on PrEP users' PrEP care experiences and preferences, Belgium, 2020-2022.

	Total N=315	Experienced barriers to care					
		Direct cost associated with PrEP care n (%*)		Visit frequency n (%*)		Duration of visit n (%*)	
	n (%)	Major/minor barrier	p-value§	Major/minor barrier	p-value§	Major/minor barrier	p-value§
Total	315 (100)	114 (36.2)	/	84 (26.7)	/	82 (26.0)	/
Socio-demographics							
Age group in years			**0.002**		0.465		**0.043**
<25	8 (2.5)	6 (75.0)		2 (25.0)		2 (25.0)	
25-34	73 (23.2)	35 (47.9)		23 (31.5)		26 (35.6)	
35-44	102 (32.4)	40 (39.2)		29 (28.4)		31 (30.4)	
45-54	87 (27.6)	21 (24.1)		17 (19.5)		15 (17.2)	
≥55	45 (14.3)	12 (26.7)		13 (28.9)		8 (17.8)	
Sex at birth			1.000		1.000		1.000
Male	313 (99.4)	113 (36.1)		84 (26.8)		81 (25.9)	
Female	2 (0.6)	1 (50.0)		0 (0)		1 (50.0)	
Born in Belgium			0.435		0.178		0.143
Yes	269 (85.4)	95 (35.3)		68 (25.3)		66 (24.5)	
No	46 (14.6)	19 (41.3)		16 (34.8)		16 (34.8)	
Educational attainment°			0.061		0.194		**0.037**
Secondary or lower	60 (19.0)	28 (46.7)		20 (33.3)		22 (36.7)	
Higher education	255 (81.0)	86 (33.7)		64 (25.1)		60 (23.5)	
Occupational status$			0.201		0.245		0.187
Employed	260 (82.5)	92 (35.4)		74 (28.5)		73 (28.1)	
Unemployed	51 (16.2)	22 (43.1)		10 (19.6)		9 (17.6)	
Other	4 (1.3)	0 (0)		0 (0)		0 (0)	
Financial comfort			**<0.001**		0.683		0.936
Very comfortable or comfortable on present income	214 (67.9)	62 (29.0)		59 (27.6)		56 (26.2)	
Not comfortable or struggling on present income	101 (32.1)	52 (51.5)		25 (24.8)		26 (25.7)	

PrEP use						
PrEP use – regimen over the past 3 months			0.581	0.110		0.395
Daily use	151 (47.9)	57 (37.7)		34 (22.5)	36 (23.8)	
Non-daily or no use	164 (52.1)	57 (34.8)		50 (30.5)	46 (28.0)	
PrEP care utilisation						
Settings visited for PrEP follow-up since start PrEP use			0.177	0.710		0.453
HIV clinic -only	275 (87.3)	96 (34.9)		75 (27.3)	70 (25.5)	
HIV clinic and FP	22 (7.0)	12 (54.5)		4 (18.2)	5 (22.7)	
Other[£]	18 (5.7)	6 (33.3)		5 (27.8)	7 (38.9)	
Frequency of PrEP follow-up visits since start PrEP use			0.229	**0.033**		0.490
At least 3 monthly	221 (70.2)	81 (36.7)		51 (23.1)	53 (24.0)	
4-6 monthly	78 (24.8)	27 (34.6)		25 (32.1)	23 (29.5)	
Less than 6 monthly	8 (2.5)	1 (12.5)		3 (37.5)	3 (37.5)	
Other	8 (2.5)	5 (62.5)		5 (62.5)	3 (37.5)	
PrEP care satisfaction[†]			**0.003**	**<0.001**		**<0.001**
>7/10	252 (80.0)	81 (32.1)		51 (20.2)	51 (20.2)	
≤7/10	63 (20.0)	33 (52.4)		33 (52.4)	31 (49.2)	

FP: family physician, PrEP: pre-exposure prophylaxis, STI: sexually transmitted infection, values in bold indicate p-values < 0.05.
** % of row total*
§ P-value of chi-square test or Fisher's exact test
° 'Higher education' means college or university and includes higher education long type (i.e. more than 3 years) and short type (i.e. 3 years or less).
$ 'unemployed' includes long-term sick/leave/medically retired, technical unemployed, retired, student, and unemployed. 'employed' includes employed full-time, employed part-time and self-employed.
£ 'Other' includes combinations involving a community health centre and/or sourcing PrEP either informally (e.g. online) or through services across national borders (e.g. through public health services in the Netherlands).
† Scale 0-10, 10=very satisfied

	Total N=315 n (%)	Experienced barriers to care (ctd.)					
		Difficulty taking off from work n (%*)		Clinic location is too far n (%*)		Feeling unable to talk about all their problems with providers n (%*)	
		Major/minor barrier	p-value§	Major/minor barrier	p-value§	Major/minor barrier	p-value§
Total	315 (100)	143 (45.4)	/	75 (23.8)	/	53 (16.8)	/
Socio-demographics							
Age group in years			**0.003**		**0.013**		0.057
<25	8 (2.5)	7 (87.5)		5 (62.5)		2 (25.0)	
25-34	73 (23.2)	35 (47.9)		17 (23.3)		17 (23.3)	
35-44	102 (32.4)	55 (53.9)		28 (27.5)		20 (19.6)	
45-54	87 (27.6)	28 (32.2)		12 (13.8)		7 (8.0)	
≥55	45 (14.3)	18 (40.0)		13 (28.9)		7 (15.6)	
Sex at birth			1.000		1.000		**0.027**
Male	313 (99.4)	142 (45.4)		75 (24.0)		51 (16.3)	
Female	2 (0.6)	1 (50.0)		0 (0)		2 (100.0)	
Born in Belgium			0.187		0.443		0.752
Yes	269 (85.4)	118 (43.9)		62 (23.0)		46 (17.1)	
No	46 (14.6)	25 (54.3)		13 (28.3)		7 (15.2)	
Educational attainment°			0.826		0.361		0.265
Secondary or lower	60 (19.0)	28 (46.7)		17 (28.3)		13 (21.7)	
Higher education	255 (81.0)	115 (45.1)		58 (22.7)		40 (15.7)	
Occupational status$			0.223		0.151		0.785
Employed	260 (82.5)	119 (45.8)		58 (22.3)		43 (16.5)	
Unemployed	51 (16.2)	24 (47.1)		17 (33.3)		10 (19.6)	
Other	4 (1.3)	0 (0.0)		0 (0.0)		0 (0.0)	
Financial comfort			0.971		0.403		0.332
Very comfortable or comfortable on present income	214 (67.9)	97 (45.3)		48 (22.4)		33 (15.4)	
Not comfortable or struggling on present income	101 (32.1)	46 (45.5)		27 (26.7)		20 (19.8)	
PrEP use							
PrEP use in last 3 months			0.901		0.233		0.631
Daily use	151 (47.9)	68 (45.0)		31 (20.5)		27 (17.9)	

Non-daily or no use	164 (52.1)	75 (45.7)		44 (26.8)	26 (15.9)	
PrEP care utilisation						
Settings visited for PrEP follow-up since start PrEP use			0.903		0.220	0.741
HIV clinic -only	275 (87.3)	126 (45.8)		68 (24.7)	45 (16.4)	
HIV clinic and FP	22 (7.0)	9 (40.9)		2 (9.1)	4 (18.2)	
Other[£]	18 (5.7)	8 (44.4)		5 (27.8)	4 (22.2)	
Frequency of PrEP follow-up visits since start PrEP use			0.131		**0.015**	0.571
At least 3 monthly	221 (70.2)	95 (43.0)		44 (19.9)	34 (15.4)	
4-6 monthly	78 (24.8)	40 (51.3)		24 (30.8)	16 (20.5)	
Less than 6 monthly	8 (2.5)	2 (25.0)		2 (25.0)	1 (12.5)	
Other	8 (2.5)	6 (75.0)		5 (62.5)	2 (25.0)	
PrEP care satisfaction[†]			**0.003**		**<0.001**	**<0.001**
>7/10	252 (80.0)	104 (41.3)		49 (19.4)	29 (11.5)	
≤7/10	63 (20.0)	39 (61.9)		26 (41.3)	24 (38.1)	

FP: family physician, PrEP: pre-exposure prophylaxis, STI: sexually transmitted infection, values in bold indicate p-values < 0.05.

** % of row total*

[§] P-value of chi-square test or Fisher's exact test

[°] 'Higher education' means college or university and includes higher education long type (i.e. more than 3 years) and short type (i.e. 3 years or less).

[$] 'unemployed' includes long-term sick/leave/medically retired, technical unemployed, retired, student, and unemployed. 'employed' includes employed full-time, employed part-time and self-employed.

[£] 'Other' includes combinations involving a community health centre and/or sourcing PrEP either informally (e.g. online) or through services across national borders (e.g. through public health services in the Netherlands).

