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secondary outcomes of a randomized controlled trial

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Impact of reduced-frequency monitoring among users of HIV pre-exposure prophylaxis on sexually transmitted infections and associated care: secondary outcomes of a randomized controlled trial

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Abstract

Background Oral HIV pre-exposure prophylaxis (PrEP) users are generally screened for sexually transmitted infections (STIs) every 3 months. The need for such frequent screening is debatable. We compared STI diagnoses and associated care between PrEP users who underwent 6-monthly versus 3-monthly PrEP monitoring.

Methods We conducted a secondary analysis of the EZI-PrEP study— a 2×2 factorial randomized controlled trial examining 6-monthly versus 3-monthly and online versus in-clinic PrEP monitoring among men who have sex with men (MSM) and transgender or gender-diverse persons in the Netherlands (2021–2024). Participants were followed for 24 months. Scheduled PrEP monitoring included bacterial STI screening (i.e., *Neisseria gonorrhoeae* (NG), *Chlamydia trachomatis* (CT), syphilis). Unscheduled STI testing in-between monitoring visits was permitted. This secondary analysis compared several outcomes between the 6-monthly and 3-monthly monitoring groups, using Poisson regression: (i) visit rates as number of visits per person-year (PY), (ii) STI detection rates as number of STI diagnoses per 100PY (to assess STI detection and potential (over)treatment), and (iii) STI positivity as number of STI diagnoses per 100 visits (as proxy for diagnostic delay). We stratified outcomes by visit type (i.e., scheduled/unscheduled) and adjusted for sexual behavior.

Results 451 participants (99% MSM) were followed for median 22.7 months (IQR 19.2–23.8). Compared to 3-monthly PrEP monitoring, 6-monthly monitoring led to 31% fewer visits in total (rate ratio = 0.69, 95%CI = 0.64–0.74), but 67%

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more unscheduled visits (rate ratio = 1.67, 95%CI = 1.42–1.98). The STI detection rate was 18% lower in the 6-monthly monitoring group (adjusted rate ratio = 0.82, 95%CI = 0.70–0.95). STI positivity at PrEP monitoring visits did not differ between monitoring groups (6-monthly: 23.8 STIs/100 visits; 3-monthly: 23.2 STIs/100 visits; adjusted positivity ratio = 1.09, 95%CI = 0.90–1.30).

Conclusions Reduced-frequency PrEP monitoring resulted in fewer total clinic visits, but more self-initiated STI testing. Furthermore, fewer STIs were diagnosed during follow-up, yet the number of STIs detected per scheduled monitoring visit was similar between groups. These findings suggest that less frequent PrEP monitoring could reduce the burden of PrEP care and the number of STIs that are detected and treated, without leading to a substantial rise in STIs.

Trial registration The trial has been registered with ClinicalTrials.gov, trial number NCT05093036 (https://clinicaltrials.gov/study/NCT05093036).

Keywords HIV preexposure prophylaxis, Sexually transmitted infections, Screening frequency, Antibiotics

Background

The incidence of sexually transmitted infections (STI) is high among populations who use HIV pre-exposure prophylaxis (PrEP) [1–3]. Many PrEP guidelines, including those from the Netherlands from 2016–2024, have recommend screening users for bacterial STIs every three months [4, 5]. However, there is growing debate about the potential benefits and harms of such frequent STI screening. First, three-monthly screening is costly and intensive for both PrEP care providers and PrEP users [6–8], whilst some PrEP users are rarely diagnosed with an STI [2, 3, 9, 10]. Second, serious sequelae in men are rare for chlamydia and gonorrhea, and rare for syphilis when diagnosed and treated within six months [11]. Third, frequent use of antibiotics can drive antimicrobial resistance (AMR) and disturb the microbiome [12–14]. Fourth, studies aiming to assess the (potential) effect of frequent STI screening draw contrasting conclusions [6, 15–22].

Several modelling studies suggest that frequent screening can reduce STI prevalence among men who have sex with men (MSM), by reducing diagnostic delay and thus ongoing transmission [6, 15, 16]. Moreover, two scenario analyses estimated that 30–35% of STIs would be diagnosed with delay if PrEP users were screened for STIs every 6 months rather than every 3 months [17, 18]. However, there is a dearth of real-world evidence demonstrating that more frequent screening is associated with a reduced prevalence of gonorrhea and chlamydia among MSM [19–21]. A recent observational study from Belgium showed no increases in the incidence of symptomatic gonorrhea or chlamydia among MSM using PrEP after asymptomatic screening for these STIs was ceased in this population in 2023 [22].

To the best of our knowledge, no randomized trial has examined the effect of 6-monthly versus 3-monthly PrEP monitoring on STIs and its associated care. The EZI-PrEP study is a randomized controlled trial that examined the effectiveness, feasibility, and acceptability of online (versus in-clinic) and 6-monthly (versus 3-monthly) PrEP monitoring [23]. The primary objective of the EZI-PrEP trial was to assess whether online and 6-monthly monitoring are non-inferior to the standard of care in terms of PrEP adherence; non-inferiority was established for both interventions [24]. Here, we evaluate one of the secondary objectives of the trial, which was to assess differences in the incidence of bacterial STIs between PrEP care modalities. In the current analysis, we aimed to examine the impact of reduced-frequency monitoring on four key aspects of STIs and the associated care: (i) STI testing behavior and the burden on PrEP care (by comparing visit rates), (ii) the total number of STIs that would be detected and treated (by comparing STI detection rates), (iii) antibiotic use (by comparing the volume of prescribed antibiotics), and (iv) the potential extent of diagnostic delay when screening less frequently (by comparing the number of STIs diagnosed per 100 visits).

Methods

Study design, setting, and participants

The EZI-PrEP study (conducted from 2021–2024) was a 2 × 2 factorial, open-label, multicenter, randomized controlled trial with four arms: (i) in-clinic monitoring every 3 months, (ii) in-clinic monitoring every 6 months, (iii) online-mediated monitoring every 3 months, or (iv) online-mediated monitoring every 6 months [23]. The primary objective of the EZI-PrEP study was to assess the non-inferiority of online (versus in-clinic) and 6-monthly (versus 3-monthly) PrEP monitoring in terms of PrEP adherence; non-inferiority of the primary outcome had been established [24]. A secondary objective of the trial was to assess differences in the incidence of bacterial STIs between PrEP care modalities. As we did not expect that online monitoring would have an effect on STI incidence, this analysis focuses exclusively on the comparison between 6-monthly and 3-monthly PrEP monitoring.

EZI-PrEP was embedded in the Dutch national PrEP pilot program (NPP). The NPP offered free-of-charge

PrEP care and subsidized PrEP tablets to PrEP-eligible individuals (i.e., individuals who engaged in condomless anal sex with a male partner with unknown or detectable viral load, had a rectal STI, or used HIV post-exposure prophylaxis (PEP) in the past 6 months) via centers for sexual health [25]. Four centers for sexual health participated in EZI-PrEP: Amsterdam, Rotterdam, The Hague, and Nijmegen.

Individuals eligible for EZI-PrEP participation were MSM or TGD persons without HIV, aged 18 years or older, who were eligible for the NPP, living in the catchment area of a participating center, and who provided written informed consent for study participation [23]. Both PrEP starters and experienced PrEP users were eligible for EZI-PrEP. In this analysis, we included data of EZI-PrEP participants who had at least one follow-up monitoring visit.

Sample size

The sample size was calculated based on the trial's primary outcome (i.e., PrEP adherence); calculations are described in the protocol [23].

Randomization and masking

This study was open-label and non-blinded to participants and researchers. Participants were randomly allocated to one of the four study arms in a 1:1:1:1 ratio, in permuted blocks of 4, stratified by participating center and PrEP experience, by an independent statistician.

NPP procedures

NPP participants could choose to take oral PrEP as a daily or event-driven regimen (i.e., two tablets 2–24 h before sex, one tablet 24 h after, and 1 tablet 48 h after); regimen switches were allowed. In the NPP, scheduled PrEP monitoring occurred every 3 months. Unscheduled, additional STI/HIV testing in-between monitoring visits was permitted (e.g., after symptoms, partner notification, or behaviors associated with STIs).

