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Trends in Sexual Behavior and Sexually Transmitted Infections After Initiating Human Immunodeficiency Virus Pre-Exposure Prophylaxis in Men Who Have Sex with Men from Amsterdam, the Netherlands: A Longitudinal Exposure-Matched Study

Liza Coyer, MSc,[1,2] Maria Prins, PhD,[1,2] Udi Davidovich, PhD,[1,3] Ward P.H. van Bilsen, MD, PhD,[1] Maarten F. Schim van der Loeff, PhD,[1,2] Elske Hoornenborg, MD, PhD,[1] Amy Matser, PhD,[1,2,*] and Anders Boyd, PhD[1,4,*]

Abstract

Men who have sex with men (MSM) initiating human immunodeficiency virus (HIV) pre-exposure prophylaxis (PrEP) may increase condomless anal sex (CAS) and number of partners, and, consequently, more often acquire sexually transmitted infections (STIs). Using data from the Amsterdam Cohort Studies, we compared sexual behavior and STI among MSM after PrEP-initiation with controls not initiating PrEP. The MSM reported on sexual behavior and were tested for HIV, chlamydia, gonorrhea, and syphilis semi-annually. We matched MSM who initiated PrEP between January 1, 2015 and December 31, 2019 1:1 to MSM who did not use time-dependent propensity scores based on age, sexual behavior, and STI. Primary end-points were number of casual partners, and proportion with CAS and receptive CAS (rCAS) with casual partners, sexualized drug use (SDU), any STI, and anal STI. We modeled end-points during the 4 years before and 2 years after PrEP-initiation or matched PrEP-initiation timepoint by using logistic regression (dichotomous end-points) or negative binomial regression (count end-point), adjusted for calendar year. Two hundred twenty-eight out of the 858 (26.6%) MSM initiated PrEP. We matched 198 out of 228 (86.8%) to a control. Before PrEP-initiation, end-points increased over time in both groups, with no statistically significant difference. The odds of CAS, rCAS, and anal STI were on average higher after than before PrEP-initiation in PrEP initiators, whereas after versus before differences were not observed in controls. After PrEP-initiation, PrEP initiators had statistically significantly more casual partners, and higher odds of CAS, rCAS, SDU, any STI, and anal STI than controls. These findings support frequent STI screening and counseling in MSM using PrEP.

Keywords: pre-exposure prophylaxis, sexually transmitted infections, sexual behavior, prospective studies, men who have sex with men, homosexuality, male

[1]Department of Infectious Diseases, Public Health Service of Amsterdam, Amsterdam, the Netherlands.
[2]Department of Infectious Diseases, Amsterdam Institute for Infection & Immunity (AII), Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands.
[3]Department of Social Psychology, University of Amsterdam, Amsterdam, the Netherlands.
[4]Stichting HIV Monitoring, Amsterdam, the Netherlands.
*These two authors contributed equally to this work.

Introduction

Oral pre-exposure prophylaxis (PrEP) is an effective biomedical measure to prevent human immunodeficiency virus (HIV) acquisition.[1] The PrEP can be taken every 24 h (i.e., daily) or before and after sexual contact (i.e., event-driven). In the Netherlands, 61% of new HIV diagnoses in 2019 were made in men who have sex with men (MSM),[2] making this key population the highest at risk of infection. Accordingly, PrEP use in the Netherlands is targeted mainly to MSM, as is the case in many high-income countries.[3]

A systematic review of open-label PrEP studies conducted in mostly North America, the United Kingdom, and Australia concluded that condom use decreased in MSM after PrEP-initiation compared with before.[4] The same review also showed that the use of PrEP by MSM was associated with increased diagnoses of bacterial sexually transmitted infections (STIs). However, studying the effect of PrEP on sexual behavior and STI is challenging.

First, comparisons between after versus before PrEP-initiation can be biased by a different frequency of STI testing between periods. Second, population-level increases in condomless anal sex (CAS) and STI in MSM started before the widespread implementation of PrEP, and increases after PrEP-initiation could partly be due to a continuation of these trends.[5] Third, comparisons of sexual behavior and STI between MSM using and not using PrEP are hampered by the lack of adequate longitudinal data in non-PrEP users. Last, differences in sociodemographic and sexual behaviors between PrEP and non-PrEP users[6] make identifying comparable groups of MSM difficult.

In the Netherlands, PrEP became available to a limited number of MSM and transgender people through a demonstration project in 2015.[7] The PrEP use outside of study contexts increased, particularly after generic PrEP became available at the beginning of 2018 and the price of PrEP steeply declined.[6] The PrEP was formally implemented as a national pilot through sexual health centers in August 2019.[8] The Amsterdam Cohort Studies (ACS) has consistently monitored sexual behavior, PrEP use, and HIV/STI in MSM through semi-annual questionnaires and HIV/STI testing. Using these unique longitudinal data, we assessed changes in sexual behavior and diagnosed STI from before to after PrEP-initiation in MSM who initiated PrEP, and we compared these with a matched group of MSM who did not initiate PrEP.

Methods

Study design and participants

The ACS is an ongoing, open prospective cohort study among MSM, which was initiated in 1984.[9] The aim of the ACS is to investigate the epidemiology, psychosocial determinants, pathogenesis and course of HIV-1 infection, STI, and blood-borne infections other than HIV, and to evaluate the effect of interventions. Men aged ≥18 years were eligible for participation if they self-reported sex with men in the 6 months before recruitment and living in the Amsterdam region or regularly participated in MSM-related activities in the area. Participation was voluntary, and each participant provided written informed consent before enrollment. The ACS has been approved by the Medical Ethics Review Board of the Amsterdam University Medical Centers, location Academic Medical Center, the Netherlands (MEC 07/182).