[†] Scale 0-10, 10=very satisfied

Chapter 5

General discussion and conclusion

Individually-randomised controlled trials confirmed that PrEP significantly reduces the risk of acquiring HIV. Translating this evidence of efficacy into population-level effectiveness continues to be challenging as uptake and adherence remain inadequate. In this thesis, I focused on gaining insights into how users engage with PrEP, to better understand factors that can influence the success of PrEP implementation. We described the sociodemographic characteristics of PrEP users, PrEP dispensing practices, uptake of testing for three bacterial STIs (i.e. gonorrhoea, chlamydia and syphilis) and HIV, and HIV and STI incidence among PrEP users to provide insights that can enable optimising the roll-out of PrEP in Belgium **(Chapter 2)**. Next, we described trends in PrEP and condom use and related sexual behaviours, together with attitudes towards condoms as an STI prevention tool to understand PrEP users' sexual behaviour **(Chapter 3)**. Finally, we elicited experiences with, and preferences for, PrEP service delivery among PrEP users, to capture insights into users' views on how to deliver PrEP care **(Chapter 4)**.

In this chapter, the main findings of this thesis and their implications are discussed, followed by future directions for prevention and research in the field of HIV and STI prevention.

5.1 POTENTIAL IMPLICATIONS FOR PrEP IMPLEMENTATION

In subsequent paragraphs, I present potential implications of the main results. These implications are primarily applicable to the Belgian context, considering the focus of this thesis. However, they might also prove of interest to other countries with similar target populations and service delivery characteristics, as such, in particular other Western European countries.

5.1.1 Addressing disparities and expanding PrEP uptake

In **Chapter 2**, we showed that, between 2017 and 2019, nearly 4600 individuals started using PrEP in Belgium. Furthermore, we learned that PrEP users in the HIV clinic in Antwerp were almost exclusively MSM whose self-reported sexual behaviours increased their vulnerability to and risk of HIV infection (**Chapter 3.1**). These results suggest that the national PrEP programme is successfully reaching individuals who are

likely to benefit from using PrEP. Yet, compared to the Belgian HIV epidemiological trends, our results highlight areas where uptake can be improved.(1)
Current PrEP implementation strategies are mainly reaching individuals who are employed and highly educated. Only about one in ten individuals in the national PrEP cohort was entitled to an increased healthcare allowance (i.e. an indicator of lower income) while this is about one in five people in the general national population **(Chapter 2 and 3.1)**. This suggests that PrEP is not financially accessible to those who are socio-economically vulnerable or that they are less likely to be aware of PrEP. This aligns with the inverse equity hypothesis, which states that when a new innovation is introduced, it is typically the wealthier and more educated individuals who benefit first, leading to increased inequalities before more widespread access is achieved.(2) As such, there is a need to address this disparity in health equity.

Despite the majority of new users gaining access to PrEP annually since 2017 being MSM born in Belgium **(Chapter 2)**, the number of Belgian MSM who could benefit from using PrEP reached may still be insufficient. Belgian MSM with multiple sex partners remain to be targeted, as a phylogenetic study suggests that the Belgian epidemic is primarily driven by these sexual networks.(3) In addition, in 2021, there was an increase in the number of diagnoses of acute HIV infections among Belgian MSM, although the trend over several years remains downward overall.(1) This could be indicative of an increase in HIV transmission, however, a potential after-effect from COVID-19 (i.e. reduced HIV testing in 2020) and its implications cannot be excluded.

Our results revealed that populations, such as MSM who were not born in Belgium, are underrepresented, despite being vulnerable to HIV acquisition. Belgian MSM accounted for almost half of new HIV diagnoses among MSM in 2021, while MSM from other European countries accounted for 21% and from Latin America for 18% of new diagnoses.(1) Some of these individuals might already have been infected prior to arriving in Belgium, nevertheless MSM with a migrant background might be an important population to reach with PrEP. Concurrently, heterosexual individuals vulnerable to HIV acquisition, such as individuals from the sub-Saharan diaspora communities were underserved **(Chapter 2 and 3.1)**, yet this population accounted for 45% of HIV infections confirmed as heterosexual transmissions in 2021.(1)

Increasing awareness and ensuring a positive attitude towards PrEP use among individuals for whom PrEP use is indicated and desired could be an important approach to increase PrEP uptake.(4) PrEP promotion campaigns and research initiatives have often been targeted towards MSM only.(5,6) Additionally, PrEP reimbursement criteria have a particular focus on MSM.(7) This likely contributed to PrEP being predominantly used by MSM, as shown in this thesis. Such a narrow focus might limit the awareness of PrEP among the general population, lead to the misconception that PrEP is only appropriate for MSM and even stigmatise MSM.(8) Optimising the communication around PrEP could, therefore, help to increase awareness and motivate individuals other than MSM to adopt this HIV prevention strategy. PrEP use should be normalised and promoted more widely among the general population. Framing PrEP in a more inclusive way could lead to enhanced public and social support for PrEP use.(9,10) Feeling supported by friends and family has shown to positively influence PrEP uptake and continuation.(11) A similar strategy was adopted by the Centers for Disease Control & Prevention 2021 PrEP guidelines, which include a recommendation to inform all sexually active adults and adolescents about PrEP.(12) Gain-framing of PrEP is another strategy to increase awareness and encourage potential users to use PrEP. Gain-framed messaging involves focusing on the protection and benefits of PrEP, including providing additional safety and improving sexual health and wellbeing.(13,14) Inclusive and gain-framed messaging could involve the use of mass media campaigns using modern media strategies (e.g. social media) and showcasing PrEP users as diverse with regards to gender, ethnicity, education, and other sociodemographic characteristics.(8,15) Involving all relevant stakeholders in the design of communication strategies and promotion or education campaigns will be pivotal for success.(16)

To verify PrEP eligibility, PrEP reimbursement criteria are based on HIV risk, which could prevent PrEP uptake in two ways: some individuals may not identify with these criteria, e.g. using psychoactive substances during sexual activity; not all individuals might feel comfortable in disclosing private and sensitive information about their sexual lives and thus might be classified as ineligible for PrEP. Hence, eligibility criteria should not be restrictive if an individual feels they could benefit from PrEP.

5.1.2 The importance of effective use and choice

When studying the patterns of PrEP use, we identified more diverse categories of use, going beyond daily and on-demand use to daily use, short-period use (shorter than a week), and many variants in between. Switching between identified categories and stopping and re-starting PrEP were also observed **(Chapter 3.1 and 3.2)**. We found that PrEP use was associated with sexual behaviour, suggesting that MSM are able to adapt their PrEP use to their evolving HIV risk. As such, instead of addressing PrEP from a two-regimen dichotomy (i.e. daily vs. on-demand use), the focus should be on supporting effective PrEP use during periods of potential exposure to HIV. Effectively starting, stopping and re-initiating PrEP will be essential to reach optimal protection.(17) In **Chapter 3.4**, we revealed that knowledge on how to start and stop PrEP among PrEP users is sub-optimal. One-third of participants, assigned male at birth, failed to correctly answer questions on effectively starting and stopping PrEP. This suggests that PrEP users need to be better informed about how to start and stop use, irrespective of dosing regimen.(18)

In **Chapter 3.2**, we demonstrated that, although condom use was relatively low among PrEP users, their behaviours differed with regards to when they used and combined PrEP and condom use. Patterns of use differed over time and by the type of partner with whom men reported anal sex. Anal sex acts with casual or anonymous sex partners that were not covered by condoms or PrEP were rarely reported, and mostly occurred with steady sexual partners. This suggests that users are well protected against HIV during anal sex with casual and anonymous partners, but they are probably more at risk from their steady sexual partner – unless they can be certain these steady partners are monogamous or are equally using PrEP and/or condoms with other partners. Also, it suggests that MSM use HIV prevention measures either simultaneously or choose one depending on the specific context, and according to their preferences. Having the option to choose between HIV prevention strategies might increase the overall population level protection offered by combination prevention methods, also referred to as 'net prevention coverage'.(19) Such an increase in net prevention coverage has been demonstrated among MSM in Australia, and likely contributed to declines in HIV infections, despite a reduction in condom use.(19) Offering more choice in how PrEP can be used, beyond oral PrEP, could enhance the acceptability of the prevention

method, thereby increasing uptake, continuation and effective use. Several new biomedical prevention products are becoming available (e.g. dapivirine vaginal rings for women and long-acting injectable cabotegravir) and more are in the pipeline (e.g. other long-acting injectable antiretrovirals and implants). As an individual's exposure to HIV changes over time so may their HIV prevention needs. Available prevention options should thus be tailored to each individual's circumstances and vulnerability to HIV, whereby timing and frequency of use being important elements in choosing the most appropriate prevention method.(20) For example, injectable PrEP might be more appropriate for men with frequent sexual contacts, and prefer not to take daily pills and/or who have difficulties with adhering to oral PrEP.

