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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

Anke Rotsaert[1*], Tom Smekens[1], David Jaminé[2], Tonio Di Zinno[2], Jessika Deblonde[3], Marie-Laurence Lambert[4], Eric Florence[5,6], Thijs Reyniers[1], Jef Vanhamel[1], Catherine Lucet[7], Maarten Schim van der Loeff[8,9,10,11], Bernadette Hensen[1] and Bea Vuylsteke[1]

Abstract

Background 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 Analysis of 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). 18% (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 rates for bacterial STIs and HIV were 4.2 tests per person-year (95% CI 4.1–4.2) and 3.6 tests per person-year (95% CI 3.5–3.6), respectively. Twelve individuals were identified to have seroconverted during the study period, resulting in 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).

*Correspondence:
Anke Rotsaert
arotsaert@itg.be

Full list of author information is available at the end of the article

Conclusions The study highlights challenges in PrEP persistence and a high incidence of bacterial STIs among individuals receiving PrEP. Tailored prevention support is crucial for individuals with ongoing HIV risk to optimise PrEP effectiveness. Integrated STI testing and prevention interventions within PrEP care are necessary to mitigate STI acquisition and transmission among PrEP users.

Keywords HIV prevention, Pre-exposure prophylaxis (PrEP), HIV incidence, STI, Longitudinal, Claims data

Background

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 60–74% 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 individuals who obtained reimbursed PrEP 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 (i.e. first PrEP dispensing date), 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].

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 (i.e. first-time PrEP dispensing events) 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.

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. 5% 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.

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 (5.8)	61 (28.8)	Ref	-
25–34	1573 (34.5)	1237 (34.0)	265 (21.4)	0.64 (0.49–0.83)	-
35–44	1496 (32.8)	1206 (33.2)	193 (16.0)	0.47 (0.36–0.62)	-
45–54	807 (17.7)	664 (18.3)	85 (12.8)	0.39 (0.29–0.52)	-
≥55	404 (8.9)	316 (8.7)	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 (92.4)	580 (17.3)	Ref	Ref
Non-active	341 (7.5)	275 (7.6)	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 (88.1)	547 (17.1)	Ref	Ref
Yes	514 (11.4)	396 (10.9)	99 (25.0)	1.62 (1.26–2.06)	1.45 (1.13–1.86)
Missing	39	36 (1.0)	11		
Semester of initiation					
June 2017	92 (2.0)	92 (2.5)	7 (7.6)	0.49 (0.20–1.00)	0.49 (0.20–1.02)
July 2017 – Dec 2017	973 (21.3)	973 (26.8)	141 (14.5)	Ref	Ref
Jan 2018 – June 2018	899 (19.7)	899 (24.7)	152 (16.9)	1.20 (0.94–1.54)	1.18 (0.92–1.52)
July 2018 – Dec 2018	814 (17.9)	814 (22.4)	161 (19.8)	1.45 (1.14–1.87)	1.44 (1.12–1.85)
Jan 2019 – June 2019	858 (18.8)	858 (23.6)	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

[*] PrEP initiation was defined as first PrEP dispensing date, [†] 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

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

[£] PrEP initiation was defined as first PrEP dispensing date, [†] 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% profile likelihood confidence intervals and were obtained from Poisson regression, either with no explanatory variables (column TOTAL) or semester of PrEP initiation as explanatory variable and without intercept (other columns), and the log of follow-up time as exposure variable

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, with a median of 30 pills dispensed per dispensing event. PrEP users who were $\geq$ 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)

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 and 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. The number of PrEP pills dispensed at the last PrEP dispensing event ranged from 30 to 120 pills.

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 (3.5–3.7)	3.5 (3.4–3.6)	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. [£] PrEP initiation was defined as first PrEP dispensing date, [†] 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% profile likelihood confidence intervals and were obtained from Poisson regression, either with no explanatory variables (column TOTAL) or semester of PrEP initiation as explanatory variable and without intercept (other columns), and the log of follow-up time as exposure variable

Discussion

Between June 2017 and December 2019, 4559 individuals in Belgium were dispensed 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 who were dispensed 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