Information on sociodemographic characteristics (e.g., date and country of birth, education level, sexual orientation, and living situation) was collected at enrollment. During each semi-annual study visit at the Public Health Service of Amsterdam (PHSA), participants attended a face-to-face consultation and completed a self-administered questionnaire on behaviors in the past 6 months, including sexual behavior and recreational drug use. From the second half of 2015 onward, all semi-annual questionnaires included questions on PrEP use. Most PrEP-initiators initiated PrEP (self-obtained or provided through other studies) between study visits, as the ACS did not prescribe PrEP before August 2019.

Since August 2019, ACS participants can obtain PrEP through the ACS as part of the national PrEP pilot. Participants were tested free of charge for HIV at each study visit since 1984 and for syphilis and pharyngeal, urethral, and anal gonorrhea and chlamydia since 2008. Detailed sampling and laboratory testing and storage procedures have been described elsewhere.[10] For individuals experiencing symptoms or who received partner notification of a possible exposure to an STI, HIV and STI tests could be performed during additional, non-study, visits at the Centre for Sexual Health of the PHSA; the results from these tests were also included in the analysis.

Matching

We distinguished two exposure groups: HIV-negative MSM who initiated PrEP between January 1, 2015 and December 31, 2019 (i.e., PrEP initiators) and HIV-negative MSM who did not (i.e., potential controls). As PrEP-initiation, sexual behavior, and STI varied over calendar time, the aim of the matching procedure was to identify the study visit at which a PrEP initiator most closely resembled a control, specifically around the moment of PrEP-initiation. To achieve this, we used a time-dependent propensity score[11] based on the time-varying covariates current age, number of casual partners, specific sexualized drug use (SDU), receptive CAS (rCAS) with casual partners, and any bacterial STI diagnosis, all in the past 6 months.

Propensity scores were calculated from a Cox proportional hazards regression model with the outcome PrEP-initiation and the matching criteria as independent variables. Observation time for the propensity score model started on January 1, 2015 (assuming no PrEP-initiation had occurred before this date) or the first ACS visit if enrolled after this date and ended on the first visit after PrEP-initiation (for PrEP initiators) or on the first HIV-positive visit or the last follow-up visit before December 31, 2019 (for potential controls).

Predicted hazards were estimated at the last visit before PrEP-initiation (for PrEP initiators) or at each visit between January 1, 2015 and December 31, 2019 (for potential controls). We sequentially matched PrEP initiators 1:1 to controls without replacement by choosing the closest total distance in predicted hazards within matched sets. No maximum distance was specified. The date of the matched PrEP-initiation timepoint for controls was calculated based on the time between the last visit before PrEP-initiation and the date of PrEP-initiation from the matched PrEP initiator. Baseline was subsequently defined as the date of PrEP-initiation for PrEP initiators or the matched PrEP-initiation timepoint for controls.

Outcomes

We examined the following end-points: (1) number of casual partners, and proportion with (2) CAS with casual partners, (3) rCAS with casual partners, (4) specific SDU, (5) any bacterial STI, and (6) any anal STI, all in the past 6 months. Specific SDU was defined as the use of mephedrone, methamphetamine, gamma hydroxybutyrate (GHB)/gamma butyrolactone (GBL), ketamine, amphetamine, cocaine, and/or ecstasy (XTC)/methylenedioxy-methylamphetamine (MDMA) during sex.[12] Any STI was defined as having a newly diagnosed chlamydia, gonorrhea, or syphilis, whereas any anal STI was defined as having a newly diagnosed anal chlamydia or anal gonorrhea.

Statistical analysis

We used a three-way interaction model between group (PrEP initiator/control), period (before/after baseline), and follow-up time to model each end-point during the 4 years before and 2 years after baseline. The censoring date was December 31, 2019. Post-baseline follow-up was restricted to 2 years, because a few PrEP initiators achieved more than 2 years of follow-up after PrEP-initiation. From each model, we compared (1) linear changes over the two follow-up periods, separately, within each group, (2) overall changes after versus before baseline within each group, and (3) overall difference between groups within each period.

Dichotomous end-points were modeled by using logistic regression with Generalized Estimating Equations (GEE). From these models, we calculated marginal predicted probabilities of end-points per 6-month interval, and odds ratios comparing odds of an end-point between intervals, with 95% confidence intervals (CIs). Count end-points were modeled by using negative binomial regression with GEE. From these models, we calculated the marginal predicted number of casual partners per 6-month interval, and parameter estimates comparing the number of casual partners per between intervals, which were interpreted as relative ratios, with 95% CIs.

We specified an exchangeable working correlation structure to account for the repeated observations within each participant. All models were corrected for calendar year (as restricted cubic spline with three knots), and STI models were additionally corrected for testing frequency (i.e., number of STI tests in the past 6 months).

We conducted two sensitivity analyses. First, we repeated the matching procedure and analysis for PrEP users and matched controls with a study visit at least 1.5 years after baseline to evaluate the effect of differential follow-up on results. Second, we additionally included having a steady partner and specific SDU as additional covariates in the STI models of the main analysis to evaluate whether these explained the associations between PrEP-initiation and STI end-points.

$p < 0.05$ was considered statistically significant. We performed analyses by using STATA IC 15.1 (College Station, TX).

Results

PrEP-initiation and use

A total of 858 HIV-negative MSM had a study visit between January 1, 2015 and December 31, 2019, of whom 228 initiated PrEP and 617 did not (Fig. 1); for 13 MSM, no or unclear information on PrEP use was available. The PrEP use increased over time between 2015 and 2019 ($p < 0.001$ for linear trends) (Fig. 1). In the second half of 2015, 2.2% (95% CI 1.3–3.7) of the MSM indicated having used PrEP in the past 6 months. This proportion increased to 29.1% (95% CI 25.3–33.1) in the second half of 2019.