Monitoring visits included counselling, screening for HIV and bacterial STIs (i.e., gonorrhea, chlamydia, and syphilis), and a questionnaire on sexual behavior. For *Neisseria gonorrhoeae* (NG) and *Chlamydia trachomatis* (CT), anorectal, urogenital, and oropharyngeal samples were obtained and analyzed. In case of an anorectal chlamydia diagnosis, individuals were tested for lymphogranuloma venereum (LGV). If an STI was detected, free-of-cost treatment was provided following national guidelines [26, 27]. Treatment usually consisted of ceftriaxone for gonorrhea, doxycycline or azithromycin for chlamydia, and benzathine penicillin for syphilis. Routine questionnaires included, but were not limited to, questions on number of partners, condomless sex, group sex, and sexualized drug use. We defined chemsex as the use of crystal methamphetamine, gamma-hydroxybutyrate (GHB)/gamma-butyrolactone (GBL), mephedrone or ketamine around the time of sex.

Data on HIV/STI testing and diagnoses and sexual behavior were pseudonymized and sent to the national STI surveillance database (SOAP) for monitoring and surveillance purposes. Informed consent to transfer data with SOAP was obtained through an op-out procedure; data were handled in accordance with European privacy legislation.

Study-specific procedures

Study procedures have been described previously [23]. In brief, scheduled PrEP monitoring occurred every 3 or 6 months, depending on the study arm, for a total of 24 months. With respect to PrEP monitoring visits and unscheduled testing visits, routine NPP procedures were followed. At baseline and every six months thereafter, participants were asked to complete questionnaires on PrEP intake, sexual behavior, and mental health. In case of early study discontinuation, we recorded reasons for discontinuation. Deviations from the study protocol include (i) enrolment of six more individuals than planned in Rotterdam and (ii) no longer testing for pharyngeal chlamydia at the Centres of Sexual Health in November 2023, following changes in the national guidelines [28]. For this study, we used data from the baseline and follow-up questionnaires of the EZI-PrEP study, data on STI testing and diagnoses from SOAP. For the research question on antibiotic prescriptions, we extracted routinely registered prescription data from two study sites - Amsterdam and The Hague.

Outcomes

We used the term 'monitoring visits' to refer to PrEP monitoring visits that were scheduled every 3 or 6 months, depending on study arm. We used 'unscheduled visits' to refer to visits to a sexual health clinic that occurred in-between monitoring visits, were initiated by the participant, and where an STI test was performed (excluding test-of-cure visits). We used 'total visits' to refer to visits that were scheduled or unscheduled.

To examine STI testing, we assessed the number of total visits, scheduled visits, and unscheduled visits. We calculated visit rates as the number of visits divided by the person-years (PY) of follow-up. We report reasons for unscheduled visits.

For each specific STI and STI grouping, we calculated STI detection rates per 100PY of follow-up (i.e., with person-time as the denominator) and the STI positivity per 100 visits (i.e., with number of visits as the denominator). We calculated STI detection rates to gain insight into the number of detected STIs, spontaneous clearance of STIs, and the potential extent of overtreatment

when monitoring every 3 months (Fig. 1). We calculated STI positivity to gain insight into the potential extent of diagnostic delay in the 6-monthly monitoring group. Here, we focus on STI positivity at monitoring visits for the following reason: assuming that both groups have a constant and identical STI acquisition rate, neither group initiates unscheduled STI testing, and no spontaneous STI clearance takes place, all STIs diagnosed at month 3, 9, 15, or 21 in the 3-monthly monitoring group would be diagnosed with delay in the 6-monthly monitoring group (i.e., at month 6, 12, 18, and 24). In that case, the STI positivity at monitoring visits would be approximately twice as high in the 6-monthly monitoring group compared to the 3-monthly monitoring group, reflecting diagnostic

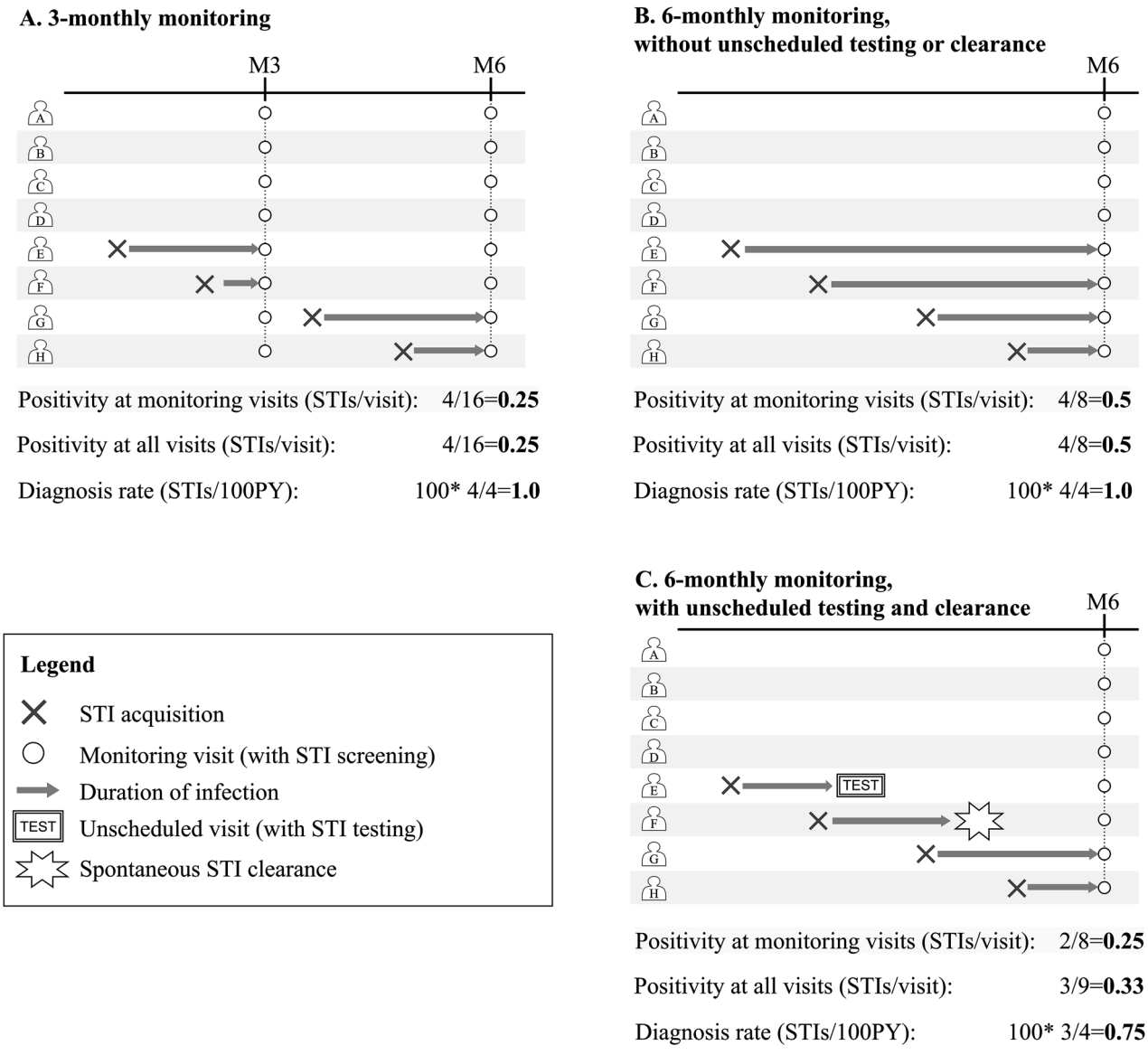

Fig. 1 Visual example of the STI positivity and detection rate for 6-monthly versus 3-monthly PrEP monitoring, in the absence and presence of unscheduled testing and STI clearance. *Abbreviations: EZI-PrEP: E-Health for Zero Infections - facilitating access to and use of Pre-Exposure Prophylaxis in the Netherlands; M, month; PY, person-years; STI, sexually transmitted infection.* **A** depicts the standard scenario of 3-monthly STI screening. **B** depicts a scenario where individuals undergo 6-monthly STI screening and do not present for additional testing nor experience spontaneous STI clearance. **C** depicts a scenario where individuals undergo 6-monthly STI screening, some present for additional testing (and treatment), and some experience spontaneous STI clearance. Below each subfigure, STI positivity is expressed as the number of diagnosed STIs / number of visits with an STI test. In **B** (i.e., reduced screening without clearance or additional risk-informed testing), both the overall STI positivity and the STI positivity at scheduled monitoring visits are higher than in **A** (i.e., reference scenario). In **C** (i.e., reduced screening with clearance and additional risk-informed testing), the overall STI positivity is higher than in **A**, but the positivity at scheduled monitoring visits is the same – reflecting the lack of delayed diagnoses in this scenario. The detection rates, calculated as number of STI diagnoses per 100PY, are the same in **A** and **B**. The detection rate is lower in **C** since one STI spontaneously cleared but the observation time remained the same