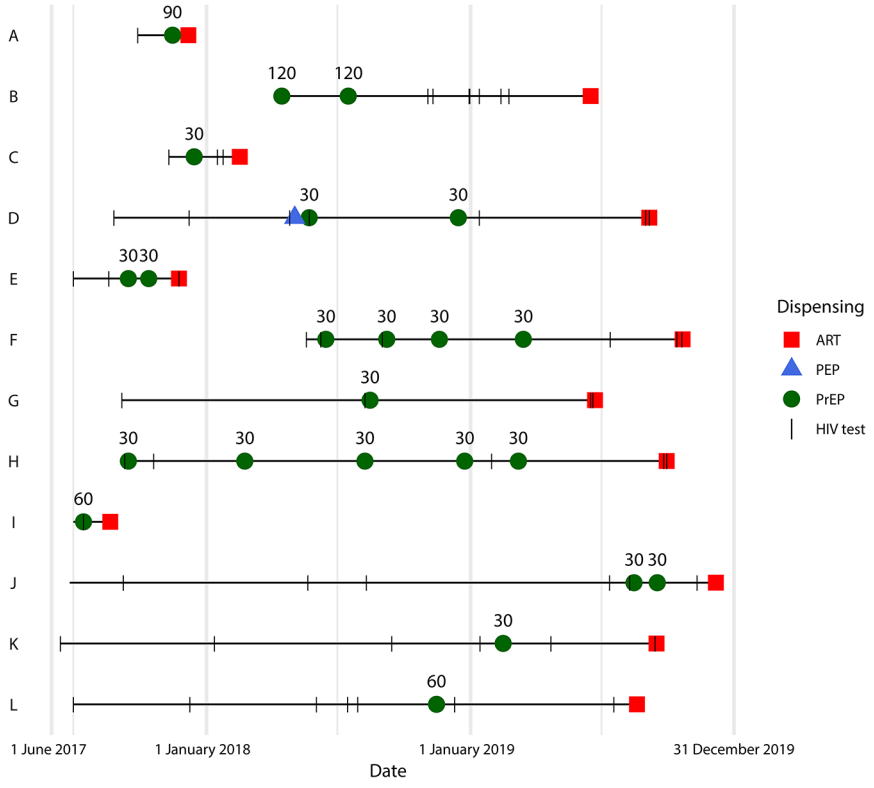

Fig. 1 Trajectories of individuals who seroconverted after PrEP initiation, indicated by letter codes (A through L), in Belgium, between 1 June 2017 and 31 December 2019 (*N* = 12). ART: antiretroviral treatment, PEP: post-exposure prophylaxis, PrEP: pre-exposure prophylaxis. The numbers indicate the number of pills dispensed per PrEP dispensing event. PrEP initiation was defined as first PrEP dispensing date

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, dependent on the number of PrEP pills dispensed at the last dispensing event, 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

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)	48.9 (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 (0.0–50.0)
Chlamydia							
Infection events	2732	144	1115	715	397	247	114
Rate per 100 PY, 95%CI	56.6 (54.5–58.8)	68.0 (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 (0.0-23.9)
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)

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

PrEP initiation = first PrEP dispensing date. 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% profile likelihood confidence intervals and were obtained from Poisson regression, either with no explanatory variables (column TOTAL) or semester of PrEP initiation as explanatory variable and without intercept (other columns), and the log of follow-up time as exposure variable. Where the number of events is zero, we approximated the upper limit of the confidence interval by taking 3.7 divided by person-time at risk (PY divided by 100)

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.

Conclusions

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.

Abbreviations

ART	Antiretroviral therapy
CI	Confidence interval
HIV	Human immunodeficiency virus
IQR	Interquartile range
IMA	Intermutualistic Agency
MSM	Men who have sex with men
PEP	Post-exposure prophylaxis
PrEP	Pre-exposure prophylaxis
PY	Person-year
SD	Standard deviation
STI	Sexually transmitted infections
TDF-FTC	Tenofovir disoproxil fumarate and emtricitabine

Supplementary Information

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Supplementary Material 1

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Author 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

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).

Declarations

Ethics approval and consent to participate

This study received ethical approval by the Institutional review board of the Institute of Tropical Medicine, Antwerp, Belgium (1427/20). In addition, the Belgian Information Security Committee judged this study positively on its proportionality and finality to use personal and medical data (IVC/KSZG/21/312). In the same context, a third party, the Belgian Health Care Knowledge Centre (KCE) performed a small-cell risk analysis to evaluate the risk of unintentional disclosure of personal information versus the proportionality and finality of the study. For variables with a risk of individual identification, such as sex at birth and residency, we received data in aggregated format. IMA pseudonymized all data and converted exact dates of first PrEP dispensing into month-year dates and for all other healthcare expenditures the number of days since first PrEP dispensing were registered to secure the privacy of each individual. As outlined in Article 14(5)(b) General Data Protection Regulation - European Regulation 2016/679 of April 27, 2016, and confirmed by the Institutional Review Board and Belgian Information Security Committee, the data controller is exempt from the obligation to provide information to the individuals whose personal data is processed.

Consent for publication

Not applicable.

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.

Author details

[1]Department of Public Health, Institute of Tropical Medicine, Nationalestraat 155 Antwerp, Antwerp 2000, Belgium
[2]Intermutualistisch Agentschap, Brussels, Belgium
[3]Epidemiology of Infectious Diseases, Sciensano, Brussels, Belgium
[4]INAMI/RIZIV, Brussels, Belgium
[5]Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp, Belgium
[6]Department of General Internal Medicine, Infectious Diseases and Tropical Medicine, University Hospital Antwerp, Antwerp, Belgium
[7]Solidaris Mutualité, Brussels, Belgium
[8]Department of Infectious Diseases, Research and Prevention, Public Health Service of Amsterdam, Amsterdam, The Netherlands

[9]Department of Internal Medicine, Amsterdam UMC location University of Amsterdam, Meibergdreef 9, Amsterdam, The Netherlands
[10]Amsterdam Institute for Infection and Immunity (AII), Amsterdam, the Netherlands
[11]Amsterdam Public Health Research Institute (APH), Amsterdam, the Netherlands

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