5.1.3 A call for differentiated service delivery models

In **Chapter 4**, we showed that most PrEP users were satisfied with the PrEP care they received in specialised HIV clinics. Yet, the care experiences were also influenced by service delivery barriers, including limited provider-client interaction (e.g. due to high staff turnover), difficulties incorporating follow-up visits into private and professional life and out-of-pockets costs. Furthermore, our results highlight differing user preferences in terms of settings (e.g. specialised HIV clinics vs. community based organisations), providers (e.g. specialised HIV clinician vs. family physician), formats (e.g. remote vs. in-person) and frequency of follow-up visits (e.g. needs-based vs. quarterly) to receive PrEP care. To accommodate these diverse needs and preferences, and to reduce the burden of a growing population of PrEP users on HIV clinics, it will be necessary to move from a centralised service delivery model towards differentiated service delivery (DSD) models. DSD is a client-centred approach that has been widely promoted in HIV care, and that is now increasingly recognised as a way to make PrEP services more acceptable and accessible.(18,21)

Our findings provide guidance for policy and programmers on which DSD model to prioritise. A potential strategy would be to engage family physicians in PrEP follow-up, considering PrEP users' willingness to involve family physicians **(Chapter 4)**. By offering services through family physicians, it is likely that practical barriers to care might decrease (e.g. improved proximity), while client-centredness and affordability will increase. This could lead to fewer users discontinuing PrEP early **(Chapter 2)**. Providing

more flexibility (e.g. opening hours) and choice might additionally facilitate access to PrEP services. In terms of service package, our findings revealed that PrEP users highly valued regular STI/HIV testing **(Chapter 4)**, which confirms the need for integration of STI prevention services in PrEP care.(18) Counselling on mental health issues and 'chemsex' were other services deemed necessary as part of holistic PrEP care services **(Chapter 4)**. Providing a comprehensive, yet tailored PrEP care package might support longer-term engagement with care.

5.1.4 Moving beyond consistent condom use counselling for STI prevention

In **Chapter 2**, we demonstrated a high incidence of curable bacterial STIs (i.e. syphilis, gonorrhoea and chlamydia) among individuals who were dispensed PrEP at least once between 2017 and 2019. Similarly, in **Chapter 3.3**, one in three study participants reported having been diagnosed with at least one STI in the previous six months. These results indicate that curable bacterial STIs are a public health concern among PrEP users in Belgium. While condom use remains the main strategy available for STI prevention, we showed in **Chapter 3.2 and 3.3** that most PrEP users either reported never using condoms or occasionally using condoms when using PrEP during anal sex with casual or anonymous partners. Although PrEP users acknowledged condoms as a valuable STI prevention option, the preference to use condoms as a means to protect against STIs resulted from balancing perceived severity of, susceptibility to, and concerns towards STIs against sexual pleasure of condomless sex, protective benefits of condoms, and perceived social norms and practices.

Interestingly, about 75% of PrEP users indicated counselling on sexual risk reduction during PrEP care follow-up as a preferred care component to be included in PrEP care services, while only half of PrEP users indicated condom counselling **(Chapter 4)**. This may be explained by the fact that PrEP users also reported using differing STI prevention strategies besides condoms (e.g. asking whether a sexual partner had an STI or not) and because PrEP users felt that condom counselling does not impact their condom use **(Chapter 3.3)**. These results emphasise that healthcare providers should take the opportunity during PrEP care visits to discuss sexual health promotion strategies beyond PrEP. It might also be recommended to move beyond promoting consistent and concurrent condom use among PrEP users. A contextual, strategic

condom use counselling could be advised whereby type of sexual partner, positioning, type of sexual act, sexual network, values of PrEP users towards STI prevention, and other STI prevention strategies (e.g. doxycycline prophylaxis) used are taken into account. Such counselling should be done in a non-judgemental and empathetic manner, using an interactive approach tailored to the individual situation, e.g. integrated next step counselling or motivational interviewing.(22,23)

5.2 FUTURE DIRECTIONS FOR PREVENTION AND RESEARCH

5.2.1 Defining and refining indicators for monitoring of PrEP use

Routine monitoring of PrEP programmes is imperative to measure their performance and effectiveness.(24) However, as shown in this thesis, PrEP is being used varyingly, according to users' needs and preferences, making monitoring patterns of PrEP use challenging. Measuring effective use of PrEP requires detailed individual-level data on the individual's exposures to HIV, objective measures of PrEP adherence (i.e. drug level concentrations) and the combination with other HIV prevention methods. As such, stopping PrEP can still be considered effective as individuals may do so for various reasons (e.g. no sexual contacts or using condoms consistently instead of PrEP during sexual contacts). The implementation of new PrEP modalities such as long-acting injectable PrEP will further complicate monitoring as individuals could switch between PrEP modalities. Correspondingly, the implementation of multiple delivery model approaches increases the risk of double-counting individuals when they visit multiple settings for PrEP. Ensuring the feasibility of operationalising indicators on patterns of PrEP use, without overburdening healthcare providers with data collection, requires the formulation of appropriate proxy measures.(24,25) In **Chapter 2,** we considered PrEP dispensing events as PrEP use by using claims data which included unique identifiers to track PrEP users. HIV seroconversions within one year of last PrEP dispensing were considered as an indicator of ineffective use.

Since PrEP is increasingly being implemented in national HIV prevention programmes, examples from countries and studies investigating and implementing new monitoring and evaluation indicators are emerging.(25–29) For example, newly proposed indicators (e.g. 'PrEP dispensed' and 'PrEP visits') by the monitoring and evaluation

working group of USAID are being pilot tested in MOSAIC (i.e. Maximizing Options to Advance Informed Choice for HIV Prevention) demonstration projects.(27) 'PrEP coverage' and 'PrEP continuation' were another set of indicators proposed by the European Centre for Disease Prevention and Control.(25,30) Given the limited literature available regarding PrEP monitoring and evaluation, more investments and evidence will be required to define and refine indicator definitions while ensuring easy and reproducible longitudinal data collection, which allows sufficient level of disaggregation.

5.2.2 Preparing for the introduction of new PrEP modalities

One recent and promising addition to the biomedical HIV prevention options is a long-acting injectable integrase strand-transfer inhibitor called cabotegravir (CAB-LA). CAB-LA entails intramuscular injections of 600mg cabotegravir. The first two injections are administered four weeks apart, and are followed by an injection every eight weeks thereafter. In 2020, the HPTN 083 and 084 randomised clinical trials found that the use of CAB-LA is efficacious and resulted in a combined 79% reduction in risk of HIV acquisition among study participants receiving CAB-LA compared with participants receiving daily oral PrEP (TDF/FTC).(31–33) HPTN 083 enrolled cisgender MSM and transgender women, while HPTN 084 enrolled cisgender women. In December 2021, the United States Food and Drug Administration approved CAB-LA for HIV prevention in the USA.(34) In July 2022, WHO recommended CAB-LA as an additional prevention option.(35) For the European region, the European Medicines Agency approved ViiV Healthcare's (i.e. manufacturer of CAB-LA) marketing authorisation application in July 2023.(36) To date, CAB-LA has been granted marketing authorisation in various countries, including the United States, Australia, Zimbabwe, South-Africa, and Malawi, and is under review in other countries.(37)

For CAB-LA to transform from an additional biomedical prevention option to a real choice for potential users, several recognised impediments will need to be addressed.(38,39) Lessons can be learned from the introduction of oral PrEP as several barriers at individual, interpersonal and structural level limiting oral PrEP uptake and prevention effective use, may similarly impact CAB-LA.(15,38) An example could be, as suggested in this thesis, the disparities in uptake among sub-populations which could

be reduced by more inclusive, gain-framed communication and by improving accessibility through differentiated delivery models. Nevertheless, particular implementation concerns related to CAB-LA were raised during the clinical trials phase, including service delivery organisation and affordability of the new PrEP modality.

Compared to oral PrEP, CAB-LA requires more frequent in-person visits with trained healthcare professionals to administer the 2-monthly injections, to conduct more specialised HIV testing for the earlier detection of HIV seroconversions (i.e. nucleic acid technologies testing), and for the prevention of drug resistance in case of HIV infection during suboptimal drug concentrations (e.g. infection during tail phase, i.e. the period starting eight weeks after the last injection during which there are gradually declining drug concentrations over time).(35,40,41) This will impact how service delivery could be organised. Reports from in-depth interviews with PrEP providers globally showed that most providers felt that CAB-LA would lead to a re-medicalisation of PrEP services into clinical settings.(42) The availability of DSD models for oral PrEP, responsive to the needs and preferences of users, may therefore be less feasible for CAB-LA. Hence, implementation research will be required to investigate the feasibility and effectiveness of providing CAB-LA in various settings. Additionally, generating evidence on alternative injection schedules and anatomic sites for injections, HIV testing algorithms, and safety concerns will be needed to support differentiated service delivery and scale-up.(35,43) Further research will be needed to evaluate if CAB-LA can indeed increase the net prevention coverage.