Characteristics of included PrEP initiators and matched controls

Of the 228 MSM who initiated PrEP, we matched 199 (87.3%) to a control (Fig. 2). Characteristics of matched groups are presented in Table 1. The matched PrEP-initiation timepoint was a median of 0.6 years before the date of PrEP-initiation (IQR 1.9 before to 0.4 after). The median age of PrEP initiators was 41.9 years at the last visit before PrEP-initiation [interquartile range (IQR), 34.1 to 48.7], and the majority was born in the Netherlands (85.9%), had a college or university degree (78.9%), identified as exclusively homosexual (81.3%), and lived in Amsterdam (85.9%).

The median number of casual partners among PrEP initiators was 12 (IQR 5 to 25), 63.3% reported CAS with a casual partner, 51.8% specific SDU, and 23.6% had been diagnosed with any STI in the 6 months before the match visit. The characteristics and behaviors of controls were comparable to those of PrEP initiators as the result of matching. Overall, 74.2% of PrEP initiators acquired PrEP outside of study settings at PrEP-initiation. Of those with a known PrEP regimen, 51.4% exclusively used an event-driven regimen in the first months after PrEP-initiation, 41.2% used daily PrEP, and 7.4% used both. There were six HIV seroconversions, all in controls within 1.5 years after baseline. The median follow-up time before and after baseline was 3.9 years (IQR 3.0 to 4.0) and 1.4 years (IQR 0.7 to 1.9), respectively, for PrEP initiators, and 3.8 years (IQR 2.9 to 4.0) and 1.7 years (IQR 0.9 to 2.0) for controls.

Changes in sexual behavior

Figure 3A and Table 2 show changes in sexual behavior end-points both before and after baseline. When studying linear changes within each group during the follow-up period before baseline, all sexual behavior end-points increased in both groups. No statistically significant linear change was observed in end-points during the follow-up period after baseline in either group. Comparing end-points after versus before baseline within each group, in PrEP initiators, the odds of reporting CAS [adjusted odds ratio (aOR) = 1.49, 95% CI 1.01–2.21] and rCAS (aOR = 1.62, 95% CI 1.01–2.29) with casual partners were on average higher after baseline compared with before.

No statistically significant change was observed in the number of casual partners and odds of specific SDU. In controls, all sexual behavior end-points were on average decreased after baseline compared with before. Comparing end-points between groups before baseline, there was no statistically significant difference in sexual behavior end-points, although all end-points except rCAS with casual partners were slightly increased in PrEP initiators. Comparing end-points between groups after baseline, PrEP initiators had a higher number of casual partners (aOR = 1.85, 95% CI 1.45–2.35), and higher odds of CAS (aOR = 5.93, 95% CI 4.08–8.62), rCAS (aOR = 4.75, 95% CI 3.25–6.93), and specific SDU (aOR = 2.26, 95% CI 1.52–3.36) than controls.

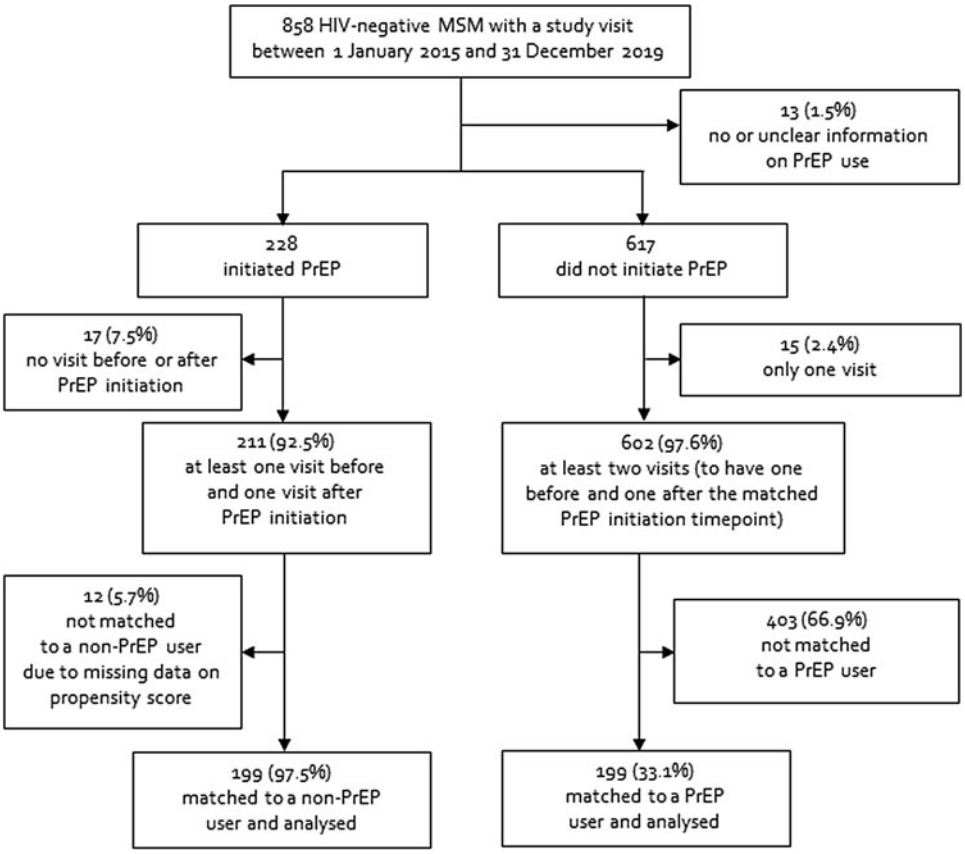

FIG. 1. Flowchart of inclusion into the analysis and matching of PrEP initiators to controls, Amsterdam Cohort Studies, the Netherlands. PrEP, pre-exposure prophylaxis.

Sensitivity analysis showed similar results with respect to the direction of effects, although conclusions of significance sometimes differed (Table 3).

Changes in STI

Crude incidence of any STI before and after baseline was 33.0/100 person-years (PY) and 76.2/100PY, respectively, in PrEP initiators, and 27.9/100PY and 26.9/100PY in controls. Crude incidence of any anal STI before and after baseline was 18.6/100PY and 48.3/100PY, respectively, in PrEP initiators, and 16.3/100PY and 19.2/100PY in controls.