delay (Fig. 1). The difference in STI positivity at monitoring visits may dissipate if participants in the 6-monthly monitoring group experience spontaneous STI clearance of STIs that would have otherwise been detected at quarterly monitoring visits, or receive testing and treatment in-between monitoring visits (Fig. 1). In the latter scenario, the STI positivity at any visit may still be somewhat higher in the 6-monthly monitoring group than the 3-monthly monitoring group, but could indicate more efficient STI testing (i.e., a favorable outcome) rather than more delayed STI diagnoses (i.e., an unfavorable outcome).

As STI outcomes, we assessed the number of diagnoses of gonorrhea, chlamydia (including lymphogranuloma venereum (LGV)), and infectious syphilis (stage 1, 2 or early latent syphilis). We defined any bacterial STI as the diagnosis of gonorrhea, chlamydia, or infectious syphilis, whereby concurrent infections with different bacteria (e.g., anorectal gonorrhea and anorectal chlamydia) were counted separately, and infections with the same bacterium at different anatomical sites (e.g., urogenital gonorrhea and anorectal gonorrhea) were counted as one. We defined anal STI as the diagnosis of anorectal gonorrhea or anorectal chlamydia, whereby concurrent diagnoses were counted separately. We describe the number of STI diagnoses (in total, stratified by visit type, and stratified by the presence of symptoms) and the distribution of STI diagnoses across participants.

For antibiotic prescription outcomes, we calculated the number of defined daily doses (DDD) of antibiotics prescribed per 1000 person-days of follow-up, following World Health Organization (WHO) methodology [29]. Detailed methods and results can be found in Additional file 1.

Statistical analysis

We performed a modified intention-to-treat analysis including participants who were randomized and attended at least one follow-up monitoring visit. The 3-monthly monitoring group included participants randomized to in-clinic or online monitoring every 3 months (i.e., arm 1 and 3). The 6-monthly monitoring group included participants randomized to in-clinic or online monitoring every 6 months (i.e., arm 2 and 4). Follow-up began at study enrolment (i.e., 'baseline') and continued until the 24 month visit or the visit (scheduled or unscheduled) prior to study discontinuation. Among participants who discontinued the study before month 24, we excluded person-time after their last monitoring visit, to avoid overestimating rates of unscheduled visits and STI detection. We used Cox proportional hazards regression to examine whether study attrition or its determinants differed by monitoring frequency. Detailed methods and results can be found in Additional file 2.

We calculated visit rates per PY of follow-up along with 95% confidence intervals (CI) based on a Poisson distribution, overall and stratified by visit type. We calculated visit rate ratios along with 95%CI to compare visit rates between the 6-monthly and 3-monthly monitoring groups and used a Wald χ^2 test to test for differences. We described the distribution on unscheduled visits across individuals, and assessed determinants of unscheduled visits using Poisson regression. Detailed methods and results can be found in Additional file 3.

We calculated STI detection rates per 100PY of follow-up along with 95%CI based on a Poisson distribution. In calculating PY for STI detection rates, we assumed that infection occurred at the date of positive test. We calculated the detection rate ratio along with 95%CI to compare detection rates across monitoring groups and used a Wald χ^2 test to test for differences.

We report the positivity of STIs at monitoring visits, unscheduled visits, and any visit. Using Poisson regression, we estimated the positivity ratio (PR) along with 95%CI to compare STI positivity between the 6-monthly and 3-monthly monitoring groups, and used a Wald χ^2 test to test for differences.

For all outcomes, we calculated unadjusted estimates and estimates adjusted for post-randomization imbalances in sexual behavior through participant weights. Weights were calculated by modelling the probability of being randomized to 6-monthly (versus 3-monthly) monitoring on the covariates number of sex partners (in quartiles), chemsex (yes/no), and group sex (yes/no) – all in the 6 months preceding baseline - using logistic regression and taking the inverse of this probability. Because we observed no interactions between monitoring frequency and modality (i.e., online or in-clinic), we did not stratify analyses by monitoring modality (Additional file 4). We descriptively summarized data on antibiotic prescriptions by monitoring group.

Ethics approval

The EZI-PrEP Trial was approved by the medical ethics committee of the Amsterdam University Medical Center, file number 2020_154 - NL74494.018.20. The trial has been registered with ClinicalTrials.gov, trial number NCT05093036 (https://clinicaltrials.gov/study/NCT05093036).

Results

Description of the study participants

Between 21 September 2021 and 9 August 2022, 469 individuals were enrolled in EZI-PrEP and had a baseline visit (Fig. 2). Their characteristics were previously described [30]. After excluding 18 individuals without any follow-up monitoring visits, 451 were included in this secondary analysis: 224 (49.7%) in the 6-monthly