The potential of CAB-LA to impact the HIV epidemic might be limited by its cost. At present, the US price of one injection is set at $ US 3755.50 or an annual cost of about $ US 22 000.(44) The annual out-of-pocket cost for TDF/FTC in Belgium, when eligible for reimbursement through healthcare insurance, is about 60 euros, considering daily use. While ViiV Healthcare enables, by signing the Medicine Patents Pools, the development of generic versions of CAB-LA in 90 countries in the global South, it does not ensure injectable PrEP's affordability globally. With oral PrEP being highly effective, safe, and available at a significantly lower cost, it has been questioned how much a society or public health ministry should be willing to pay for the additional clinical benefits of CAB-LA.(45) To leverage the purchasing power to secure lower prices, the Belgian

government should engage in European-level collaborations to collectively negotiate drug prices with pharmaceutical companies.

5.2.3 Enabling the implementation of differentiated service delivery models

Comparable to the Belgian PrEP delivery model, specialised infectious diseases clinics are the most frequently reported delivery setting in other European countries.(46) In order to encourage and ensure the shift towards DSD, more evidence is needed on which delivery models will be most acceptable, feasible and cost-effective for whom. It will be important to conduct such context-specific research on needs and preferences across multiple geographical regions and populations (e.g. current and potential users with differing sociodemographic backgrounds and sexual behaviours) and to consider the newly available PrEP modalities with their own implementation particularities (e.g. CAB-LA requires 2-monthly follow-up visits). Furthermore, the introduction of DSD models would require an enabling legal framework and environment for healthcare providers to collaborate. For example, initially only specialised hospital practitioners could initiate a person on PrEP in France. Since June 2021, authorities have extended it to all prescribing physicians in order to facilitate access to diverse groups of beneficiaries.(47) To date, family physicians in Belgium, do not have this legal authority.

5.2.4 Tailored and targeted STI screening strategies

Integration of STI prevention and care into PrEP care services offers important opportunities for STI prevention and control by leveraging resources and synergising interventions.(48) Currently, international guidelines recommend a 3-monthly, 3-site (i.e. urethra, pharynx and anorectum) screening intensity for bacterial STIs for MSM taking PrEP.(49) Our findings indicated that PrEP users highly value the opportunity to receive such regular STI testing **(Chapter 4)**. However, some of our results may suggest the need for a more tailored and targeted testing and prevention approach as proposed in the literature.(50) The recommended screening guidelines for entire populations such as all MSM using PrEP may lead to greater testing coverage and frequency, but, it may not be sustainable among a growing population of PrEP users and may negatively impact cost and cost-effectiveness of sexual health services.(50) In Belgium, and in other European countries, STI laboratory tests are not always (fully) reimbursed, which

requires out-of-pocket costs for PrEP users.(46) Costs were often reported as burdensome by the PrEP users in our studies **(Chapter 4)**. Socio-economically disadvantaged (potential) PrEP users may be discouraged to seek care, despite being at risk of HIV acquisition. Additionally, some PrEP users suggested to align the frequency of PrEP follow-up visits, and as such STI testing, with their PrEP use and associated sexual behaviour, e.g. STI testing when there have been sexual contacts since previous STI testing **(Chapter 4)**.

Moreover, evidence regarding the effectiveness of the current STI screening strategy on STI prevalence is mixed.(51–53) High frequency screening can also lead to the diagnosis of many asymptomatic STIs, which might have otherwise self-cleared. This can result in higher antibiotic consumption, increasing the risk of developing antimicrobial resistance.(54,55) The bacterial STI re-infection rates reported in **Chapter 2**, might be indicative of users at higher risk for STI acquisition and transmission.(56) A targeted screening approach for individuals at higher risk for curable STI acquisition may decrease testing frequencies and thereby reduce antibiotic consumption.(53) Future research should investigate how STI testing frequency and strategies can be optimised.

5.2.5 Investment in innovative curable bacterial STI prevention strategies

This thesis reported on the perceived disadvantages related to condom use to prevent curable bacterial STIs **(Chapter 3.3)**, including hindering pleasurable sex, impracticality and inadequacy to protect during all types of sexual techniques; e.g. condoms are not frequently used during oral sex among MSM. This suggests the need to invest in the development of innovative STI prevention interventions to address the burden of curable STIs.(21)

One such strategy, which is subject to ongoing research, is the use of doxycycline prophylaxis to prevent bacterial STI acquisition.(57) Results from a recent open-label RCT in the United States among MSM and transgender women, taking 200 mg doxycycline within 72 hours of condomless sex, showed a two-thirds reduction in the combined incidence of syphilis, gonorrhoea, and chlamydia among those taking doxycycline post-exposure prophylaxis (doxy-PEP) compared to no intervention.(58)

Preliminary results from the DOXYVAC RCT in France among MSM taking PrEP, similarly taking 200 mg doxycycline within 72 hours of condomless sex, demonstrated an efficacy of 79% against syphilis, 89% against chlamydia, and 51% against gonorrhoea in the doxy-PEP arm compared to the no intervention arm.(59) The results from abovementioned and recently completed doxy-PEP studies, together with reports from PrEP-using MSM who are informally using antibiotics to prevent STI acquisition, urge international health organisations to formulate recommendations aligned with the latest evidence on the use of doxy-PEP.(57,60–62) Hence, the Centers for Disease Control and Prevention issued proposed guidelines for using doxy-PEP to prevent bacterial STIs.(63) These guidelines recommend to take a single 200 mg dose of oral doxycycline within 72 hours after a sexual contact. The recommendation only applies to gay, bisexual and other MSM and transgender women who have had gonorrhoea, chlamydia or syphilis at least once during the past year as there is insufficient evidence among other populations. Yet, additional research is needed to ascertain the net benefits and risks of doxy-PEP as an STI prevention strategy on population level, including the long-term impact of doxy-PEP on antimicrobial resistance and the microbiome.(64,65) Complementary, future studies should investigate the implementation of doxy-PEP into PrEP care services and more broadly into comprehensive sexual healthcare packages.

5.3 CONCLUSION

Enhancing the success of the Belgian PrEP programmes in preventing new HIV infections will require a multifaceted approach along the PrEP cascade. Larger impact will be achieved by increasing the number of individuals who could benefit from PrEP and by diversifying the populations reached. Concurrently, effective PrEP use and engagement with sexual health care should be optimised, whereby PrEP is offered as part of a comprehensive sexual healthcare package. This package should be easily accessible, tailored to the individual and enable informed HIV and STI prevention choices. Well-formulated programmatic indicators will be essential to guide programmatic changes and improve long-term outcomes of PrEP. In addition, applying lessons learned from oral PrEP to the newly available HIV and STI prevention options will enable us to accelerate progress towards reducing annual HIV infections to fewer than 370 000 worldwide by 2025 and ensure that 95% of people at risk for HIV have access to HIV prevention options.

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Appendices

Summary

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Summary

Oral HIV pre-exposure prophylaxis (PrEP) in Belgium: understanding PrEP users' behaviours, attitudes and care needs

Over the past decade, the HIV prevention landscape has evolved substantially with the advent of oral HIV PrEP. Although the biomedical tool represents a promising development for primary prevention, its full potential in ending the HIV epidemic has not yet been realised. To understand how PrEP implementation can be optimised, it is essential to explore behaviours, attitudes, and care needs of those who can benefit from this prevention method. Therefore, in this thesis, we aimed to explore the PrEP user's perspective in Belgium. We provided a more nuanced understanding of who is using PrEP, how they use PrEP, and their experiences and preferences regarding PrEP care delivery. In parallel, we aimed to explore condom use and attitudes towards sexually transmitted infection (STI) prevention among PrEP users.

General introduction

In **Chapter 1**, we described the global HIV epidemic and how HIV affects men who have sex with men (MSM). We summarised the advances and challenges in HIV prevention over time, with a focus on MSM. We described the advent of PrEP, gave an overview of how randomised controlled trials demonstrated the efficacy and safety of PrEP, and how demonstration and implementation projects demonstrated its feasibility and acceptability. We elaborated on the roll-out of PrEP in practice, demonstrating the effectiveness at population-level and the challenges related to PrEP uptake, use, and available delivery models. We highlighted the divergent HIV and STI trends, showing an increase in curable bacterial STIs and a decrease in HIV infections. We described the HIV and STI epidemics in Belgium and how PrEP has been implemented there since 2015. We introduced the aim and objectives, and the outline of this thesis. Finally, we gave an overview of the methods and data sources used.