Figure 3B and Table 4 show changes in STI end-points before and after baseline. When studying linear changes within each group during the follow-up period before baseline, the odds of any STI increased in both groups (PrEP initiators aOR = 1.26 per year, 95% CI 1.06–1.51; controls aOR = 1.44 per year, 95% CI 1.19–1.74), but the odds of any

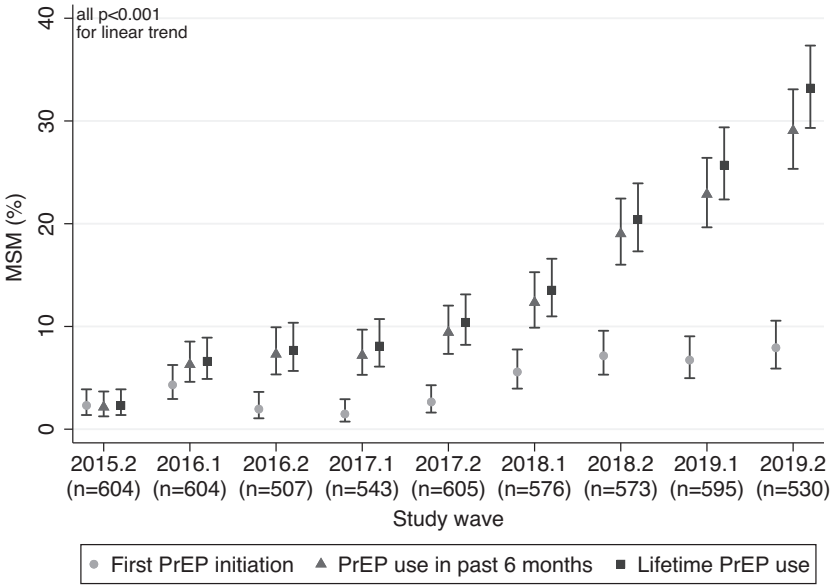

FIG. 2. PrEP use per study wave between 2015 and 2019 ($N = 845$), Amsterdam Cohort Studies, the Netherlands. Squares represent the proportion reporting the end-point; lines represent 95% confidence intervals around this proportion. Participants attended study visits semi-annually; questionnaires were updated semi-annually, giving rise to study waves. From the second half of 2015 onward, all questionnaires included questions on PrEP use. The number of participants per study wave on the x-axis represents the number of participants with data on PrEP use per study wave. Lifetime PrEP use was defined as ever reporting use of PrEP. PrEP, pre-exposure prophylaxis.

Table 1. Characteristics of Pre-Exposure Prophylaxis Initiators and Matched Controls (N = 398), Amsterdam Cohort Studies, Amsterdam, the Netherlands, 2015–2019

	PrEP initiators (n = *199*), n *(%)*	*Controls* (n = *199*), n *(%)*	p
Sociodemographic characteristics			
Age in years,[a] median [IQR]	41.9 [34.1–48.7]	43.0 [29.9–50.9]	0.93
18–34	54 (27.1)	58 (29.2)	0.36
35–44	65 (32.7)	52 (26.1)	
45+	80 (40.2)	89 (44.7)	
Born in the Netherlands[b]	171 (85.9)	163 (81.9)	0.28
College or university degree[b] (3 missing)	157 (78.9)	150 (75.8)	0.35
Exclusively homosexual[b] (1 missing)	161 (81.3)	165 (82.9)	0.68
Residence in Amsterdam[b]	171 (85.9)	172 (86.2)	0.89
Sexual behavior and STI in the past 6 months[a]			
Number of casual partners, median [IQR]	12 [5–25]	10 [5–20]	0.12
CAS with casual partner	126 (63.3)	110 (55.3)	0.10
Receptive CAS with casual partner	91 (45.7)	96 (48.2)	0.62
Specific SDU	103 (51.8)	92 (46.2)	0.27
Any STI	47 (23.6)	56 (28.1)	0.30
Anal STI	24 (12.1)	34 (17.1)	0.16
Information on match			
Calendar year of match visit			<0.001
2015	37 (18.6)	46 (23.1)	
2016	19 (9.6)	51 (25.6)	
2017	34 (17.1)	42 (21.1)	
2018	70 (35.2)	42 (21.1)	
2019	39 (19.6)	18 (9.1)	
Years between matched PrEP-initiation timepoint and date of PrEP-initiation (negative = matched timepoint was earlier than date of PrEP-initiation), median [IQR]		−0.6 [−1.9–0.4]	
Propensity score at match visit, median [IQR]	2.8 [1.8–3.6]	2.7 [1.8–3.6]	0.87
PrEP use			
Source of PrEP[c] (5 missing)			
Provided in study context outside the ACS	50 (25.8)	n.a.	
Informal or prescribed	144 (74.2)	n.a.	
PrEP regimen[d] (24 missing)			
Daily	72 (41.2)	n.a.	
Event-driven	90 (51.4)	n.a.	
Both daily and event-driven	13 (7.4)	n.a.	
HIV seroconversion during follow-up	0 (0)	6 (3.0)	

[a]At the match visit, that is, last visit before PrEP-initiation or matched PrEP-initiation timepoint.
[b]At most recent visit before the match visit, if available, or enrollment.
[c]PrEP was provided to some users in the context of a demonstration study (AMPrEP), trial (DISCOVER), and a cohort of informal PrEP users if not already prescribed PrEP. Before PrEP was widely available through prescription, some users obtained it abroad, via friends or HIV doctors. The ACS on HIV started prescribing PrEP in August 2019, with the start of the National PrEP Program (here categorized as ''prescribed'').
[d]During the first period after initiation.
ACS, Amsterdam Cohort Studies; AMPrEP, Amsterdam PrEP project; CAS, condomless anal sex; HIV, human immunodeficiency virus; IQR, interquartile range; n.a., not applicable; PrEP, pre-exposure prophylaxis; SDU, sexualized drug use; STI, sexually transmitted infection.

anal STI only increased in controls (aOR = 1.43 per year, 95% CI 1.15–1.79). No statistically significant linear change in STI end-points was observed in PrEP initiators during the follow-up after baseline, whereas any anal STI decreased after baseline in controls (aOR = 0.59 per year, 95% CI 0.36–0.96).