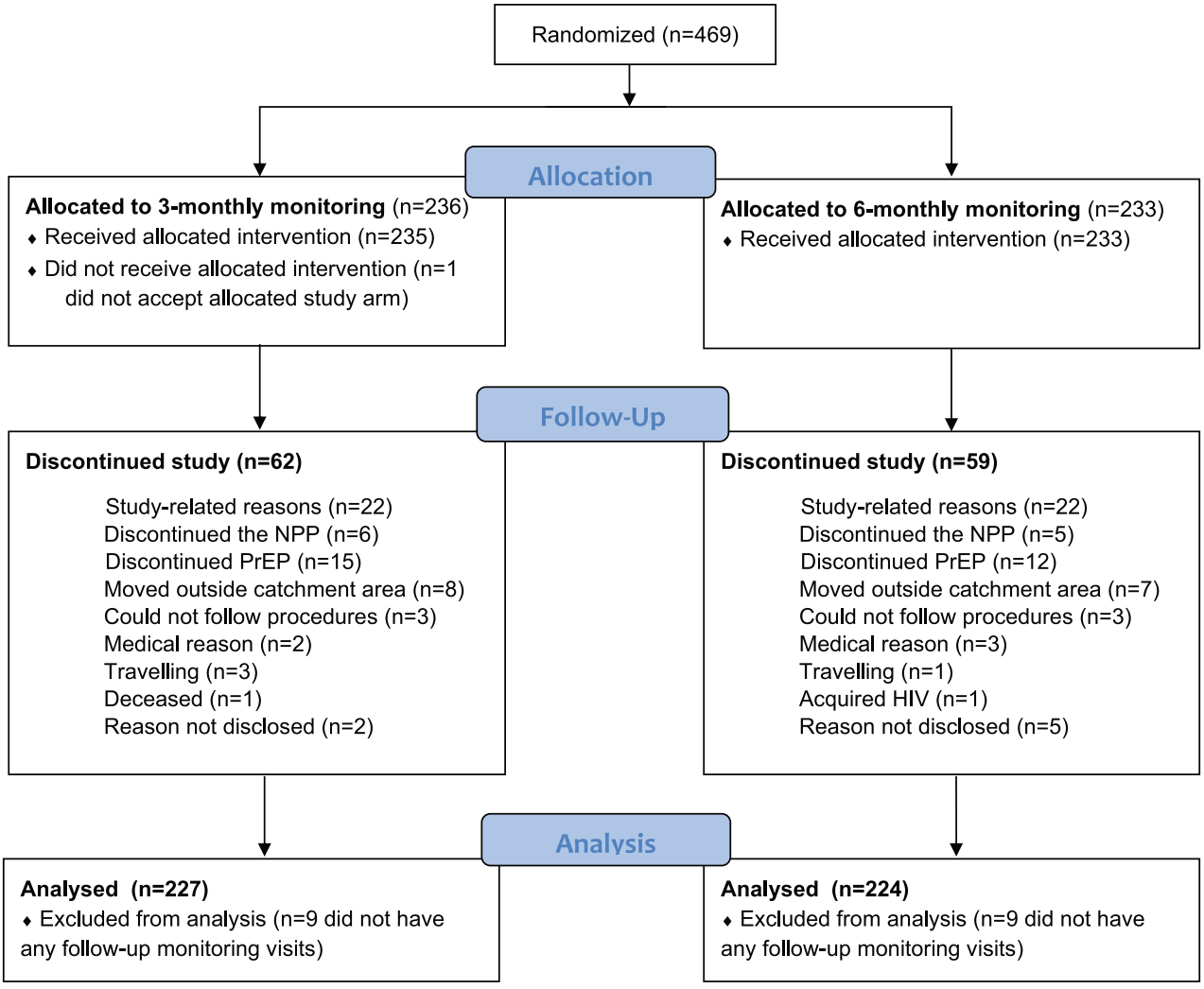

Fig. 2 CONSORT flow diagram for (EZI-PrEP, the Netherlands, 2021–2024). Abbreviations: HIV human immunodeficiency virus, NPP national PrEP pilot programme, PrEP pre-exposure prophylaxis, NB: Study-related reasons included like disliking the burden of filling in the daily diary app or 6-monthly study questionnaires

monitoring group and 227 (50.3%) in the 3-monthly monitoring group (Table 1). Most participants (n = 446, 98.9%) were cisgender MSM. Median age was 36 years (IQR 29–47), 68.3% (n = 308) of participants were born in the Netherlands, and 81.1% (n = 361) completed or were pursuing a college- or university degree. During the six months before baseline, the median number of sex partners was 7 (IQR 4–15), 39.1% (n = 165) reported group sex, and 24.7% (n = 111) reported chemsex (Table 1). Sociodemographics, sexual behavior, and STI prevalence were similar between monitoring groups.

Median follow-up time was 22.7 months (IQR 19.2–23.8), totaling 760PY of observation. 332/451 (73.6%) participants remained in the study for 24 months. Neither study attrition nor its determinants differed by monitoring frequency (Additional file 2: Table 1). Study-related factors like dissatisfaction with completing the diary or questionnaires were the primary reason for study discontinuation (Fig. 2).

Visit rates

As expected, the rate of scheduled visits was lower in the 6-monthly than 3-monthly monitoring group (visit rate ratio=0.54, 95%CI = 0.50–0.59) (Fig. 3; Additional file 5: Table 1). The rate of unscheduled visits, as well as the proportion of individuals with at least one unscheduled visit, was higher in the 6-monthly monitoring group (visit rate ratio=1.67, 95%CI = 1.42–1.98) (Fig. 3; Additional file 5: Table 1, Fig. 1). Overall, 6-monthly monitoring resulted in 31% fewer total visits (visit rate ratio=0.69, 95%CI = 0.64–0.74).

At unscheduled visits, 55% (n = 334/609) of participants reported neither symptoms nor partner notification, 25% (n = 150/609) reported only partner notification,

Table 1 Baseline socio-demographic characteristics and sexual behaviour of EZI-PrEP study participants by monitoring frequency, the Netherlands (2021)

		Total		3-monthly monitoring		6-monthly monitoring	
		N = 451		N = 227		N = 224	
		n[a]	%[a]	n[a]	%[a]	n[a]	%[a]
Sociodemographic characteristics							
Gender	Cisgender male	446	(98.9%)	224	(98.7%)	222	(99.1%)
	Transgender or genderdiverse person	5	(1.1%)	3	(1.3%)	2	(0.9%)
Age in years, median (IQR)		36	(29–47)	34	(28–47)	36	(31–47)
Age in years	<25	43	(9.5%)	24	(10.6%)	19	(8.5%)
	25–34	163	(36.1%)	90	(39.6%)	73	(32.6%)
	35–44	108	(23.9%)	48	(21.1%)	60	(26.8%)
	≥45	137	(30.4%)	65	(28.6%)	72	(32.1%)
Region of birth[b]	Netherlands	308	(68.3%)	161	(70.9%)	147	(65.6%)
	W. & Central Europe and N. America	53	(11.8%)	19	(8.4%)	34	(15.2%)
	Eastern Europe and Central Asia	14	(3.1%)	7	(3.1%)	7	(3.1%)
	Middle East and North Africa	10	(2.2%)	7	(3.1%)	3	(1.3%)
	Latin America and the Caribbean	35	(7.8%)	16	(7.0%)	19	(8.5%)
	Asia and the Pacific	22	(4.9%)	12	(5.3%)	10	(4.5%)
	Sub-Saharan Africa	9	(2.0%)	5	(2.2%)	4	(1.8%)
Completed or pursuing a college or university degree		361	(81.1%)	182	(81.3%)	179	(81.0%)
Employed at baseline[c]		388	(90.0%)	193	(89.8%)	195	(90.3%)
Income below minimum wage[d]		75	(19.1%)	39	(19.8%)	36	(18.5%)
PrEP use							
Used PrEP in 12 months prior to inclusion		399	(88.5%)	199	(87.7%)	200	(89.3%)
Intended PrEP regimen at baseline	Daily PrEP	293	(66.9%)	153	(69.9%)	140	(63.9%)
	Event-driven PrEP	145	(33.1%)	66	(30.1%)	79	(36.1%)
Sexual behaviour in the preceding 6 months							
Number of sex partners, median [IQR]		7	(4–15)	8	(4–15)	6	(4–13)
Any condomless anal sex		428	(95.3%)	216	(95.6%)	212	(95.1%)
Never used a condom during anal sex		162	(36.1%)	85	(37.6%)	77	(34.5%)
Had sex in return for money or goods		3	(0.7%)	2	(0.9%)	1	(0.5%)
Had group sex		165	(39.1%)	87	(41.4%)	78	(36.8%)
Had chemsex[e]		111	(24.7%)	60	(26.5%)	51	(22.8%)
Bacterial STI diagnoses at inclusion							
Any bacterial STI[f]		81	(18.2%)	42	(18.8%)	39	(17.6%)
Gonorrhoea		44	(10.1%)	25	(11.3%)	19	(8.8%)
Chlamydia		39	(8.9%)	19	(8.6%)	20	(9.3%)
Infectious syphilis[g]		7	(1.6%)	2	(0.9%)	5	(2.3%)
Mental wellbeing							
PHQ-9 score, median (IQR)		4	(2–7)	4	(2–8)	4	(2–7)
Indication for clinical depression[h]		59	(14.0%)	29	(13.7%)	30	(14.3%)
Indication for sexual compulsivity[i]		84	(19.3%)	46	(21.1%)	38	(17.5%)
AUDIT score	No or low risk alcohol use (0–7)	290	(67.0%)	142	(65.7%)	148	(68.2%)
	Hazardous alcohol use (8–15)	116	(26.8%)	61	(28.2%)	55	(25.3%)
	Harmful alcohol use (16–19)	15	(3.5%)	8	(3.7%)	7	(3.2%)
	Likely dependent on alcohol (≥20)	12	(2.8%)	5	(2.3%)	7	(3.2%)
DUDIT score	No drugs related problems (0–5)	247	(57.4%)	128	(59.8%)	119	(55.1%)

Table 1 (continued)

	Total		3-monthly monitoring		6-monthly monitoring	
	N = 451		N = 227		N = 224	
	n[a]	%[a]	n[a]	%[a]	n[a]	%[a]
Harmful drug use (6–24)	175	(40.7%)	81	(37.9%)	94	(43.5%)
Likely dependent on drugs (≥25)	8	(1.9%)	5	(2.3%)	3	(1.4%)