The roll-out of PrEP in Belgium

By analysing routinely collected Belgian social health insurance claims data, we provided a nationwide and comprehensive longitudinal overview of all PrEP users with social health insurance in **Chapter 2**. We found that 4559 individuals were dispensed

PrEP at least once between June 2017 and December 2019. When assessing the PrEP dispensing practices, we demonstrated a high proportion of early PrEP discontinuation, as about one-fifth of PrEP users had only one PrEP dispensing event in the first six months of PrEP use. Early discontinuation of PrEP occurred more often among users who were younger, unemployed, or covered by an increased healthcare allowance (i.e. individuals with lower incomes). Twelve individuals acquired HIV, giving an estimated incidence rate of 0.21 per 100 person-years among individuals initiating PrEP. Their individual PrEP use trajectories demonstrated that seroconversions either occurred prior to or around the time of PrEP initiation, or more than seven months after a last PrEP dispensing event, suggesting missed HIV prevention opportunities within the PrEP programme. In addition, we reported a high incidence of bacterial STIs (i.e. gonorrhoea, chlamydia and syphilis). These results suggest the need to enhance PrEP (re-)initiation for individuals vulnerable to HIV acquisition together with effective use counselling to ensure optimal PrEP programme implementation. Additionally, reducing STI acquisition and transmission among PrEP users will require tailored STI testing and prevention interventions, integrated into PrEP care.

PrEP users' HIV prevention and sexual behaviours and attitudes towards condoms and STIs

Chapter 3 reports on four studies, in which we analysed PrEP users' patterns of PrEP and condom use, sexual behaviour with steady, casual and/or anonymous partners, and attitudes towards STIs and condoms.

In **Subchapter 3.1,** we assessed changes in the sociodemographic and sexual behaviour profile of individuals initiating PrEP at a large HIV centre in Belgium between June 2017 and March 2020. We described the probabilities of switching between daily and on-demand PrEP, and of interrupting PrEP. Additionally, we described dynamics of PrEP follow-up over time. This was a cohort analysis of longitudinally collected clinical record and questionnaire data. The majority of PrEP users were men and MSM, with a median age of 37 years; they were mostly born in Belgium and highly educated. About three-quarters of PrEP users remained in care after one year, with a median time of three months between PrEP follow-up visits. Early PrEP adopters reported more HIV risk behaviours as compared with PrEP users starting more than a year after PrEP was introduced in Belgium (e.g. having a higher number of sexual partners, more likely to

engage in paid sex or sex under influence of drugs). The reported PrEP regimen (i.e. daily or on-demand) remained relatively steady over time. Nevertheless, switches between PrEP regimens and (temporary) interruptions in follow-up and PrEP use occurred.

In **Subchapter 3.2,** we investigated patterns of PrEP use among PrEP users participating in a web-based longitudinal study between September 2020 and January 2022. We examined sociodemographic and sexual behaviours associated with the defined categories of use and described PrEP and concurrent condom use by partner type over time. We showed that distinct categories of PrEP use exist, going beyond the daily and on-demand dichotomy. High proportions of users reported using PrEP in a consistent manner over time, though we also observed switches between categories of use. We demonstrated the association between sexual behaviours and how PrEP is used as daily users reported more casual and anonymous sex partners and a higher frequency of anal sex with these partners compared to less frequent PrEP users. While reported condom use was low, sexual acts with casual or anonymous sex partners neither protected by condoms nor by PrEP were rarely reported; such unprotected acts were more frequent during sex with steady partners.

In **Subchapter 3.3,** we explored PrEP users' attitudes towards STIs and condoms and how these attitudes influence their condom use with non-steady partners as a method to prevent STIs. Using a mixed-methods study design, we triangulated data from in-depth interviews with data collected during the web-based longitudinal study described above. We demonstrated different concerns towards STIs and likewise variation in motivation and willingness to use a condom to prevent STIs. A minority of web-based study participants indicated consistently using condom and PrEP concurrently. For other PrEP users, condoms remained a valuable STI prevention option depending on the contextual circumstances (e.g. type of partner, venue). The decision to use condoms to prevent STIs resulted from balancing perceived severity of, susceptibility to, and concerns towards STIs against sexual pleasure, protective benefits of condoms and perceived social norms and practices.

In the last part of Chapter 3 **(Subchapter 3.4),** we assessed self-perceived and actual knowledge of effectively starting and stopping oral PrEP. In addition, we identified

factors associated with incorrect start-and-stop knowledge. Among 206 participants assigned male at birth and who completed the web-based longitudinal study, one-third failed to correctly answer questions on effectively starting and stopping PrEP, whereas the majority perceived their start-and-stop knowledge as 'very good'. Using PrEP daily was associated with incorrect start-and-stop knowledge.

The findings from the studies included in Chapter 3 indicated that PrEP users were able to adapt their PrEP use to meet their needs. However, the disparity between self-perceived and actual start-and-stop knowledge suggests PrEP users could be better informed about how to start and stop use, irrespective of the dosing regimen. Client-centred, tailored PrEP services, taking into account PrEP users' values, priorities and needs towards HIV and STI prevention, will be required to counsel PrEP users across their life course and to help to reduce the transmission of STIs.

PrEP users' perception on PrEP care

In **Chapter 4**, we provided insights into PrEP users' experiences and preferences for PrEP service delivery, including their willingness to involve their family physician in PrEP care. The mixed-methods study revealed high satisfaction with the care received in specialised HIV clinics. Nevertheless, these positive care experiences were not without challenges, as PrEP users reported barriers to the care they received, including limited provider-client interaction, difficulties incorporating follow-up visits in private and professional life, and the financial burden of out-of-pocket expenses. Moreover, we pointed out the need for a more differentiated PrEP service delivery approach to better accommodate different user preferences regarding various aspects of PrEP care, including setting (e.g. specialised HIV clinics vs. community based organisations), provider (e.g. specialised HIV clinician vs. family physician), format (e.g. remote vs. in-person) or frequency of follow-up visits (e.g. needs-based vs. quarterly). As half of PrEP users were willing to involve family physicians in PrEP care, collaborative care models between primary care providers and specialised HIV clinics should be explored. Additionally, our results suggested that tailoring the content of PrEP care packages to users' needs and preferences, e.g., mental health counselling and HIV/STI testing, is instrumental to fostering sustained engagement with care as long as users are exposed to HIV.

General discussion and conclusion

In the last part of this thesis, **Chapter 5**, we discussed the implications of the main findings. We suggested options through which PrEP implementation in Belgium might be improved. These include: (1) increasing uptake among underserved populations by enhancing awareness through inclusive and gain-framed messaging, (2) increasing knowledge of how to start and stop PrEP use among PrEP users, irrespective of dosing regimen, (3) providing alternative PrEP modalities (e.g. long-acting cabotegravir) and delivery options (e.g. involvement of family physicians) that can be tailored to users' needs and preferences, and provides users with more choice. Additionally, our findings highlight the importance of providing sexual risk reduction counselling during PrEP follow-up visits, including tailored condom use promotion.

We also proposed some future directions for HIV and STI prevention and research. To enable monitoring of performance and effectiveness of PrEP programmes, it is imperative to establish appropriate, feasible, evidence-based indicators, which take into account the fluidity of PrEP use and the diverse modalities and delivery settings available. For new PrEP modalities, such as long-acting injectable cabotegravir, it is essential to dissolve accessibility barriers to ensure a rapid implementation and an enhanced net prevention coverage. An enabling environment should be created for engaging family physicians into PrEP care and the implementation of other viable, cost-effective delivery models. In the context of curable STI prevention, we advocate for tailored and targeted STI screening strategies and further research investments for doxycycline post-exposure prophylaxis.

Nederlandse samenvatting

Orale hiv pre-expositie profylaxe (PrEP) in België: inzicht in het gedrag, de attitudes en de zorgbehoeften van PrEP-gebruikers

In de afgelopen tien jaar is het hiv-preventielandschap ingrijpend veranderd door de introductie van orale PrEP. Hoewel deze pil veelbelovend is voor primaire preventie, is het potentieel ervan om nieuwe hiv-infecties te voorkomen nog niet voldoende benut. Om te begrijpen hoe de implementatie van PrEP verbeterd kan worden, is het van essentieel belang om het gedrag, de attitudes en de zorgbehoeften van (potentiële) PrEP-gebruikers te onderzoeken. Daarom bestudeerden we in dit proefschrift het perspectief van PrEP-gebruikers in België. Het doel was om een gedetailleerd inzicht te krijgen in wie PrEP gebruikt, hoe men PrEP gebruikt en wat de ervaringen van PrEP-gebruikers met en voorkeuren t.a.v. de PrEP-zorgverlening zijn. Tegelijkertijd wilden we ook het gebruik van condooms en de houding ten opzichte van seksueel overdraagbare infectie (soi)-preventie bij PrEP-gebruikers onderzoeken.

