

**Real-life occurrence of bacterial sexually transmitted infections among PrEP users: improving the diagnosis of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* with multisite screening**

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**ABSTRACT**

PrEP users are under high risk for bacterial sexually transmitted infections (STI), including those caused by *Treponema pallidum* (Tp), *Chlamydia trachomatis* (Ct) and *Neisseria gonorrhoeae* (Ng). Ct and Ng screening at multiple anatomic sites may improve the diagnostic sensitivity among high-risk populations. We analyzed the prevalence and incidence of Ct, Ng, and Tp and investigated predictors of bacterial STI occurrence between January 2018 and November 2019 in a retrospective cohort of PrEP users in Sao Paulo, Brazil. We describe the frequency and percentage of Ct/Ng per anatomical site and calculate the percentage of missed diagnosis if molecular testing were applied only in symptomatic patients, or only in urine samples. Patients underwent syphilis testing every 3-4 months and Ct/Ng testing every 6 months. We included 413 PrEP users with a median age of 31 years. At baseline, 25% had a positive treponemal test and 7% had active syphilis; Ct and Ng were more frequently detected in the oropharynx and anus (6.4-6.9%) than in urine samples (0.7-2.6%). Twelve months after the onset of PrEP, the incidence of Tp, Ct and Ng was, respectively, 13.4%, 11.4% and 8.9%. During follow-up, 23 out of 33 Ct/Ng cases (69%, 95% CI 51-84) would have been missed if oropharynx and anus samples had not been tested. In addition, if only symptomatic cases had been tested, 30 out of 33 Ct/Ng cases (90%, 95% CI 75-98) would have been missed. Participants with incident STI had a higher baseline number of sexual partners and a longer follow-up. Our study reinforces that active and frequent screening for STI is a powerful strategy to improve the diagnostic sensitivity.

**KEYWORDS:** Pre-exposure prophylaxis. Sexually transmitted infections. *Chlamydia trachomatis*. *Neisseria gonorrhoeae*. Syphilis. *Treponema pallidum*.

**INTRODUCTION**

The pre-exposure prophylaxis (PrEP) is an HIV prevention strategy recommended for high-risk individuals including sex workers, sexual partners of people living with HIV not under antiretroviral treatment, men who have sex with men (MSM), transgender people, and people who inject drugs, among others. Since the introduction of PrEP studies back in 2008, and more strongly following its implementation as a real-life prevention strategy, there has been an intense concern about its impact on the risk of other sexually transmitted infections (STI).

Risk compensation, characterized in this context as an increase of exposure to unprotected sex following a reduction in the risk perception for HIV has not been shown in initial PrEP studies<sup>1-5</sup>. However, more recent publications have suggested

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that there may be an increase in condomless sex and in the incidence of STI among PrEP users<sup>6-13</sup>.

STI represent an enormous public health issue in Brazil and around the world. The World Health Organization estimates that more than one million STI are acquired daily worldwide<sup>14</sup>, also increasing the risk for the acquisition of HIV<sup>15</sup>. More than 300 thousand fetal and neonatal deaths are estimated per year to be caused by syphilis alone<sup>16</sup>. In addition, STI are associated with complications such as infertility and abdominal inflammatory conditions (*Chlamydia trachomatis* [Ct]), antimicrobial resistance (*Neisseria gonorrhoeae* [Ng]) and certain types of cancer (Human Papilloma Virus)<sup>16</sup>.

Although PrEP guidelines emphasize that the screening of STI is an essential component of medical care, there is inconsistency regarding the recommended frequency and type of testing for the different STI. In addition, several studies have shown that Ct and Ng screening at multiple anatomic sites may improve the diagnostic sensitivity in high-risk populations<sup>17-20</sup>. However, multiple site screening is inconsistently adopted in PrEP clinics due to financial and operational limitations. Some providers indicate that testing should be performed only in symptomatic patients, whereas others recommend that the testing of asymptomatic patients should be performed only in urine samples.