AUDIT alcohol use disorders identification test, *DUDIT* drug use disorders identification test, *EZI-PrEP* E-Health for Zero Infections - facilitating access to and use of Pre-Exposure Prophylaxis in the Netherlands, *PHQ* patient health questionnaire, *PrEP* pre-exposure prophylaxis, *IQR* interquartile range, *STI* sexually transmitted infection

Missing/unknown, respectively in the 3-monthly and 6-monthly monitoring groups*:* gender (n = 0; n = 0), age (n = 0; n = 0), region of birth (n = 0; n = 0), education (n = 3; n = 3), employment (n = 12; n = 8), income (n = 30; n = 29), PrEP use history (n = 0; n = 0), intended PrEP regimen (n = 8; n = 5), number of sex partners (n = 4; n = 4), condomless anal sex (n = 1; n = 1), sex in return for money or goods (n = 10; n = 10), group sex (n = 17; n = 12), chemsex (n = 1; n = 0), bacterial STI (n = 3; n = 3), gonorrhea (n = 6; n = 8), chlamydia (n = 6; n = 9), syphilis (n = 3; n = 3), PHQ-9 score (n = 10; n = 7), sexual compulsivity (n = 9; n = 7), AUDIT score (n = 12; n = 7), DUDIT score (n = 12; n = 8)

[a]Unless stated otherwise; percentages are based on complete data

[b]Based on World Bank Regions (https://datatopics.worldbank.org/sdgatlas/archive/2017/the-world-by-region.html)

[c]Student/in school (n = 21), volunteer (n = 3), unemployed (n = 8), unable to work (n = 4), retired (n = 7)

[d]https://www.rijksoverheid.nl/onderwerpen/minimumloon/bedragen-minimumloon/bedragen-minimumloon-2021

[e]Chemsex: sex under influence of one or more of the following drugs: crystal meth ('Tina'); mephedrone ('miau miau'); GHB/GBL; ketamine

[f]Any diagnosis of gonorrhea, chlamydia, or infectious syphilis (stage 1, stage 2, or early latent infection)

[g]Infectious syphilis: stage 1, stage 2, or early latent infection

[h]Patient Health Questionnaire-9 (PHQ- 9) score ≥10

[i]Sexual compulsivity scale (SCS) score ≥24

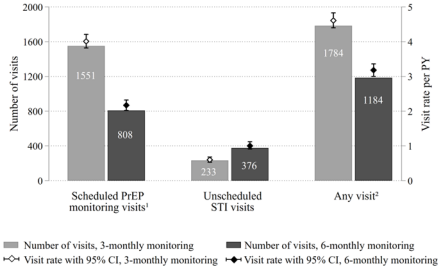

Fig. 3 Number of visits and visit rates among EZI-PrEP participants randomized to receive 3-monthly or 6-monthly PrEP monitoring (2021–2024, the Netherlands). Abbreviations: CI confidence interval, EZI-PrEP E-Health for Zero Infections - facilitating access to and use of Pre-Exposure Prophylaxis in the Netherlands, PrEP pre-exposure prophylaxis, PY person-years, STI sexually transmitted infection. *1. Including n = 51 month-1 monitoring visits among participants starting or restarting PrEP. 2. Including n = 71 visits where no STI tests were taken or test results were unavailable*

13% (n = 81/609) reported only symptoms, and 7% (n = 44/609) reported both symptoms and partner notification STI positivity at unscheduled visits was lowest when participants reported neither symptoms nor partner notification (i.e., 31.1 STIs/100 visits) and highest when they reported both (i.e., 73.3 STIs/100 visits) (Fig. 4). Sociodemographic determinants of seeking unscheduled STI tests included age under 45 years, having or pursuing a university or college degree, and being born outside the Netherlands; behavioral determinants included a higher number of sex partners, engagement in group sex, and having had a bacterial STI diagnosis at enrolment (Additional file 3: Table 1). Participants who sought unscheduled testing in the absence (versus presence) of symptoms or a partner notification had a higher median number of sexual partners, more often engaged in group sex, were more often PrEP-experienced, and more often had a college- or university education (Additional file 3: Table 2).

STI detection rate and antibiotic prescriptions

In total, 773 incident bacterial STIs (n = 396 gonorrhea, n = 326 chlamydia (including 32 LGV), and n = 51 infectious syphilis) were detected over 760PY (Additional file 5: Table 2). Most (82.2%; n = 635/773) STIs were asymptomatic, although this varied across STIs and anatomical locations (Additional file 5: Table 3). 63.6% (n = 287/451) of participants had at least one incident STI diagnosis during the study period, yet 16.4% (n = 74/451) of participants accounted for 49.9% (n = 388/773) of diagnoses (Additional file 5: Table 2, Figs. 2; 3). The detection rate of bacterial STIs was lower in the 6-monthly monitoring group (88.2/100PY) than the 3-monthly monitoring group (114.8/100PY; adjusted detection rate ratio=0.82, 95%CI = 0.70–0.95) (Fig. 5**;** Additional file 5: Table 2). The detection rates of any gonorrhea and of pharyngeal chlamydia were also lower in the 6-monthly monitoring group (Additional file 5: Table 2). We did not observe any statistically significant differences in the detection rate of anal chlamydia, genital chlamydia or infectious syphilis between monitoring groups.

As measured in two of the centers with available data, third generation cephalosporin prescription was 20.0% lower in the 6-monthly (versus 3-monthly) monitoring group (respectively, 0.43 and 0.54 DDD/1000 person-days; Additional file 1: Table 4). Tetracycline prescription