The odds of any STI also decreased during follow-up in controls, but the effect was not statistically significant. Comparing end-points after versus before baseline within each group, in PrEP initiators, the odds of any anal STI were on average higher after baseline compared with before (aOR = 2.18, 95% CI 1.20–3.96), whereas the odds of any STI were on average higher, but the effect was not statistically significant (aOR = 1.24, 95% CI 0.78–1.98). In controls, STI end-points were on average decreased after baseline compared with before (any STI aOR = 0.50, 95% CI 0.32–0.79; any anal STI aOR = 0.56, 95% CI 0.32–0.97).

Comparing end-points between groups before baseline, STI end-points did not differ between the two groups. Comparing end-points between groups after baseline, PrEP initiators had on average higher odds of any STI (aOR = 2.00, 95% CI 1.36–2.93) and any anal STI (aOR = 1.93, 95% CI 1.25–2.98) than controls.

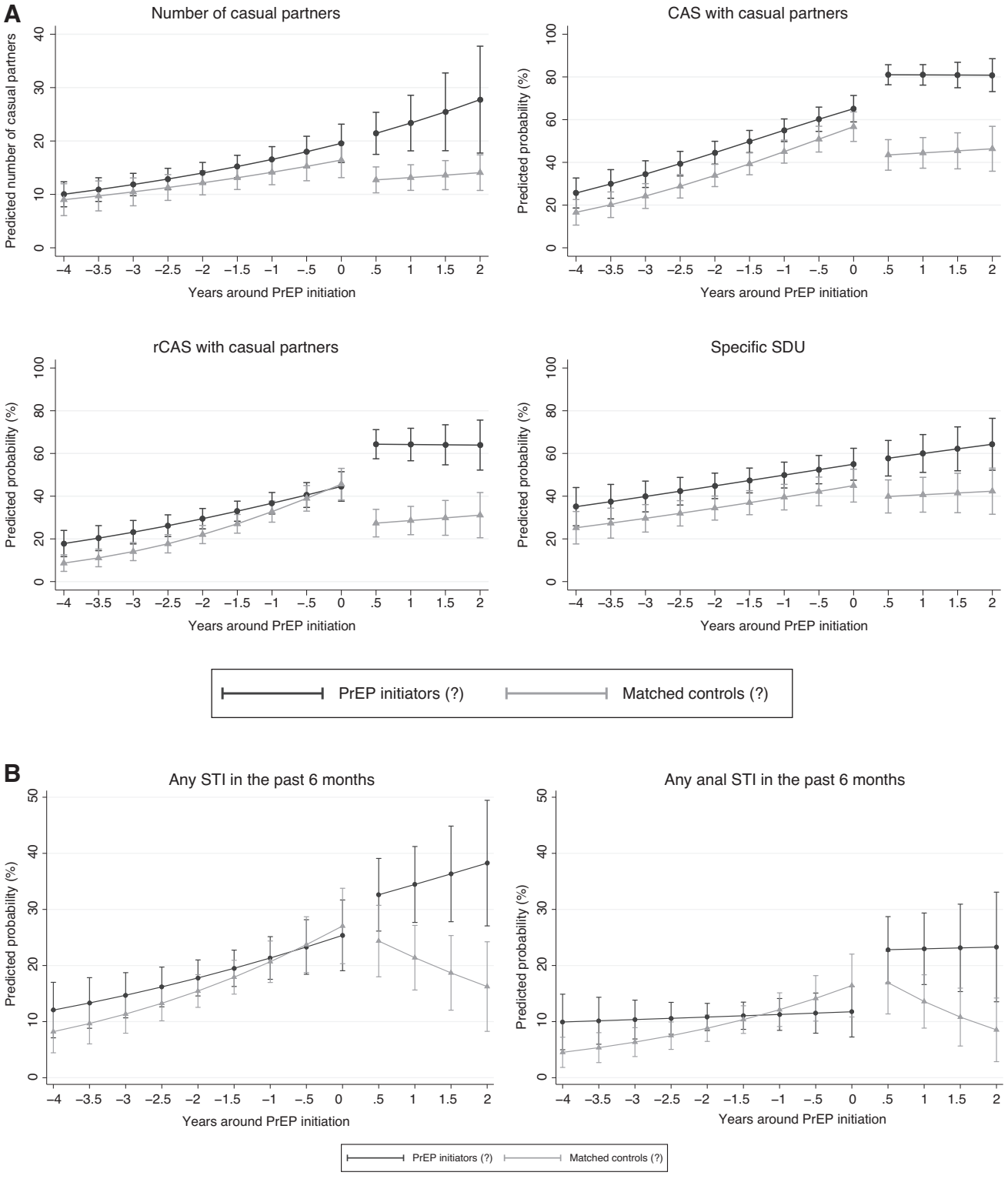

FIG. 3. Modeled changes in **(A)** sexual behavior and **(B)** sexually transmitted infections over time in the 4 years before and 2 years after baseline among PrEP initiators and matched controls ($N = 398$), Amsterdam Cohort Studies, the Netherlands. Lines represent 95% confidence intervals. $T = 0$ represents baseline, defined as the date of PrEP-initiation for PrEP initiators or matched PrEP-initiation timepoint for controls. PrEP, pre-exposure prophylaxis.

