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Bacterial sexually transmitted infections are concentrated in subpopulations of men who have sex with men using HIV pre-exposure prophylaxis

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Objective: Studies have shown varying trends in incidence of sexually transmitted infections (STIs) among individuals using HIV pre-exposure prophylaxis (PrEP). Characterization of individuals at increased risk for STIs may offer an opportunity for targeted STI screening.

Design: Group-based trajectory modeling

Methods: We screened participants from the AMPrEP demonstration project (2015–2020) for urogenital, anal, and pharyngeal chlamydia and gonorrhea, and syphilis every 3 months and when needed. We identified trajectories of STI incidence within individuals over time and determinants of belonging to a trajectory group. We calculated cumulative proportions of STIs within STI trajectory groups.

Results: Three hundred and sixty-six participants with baseline and at least one screening visit during follow-up were included (median follow-up time = 3.7 years [interquartile range, IQR = 3.5–3.7]). We identified three trajectories of STI incidence: participants with a mean of approximately 0.1 STIs per 3 months ('low overall', 52% of the population), participants with a mean 0.4 STI per 3 months ('medium overall', 43%), and participants with high and fluctuating (between 0.3 and 1 STIs per 3 months) STI incidence ('high and fluctuating', 5%). Participants in the 'low overall' trajectory were significantly older, and reported less chemsex and condomless anal sex with casual partners than participants in the other trajectories. Participants in the 'high and fluctuating' and 'medium overall' groups accounted for respectively 23 and 64% of all STIs observed during follow-up.

Conclusions: STI incidence was concentrated in subpopulations of PrEP users who were younger, had more chemsex and condomless anal sex. Screening frequency for STIs could be reduced for subpopulations with low risk for incident STIs.

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Keywords: HIV prevention & control, men who have sex with men, pre-exposure prophylaxis, sexually transmitted infections

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Introduction

While pre-exposure prophylaxis (PrEP) is highly effective against HIV acquisition [1,2], it does not offer protection against other sexually transmitted infections (STIs). Since the introduction of PrEP, condomless anal sex continues to increase among men who have sex with men (MSM) [3–5] and STI incidence is high among MSM on PrEP [3,5–9]. Therefore, Dutch and international PrEP guidelines advise to screen PrEP users for STIs on a 3–6 monthly basis [10–12].

While 3-monthly STI screening leads to earlier diagnosis and treatment of, primarily, asymptomatic bacterial STIs compared to 6-monthly screening [13,14], not all PrEP users may need testing at this frequency. Previous studies from Australia found that half of their participants were not diagnosed with any STI within one year of follow-up and that the majority of STIs were concentrated within a small subpopulation [7,9]. In addition, certain socio-demographic and behavioral characteristics (e.g. younger age, use of chemsex and condomless anal sex) have been associated with an increased risk of bacterial STIs [7,14]. Further characterization of subpopulations of PrEP users at increased risk for STIs may offer an opportunity for more targeted bacterial STI screening, which could reduce monitoring burden for PrEP users and costs.

To this end, we assessed whether the incidence of STIs was concentrated within subpopulations within the Amsterdam PrEP (AMPrEP) study using longitudinal data of individuals using PrEP for up to 45 months. We also examined which socio-demographic and behavioral characteristics were associated with belonging to these subpopulations.

Methods

Study design and participants

The AMPrEP study was a demonstration project that assessed the uptake and feasibility of daily and event-driven PrEP among MSM and transgender persons in Amsterdam, the Netherlands [15]. Participants were enrolled between 3 August 2015 and 31 May 2016. HIV-negative MSM and transgender persons were eligible for inclusion if they were at least 18 years old and reported any of the following in the preceding 6 months: condomless anal sex with casual partners, one or more diagnosed bacterial STI, postexposure prophylaxis use, or sex with a partner living with HIV with a detectable or unknown viral load. Data collection ended in December 2020. Because the coronavirus disease 2019 (COVID-19) epidemic started on 6 March 2020 in the Netherlands, and at that date all participants had had the opportunity to complete their month-45 visit, we censored data after the month-45 study visit; hence we included data from 3 August 2015 until 6 March 2020.