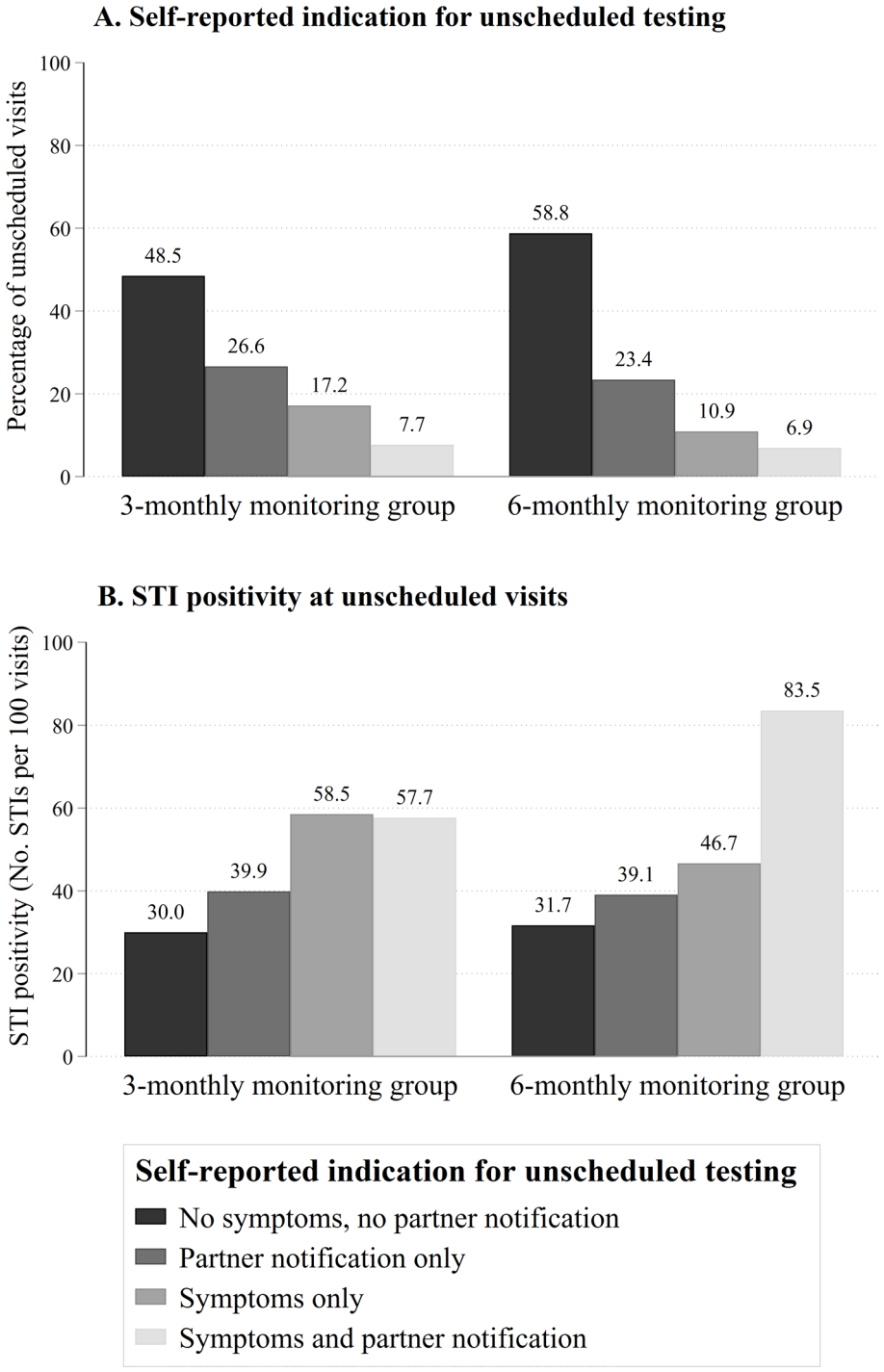

Fig. 4 Prevalence of self-reported symptoms or partner notification and STI positivity at unscheduled visits among EZI-PrEP participants (2021–2024, the Netherlands). STI positivity was defined as the number of bacterial STIs (gonorrhea, chlamydia, or infectious syphilis) diagnosed per 100 unscheduled STI testing visits. Unscheduled STI testing in-between monitoring visits was available free-of-charge through Sexual Health Centers of Public Health Services and through online testing service 'Testlab'

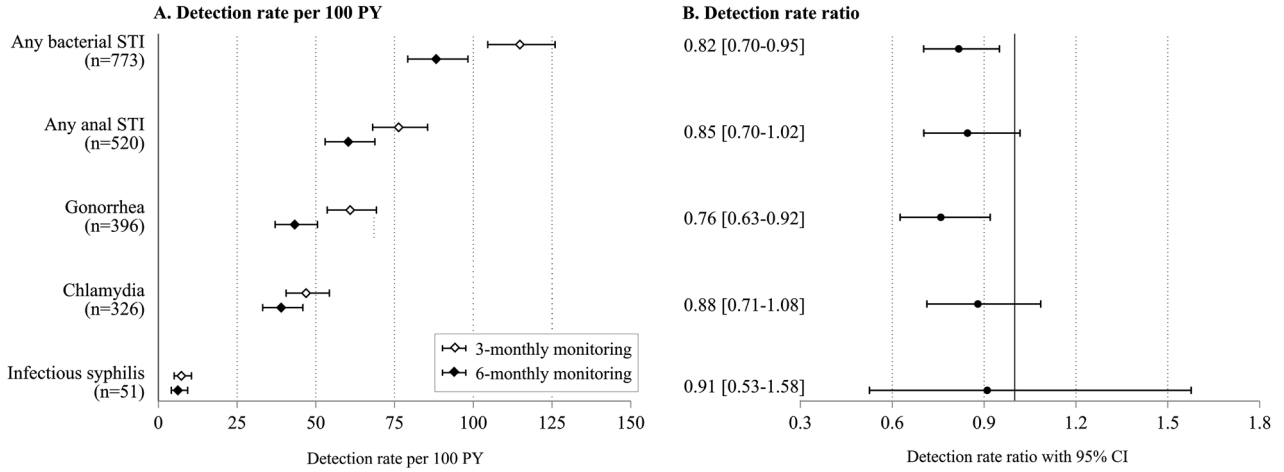

Fig. 5 STI detection rates and adjusted detection rate ratio among EZI-PrEP participants randomized to receive 6-monthly (compared to 3-monthly) PrEP monitoring (2021–2024, the Netherlands). Abbreviations: EZI-PrEP E-Health for Zero Infections - facilitating access to and use of Pre-Exposure Prophylaxis in the Netherlands, PY person-years, STI sexually transmitted infection. Panel **A** displays the detection rates per 100 person-years in the 3-monthly and 6-monthly monitoring groups for five STI outcomes. Panel **B** displays the detection rate ratio (6-monthly versus 3-monthly monitoring) for those five outcomes, adjusted for number of sex partners, chemsex, and group sex, all in the six months preceding enrolment, through inverse-propensity score weighting for allocated monitoring frequency based on logistic regression

was 11.9% lower (respectively, 13.5 and 15.2 DDD/1000 person-days). Macrolide prescription was 38.8% lower (respectively, 0.56 and 0.92 DDD/1000 person-days). Beta-lactam prescription was 10.4% higher in the 6-monthly monitoring group (respectively, 0.10 and 0.09 DDD/1000 person-days), mainly due to a higher incidence of inaccurate presumptive treatment.

STI positivity

Most STIs (69.3%, n = 536/773) were diagnosed at PrEP monitoring visits, although this proportion was lower in the 6-monthly (56.2%, n = 185/329) than 3-monthly monitoring group (79.1%, n = 351/444), and differed across STIs (Table 2).

STI positivity stratified by visit type did not differ between monitoring groups (Table 2). At monitoring visits, STI positivity was 23.8 STIs/100 visits in the 6-monthly monitoring group and 23.2 STIs/100 visits in the 3-monthly monitoring group (adjusted PR = 1.09, 95%CI = 0.90–1.30). At unscheduled visits, STI positivity was 38.0 STIs/100 visits in the 6-monthly monitoring group and 39.6 STIs/100 visits in the 3-monthly monitoring group (adjusted PR = 0.98, 95%CI = 0.77–1.24). When combining all visits, STI positivity was higher in the 6-monthly (28.5 STIs/100 visits) than 3-monthly monitoring group (25.4 STIs/100 visits; adjusted PR = 1.18, 95%CI = 1.02–1.36).

When stratifying by visit type, we did not observe differences in the positivity of specific bacterial STIs (Table 2). When combining all visits, chlamydia positivity was higher in the 6-monthly group (adjusted PR = 1.27, 95%CI = 1.00–1.60). When looking exclusively at asymptomatic STIs, findings were comparable to the main analysis (Additional file 5: Table 4). When looking over time, STI positivity remained stable (Additional file 5: Table 5).

Discussion

In this randomized trial among PrEP users in the Netherlands, we found that 6-monthly (compared to 3-monthly) monitoring led to fewer total visits, but more frequent unscheduled STI testing. Moreover, 6-monthly monitoring led to fewer STI diagnoses and fewer prescriptions of antibiotics associated with NG/CT treatment, whilst STI positivity at scheduled monitoring visits did not differ by monitoring frequency. These findings suggest that, in a setting where STI testing in-between monitoring visits is available and accessible, 6-monthly PrEP monitoring may reduce PrEP care burden and antibiotic prescriptions without resulting in substantial increases in STIs.