In this study, we evaluated a cohort of HIV-uninfected patients referred for PrEP in Sao Paulo, Brazil. We describe the baseline prevalence and incidence of STI in this population and investigated demographic and clinical predictors of the occurrence of STI. We have also describe the frequency and percentage of Ct/Ng detection per anatomical site and calculate the percentage of missed diagnosis if molecular tests for Ct/Ng were applied only for symptomatic patients, or if this screening were performed in urine samples only.

## MATERIALS AND METHODS

We conducted a retrospective cohort study including HIV-uninfected patients admitted to the PrEP outpatient service of Hospital das Clinicas, in Sao Paulo, Brazil, from January 2018 to November 2019.

Our facility follows the Brazilian PrEP guidelines<sup>21</sup>, which defines the following subgroups as the eligible population for PrEP: MSM, transgender people and sex workers who reported condomless sex; people with prior STI and/or use of HIV post-exposure prophylaxis (PEP); and people in serodiscordant relationships, that do not use condoms regularly. People younger than 18 years old, those with a history of bone fractures not related to trauma, and those with impaired kidney function who not eligible for

PrEP according to national guidelines. In this study, we have also excluded participants who failed to attend at least one follow-up appointment after the onset of PrEP. We retrieved data from laboratory reports, medical charts, and electronic standardized forms including reports of potential risk factors for STI that are routinely collected from PrEP users during medical consultations.

All patients had an initial medical appointment when PrEP was first prescribed, a second visit in approximately 30 days, and routine appointments every 90-120 days. The baseline visit comprised a clinical assessment and laboratory tests including rapid tests for HIV and serological tests for syphilis. Since November 2018, our service has also been providing out molecular tests for Ct and Ng in both symptomatic and asymptomatic patients using urine samples, anal swabs, oropharynx swabs and cervicovaginal swabs if applicable. Prior to November 2018, a few PrEP users had access to molecular biology tests through private laboratories and only in urine specimens. At each routine visit, patients were tested for HIV and Tp; a multisite testing for Ct and Ng was conducted every 6 months among asymptomatic patients and as needed when symptoms were reported. Moreover, some patients had more frequent urine testing through private laboratories. For personal reasons, not all patients complied with the requested tests. Regardless of symptoms, all patients with positive STI tests received antimicrobial treatment according to the national STI guidelines<sup>22</sup>.

Molecular tests for Ct and Ng were performed using the real time polymerase chain reaction (PCR; Abbott Real Time Ct/Ng assay). Specimens included urine samples, anal, oropharynx and cervicovaginal swabs for asymptomatic patients; samples from urethral and cervical secretion were collected from symptomatic patients.

Commercial immunochromatography rapid tests were used for the baseline screening tests (Wama [Wama Diagnostica, Brussels, Belgium] for syphilis; Bioeasy [Shenzhen Bioeasy Biotechnology Co., Shenzhen, China] for HIV; and TR DPP [BioManguinhos, Rio de Janeiro, Brazil] for the confirmatory HIV test). All non-negative results were confirmed using serological tests; (ECLIA [DiaSorin, Sao Paulo, Brazil], VDRL [LaborClin, Pinhais, Brazil] and FTA-Abs [Wama, Sao Carlos, Brazil] for syphilis; ECLIA, HIV combi PT [Roche, Mannheim, Germany] for HIV). At baseline, we defined active syphilis for all patients with a first positive treponemal and/or nontreponemal test without a history of previous treatment; a VDRL titer greater than 1:8 (except if there are decreasing titers following treatment); and any symptomatic cases with a positive laboratory test. Incident syphilis was defined as a first positive treponemal test or a  $\geq 4$ -fold increase in consecutive titers of non-treponemal tests after the second

medical visit 30 days after the onset of PrEP. Follow-up tests for HIV were carried out using immunochromatography rapid tests; tests for syphilis were performed using VDRL/ELISA.