The AMPrEP study was approved by the ethics board of the Amsterdam University Medical Centers, location Academic Medical Center, the Netherlands (NL49504.018.14) and was registered with the Netherlands Trial Registry (NL5302). Written informed consent was obtained from all participants.

Procedures

At baseline and every 3-monthly visit, participants could choose and switch between daily and event-driven PrEP regimens. PrEP was provided free-of-charge throughout the study period.

Participants attended 3-monthly study visits at which they were screened for chlamydia, gonorrhea, and syphilis. Additional STI screening was available between study visits for those presenting with STI-related symptoms or for those notified for having a recent sexual partner diagnosed with an STI. All STI testing was free-of-charge. Serology testing for syphilis was done using the LIAISON Treponema Screen assay for primary infections (DiaSorin, Saluggia, Italy), and VDRL (RPR-Nosticon II; bioMérieux) for reinfections. Urine, anal and pharyngeal swabs were tested for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* using nucleic amplification testing (Aptima Combo 2 assay; Hologic, San Diego, CA, USA). If an STI was diagnosed, immediate, free-of-charge treatment was provided.

At baseline and the 3-monthly study visits, participants completed a questionnaire on sexual behavior [15]. A separate questionnaire on substance use (both in general and in sexual settings) was completed at baseline and yearly thereafter. We defined chemsex as ever having used gamma-hydroxybutyrate (GHB)/gamma-butyrolactone (GBL), mephedrone or crystalized methamphetamine around the time of sex during follow-up [16].

Statistical analysis

We included data of participants who had at least two study visits (i.e. baseline and one additional study visit). Follow-up started at PrEP initiation (i.e. baseline) and continued until PrEP discontinuation (as indicated by the participant) or at the month-45 study visit, whichever occurred first.

We used group-based trajectory modeling to identify groups of participants who had similar individual-level trajectories of STI incidence during the study period [17]. Group-based trajectory models are a form of finite-mixture models that use a multinomial modeling strategy to identify clusters of trajectories within a study population. The shape of the trajectories was described as a polynomial function of time, which could either be constant (zero-order), linear, quadratic or cubic. We fitted

the group-based trajectory models using the Stata 'traj' plug-in. We fitted a zero-inflated Poisson model using the cumulative number of STIs (any chlamydia or gonorrhea, or primary, secondary, or early latent syphilis) diagnosed during a 3-month period (i.e. STIs diagnosed at a study visit and at additional STI visits in the 3 months since the previous study visit) as the outcome. Chlamydia and gonorrhea infections diagnosed at multiple anatomical locations were counted as one infection; simultaneous infections with chlamydia, gonorrhea or syphilis at the same visit were taken into account as the actual number of infections at that visit (i.e. if someone was diagnosed with chlamydia and gonorrhea at the same visit, this counted as two infections in the outcome variable). Study visits at which participants were absent were considered missing and data in the 3-month period prior to and at missing visits were not included in the model. To assess the effect of loss to follow-up on the results, we ran a sensitivity analysis in which only participants who attended the month-45 study visit were included.

We ran a series of group-based trajectory models with increasing numbers of groups (i.e. $k = 1, 2, \ldots, 5$) and determined the optimal number of groups from the model resulting in the Bayesian Information Criteria (based on the number of persons) closest to 0, highest entropy values, and all trajectories having a marginal prevalence of >5% [17]. Based on this procedure, a total of three distinct trajectories were identified (Table 1, Supplemental Digital Content, http://links.lww.com/QAD/C944). We plotted the group-based trajectories and observed group means of STI incidence using the 'trajplot' command in Stata.

We assigned participants to a trajectory based on the highest *a posteriori* probability of group membership. As group-membership is based on a finite-mixture distribution (i.e. group membership contains some degree of misclassification), we modeled the probability of belonging to each group across several covariates directly in the group-based trajectory models. Univariable odds ratios (ORs) of time-stable covariates associated with group membership, and their 95% confidence intervals (CIs), were calculated from the main model. We constructed a multivariable model by adding covariates with a $P < 0.20$ in univariable analysis. We removed covariates that were not significant at $P < 0.05$ in all groups from the multivariable model in backward-stepwise fashion.