Given previous observational scenario studies, we expected that reducing the frequency of PrEP monitoring from 3-monthly to 6-monthly would lead to a 30–35% higher STI positivity, reflecting diagnostic delay [17, 18]. In contrast, our results indicated a limited impact of reduced monitoring on STI positivity. The explanation for this unexpected finding is three-fold. First, as observed in this and other studies, STIs are concentrated in a small fraction of PrEP users [2, 9]. PrEP users who never acquire an STI could receive less frequent screening without experiencing any diagnostic delay. Second, 3-monthly monitoring may more often lead to diagnosis of an asymptomatic NG/CT infection that would have cleared naturally within weeks or months. Prior studies have observed spontaneous clearance for 11–33% of NG and 4–21% of anogenital CT infections in the 10

Table 2 Positivity of bacterial STIs per 100 visits among EZI-PrEP participants receiving 3-monthly or 6-monthly PrEP monitoring (2021–2024, the Netherlands)

	Total (n = 451)			3-monthly monitoring (n = 227)			6-monthly monitoring (n = 224)						
	No. STIs	No. visits	Positivity (STIs / 100 visits)	No. STIs	No. visits	Positivity (STIs / 100 visits)	No. STIs	No. visits	Positivity (STIs / 100 visits)	Crude positivity ratio [95% CI]	p-value	Adjusted positivity ratio [95% CI][f]	p-value
Scheduled monitoring visits													
Bacterial STI[a]	536	2291	23.4	351	1514	23.2	185	777	23.8	1.03 [0.86–1.23]	0.78	1.09 [0.90–1.30]	0.38
Anal STI[b]	362	2284	15.8	232	1509	15.4	130	775	16.8	1.09 [0.87–1.36]	0.45	1.15 [0.91–1.43]	0.24
Gonorrhea	265	2285	11.6	179	1510	11.9	86	775	11.1	0.94 [0.71–1.24]	0.64	0.99 [0.75–1.31]	0.96
Chlamydia	236	2285	10.3	150	1510	9.9	86	775	11.1	1.12 [0.84–1.48]	0.44	1.17 [0.89–1.56]	0.26
LGV[c]	17	2257	0.8	14	1491	0.9	3	766	0.4	0.42 [0.12–1.43]	0.17	0.45 [0.13–1.55]	0.21
Infectious syphilis[d]	35	2284	1.5	22	1511	1.5	13	773	1.7	1.15 [0.58–2.27]	0.68	1.23 [0.63–2.44]	0.54
Unscheduled visits[e]													
Bacterial STI[a]	237	614	38.6	93	235	39.6	144	379	38.0	0.96 [0.75–1.22]	0.73	0.98 [0.77–1.24]	0.86
Anal STI[b]	158	611	25.9	63	235	26.8	95	376	25.3	0.89 [0.65–1.21]	0.46	0.91 [0.67–1.24]	0.56
Gonorrhea	131	613	21.4	56	235	23.8	75	378	19.8	0.83 [0.61–1.13]	0.24	0.86 [0.63–1.17]	0.33
Chlamydia	90	613	14.7	31	235	13.2	59	378	15.6	1.18 [0.77–1.82]	0.44	1.19 [0.78–1.82]	0.42
LGV[c]	15	554	2.7	4	204	2.0	11	350	3.1	1.60 [0.51–5.05]	0.42	1.65 [0.53–5.18]	0.39
Infectious syphilis[d]	16	603	2.7	6	228	2.6	10	375	2.7	1.02 [0.39–2.67]	0.96	1.03 [0.39–2.70]	0.96
Any visit													
Bacterial STI[a]	773	2905	26.6	444	1749	25.4	329	1156	28.5	1.12 [0.97–1.30]	0.12	1.18 [1.02–1.36]	0.027
Anal STI[b]	520	2895	18.0	295	1744	16.9	225	1151	19.5	1.16 [0.97–1.39]	0.10	1.22 [1.02–1.46]	0.031
Gonorrhea	396	2898	13.7	235	1745	13.5	161	1153	14.0	1.04 [0.84–1.28]	0.74	1.09 [0.88–1.35]	0.42
Chlamydia	326	2898	11.2	181	1745	10.4	145	1153	12.6	1.21 [0.96–1.53]	0.11	1.27 [1.00–1.60]	0.049
LGV[c]	32	2805	1.1	18	1675	1.1	14	1112	1.3	1.18 [0.67–2.58]	0.67	1.30 [0.60–2.84]	0.51
Infectious syphilis[d]	51	2887	1.8	28	1739	1.6	23	1148	2.0	1.24 [0.72–2.16]	0.44	1.31 [0.76–2.28]	0.33

CI confidence interval, *EZI-PrEP* E-Health for Zero Infections - facilitating access to and use of Pre-Exposure Prophylaxis in the Netherlands, *LGV* lymphogranuloma venereum, *No.* number, *PrEP* pre-exposure prophylaxis, *PY* person-years, *STI* sexually transmitted infection

[a]Diagnosis of gonorrhea, chlamydia or infectious syphilis. Concurrent diagnoses of infections with different bacteria were counted separately, and diagnoses of infections with the same bacterium at different anatomical sites were counted as one

[b]Diagnosis of anal gonorrhea or anal chlamydia. Concurrent diagnoses of anal gonorrhea and anal chlamydia were counted separately

[c]The denominator for LGV included visits where either an LGV test was taken or the anal CT test result was negative (assuming no LGV in the absence of any anal CT). Visits where an LGV test was taken but LGV-PCR could not be assessed were excluded from the numerator and denominator

[d]Stage 1, stage 2, and early latent syphilis

[e]N = 6 month 1 PrEP monitoring visits were an STI test was taken were categorised as additional STI testing visit, as STI screening is not standard at month 1 PrEP visits

[f]Adjusted for sexual behavior, by weighting participants for the inverse probability of being allocated to 6-monthly monitoring logistic regression with covariates number of sex partners, chemsex and group sex (all referring to the 6 months preceding enrolment)

days between the initial diagnosis and treatment initiation [31–35]. In our study, the finding that the difference in STI positivity between monitoring groups was smallest for gonorrhea (which clears relatively fast), larger for chlamydia (which clears more slowly), and greatest for syphilis (which rarely clears spontaneously) [11] also supports more frequent STI clearance in the 6-monthly groups. Third, we observed that more participants in the 6-monthly monitoring group sought unscheduled, additional STI testing, even in the absence of symptoms or partner notification. These tests appeared to be sought following behavior associated with STI acquisition: STI positivity was high at unscheduled visits in both the 6-monthly and 3-monthly monitoring groups. Taken together, while prior scenario studies expected that 6-monthly monitoring would lead to delayed STI diagnoses [17, 18], we rather observed that it led to (i) a substantial reduction in the number of visits at which no STIs were diagnosed and (ii) a shift from diagnosing most STIs at PrEP monitoring visits to diagnosing STIs at self-initiated visits, when they deemed their chance of an STI to be high.

We observed an 18% lower STI detection rate in the 6-monthly monitoring group than the 3-monthly monitoring group. This is unlikely to reflect actual differences in STI acquisition: participants were randomly allocated to a monitoring frequency, detection rates were adjusted for any coincidental imbalances in sexual behavior, and sexual networks likely overlapped between groups. Our findings rather suggest that 3-monthly monitoring was more likely to result in the detection of an asymptomatic STI that would have otherwise cleared spontaneously within weeks or months. Again, this hypothesis is supported by the finding that detection rates differed most for gonorrhea, less for anogenital chlamydia, and least for syphilis. As such, the lower detection rates in the 6-monthly monitoring group may be considered a proxy for averted overtreatment (i.e., of STIs that would clear spontaneously) rather than underdiagnosis. In our study, there were indeed fewer prescribed doses of antibiotics used to treat NG and CT, as expected [22, 36, 37]. Reduced CT/NG STI screening among PrEP users would then align with the principles of antibiotic stewardship: achieving effective treatment of disease whilst preventing antibiotic resistance and protecting patients from the harms associated with unnecessary antibiotic use [38].