Algemene inleiding

In **Hoofdstuk 1** beschreven we de wereldwijde hiv-epidemie en de impact van hiv op mannen die seks hebben met mannen (MSM). We gaven een overzicht van de vooruitgang en uitdagingen voor hiv-preventie in de loop van de tijd, met een specifieke focus op MSM. Daarnaast beschreven we de introductie van PrEP. We gaven een samenvatting van hoe gerandomiseerde gecontroleerde studies de werkzaamheid en veiligheid van PrEP hebben aangetoond en hoe demonstratie- en implementatieprojecten de haalbaarheid en aanvaardbaarheid ervan hebben aangetoond. We gingen dieper in op de implementatie van PrEP in de praktijk, waarbij we de effectiviteit op populatieniveau belichtten en de uitdagingen met betrekking tot het starten met en het gebruik van PrEP en de beschikbare modellen van PrEP-zorg beschreven. We benadrukten de uiteenlopende trends van hiv- en seksueel overdraagbare aandoeningen (soa), waarbij het aantal behandelbare bacteriële soa's stijgt en het aantal hiv-infecties daalt. We beschreven de hiv- en soa-epidemieën in België en de implementatie van PrEP sinds 2015. We introduceerden de doelen en de opzet van dit proefschrift. Tot slot gaven we een overzicht van de gehanteerde methoden en gegevensbronnen.

De uitrol van PrEP in België

Aan de hand van een analyse van routinematig verzamelde declaratiegegevens van de Belgische sociale ziektekostenverzekering, gaven we in **Hoofdstuk 2** een nationaal en longitudinaal overzicht van alle PrEP-gebruikers met een sociale ziektekostenverzekering. We observeerden dat tussen juni 2017 en december 2019 aan 4559 personen ten minste één keer PrEP werd verstrekt. Door de distributie van PrEP te onderzoeken stelden we vast dat een hoog percentage PrEP-gebruikers vroegtijdig stopte met het nemen van PrEP: ongeveer een vijfde van de PrEP-gebruikers ontving slechts één keer PrEP in de eerste zes maanden van PrEP-gebruik. Het vroegtijdig stoppen met PrEP kwam vaker voor bij jonge gebruikers, werklozen of bij mensen met een verhoogde ziektekostenvergoeding (d.w.z. mensen met lagere inkomens). Twaalf personen liepen hiv op; de geschatte hiv-incidentie was 0,21 per 100 persoonsjaren onder personen die gestart zijn met PrEP. Een analyse van individuele PrEP-gebruikspatronen van mensen die toch een hiv-infectie opliepen toonde aan dat de seroconversies plaatsvonden vóór of rond de tijd dat ze met PrEP begonnen, of meer dan zeven maanden na een laatste afgifte van een PrEP-voorschrift. Dit wijst op gemiste kansen voor hiv-preventie binnen het PrEP-programma. Daarnaast vonden we een hoge incidentie van bacteriële soi's (d.w.z. gonorroe, chlamydia en syfilis). Deze resultaten onderstrepen de noodzaak om PrEP (her)start te vergemakkelijken voor individuen die kwetsbaar zijn voor hiv, in combinatie met counseling omtrent therapietrouw om te zorgen voor een optimale implementatie van het PrEP-programma. Daarnaast zijn aangepaste preventie en test-interventies nodig, geïntegreerd in de PrEP-zorg, om het aantal soi's onder PrEP-gebruikers te verminderen.

Hiv-preventie en seksueel gedrag en attitudes ten aanzien van condooms en seksueel overdraagbare infecties van PrEP-gebruikers

Hoofdstuk 3 rapporteert de resultaten van vier onderzoeken waarin we de patronen van PrEP- en condoomgebruik, seksueel gedrag met vaste, losse en/of anonieme partners en de houding ten opzichte van soi's en condooms van PrEP-gebruikers analyseerden.

In **Subhoofdstuk 3.1** onderzochten we veranderingen omtrent sociodemografische gegevens en seksueel gedrag in de profielen van personen die met PrEP gestart zijn in een grote hiv-kliniek in België tussen juni 2017 en maart 2020. We beschreven de kans

om te wisselen tussen dagelijks PrEP-gebruik en PrEP-gebruik rondom de seks, en op het onderbreken van PrEP. Daarnaast beschreven we de PrEP-vervolgbezoeken in de loop van de tijd. Deze analyse was gebaseerd op gegevens die longitudinaal werden verzameld via medische dossiers van patiënten en vragenlijsten. De meerderheid van de PrEP-gebruikers waren MSM, met een mediane leeftijd van 37 jaar; ze waren meestal geboren in België en hoogopgeleid. Ongeveer driekwart van de PrEP-gebruikers was na een jaar nog in zorg, met een mediane tijd van drie maanden tussen PrEP-vervolgbezoeken. Mensen die al snel na de introductie van PrEP in België begonnen met PrEP rapporteerden meer hiv-risicogedrag in vergelijking met gebruikers die meer dan een jaar na de introductie van PrEP begonnen (bijv. een hoger aantal seksuele partners, meer kans op betaalde seks of seks onder invloed van drugs). Het gerapporteerde PrEP-regime (d.w.z. dagelijks of rondom de seks) bleef relatief stabiel in de loop van de tijd. Niettemin werd er gewisseld tussen PrEP-regimes en waren er (tijdelijke) onderbrekingen in de zorgopvolging en het PrEP-gebruik.

In **Subhoofdstuk 3.2** onderzochten we patronen van PrEP-gebruik onder PrEP-gebruikers die tussen september 2020 en januari 2022 deelnamen aan een online longitudinale studie. We onderzochten associaties tussen sociodemografische kenmerken en seksueel gedrag en verschillende PrEP-gebruik categorieën en beschreven PrEP- en gelijktijdig condoomgebruik per partnertype in de loop van de tijd. We toonden aan dat er diverse categorieën van PrEP-gebruik bestaan, die verder gaan dan de tweedeling 'dagelijks' en 'rondom de seks'. Een aanzienlijk aantal gebruikers gaf aan dat ze PrEP op een consistente manier gebruikten in de loop van de tijd, hoewel we ook zagen dat er gewisseld werd tussen PrEP-gebruik categorieën. We toonden een verband aan tussen seksueel gedrag en de manier waarop PrEP werd gebruikt: dagelijkse gebruikers rapporteerden meer losse en anonieme sekspartners en hadden vaker anale seks met deze partners in vergelijking met minder frequente PrEP-gebruikers. Terwijl het gerapporteerde gebruik van condooms laag was, waren seksuele handelingen met losse of anonieme sekspartners die noch door condooms noch door PrEP beschermd waren zeldzaam; dergelijke onbeschermde situaties kwamen vaker voor tijdens seks met vaste partners.

In **Subhoofdstuk 3.3** onderzochten we de attitudes van PrEP-gebruikers ten aanzien van soi's en condooms en hoe deze attitudes hun condoomgebruik met niet-vaste

partners beïnvloeden om soi's te voorkomen. Met behulp van een onderzoeksopzet waarbij we van verschillende methoden gebruikt maakten ('mixed methods') hebben we gegevens uit diepte-interviews vergeleken met gegevens die zijn verzameld tijdens het eerder beschreven online longitudinale onderzoek. Onze bevindingen gaven inzichten omtrent uiteenlopende zorgen over soi's en een variatie inzake motivatie en bereidheid om condooms te gebruiken om soi's te voorkomen. Een minderheid van de deelnemers aan het online onderzoek gaf aan consequent condoom en PrEP tegelijkertijd te gebruiken. Voor andere PrEP-gebruikers bleven condooms een waardevolle soi-preventieoptie, afhankelijk van de contextuele omstandigheden (bijv. type partner, locatie). De beslissing om condooms te gebruiken en zo soi's te voorkomen was het resultaat van een afweging tussen de gepercipieerde ernst van, vatbaarheid voor en bezorgdheid over soi's enerzijds en seksueel plezier, de beschermende voordelen van condooms en waargenomen sociale normen en praktijken anderzijds.

In het laatste deel van hoofdstuk 3 (**Subhoofdstuk 3.4**) hebben we de zelfwaargenomen en werkelijke kennis van het effectief starten en stoppen met orale PrEP geëvalueerd. Daarnaast identificeerden we factoren die samenhingen met onjuiste kennis over starten en stoppen. Van de 206 mannen die het online longitudinale onderzoek invulden, beantwoordde een derde de vragen over het effectief starten en stoppen met PrEP niet correct, terwijl de meerderheid hun start-en-stopkennis als 'zeer goed' beoordeelde. Dagelijks gebruik van PrEP was geassocieerd met onjuiste kennis over het starten en stoppen.