We estimated the cumulative number of STIs up until the 45-month study visit for each individual. Individuals were ranked from lowest to highest cumulative number, from which the cumulative proportion of STIs overall and cumulative proportion of individuals could be calculated. These two cumulative proportions were plotted and fitted as a Lorenz curve function using the 'lorenz' plug-in in Stata [18]. We then calculated these cumulative proportions within group-based STI trajectory groups, as assigned by the *a posteriori* probability. From the Lorenz curve, we estimated the Gini coefficient as an estimate for inequality using the 'lorenz' plug-in [18]. The Gini curve was estimated as the area between the 'line of equality' (i.e. a diagonal line from a cumulative proportion of 0 to 1 with slope of 1) and the fitted Lorenz curve (A) divided by the total area under the 'line of equality' ($A + B$) (i.e. $\frac{A}{A+B}$. The Gini coefficient can range from 0 (perfect equality) to 1 (perfect inequality). Since the cumulative proportions are calculated from baseline until a given time point, any individual with follow-up time ending before this time point will likely have a biased underestimation of cumulative STIs. Therefore, all individuals who did not reach their month-45 study visit were excluded from these analyses.

All analyses were performed using Stata (v15.1, StataCorp, College Station, Texas, USA).

Results

Between August 2015 and May 2016, 376 participants were included in the AMPrEP study. Of these, nine (2%) did not have any follow-up data, and one (0.3%) was diagnosed with HIV shortly after enrolment; these 10 were excluded from analyses. Of the 366 included participants, 99% identified as male (Table 2, Supplemental Digital Content, http://links.lww.com/QAD/C944). Median age at baseline was 40 years [interquartile range (IQR) 32–48]. Median number of anal sex partners in the preceding three months was 12 [IQR 6–25] and 155 (43%) participants reported chemsex in the three months prior to baseline. Seventy-one (20%) participants had a bacterial STI detected at baseline. At baseline, 268 (73%) participants chose the daily PrEP regimen.

Median follow-up time was 3.7 years [IQR 3.5–3.7, range 0.3–4.4]. Participants attended a median of 16 study visits [IQR 14–16] and one additional STI visit [IQR 0–3] during follow-up. Three distinct trajectories of STI incidence were identified (Fig. 1). Misclassification (i.e. the individual probability to belong to a group other than the assigned group) within the trajectories is shown in Figure 1, Supplemental Digital Content, http://links.lww.com/QAD/C943. One hundred and eighty-nine of the 366 (52%) participants had a mean of approximately 0.1 STIs for every 3-month period (hereafter 'low overall' group), for 158 (43%) STI incidence was a mean of approximately 0.4 STIs for every 3-month period ('medium overall' group), and for 19 (5%) STI incidence increased during the first 18 months of follow-up to a mean of approximately one STI per 3-month period and then decreased to a mean of approximately 0.3 STIs per 3 months at month 45 ('high and fluctuating' group). There was little variation in the number of STIs diagnosed during the 3-month periods among those with 'low