Table 2. Modeled Changes in Sexual Behavior Over Time in the 4 Years Before and 2 Years After Baseline Among Pre-Exposure Prophylaxis Initiators and Matched controls ($N=398$), Amsterdam Cohort Studies, the Netherlands

	Number of casual partners[a]			*CAS with casual partners*[a]			*Receptive CAS with casual partners*[a]			*Specific SDU*[a]		
	aRR	*95% CI*	p	*aOR*	*95% CI*	p	*aOR*	*95% CI*	p	*aOR*	*95% CI*	p
Within PrEP initiators												
Before PrEP-initiation (per year)	1.18	1.09–1.28	<0.001	1.55	1.37–1.77	<0.001	1.39	1.21–1.60	<0.001	1.23	1.08–1.40	0.002
After PrEP-initiation (per year)	1.19	0.99–1.42	0.061	1.00	0.73–1.36	0.96	0.99	0.76–1.29	0.93	1.20	0.92–1.57	0.17
After compared with before (ref.) baseline	1.01	0.84–1.21	0.91	1.49	1.01–2.21	0.042	1.62	1.01–2.29	0.007	1.00	0.76–1.32	0.98
Within matched controls												
Before PrEP-initiation (per year)	1.16	1.05–1.29	0.003	1.63	1.40–1.89	<0.001	1.73	1.14–2.04	<0.001	1.25	1.09–1.42	0.001
After PrEP-initiation (per year)	1.07	0.93–1.23	0.34	1.08	0.84–1.40	0.55	1.13	0.83–1.53	0.44	1.07	0.87–1.31	0.51
After compared with before (ref.) baseline	0.69	0.57–0.83	<0.001	0.37	0.27–0.52	<0.001	0.27	0.19–0.39	<0.001	0.67	0.51–0.90	0.007
PrEP initiators compared with controls (ref.) within each period												
Before baseline	1.26	0.95–1.66	0.10	1.47	0.91–2.39	0.11	0.81	0.49–1.33	0.40	1.52	0.96–2.39	0.071
After baseline	1.85	1.45–2.36	<0.001	5.93	4.08–8.62	<0.001	4.75	3.25–6.93	<0.001	2.26	1.52–3.36	<0.001

Baseline was defined as the date of PrEP-initiation for PrEP initiators or matched PrEP-initiation timepoint for controls.
[a]In the past 6 months and adjusted for calendar year.
aOR, adjusted odds ratio; aRR, adjusted relative ratio; CAS, condomless anal sex; CI, confidence interval; PrEP, pre-exposure prophylaxis; SDU, sexualized drug use.

Table 3. Modeled Changes in Sexual Behavior Over Time in the 4 Years Before and 2 Years After Baseline Among Pre-Exposure Prophylaxis Initiators and Matched Controls with a Visit At Least 1.5 Years After Baseline ($N=150$), Amsterdam Cohort Studies, the Netherlands

	Number of casual partners[a]			*CAS with casual partners*[a]			*Receptive CAS with casual partners*[a]			*Specific SDU*[a]		
	aRR	*95% CI*	p	*aOR*	*95% CI*	p	*aOR*	*95% CI*	p	*aOR*	*95% CI*	p
Within PrEP initiators												
Before PrEP-initiation (per year)	1.12	0.98–1.28	0.11	1.61	1.26–2.06	<0.001	1.40	1.07–1.82	0.015	1.21	0.98–1.54	0.11
After PrEP-initiation (per year)	1.30	1.08–1.57	0.005	0.92	0.58–1.46	0.72	0.90	0.63–1.29	0.56	1.24	0.91–1.69	0.18
After compared with before (ref.) baseline	1.10	0.86–1.41	0.43	1.30	0.65–2.59	0.46	1.64	0.90–2.97	0.10	0.93	0.60–1.40	0.75
Within matched controls												
Before PrEP-initiation (per year)	1.10	0.97–1.25	0.13	1.47	1.13–1.90	0.004	1.49	1.14–1.95	0.003	1.21	0.96–1.42	0.081
After PrEP-initiation (per year)	1.04	0.94–1.16	0.45	1.13	0.88–1.46	0.33	0.99	0.78–1.26	0.92	1.05	0.81–1.40	0.56
After compared with before (ref.) baseline	0.72	0.53–0.97	0.030	0.34	0.19–0.59	<0.001	0.32	0.18–0.57	<0.001	0.55	0.51–1.04	0.030
PrEP initiators compared with controls (ref.) within each period												
Before baseline	1.38	0.98–1.95	0.067	2.49	1.14–5.42	0.022	1.15	0.47–2.51	0.73	1.73	1.01–3.97	0.15
After baseline	2.12	1.57–2.85	<0.001	9.59	5.49–16.73	<0.001	6.00	3.46–10.3	<0.001	2.95	1.46–4.31	<0.001

Baseline was defined as the date of PrEP-initiation for PrEP initiators or matched PrEP-initiation timepoint for controls.
[a]In the past 6 months and adjusted for calendar year.
aOR, adjusted odds ratio; aRR, adjusted relative ratio; CAS, condomless anal sex; CI, confidence interval; PrEP, pre-exposure prophylaxis; SDU, sexualized drug use.

Table 4. Modeled Changes in Sexually Transmitted Infection Over Time in the 4 Years Before and 2 Years After Baseline Among Pre-Exposure Prophylaxis Initiators and Matched Controls ($N=398$), Amsterdam Cohort Studies, the Netherlands

	Any STI diagnosis[a]			*Any anal STI diagnosis*[a]		
	aOR	*95% CI*	p	*aOR*	*95% CI*	p
Within PrEP initiators						
Before PrEP-initiation (per year)	1.26	1.06–1.51	0.009	1.05	0.84–1.31	0.67
After PrEP-initiation (per year)	1.19	0.87–1.61	0.27	1.02	0.75–1.39	0.91
After compared with before (ref.) baseline	1.24	0.78–1.98	0.35	2.18	1.20–3.96	0.011
Within matched controls						
Before PrEP-initiation (per year)	1.44	1.19–1.74	<0.001	1.43	1.15–1.79	0.034
After PrEP-initiation (per year)	0.71	0.47–1.06	0.090	0.59	0.36–0.96	0.040
After compared with before (ref.) baseline	0.50	0.32–0.79	0.003	0.56	0.32–0.97	0.045
PrEP initiators compared with controls (ref.) within each period						
Before baseline	0.81	0.43–1.51	0.50	0.49	0.23–1.06	0.070
After baseline	2.00	1.36–2.93	<0.001	1.93	1.25–2.98	0.003

Baseline was defined as the date of PrEP-initiation for PrEP initiators or matched PrEP-initiation timepoint for controls.
[a]In the past 6 months and adjusted for calendar year and number of tests in the past 6 months.
aOR, adjusted odds ratio; CI, confidence interval; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection.