Demographic and clinical characteristics of study participants were presented using frequencies and percentages for categorical variables and medians and interquartile ranges (IQR) for numeric variables. We used Kaplan-Meier survival curves to assess the cumulative incidence of bacterial STI. The length of follow-up for the study participants was all the available time under PrEP between January 2018 and November 2019. We included as outcome only the first STI of each patient and they were excluded for future events. Comparisons between participants with and without incident STI were performed using Wilcoxon rank-sum tests for numeric variables and chi-squared tests or Fisher’s exact tests for categorical variables. The improvement in the diagnostic sensitivity with the multisite screening for Ct and Ng was estimated by percentages and 95% confidence intervals of missed diagnoses if each site or asymptomatic cases were left with

no screening. We used the statistical software Stata version 15.1 (StataCorp, College Station, TX, USA) with a two-tailed alpha error of 0.05 in all analyzes.

The institutional Ethics Review Board approved this study with exemption of informed consent (approval N° CAAE 17284119.1.0000.0068). All personal identifiable information was kept confidential throughout the study.

**RESULTS**

**Baseline characteristics of study participants**

Between January 2018 and November 2019, 493 participants who initiated PrEP in our outpatient clinic were identified through the review of medical charts and electronic forms. In total, 80 participants who failed to attend at least one follow-up visit were excluded. The final analysis included 413 participants. Most participants reported that they had never used PrEP before (85%). Demographic and vulnerability characteristics are described in [Table 1](#), overall and according to incident STI. The

**Table 1** - Demographics and vulnerability characteristics among study participants overall and according to incident STI during routine visits.

	All participants N=413	Participants with incident STI# N=64	Participants without incident STI N=349	p-value
Median age in years (IQR)	31 (27-37)	31 (27-36)	31 (27-37)	0.830
Schooling in years (%)				
4-7	2 (<1)	0 (0)	2 (1)	0.879
8-11	47 (11)	8 (13)	39 (11)	
≥12	364 (88)	56 (88)	308 (88)	
Skin color (%)				
White	298 (72)	46 (72)	252 (72)	0.851
Black	31 (8)	4 (6)	27 (8)	
Mixed	79 (19)	13 (20)	66 (19)	
Asian	4 (1)	1 (2)	3 (1)	
Native	1 (<1)	0 (0)	1 (<1)	
Median number of sexual partners*1 (IQR)	7 (3-15)	10 (6-25)	6 (3-14)	<0.001
Condom use (%)				
Always	95 (23)	13 (20)	82 (24)	0.382
Most of the times	173 (42)	27 (42)	146 (42)	
Half of the times	53 (13)	7 (11)	46 (13)	
Less than half of the times	60 (15)	14 (22)	46 (13)	
Never	32 (8)	3 (5)	29 (8)	
PEP in the past 12 months (%)	156 (38)	29 (45)	127 (36)	0.176
Alcohol use*2 (%)	275 (67)	45 (70)	230 (66)	0.510
Marijuana use*1 (%)	174 (42)	33 (52)	141 (40)	0.096
Club drugs use*1 (%)	152 (37)	27 (42)	125 (36)	0.331
Median follow-up days (IQR)	293 (175-447)	399 (265-517)	265 (167-412)	<0.001

STI = sexually transmitted infection; IQR = interquartile range; PEP = post-exposure prophylaxis; #Incident STI identified during routine appointments after the 30-day follow-up visit; \*1in the past 3 months; Club drugs include ketamin, ecstasy, LSD, and gamma-hydroxybutyrate; \*2≥5 doses over a 2-hour period in the past 3 months.

median age of participants was 31 years-old (range 18-67), most were white/Caucasian (72%) and declared at least 12 years of schooling (88%); 408 (97%) self-identified as cisgender men, while five participants self-identified as transgender women; 86% reported being homosexuals. The median number of sexual partners in the past three months was seven (interquartile range [IQR] 3-15); only 23% reported a consistent use of condoms in the three months prior to PrEP onset and 38% had already used HIV post-exposure prophylaxis in the past year, corroborating their suitability for PrEP use.