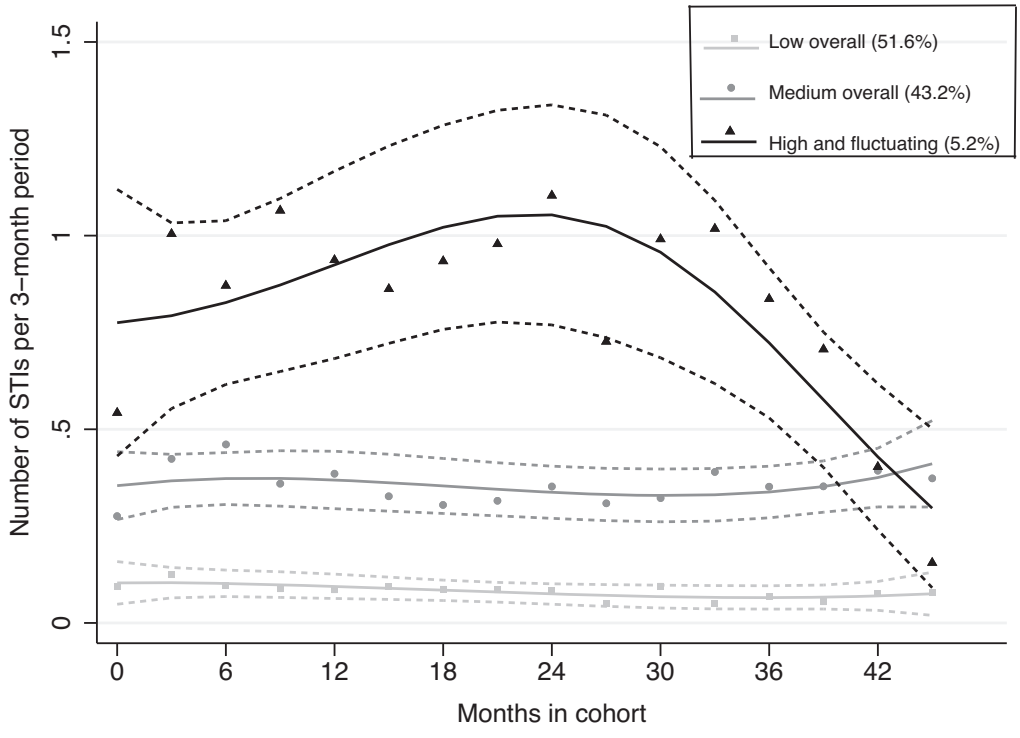

Fig. 1. Trajectories of sexually transmitted infection (STI) incidence over 45 months among PrEP users, 17 August 2015 to 6 March 2020, AMPrEP, Amsterdam, the Netherlands. Plotted symbols indicate the observed group mean number of STIs per 3 month period within each trajectory; the solid lines indicate the trajectory; dashed lines indicate the 95% confidence intervals of the trajectory. PrEP, pre-exposure prophylaxis.

overall' STI incidence, whereas in the other two groups more variation over time was seen (Fig. 2). Among the group with 'low overall' STI incidence, 67 of 189 (35%) participants did not have any STIs diagnosed during follow-up. In sensitivity analysis including only participants who completed the month-45 study visit, the modeled trajectories were not different (Figure 2, Supplemental Digital Content, http://links.lww.com/QAD/C943).

Follow-up time did not differ between the three groups ($P = 0.293$, Table 1). Participants with 'high and fluctuating' STI incidence were significantly younger than those in the other groups ($P < 0.001$). Additionally, participants with 'high and fluctuating' STI incidence had more anal sex acts and more condomless anal sex acts per year of follow-up both in general ($P < 0.001$) and with casual partners ($P < 0.001$) than the other two groups. Significantly fewer participants with 'low overall' STI incidence reported chemsex compared to those with "medium overall" and 'high and fluctuating' STI incidence. Participants with 'low overall' STI incidence more often had chosen the event-driven PrEP regimen at baseline.

The univariable association of determinants, when modelling the finite-mixture distribution of trajectory membership in the group-based trajectory model, are shown in Table 3, Supplemental Digital Content, http://links.lww.com/QAD/C944. The multivariable model showed that, compared to participants with 'low overall' STI incidence, participants in the other groups were younger (both $P < 0.001$), more often reported chemsex (group 2: $P < 0.001$, group 3: $P = 0.038$) and reported more condomless anal sex acts with casual partners (both $P < 0.001$) (Table 2).

Among participants ($n = 254$) who attended the month-45 study visit, the Gini coefficient was 0.48, indicating high disparity in STI incidence within the population. The Lorenz curve showed that 20% of the population accounted for 49% of the STIs over time (Fig. 3a). Participants in the 'high and fluctuating' and 'medium overall' groups were diagnosed with 23 and 64%, respectively, of all STIs observed during follow-up (Fig. 3b).

Discussion

Using data from up to 45 months of follow-up since PrEP initiation, we identified three distinct trajectories of STI incidence as they occurred over time. These trajectories included one with a very low STI incidence consistently during follow-up and another with an increasingly high