Sensitivity analysis showed similar results with respect to the direction of effects, although conclusions of significance sometimes differed (Tables 5 and 6).

Discussion

This longitudinal analysis of sexual behavior and STI in a cohort of HIV-negative MSM in Amsterdam shows that the proportion with CAS, rCAS, and anal STI increased in PrEP initiators during the first 2 years after PrEP-initiation, both compared with the 4 years before PrEP-initiation and with matched controls who did not initiate PrEP.

A major strength of this study is that we were able to compare end-points in MSM who initiated PrEP during follow-up with those of comparable MSM from the same cohort who did not initiate PrEP. To the best of our knowledge, this is the first study to include data on the period before PrEP-initiation for PrEP initiators and for a similar period in a matched control group. The vast majority of previous studies did not include a control group of non-PrEP users or controls were insufficiently matched, whereas most had no or limited follow-up time before PrEP-initiation.[3,4] Another major strength is that both groups were regularly tested for HIV and STI for several years, at least every 6 months or more often in the case of symptoms or partner notification.

To further limit ascertainment bias, we accounted for increased STI screening in PrEP users (three-monthly instead of six-monthly) by reducing our end-point ascertainment to a single common frequency (i.e., six-monthly) and by adjusting for the number of STI tests.

The proportion of PrEP initiators with CAS and rCAS with casual partners increased after PrEP-initiation, which suggests risk compensation in the context of PrEP (i.e., decline in condom use due to decreased perceived HIV risk). This is in line with most open-label studies comparing periods before and after PrEP-initiation.[4,13] In addition, we found an increased proportion of PrEP initiators diagnosed with an anal STI after PrEP-initiation, which further corroborates the increased proportion of self-reported CAS and rCAS.

As this increase in STI was not observed in controls and independent of changes over the calendar year, it is unlikely caused by temporal trends. A similarly designed study conducted in Seattle, Washington, among PrEP-using MSM, who were compared with propensity score matched historical controls, also observed a higher STI incidence after PrEP-initiation.[14] Taken together, these findings support PrEP guidelines in recommending frequent (i.e., quarterly), routine STI screening and sexual behavior counseling in PrEP users.[15] More pleasurable sex, without fear of HIV, is an important reason for MSM to use PrEP and not all MSM are willing to use condoms while using PrEP as it might interfere with sexual pleasure.[16,17]

Alongside promoting adherence to condoms as part of HIV/STI prevention services, additional STI prevention strategies should be explored, such as risk-reduction interventions and non-condom based prevention such as point-of-care testing, at-home self-sample STI tests, and doxycycline prophylaxis.[18–20] Further, increased STI screening and treatment might result in decreased STI incidence in MSM, even in the context of risk compensation.[21,22]

Although the trends illustrated in this study are at the population level, increases in CAS and STI rates are known to be driven by certain characteristics and behaviors. A previous study of early adopting PrEP users in Amsterdam showed that older MSM, MSM who report chemsex or post-exposure prophylaxis use before PrEP-initiation, and MSM who chose daily PrEP were more likely to increase rCAS with casual partners after PrEP-initiation.[13] Moreover, a previous analysis within our cohort showed strong associations between specific SDU and CAS, HIV, and STI.[12] This suggests that MSM with these characteristics could be specifically targeted for sexual behavior counseling that targets the prevention and management of STI, including counseling on sexual behavior in the context of SDU.

Although our results give reason to believe that PrEP-initiation induced an increase in CAS and STI, it also suggests that PrEP prevented several incidents of HIV infections. We observed six HIV seroconversions in controls and none in PrEP users. These infections might have been prevented had

Table 5. Modeled Changes in Sexually Transmitted Infection Diagnoses Over Time in the 4 Years Before and 2 Years After Baseline Among Pre-Exposure Prophylaxis Initiators and Matched Controls with a Visit At Least 1.5 Years After Baseline ($N=150$), Amsterdam Cohort Studies, the Netherlands

	Any STI diagnosis[a]			*Any anal STI diagnosis*[a]		
	aOR	*95% CI*	p	*aOR*	*95% CI*	p
Within PrEP initiators						
Before PrEP-initiation (per year)	1.45	1.10–1.92	0.010	1.19	0.78–1.81	0.43
After PrEP-initiation (per year)	0.92	0.61–1.38	0.78	0.88	0.58–1.35	0.57
After compared with before baseline (ref.)	0.69	0.37–1.30	0.39	1.97	0.73–5.30	0.18
Within matched controls						
Before PrEP-initiation (per year)	1.24	0.94–1.65	0.13	1.35	1.01–1.82	0.044
After PrEP-initiation (per year)	0.97	0.71–1.33	0.23	0.93	0.64–1.34	0.69
After compared with before (ref.) baseline	0.29	0.14–0.61	0.035	0.32	0.13–0.77	0.011
PrEP initiators compared with controls (ref.) within each period						
Before baseline	1.58	0.68–3.66	0.25	0.59	0.17–2.02	0.40
After baseline	3.71	2.06–6.69	<0.001	3.65	1.83–7.29	<0.001

Baseline was defined as the date of PrEP-initiation for PrEP initiators or matched PrEP-initiation timepoint for controls.
[a]In the past 6 months and adjusted for calendar year and number of tests in the past 6 months.
aOR, adjusted odds ratio; CI, confidence interval; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection.