De bevindingen van de onderzoeken in **Hoofdstuk 3** toonden aan dat PrEP-gebruikers in staat zijn om hun PrEP-gebruik aan te passen aan hun behoeften. Het verschil tussen zelfwaargenomen en werkelijke start-en-stopkennis suggereert echter dat PrEP-gebruikers beter geïnformeerd zouden kunnen worden over hoe te starten en te stoppen met het gebruik, ongeacht het doseringsschema. Cliëntgerichte, aangepaste PrEP-zorgverlening, die rekening houdt met de waarden, prioriteiten en behoeften van PrEP-gebruikers ten aanzien van hiv- en soi-preventie, zullen nodig zijn om PrEP-gebruikers gedurende hun hele leven te begeleiden en om de verspreiding van soi's te helpen verminderen.

De perceptie van PrEP-gebruikers over PrEP-zorg

In **Hoofdstuk 4** gaven we meer inzichten in de ervaringen en voorkeuren van PrEP-gebruikers t.a.v. PrEP-zorgverlening, inclusief hun bereidheid om hun huisarts bij de PrEP-zorg te betrekken. Uit het mixed-methoden onderzoek bleek een hoge tevredenheid over de zorg die werd aangeboden in gespecialiseerde hiv-klinieken. Toch waren deze positieve ervaringen met de zorg niet zonder uitdagingen, aangezien PrEP-gebruikers enkele barrières meldden over de zorg die ze ontvingen, waaronder de beperkte interactie tussen de zorgverlener en de cliënt, problemen met het inplannen van vervolgbezoeken in het privé- en beroepsleven en de financiële last van de directe onkosten. We benadrukten dat een meer gedifferentieerde aanpak van PrEP-zorgverlening noodzakelijk is om beter tegemoet te komen aan de diverse voorkeuren van gebruikers met betrekking tot diverse aspecten van PrEP-zorg, waaronder de setting (bijv. gespecialiseerde hiv-klinieken vs. eerste of nulde lijn organisaties), de zorgverlener (bijv. hiv-specialist vs. huisarts), de modus (bijv. op afstand vs. in persoon) of de frequentie van vervolgbezoeken (bijv. op basis van behoefte vs. per kwartaal). Aangezien de helft van de PrEP-gebruikers bereid was om hun huisartsen in de PrEP-zorg te betrekken, zou het zinvol kunnen zijn om zorgmodellen die de samenwerking tussen eerstelijnszorgverleners en gespecialiseerde hiv-klinieken bevorderen verder te onderzoeken. Daarnaast suggereren onze resultaten dat het beter afstemmen van de inhoud van PrEP-zorgpakketten op de behoeften en voorkeuren van gebruikers, bijvoorbeeld counseling op het gebied van mentale gezondheid en hiv/soi-testen, van groot belang is voor het bevorderen van een langdurige betrokkenheid bij de zorg, zolang gebruikers risico lopen op hiv.

Algemene discussie en conclusie

In het laatste deel van dit proefschrift, **Hoofdstuk 5**, werden de implicaties van de belangrijkste bevindingen samengevat. We gaven aanbevelingen om de implementatie van PrEP in België te verbeteren. Deze omvatten: (1) het beter bereiken van minderbedeelde bevolkingsgroepen door de kennis over PrEP te vergroten door inclusieve berichtgeving, die de positieve aspecten van PrEP benadrukken, (2) het verbeteren van de kennis over hoe te starten en te stoppen met PrEP onder PrEP-gebruikers, ongeacht het doseringsschema, en (3) het aanbieden van alternatieve PrEP-modaliteiten (bijv. langwerkend cabotegravir) en zorginstellingen (bijv. betrokkenheid van huisartsen) die kunnen worden afgestemd op de behoeften en

voorkeuren van gebruikers en gebruikers meer keuze bieden. Daarnaast benadrukken onze bevindingen het belang van counseling tijdens PrEP-vervolgbezoeken over het verminderen van seksuele risico's, inclusief gerichte voorlichting over het gebruik van condooms.

We deden ook suggesties voor toekomstig hiv- en soi-preventie en onderzoek. Om de prestaties en effectiviteit van PrEP-programma's te kunnen monitoren, is het noodzakelijk om geschikte, haalbare indicatoren bepaald op basis van wetenschappelijk bewijs ('evidence-based') vast te stellen, die rekening houden met de variabiliteit in PrEP-gebruik en de diverse beschikbare modaliteiten en zorginstellingen. Voor nieuwe PrEP-modaliteiten, zoals langwerkend injecteerbaar cabotegravir, is het essentieel om barrières met betrekking tot toegang op te lossen om een snelle implementatie en een grotere netto dekking van preventie te waarborgen. Er moet een gunstiger klimaat worden gecreëerd om huisartsen te betrekken bij PrEP-zorg en de implementatie van andere realistische, kosteneffectieve PrEP zorgmodellen. In de context van de preventie van behandelbare soi's pleiten we voor aangepaste en gerichte soi-screeningsstrategieën en verdere investeringen in onderzoek naar doxycycline post-expositieprofylaxe.

PhD portfolio

PhD training

	Year	Workload (ECTS)
Courses		
Clinical epidemiology: systematic review, Amsterdam UMC Doctoral school, Amsterdam, the Netherlands	2023	0.7
Project management, Amsterdam UMC Doctoral school, Amsterdam, the Netherlands	2022	0.6
Design and evaluation of health programmes, ITM short course, Antwerp, Belgium	2020	5.0
Health economics and financing, ITM short course, Antwerp, Belgium	2020	5.0
How to write a data management plan (DMP & research data lifecycle), ITM PhD training programme, Antwerp, Belgium	2020	0.1
Why stakeholders matter and how to integrate them into your research, ITM PhD training programme, Antwerp, Belgium	2020	0.1
Why should I bother? Intro to using social media as a researcher, ITM PhD training programme, Antwerp, Belgium	2020	0.1
How to write a rebuttal for papers and proposals?, ITM PhD training programme, Antwerp, Belgium	2020	0.1
How to get your paper published… in the Lancet?, ITM PhD training programme, Antwerp, Belgium	2020	0.1
Academic English: Writing research papers, Linguapolis, University of Antwerp, Belgium	2020	1.0
Advanced statistical methods in epidemiology, Institute of Tropical Medicine and International Health, Berlin, Germany	2019	4.5
Qualitative and mixed methods, ITM, Antwerp, Belgium	2019	6.0
(Inter)national conferences visited		
European AIDS Conference (EACS) 2023, Warsaw, Poland	2023	0.9
AIDS 2022, Montreal, Canada	2022	1.5
BREACH spring meeting 2022, La Hulpe, Belgium	2022	0.3
BREACH 2021, virtual conference, Liège, Belgium	2021	0.3

European AIDS Conference (EACS) 2021, virtual conference, London, United Kingdom	2021	0.9
BREACH 2019, Liège, Belgium	2019	0.3
Oral Presentations		
Increasing PrEP service delivery options to reduce barriers to care: a mixed-methods study exploring PrEP care preferences among Belgian PrEP users. Oral presentation at the 15th AIDS Impact Conference, 12-14 June 2023, Stockholm, Sweden. (presented by Jef Vanhamel)	2023	0.5
Acceptability of a new 4-in-1 Abacavir/Lamivudine/Lopinavir/Ritonavir paediatric fixed-dose combination: the caregiver-child dyads' perspective. Oral presentation at HIV Pediatrics 2020, 16-17 November 2020, virtual conference. (presented by Ogara Collin)	2020	0.5
Poster presentations		
Early pre-exposure prophylaxis users in Belgium, their PrEP use trajectories and incidence of HIV and STI: a cohort analysis of insurance claims data from 2017 to 2019. 19th European AIDS Conference (EACS) 2023, Warsaw, Poland	2023	0.5
Putting 2+1+1 into practice: MSM PrEP users' knowledge about safely starting and stopping PrEP in Belgium. AIDS 2022, Montreal, Canada	2022	0.5
PrEP user profiles, dynamics of PrEP use and follow-up: a retrospective cohort analysis at a Belgian HIV centre (2017-2020). 18th European AIDS Conference (EACS) 2021, London, United Kingdom	2021	0.5
PrEP user profiles, dynamics of PrEP use and follow-up: a retrospective cohort analysis at a Belgian HIV centre (2017-2020). 9th BREACH Symposium 2021, La Hulpe, Belgium.	2021	0.5
Acceptability of Quadrimune, a new Abacavir/Lamivudine/Lopinavir/Ritonavir paediatric fixed dose combination. INTEREST 2020, virtual conference	2020	0.5
Meetings, seminars, workshops		
Scientific advisory board – PROMISE	2022, 2020	0.6
Valorisation advisory board – PROMISE – biannually	2019-2022	1.1
Public health seminar biweekly, Department of Public Health, ITM, Antwerp, Belgium	2019-2023	1.5
AVAC: Ups & Downs in the Field: Setting an agenda together for 2022	2022	0.1
WHO Global PrEP network webinar: Get PrEP done! Strategies for raising awareness, acceptability, uptake and effective use of PrEP	2021	0.1
WHO Global PrEP network webinar: Integrating HIVST and PrEP for improving access to prevention and testing services in Asia and Africa region	2021	0.1