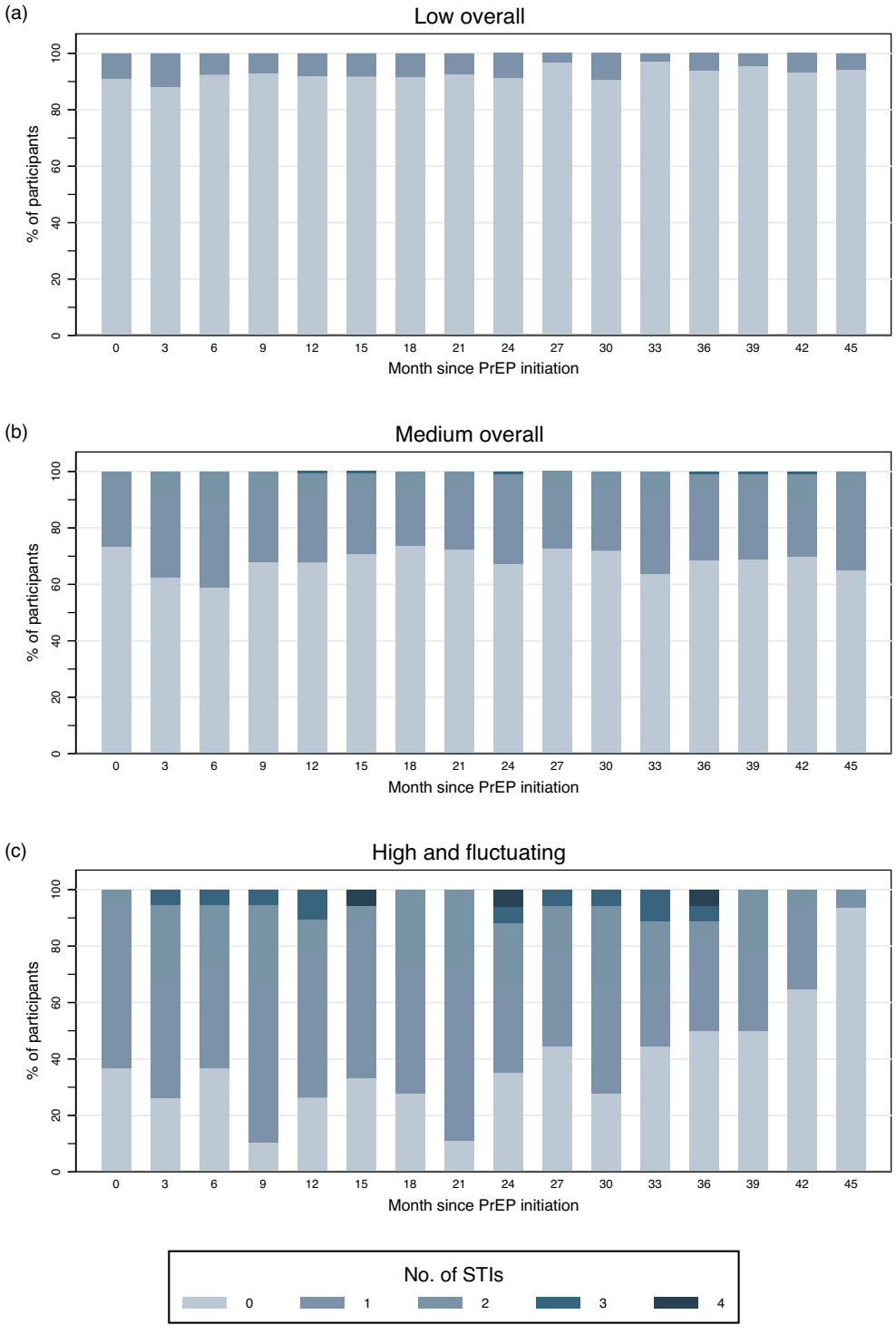

Fig. 2. Distribution of number of STIs per 3-month study period within the different trajectories of STI incidence. Data are from the AMPrEP study, 17 August 2015 to 6 March 2020, Amsterdam, the Netherlands. Figures depict the distribution of number of STIs per study visit according to the trajectories: (a) low overall, (b) medium overall, (c) high and fluctuating. STI, sexually transmitted infection.

Table 1. Socio-demographic characteristics and sexual behavior[a] of PrEP users according to STI incidence profile, 3 August 2015 to 6 March 2020, AMPrEP, Amsterdam, the Netherlands.