The use of psychoactive substances was frequent among study participants; 67% reported excessive alcohol consumption and 64% reported using at least one illicit recreational drug. Marijuana was the most commonly used substance (42%), followed by club drugs such as ketamine, ecstasy (MDMA), lysergic acid diethylamide (LSD), gamma-hydroxybutyrate (GHB) (36%), and erectile stimulants (22%). Injectable drugs use was rare in our population (<2%).

### Baseline STI

At baseline, 25% (92/361) of the study participants had a positive treponemal test and 28 of them had active syphilis infection. Ct was detected by PCR in 2.6% (4/153), 6.4% (6/93) and 6.9% (6/86) of participants in urine samples, oropharynx and anal swab samples, respectively. All participants with positive Ct PCR were asymptomatic at the moment of the medical consultation. Ng PCR had positive results in 0.7% (1/140), 6.4% (6/93) and 6.9% (6/86), respectively, in urine samples, oropharynx and anal swabs collected from asymptomatic participants. We have also identified one symptomatic participant with urethral discharge who failed to perform a molecular biology test, but had a positive Ng culture.

### Incident STI

From 413 participants included in the study, 104 had only one follow-up visit, 96 had only two follow-up visits, and 65 had only 3 follow-up visits, with the remaining 148 participants attending at least 4 follow-up visits. Details regarding the number of participants and the anatomic sites tested at each visit are described in Supplementary Table S1. Over the course of study follow-up, 64 participants had at least one incident bacterial STI (syphilis, Ct and/or Ng) after PrEP onset. We detected 39 cases of syphilis: eight in primary stage; 12 in secondary stage; 13 latent cases and six at unknown stage. The median time between PrEP onset and incident syphilis was 228 days (IQR 147-399) and the

cumulative incidence at 6 and 12 months were, respectively, 3.8% (95% confidence interval [CI] 2.1-6.9%) and 13.4% (95% CI 9.4%-18.9%). These data are shown in [Figure 1A](#)). The incidence rate was 15.4 (95% CI 11.2-21) cases per 100 person-years.