WHO Webinar: Optimising HIV Testing Services Using HIV Risk Assessment Tools	2021	0.1
WHO webinar: Bringing dual HIV/syphilis rapid tests to scale: country adoption, challenges and opportunities	2021	0.1
WHO Webinar: Integration of HIV testing and linkage in family planning services in high HIV burden settings	2021	0.1
PSI webinar: How to deliver HIVST in a sustainable manner to increase testing coverage among priority populations, experiences and lessons learned from STAR	2020	0.1
Other		
Contributor to "Safe start and stop" PrEP campaign by Sensoa	2021	0.2

Teaching

	Year	Workload (ECTS)
Tutoring, supervising		
Tutor fieldwork during qualitative and mixed methods course at ITM, Antwerp, Belgium	2022	0.7
Co-supervisor Master of Public Health student Blessing Umeigbo, thesis Master of Public Health titled: "Impact of a Quality Improvement Intervention on Viral Load Suppression Amongst Children and Adolescents Living with HIV in Adamawa State", ITM, Antwerp, Belgium	2022	0.3
Lecturing		
Guest lecturer on qualitative sampling methods during Introduction to International Health course at ITM, Antwerp, Belgium	2022	0.2
Guest lecturer on qualitative sampling methods during Introduction to International Health course at ITM, Antwerp, Belgium	2021	0.3
Guest lecturer on qualitative sampling methods during Qualitative mixed methods short course at ITM, Antwerp, Belgium	2020	0.3
Guest lecturer on qualitative sampling methods during Master of Public Health at ITM, Antwerp, Belgium	2019	0.6
Total		**37.5**

Parameters of Esteem

	Year
Scholarships	
Full scholarship to attend the AIDS conference, Montreal, Canada	2022

List of publications

Publications included in this thesis

Rotsaert A, Reyniers T, Jacobs BKM, Vanbaelen T, Burm C, Kenyon C, Vuylsteke B, Florence E. PrEP user profiles, dynamics of PrEP use and follow-up: a cohort analysis at a Belgian HIV centre (2017-2020). J Int AIDS Soc. 2022 Jul;25(7):e25953. doi: 10.1002/jia2.25953.

Rotsaert A, Smekens T, Vuylsteke B, Schim van der Loeff M, Hensen B, Nöstlinger C, Wouters E, Vanhamel J, Scheerder G, Reyniers T. Patterns of PrEP and condom use among PrEP users in Belgium: a web-based longitudinal study. BMC Public Health. 2023 May 26;23(1):970. doi: 10.1186/s12889-023-15786-6.

Rotsaert A, Nöstlinger C, Van Landeghem E, Vanbaelen T, Wouters E, Buffel, V, Scheerder G, Schim van der Loeff M, Vuylsteke B, Reyniers T. Pre-Exposure Prophylaxis Users' Attitudes About Sexually Transmitted Infections and Its Influence on Condom Use: A Mixed-Method Study in Belgium. AIDS Patient Care STDs, 2022, 36(12): 483-492. doi: 10.1089/apc.2022.0172.

Rotsaert A, Reyniers T, Vanhamel J, Van Landeghem E, Vanbaelen T, Van Mieghem H, Nöstlinger C, Laga M, Vuylsteke B. Putting 2-1-1 into Practice: PrEP Users' Knowledge of Effectively Starting and Stopping Oral PrEP Use. AIDS Behav. 2023 Jun;27(6):1793-1799. doi: 10.1007/s10461-022-03911-2.

Rotsaert A, Smekens T, Jaminé, D, Di Zinno T, Deblonde J, Lambert ML, Florence E, Reyniers T, Vanhamel J, Lucet C, Schim van der Loeff M, Hensen B, Vuylsteke B. Pre-exposure prophylaxis (PrEP) use trajectories and incidence of HIV and other sexually transmitted infections among PrEP users in Belgium: a cohort analysis of insurance claims data from 2017 to 2019. ***Submitted***

Rotsaert A, Vanhamel J, Vanbaelen T, Vuylsteke B, Schim van der Loeff M, Hensen B, Kielmann K, Callens S, Reyniers T. HIV pre-exposure prophylaxis (PrEP) care in Belgium:

a mixed-methods study on PrEP users' experiences and service delivery preferences. ***Accepted for publication in AIDS and behaviour***

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Chapter 2 - Pre-exposure prophylaxis (PrEP) use trajectories and incidence of HIV and other sexually transmitted infections among PrEP users in Belgium: a cohort analysis of insurance claims data from 2017 to 2019

Concept and design: AR, BV, TR, CL, MLL, TDZ, DJ. Statistical analysis: TS and AR. Interpretation of the data: AR, TS, BV, BH, MSVDL, DJ, JDB, TDZ, TR, EF, JV. Drafting of the manuscript: AR, TS. Supervision: BV. All authors critically reviewed and approved this manuscript.

Chapter 3.1 - PrEP user profiles, dynamics of PrEP use and follow-up: a cohort analysis at a Belgian HIV centre (2017–2020)

AR, TR and EF: conception of protocol, writing of the first draft of the manuscript, revision and editing of the present version of the manuscript. BKMJ: data collection, data analysis and reporting, writing of the first draft of the manuscript and revision of the present version of the manuscript. TV and CK: writing of the first draft of the manuscript, revision and editing of the present version of the manuscript. CB: data collection, data analysis and reporting. BV: global supervision of the protocol writing, writing of the first draft of the manuscript, revision and editing of the present version of the manuscript.

Chapter 3.2 - Patterns of PrEP and condom use among PrEP users in Belgium: a web-based longitudinal study

AR, BV, TR contributed to the study concept and design. AR performed all data analysis in collaboration with TS. AR drafted the manuscript. All authors revised the manuscript and approved the final version for publication.

Chapter 3.3 - Pre-Exposure Prophylaxis users' attitudes about sexually transmitted infections and its influence on condom use: a mixed-method study in Belgium

AR, TR, BV, EVL, CN, and TV contributed to study concept and design. AR and TR collected the data. AR performed data analyses and CN, EVL, and TR contributed to interpretation of the data. AR drafted the article. All authors critically revised and approved the final version for publication.

Chapter 3.4 - Putting 2-1-1 into practice: PrEP users' knowledge of effectively starting and stopping oral PrEP use

All authors contributed to the study concept and design. AR performed all data analysis under supervision of TR. AR drafted the manuscript. All authors critically revised the manuscript and approved the final version for publication.

Chapter 4 - HIV pre-exposure prophylaxis (PrEP) care in Belgium: a mixed-methods study on PrEP users' experiences and service delivery preferences.

AR, BV, TR, JV contributed to the study concept and design. AR, JV, TVB conducted data collection. JV and AR performed all data analysis. AR and JV drafted the manuscript. All authors revised the manuscript and approved the final version for publication.

About the author

Anke Rotsaert was born in Roeselare, Belgium on 09 September 1990. In 2013, she graduated from the University of Ghent with a Master of Pharmaceutical Sciences. Following her Master, Anke obtained a postgraduate in International Health and Tropical Medicine at the Institute of Tropical Medicine.

In 2014, she started working for a clinical research organisation in Belgium. In 2017, Anke assisted in a research project regarding Onchocerciasis in the health zone of Aketi, the Democratic Republic of the Congo, for the University of Antwerp. That same year she worked as a project pharmacy manager for a sexual reproductive health project in Bangui, Central African Republic, for the non-governmental organisation Doctors without Borders. Two other projects as project pharmacy manager followed; one in an emergency project for a diphtheria outbreak in Bangladesh and one in a post-operative and rehabilitation centre in Mosul, Iraq.

In August 2019 Anke began working as a junior researcher at the Department of Public Health of the Institute of Tropical Medicine in Antwerp under the supervision of prof. dr. Marie Laga and dr. Bea Vuylsteke. Her research focused on pre-exposure prophylaxis users in Belgium as part of the PROMISE project. Anke combined this work with a Master of Public Health – orientation health systems and disease control at the Institute of Tropical Medicine, Antwerp, Belgium, which she completed in 2020. The topic of her master thesis was HIV self-testing. In 2022, Anke officially began working towards her PhD based on the results from the PROMISE project, which are presented in this thesis.

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