	Profile[b]						
	Low overall ($n=189$)		Medium overall ($n=158$)		High and fluctuating ($n=19$)		*P*-value[c]
	n[d]	%[d]	n[d]	%[d]	n[d]	%[d]	
Follow-up time (years), median [IQR]	3.67	[3.36–3.75]	3.65	[3.55–3.73]	3.69	[3.62–3.83]	0.293
Choice of PrEP regimen							0.027
Event-driven	62	33%	32	20%	4	21%	
Daily	127	67%	126	80%	15	79%	
Age (years)							
Median [IQR]	43	[34–50]	38	[30–46]	35	[27–37]	<0.001
<35 years	50	26%	61	39%	9	47%	0.001
35–44 years	54	29%	47	30%	10	53%	
≥45 years	85	45%	50	32%	0	0%	
Self-declared racial-ethnic background							0.193
White	168	89%	131	83%	15	79%	
Nonwhite	21	11%	27	17%	4	21%	
Highest education level							0.144
No college/university	48	25%	38	24%	1	5%	
College/university	141	75%	120	76%	18	95%	
Employment							0.094
Unemployed	49	26%	26	17%	5	28%	
Employed	139	74%	130	83%	13	72%	
Steady relationship							0.249
No	99	53%	94	60%	12	67%	
Yes	89	47%	62	40%	6	33%	
Living situation							0.271
Alone	103	55%	84	53%	9	47%	
With partner	62	33%	49	31%	4	21%	
With others	24	13%	25	16%	6	32%	
Sexual identity							0.083
Exclusively homosexual	152	81%	118	75%	18	95%	
Not exclusively homosexual	36	19%	40	25%	1	5%	
Ever reported chemsex during follow-up							<0.001
No	105	56%	43	27%	4	21%	
Yes	84	44%	115	73%	15	79%	
Anal sex acts[e], median [IQR]	64	[31–101]	96	[64–159]	204	[85–273]	<0.001
CAS acts[e], median [IQR]	44	[19–84]	77	[50–119]	158	[71–257]	<0.001
CAS acts with casual partner[e], median [IQR]	28	[11–58]	58	[34–94]	133	[57–217]	<0.001

CAS, condomless anal sex; IQR, interquartile range; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection. Data missing for: employment ($n=4$), sexual identity ($n=1$), steady relationship ($n=4$) [a] All determinants were determined at baseline, except number of sex acts, number of condomless anal sex acts, and number of condomless anal sex acts with casual partners. [b] Participants were assigned to a group based on the highest posterior probability of belonging to a given class. [c] We used rank sum tests for continuous variables and Pearson's χ^2 or Fisher's exact tests for categorical variables. [d] Unless otherwise indicated. [e] Per year of follow-up.

incidence during the first 18 months and decreasing thereafter. Trajectories with higher STI incidence were associated with younger age, increased reports of chemsex and increased number of condomless anal sex acts with casual partners. We also found that, although the 'high and fluctuating' group was small (5% of the total population), they accounted for approximately a quarter of STIs.

When PrEP was introduced, concern about risk compensation arose [19]. Indeed, condomless anal sex increased since PrEP initiation [3–5] and the incidence of STIs was notably high among PrEP users [3,5–9]. Three-monthly screening was then recommended for these individuals in the Dutch national [10] and international guidelines [11,12]. In this study, we found that approximately 50% of the study population very rarely had an STI. This finding indicates that 3-monthly STI screening is unnecessarily frequent for a substantial proportion of PrEP users. Nevertheless, the debate on the optimal screening frequency for PrEP users is currently ongoing and usually focuses on screening costs and the impact of screening on STI incidence, sequelae as a result of untreated syphilis, chlamydia or gonorrhea, and antibiotic use and antimicrobial resistance.

Modelling studies have shown that more frequent screening could reduce the incidence of chlamydia, gonorrhea and syphilis [20–22], but these results have not been corroborated by empirical studies on opportunistic testing [23,24] or within low-risk subpopulations. Due to frequent screening, asymptomatic STIs are detected sooner and reducing the screening frequency (e.g. to 6-monthly) would lead to delayed diagnosis for many of

Table 2. Determinants of STI incidence profiles among PrEP users, 17 August 2015 to 6 March 2020, AMPrEP, Amsterdam, the Netherlands (multivariable analysis).