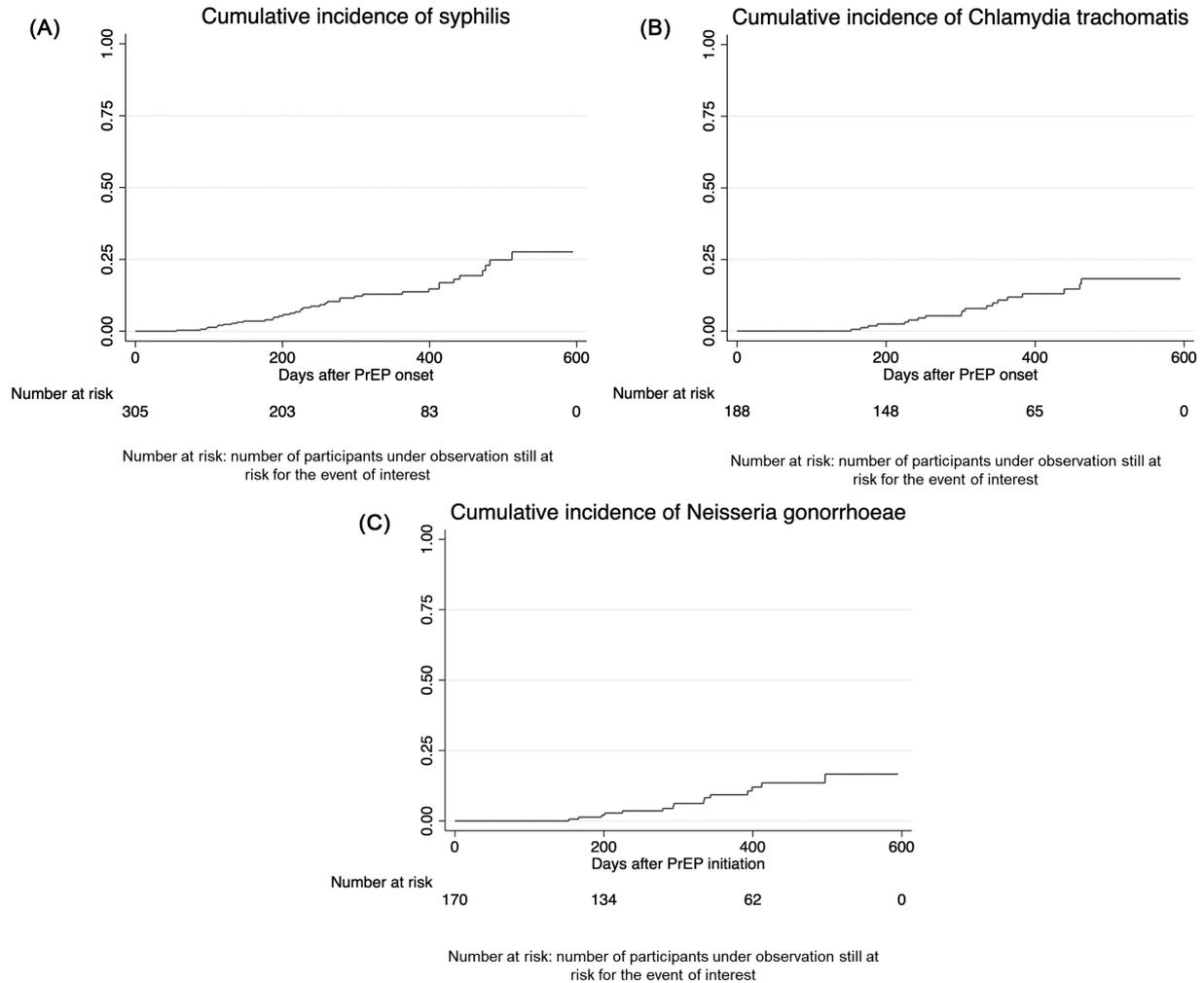
We found 20 incident cases of Ct after a median follow-up time of 304 days (IQR 227-373). The cumulative incidence of Ct was 1.7% (95% CI 0.5-5.3) at 6 months and 11.4% (95% CI 6.9-18.3) at 12 months ([Figure 1B](#)), with 11.1 (95% CI 7.2-17.2) cases per 100 person-years. Finally, we identified 16 incident cases of Ng after a median follow-up time of 294 days (IQR 201-393). The cumulative incidence was 1.2% (95% CI 0.3-5.0%) at 6 months and 8.9% (95% CI 5.0-15.7%) at 12 months ([Figure 1C](#)) comprising 9.1 (95% CI 5.5-15) cases per 100 person-years. No HIV seroconversion was identified during the study follow-up.

[Table 1](#) shows baseline characteristics of PrEP users with and without incident STI. Participants with incident STI reported a higher number of sexual partners and were followed-up for a longer period, but no additional statistically significant differences in demographics and vulnerability characteristics were found.

### Improvement in the diagnostic sensitivity with multisite screening for Ct and Ng

At the time of PrEP onset, 22 participants had asymptomatic Ct and/or Ng infections; had samples from oropharynx and anus not been tested, 17 of these cases would have been missed (77%, CI 95% 54-92). Out of 13 asymptomatic Ct infections at the baseline, nine (69%, 95% CI 38-91%) would have been missed if oropharynx and anus swabs had not been tested; for asymptomatic Ng infections at baseline, 10/11 cases (91%, 95% CI 58-99%) would have been missed. During follow-up, missed diagnosis would be of 13/21 Ct cases (61%, 95% CI 38-81%), 13/16 for Ng cases (81%, 95% CI 54-95%) and 23/33 for Ct and/or Ng cases (69%, 95% CI 51-84%).