PrEP been used. The lack of incident HIV in PrEP users, of whom more than half used event-driven PrEP, is consistent with the proven effectiveness of PrEP.[1,23] However, although uncommon, PrEP users are still at risk of HIV infections and HIV incidence rates may vary by, for example, socioeconomic status, race, ethnicity, and recreational drug use.[24] In addition, global PrEP access and uptake is still suboptimal,[25] also in the Netherlands,[26] and should be improved if HIV elimination is to be achieved.[27]

As the availability of and access to PrEP is increasing in the Netherlands, most recently through the National PrEP implementation program launched in 2019,[8] it would be expected that PrEP uptake also increases. Indeed, in our cohort, PrEP use increased from 2% in 2015 to 29% in the second half of 2019. Interestingly, the percentage of PrEP users initiating event-driven PrEP is higher than the percentage observed in the Amsterdam PrEP project,[7] but similar to that of a cohort of informal PrEP users in Amsterdam.[28]

Most open-label studies found no change in the number of partners after PrEP-initiation.[4,13] A few studies investigated changes in SDU. In our study, both the number of casual partners and the proportion reporting specific SDU did not change after PrEP-initiation compared with before in both groups. The lack of change in the proportion of PrEP initiators engaging in specific SDU is supported by an Australian study finding no new methamphetamine use in PrEP users compared with an unmatched control group.[29]

Strikingly, the proportion of controls with any or an anal STI decreased over time after hypothetical PrEP-initiation, whereas we expected a stable or slightly increasing trend from trends in the overall MSM population during the same

Table 6. Modeled Changes in Sexually Transmitted Infection Diagnoses Over Time in the 4 Years Before and 2 Years After Baseline Among Pre-Exposure Prophylaxis Initiators and Matched Controls, Additionally Adjusted for Having a Steady Partner and Specific Sexualized Drug Use ($N=398$), Amsterdam Cohort Studies, the Netherlands

	Any STI diagnosis[a]			*Any anal STI diagnosis*[a]		
	aOR	*95% CI*	p	*aOR*	*95% CI*	p
Within PrEP initiators						
Before PrEP-initiation (per year)	1.20	1.00–1.44	0.051	1.02	0.81–1.29	0.86
After PrEP-initiation (per year)	1.30	0.92–1.84	0.14	1.11	0.76–1.61	0.60
After compared with before (ref.) baseline	1.46	0.90–2.36	0.13	2.13	1.11–4.09	0.022
Within matched controls						
Before PrEP-initiation (per year)	1.37	1.13–1.67	0.001	1.37	1.08–1.73	0.008
After PrEP-initiation (per year)	0.75	0.47–1.20	0.23	0.63	0.36–1.10	0.11
After compared with before (ref.) baseline	0.57	0.35–0.93	0.024	0.60	0.33–1.12	0.11
PrEP initiators compared with controls (ref.) within each period						
Before baseline	0.75	0.39–1.43	0.38	0.50	0.22–1.13	0.096
After baseline	1.91	1.25–2.94	0.003	1.76	1.08–2.89	0.025

Baseline was defined as the date of PrEP-initiation for PrEP initiators or matched PrEP-initiation timepoint for controls.
[a]In the past 6 months and adjusted for calendar year, number of tests in the past 6 months, having a steady partner, and specific SDU.
aOR, adjusted odds ratio; CI, confidence interval; PrEP, pre-exposure prophylaxis; SDU, sexualized drug use; STI, sexually transmitted infection.

years.[5] Our sensitivity analyses suggest that this decrease is unlikely the result of differential loss to follow-up, or differences in having a steady partner or specific SDU. It is likely the result of regression to the mean. More specifically, our matching procedure could have identified controls with exceptional behaviors at a specific visit, such as a visit when the participant was between two steady relationships and the increased number of sexual partners or condomless sex with casual partners.

Any decrease observed would be an artefact of returning to an individual's average level of behavior. Alternative methods of matching to mitigate the effects of regression to the mean, such as matching based on multiple visits, would have been challenged by the high variability in end-points within a person over time and would likely have resulted in a more selective groups of controls. Moreover, since similar decreases over time after baseline were not seen in sexual behavior end-points, the extent to which regression to the mean influenced our results is unclear. Regardless, it should be mentioned that regression to the mean was not apparent in trends among PrEP users.

Our study should be interpreted in light of several limitations. First, matched individuals might not have fully represented a group at risk of initiating PrEP (i.e., the ideal control group), which could have confounded our estimated effect of PrEP-initiation on end-points. There may have been unmeasured confounding that we could not control for by matching. For example, personal circumstances, such as mental health issues, might have prevented eligible controls from initiating PrEP[30] and might also be associated with the end-points. Further, this study included mainly Amsterdam-based MSM, the majority of whom was born in the Netherlands and highly educated, and therefore may not represent the larger MSM population.

In conclusion, we showed an increase in the prevalence of CAS, rCAS, and anal STI in MSM during the 2 years after PrEP-initiation, compared with the 4 years before and compared with MSM who did not initiate PrEP. These findings support frequent STI screening and STI-specific counseling in MSM using PrEP. More research into additional, non-condom based, interventions to prevent STI should be conducted among MSM using PrEP.

Authors' Contributions

M.P. conceptualized the study. A.M., M.P., U.D., and MSvdL acquired funding. W.v.B., A.M., U.D., M.P., L.C., and M.S.v.d.L. were involved in data acquisition and study oversight. L.C. and W.v.B. cleaned the data. L.C. conducted data analysis under supervision of A.M. and A.B. L.C. drafted the article. All authors critically revised the article and approved the final version.

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Address correspondence to:
Liza Coyer, MSc
Department of Infectious Diseases
Public Health Service of Amsterdam
Nieuwe Achtergracht 100
Amsterdam 1018 WT
the Netherlands

E-mail: lcoyer@ggd.amsterdam.nl