	Profile					
	Group 2 vs. Group 1			Group 3 vs. Group 1		
	aOR	95% CI	*P*-value	aOR	95% CI	*P*-value
Age, per 10 years	0.44	(0.29–0.66)	<0.001	0.18	(0.08–0.44)	<0.001
Ever reported chemsex during follow-up						
No	REF		<0.001	REF		0.038
Yes	4.96	(2.28–10.76)		5.32	(1.10–25.73)	
CAS acts with casual partners[a]	1.38	(1.19–1.60)	<0.001	1.59	(1.31–1.94)	<0.001

Note: Univariable analysis is shown in Table 3, Supplemental Digital Content, http://links.lww.com/QAD/C944. aOR, adjusted odds ratio; CI, confidence interval; STI, sexually transmitted infection.
[a]Per year of follow-up. The odds ratios can be interpreted as the increase in odds to belong to a certain trajectory per increase in 10 condomless anal sex act with a casual partner per year.

these STIs and possible onward transmission [13,14]. However, screening for STIs, primarily chlamydia and gonorrhea, is costly and screening 6-monthly is more cost-effective than 3-monthly [25]. In addition, chlamydia and gonorrhea infections can clear spontaneously [26–29], thus may not require treatment. Moreover, unnecessary treatments might induce antimicrobial resistance. A previous study among PrEP users showed that macrolide consumption decreased by 75% when the screening frequency was decreased from 3-monthly to 6-monthly [30]. While asymptomatic STIs may remain undetected longer, the risk of serious sequela of syphilis, chlamydia or gonorrhea is limited in men if diagnosed within 6 months. Moreover, symptomatic STIs are likely diagnosed and treated regardless of screening frequency. With this in mind, screening 6-monthly and allowing interval STI testing upon symptoms could substantially decrease both costs of PrEP programs and antibiotic use.

Younger age, participating in chemsex and more frequent condomless anal sex with casual partners was associated with subpopulations with more STIs over time. These determinants are commonly associated with STIs among PrEP users [7,14], suggesting that a more focused screening approach based on these individual characteristics is possible. Healthcare professionals prescribing PrEP could use these characteristics to determine at which interval someone should be screened for STIs. However, in our previous study among AMPrEP participants, we found low predictive value for individual risk scores with the aforementioned determinants [14]. This shows the complexity in designing well functioning

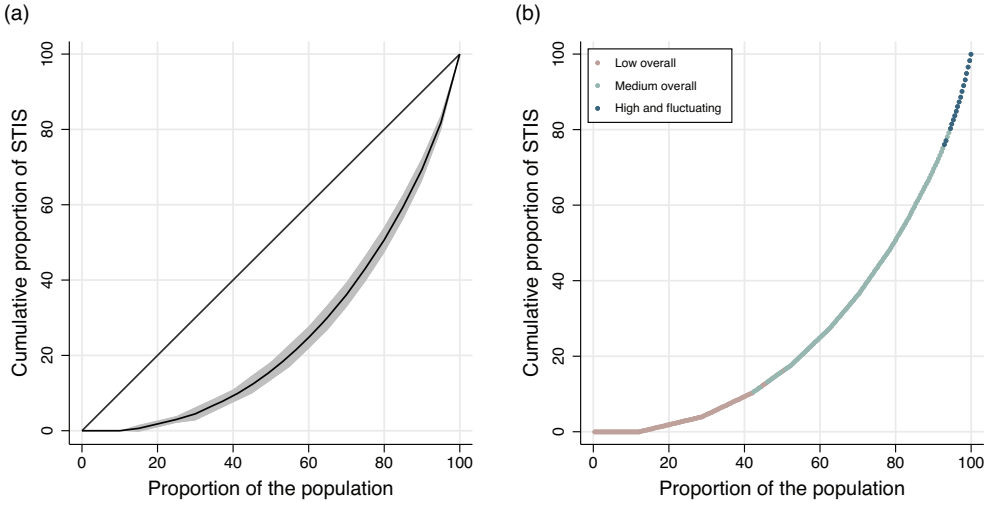

Fig. 3. Lorenz curves of the disparity in STI incidence among PrEP users who attended the 45 study visit, 17 August 2015 to 6 March 2020, AMPrEP, Amsterdam, the Netherlands. Figures are given for STI incidence in the total population (a) and cumulative STI incidence within the different trajectories (b). The straight line (i.e. the 'line of equality') indicates equal distribution of STI incidence in the population. The Lorenz curve is plotted below the straight line and shows the actual distribution in STI incidence. The grey area indicates the 95% confidence interval of the Lorenz curve. PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection.

algorithms that can be used to predict STI risk. Focused screening approaches to assist in choosing the frequency of testing should be evaluated for performance, feasibility and cost-effectiveness.