Whether it is appropriate to reduce the frequency of syphilis screening warrants separate consideration. While asymptomatic NG and CT infections (excluding LGV) in men are unlikely to cause serious sequelae [11], a syphilis infection can lead to severe late-stage complications such as stroke, dementia, paralysis, and blindness if left untreated for years [39]. Our study was underpowered to draw any meaningful conclusions on the effect of reduced screening on syphilis diagnoses, given its relatively low incidence in the Netherlands [28, 40]. However, considering the natural history of syphilis and the (non-significantly) higher STI positivity in the 6-monthly monitoring group, it is plausible that reduced-frequency screening of syphilis could lead to some delays in diagnoses. While these delays are very unlikely to result in severe complications among PrEP users themselves, they could lead to some increase in onward syphilis transmission, including to individuals who do not regularly get tested for syphilis. As such, a cautious strategy could involve reducing the frequency of NG/CT screening among PrEP users, while continuing to screen for syphilis every 3 months. However, this approach does not reduce the burden of 3-monthly clinic visits experienced by some PrEP users and subpopulations (e.g., young MSM, single parents, TGD persons in the process of transitioning, and people with a long travel distance PrEP-providing facilities), nor does it reduce the burden of PrEP care for clinics. Reducing the overall frequency of PrEP monitoring (including counselling, all STI screening, and HIV testing) to 6-monthly may facilitate PrEP uptake and continuation. The EZI-PrEP study recently showed that this approach is non-inferior to 3-monthly monitoring in terms of prevention-effective PrEP adherence [24], and was acceptable to or even preferred by users [41]. Less frequent monitoring may also lower the per-user costs of PrEP care, helping to sustain or expand access in the context of economic pressures on HIV prevention budgets. Thus, the potential benefits of reduced monitoring (i.e., improved HIV prevention through enhanced PrEP engagement) may outweigh potential disadvantages (i.e., the effect of delayed diagnosis of some syphilis and HIV infections on onward transmission). Nevertheless, the population-level impact of reduced monitoring on HIV and syphilis incidence needs more thorough understanding with modelling studies and continued research in settings where screening is reduced.

This study is not without limitations. First, while EZI-PrEP was embedded in routine care and participants generally resembled the broader population of Dutch PrEP users in terms of sexual behavior, some populations (such as people who engage in sex work, TGD persons, and migrants) were underrepresented [30]. Second, the true incidence of STI acquisitions was unknown (as in most observational studies), and the measured incidence of detected STIs was directly impacted by our intervention (i.e., the reduced frequency of PrEP monitoring). As such, any inference on potential diagnostic delay was based on a proxy measure (i.e., the relative difference in STI positivity at scheduled visits). This measure was imperfect, given that (i) we could not determine if a person acquired the same STI multiple times during an observation interval and (ii) we had no insights into the

duration of infections detected at scheduled visits, nor of infections that cleared before scheduled visits. Third, the sample size was likely too small to assess the effect of 6-monthly monitoring on the detection rate and positivity of syphilis and LGV specifically, as indicated by the wide 95% confidence intervals. Fourth, the analysis on antibiotics was limited to prescriptions issued from two participating centers, with no data on treatment adherence. However, findings mirrored that of the analysis on detection rates. Finally, findings should be interpreted whilst considering the epidemiological and healthcare context of our setting, where the incidence of gonorrhea and chlamydia was high, the incidence of syphilis was low, and STI testing was free-of-cost and accessible. Future efforts should monitor the effect of implementing 6-monthly STI screening for a broader group of PrEP users on the prevalence of STIs among PrEP users and other MSM and TGD persons, and assess the cost-effectiveness of reduced PrEP monitoring whilst accounting for the observed changes in self-initiated STI testing.

Conclusion

Reducing the frequency of PrEP monitoring from every 3 months to every 6 months resulted in fewer total visits and routine tests and an increase in self-initiated STI testing during periods of risk. While the overall number of STI diagnoses and treatments was lower in the 6-monthly monitoring group, the number of STIs detected per monitoring visit was similar across monitoring groups and over time. These findings suggest that less frequent STI screening within PrEP programs that allow easy-access, additional self-initiated testing can reduce the burden of PrEP care and use of antibiotic treatment without leading to a substantial rise in STIs.

Abbreviations

AMR	antimicrobial resistance
CI	confidence interval
CT	*Chlamydia trachomatis*
DDD	defined daily doses
EZI-PrEP	E-Health for Zero Infections - facilitating access to and use of Pre-Exposure Prophylaxis in the Netherlands
GHB	gamma-hydroxybutyrate
GBL	gamma-butyrolactone
HIV	human immunodeficiency virus
LGV	lymphogranuloma venereum
MSM	men who have sex with men
NG	*Neisseria gonorrhoeae*
NPP	national PrEP pilot programme
PEP	post-exposure prophylaxis
PrEP	pre-exposure prophylaxis
PR	positivity ratio
PY	person-years
SOAP	national STI surveillance database
STI	sexually transmitted infection
TGD	transgender or gender-diverse
WHO	World Health Organization

Supplementary information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-026-04949-y.

Additional File 1: Supplementary Methods and Results on antibiotic prescriptions within EZI-PrEP, Table 1-4. Table 1 – Defined daily doses per gram of antibiotic. Table 2- Number of STI diagnoses and prescriptions in EZI-PrEP. Table 3 - Number of defined daily doses prescribed in EZI-PrEP. Table 4 – Comparing antibiotic prescriptions by monitoring frequency

Additional file 2: Supplementary Methods and Results on loss-to-follow-up within EZI-PrEP, Table 1. Table 1 – Determinants of early study discontinuation

Additional file 3: Supplementary Methods and Results on determinants of unscheduled STI testing, Tables 1–2. Table 1 – Determinants of unscheduled STI testing. Table 2 – Unscheduled STI tests with versus without symptoms

Additional file 4: Supplementary Methods and Results assessing potential interaction effects between monitoring frequency and monitoring modality on several outcomes, Table 1-7. Table 1 – effect on the total visit rate. Table 2 – effect on the rate of scheduled visits. Table 3 – effect on the rate of unscheduled visits. Table 4 – effect on the STI detection rate. Table 5 – Effect on the overall STI positivity. Table 6 – Effect on STI positivity at scheduled visits. Table 7 – Effect on STI positivity at unscheduled visits

Additional file 5: Table 1-5, Figs. 1–3. Table 1 – Visit rates and visit rate ratio's. Figure 1 – Distribution of additional testing visits across the study population. Table 2 – STI detection rates and detection rate ratio's. Table 3 – Proportion of symptomatic versus asymptomatic STIs. Figure 2 – Distribution of incident STIs across the study population. Figure 3 – Correspondence between STI testing behavior and total STI diagnoses. Table 4 – STI positivity by monitoring frequency. Table 5 – STI positivity over time

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Author contributions

UD, MFSvdL, AB, EH, MP, HMG, FvH, KV, and MLGB contributed to study conceptualization and design. MLGB, UD, MFSvdL, VJ, LB, CvB, JW, SB, HMG, and EW contributed to data acquisition and data management. EW, MLGB, AB, VJ, UD, and MFSvdL contributed to analysis and interpretation of the data. EW drafted the original manuscript. All authors read and approved the final manuscript.

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Data availability
The EZI-PrEP data are owned by the EZI-PrEP consortium. EZI-PrEP data can be requested by submitting a study proposal to the EZI-PrEP steering committee. It will be possible to obtain a proposal format from the Public Health Services of Amsterdam datamanagersoz@ggd.amsterdam.nl. Requests for further information can also be submitted through the same email address. The EZI-PrEP steering committee will verify each proposal for compatibility with general objectives, ethical approval, and informed consent forms of the EZI-PrEP trial and potential overlap with ongoing studies. There will be no restrictions to obtaining the data and all data requests will be processed in a similar way.

Declarations

Ethics approval and consent to participate
The EZI-PrEP Trial was approved by the medical ethics committee of the Amsterdam University Medical Center, file number 2020_154 - NL74494.018.20. The trial has been registered with ClinicalTrials.gov, trial number NCT05093036 (https://clinicaltrials.gov/study/NCT05093036). Written informed consent for study participation was obtained from all participants as part of the eligibility screening procedure.

Consent for publication
Written informed consent for publication was obtained from all participants as part of the eligibility screening procedure.

Competing interests
UD received unrestricted research grants from Gilead Sciences, and participated in Advisory boards of ViiV HealthCare & Gilead Sciences, all fees and grants paid to his institute. MFSvdL participated in Advisory Boards of Merck Sharp & Dohme, for which fees were paid to his institute. MFSvdL received a research grant from GlaxoSmithKline, paid to his institute. EH received unrestricted research grants from Gilead Sciences, paid to her institute. MP received unrestricted research grants and speaker/advisory fees from Gilead Sciences and Merck Sharp & Dohme, all paid to her institute. AB received speaker's fees from Gilead Sciences. All other authors declare no competing interests.

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