Similar to previous studies performed in Australia [7,9], we found that a small subpopulation was diagnosed with a large proportion of STIs. Although STI incidence rose within this group to a mean of approximately one incident STI every 3 months during the first 18 months of follow-up, incidence started to decline thereafter. The reason for the decline in STI incidence after 18 months in this group is unclear, but may be related to increased condom use after having acquired multiple STIs [31]. However, although condoms are effective against most STIs, their popularity has stagnated over the years [4,32]. With frequent screening we are able to quickly diagnose and treat STIs within populations with high STI incidence, but other biomedical preventive measures may also be of benefit to this subpopulation. Postexposure prophylaxis with doxycycline has been shown to reduce the risk for acquiring chlamydia and syphilis [33–35], and gonorrhea to some extent [34]. Similarly, pre-exposure use of doxycycline has also been shown to reduce STI rates [36]. However, these strategies may also further contribute to antimicrobial resistance and be challenging for the prevention of gonorrhea due to growing resistance to tetracyclines [37,38]. A meningitis B vaccine is also currently being investigated for its cross-protection against gonorrhea and is showing moderate effectiveness [34].

This study has some limitations. First, AMPrEP participants were early PrEP adopters, were predominantly white and highly educated, and were at substantially increased risk for HIV acquisition before entering the study. Therefore, they may not be representative for the current population using PrEP. Second, participants sometimes missed a study visit and some participants had stopped participation before the month-45 study visit. This could have either underestimated or overestimated the monthly STI incidence. However, trajectories were not different when only including participants who attended the month-45 study visit.

In conclusion, we identified three distinct groups of participants with different trajectories of 3-monthly STI incidences over time, and higher incidence was associated with younger age, chemsex, and more condomless anal sex with casual partners. Approximately 90% of the STIs were found among 53% of the study population, which may mean that a relatively large proportion of PrEP users are over-screened for STIs based on the current guidelines. Screening for STIs could be reduced to a risk-based approach to determine screening frequency, in addition to self-initiated testing, for subpopulations with low STI incidence.

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Author's contributions: E.H., M.P., H.J.V.dV., U.D. and M.F.S.vdL. conceptualized and designed the AMPrEP demonstration project. V.J., M,F,S,vdL., M.vdE., and A. B. contributed to study design of the current study. All authors were involved in data acquisition, data analysis, or interpretation of the data. V.J. drafted the manuscript. All authors critically revised the manuscript.

Data sharing: The AMPrEP data are owned by the Public Health Service of Amsterdam. Original data can be requested by submitting a study proposal to the steering committee of AMPrEP. The proposal format can be obtained from amprep@ggd.amsterdam.nl. Request for further information can also be submitted through the same e-mail address. The AMPrEP steering committee verifies each proposal for compatibility with general objectives, ethical approval, and informed consent forms of the AMPrEP study, and potential overlap with ongoing studies. There are no restrictions to obtaining the data and all data requests will be processed in a similar way.

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Conflicts of interest

The Public Health Service of Amsterdam received the drugs for the Amsterdam PrEP study from Gilead Sciences based on an unconditional grant. U.D. received unrestricted research grants and speaker's fees from Gilead Sciences, paid to his institute. H.J.C.dV, received grants from Medigene, and advisory board and speaker fees from Gilead Sciences, Medigene, Abbvie, Janssen-Cilag, and Willpharma, all paid to his institute. M.P. received unrestricted research grants and speaker's/advisory fees from Gilead Sciences, and MSD, all paid to her institute. M.F.S.vdL. participated in Advisory Boards of MSD, for

which fees were paid to his institution. E.H. received unrestricted research grants from Gilead Sciences, paid to her institute. All other authors declare no competing interests.

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