If molecular testing had been available only for symptomatic cases, none of the 22 PrEP users with Ct and/or Ng infections at the beginning of PrEP use would have been identified, representing a percentage of missed diagnosis of 100% (95% CI 84-100%). In other words, we are 95% confident that at least 84% of Ct and/or Ng cases would have been missed if only symptomatic cases had been tested. The only participant with symptoms (urethral discharge) at baseline had a positive Ng culture and was not tested with PCR. Throughout the study, if molecular testing had been available for symptomatic cases only, 20/21 Ct cases (95%, 95% CI 76-99%), 14/16 Ng cases (87%, 95% CI 61-98%)

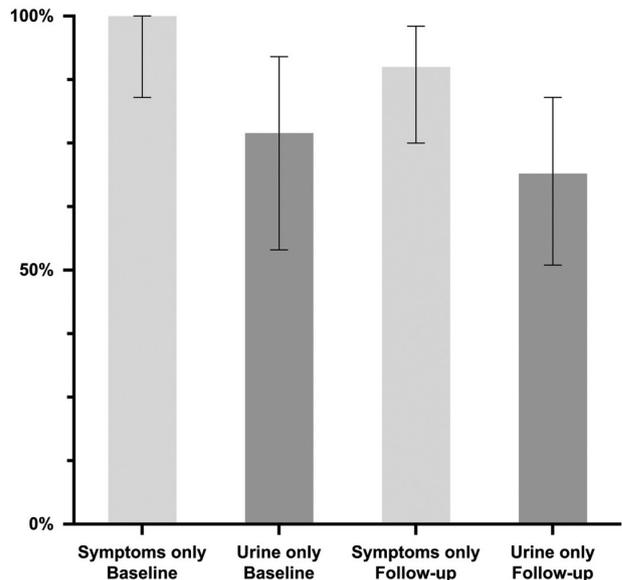


**Figure 1** - Cumulative incidence of syphilis (A), Ct (B) and Ng (C) infections during the follow-up of the participants in the study.

and 30/33 of either infections would be missed (90%, 95% CI 75-98%; **Figure 2**).

**DISCUSSION**

To our knowledge, this is the first study in Brazil that has used systematic extragenital and asymptomatic STI testing in PrEP users. This real-life study including 413 PrEP users in Sao Paulo, Brazil, had a median follow-up time of almost 10 months, with regular testing for HIV and syphilis and a multisite screening for Ct and Ng. Despite the high vulnerability of this cohort participants, we found no HIV seroconversion during follow-up, emphasizing the effectiveness of PrEP as an HIV prevention method. The sociodemographic profile found in our sample, mainly composed of white, cisgender men, older than 30 years of age with high schooling levels, suggests that access to PrEP may still face significant barriers, particularly among youths, black and transgender populations, even in the



**Figure 2** - Percentage of missed Ct/Ng diagnosis at baseline and follow-up if molecular testing had been applied only in urine samples or only to symptomatic patients. Whiskers represent 95% confidence intervals.

context of cost-free care in the public healthcare system<sup>23-26</sup>. Even though this could be interpreted as a bias of selection in our clinic, we found the same sociodemographic profile regarding schooling levels and skin color in a Brazilian national study<sup>27</sup>.

Upon admission to the PrEP clinic, 37% of our participants reported using club drugs in the past three months. Chemsex is defined as the use of psychoactive substances during sex in order to improve physical capacity and/or pleasure<sup>28,29</sup>. In our cohort, the most frequently used substances were marijuana, club drugs and erectile stimulants. Some studies have demonstrated an escalating use of club drugs and erectile stimulants among PrEP users<sup>30</sup>, and these studies have also suggested an association between club drugs and a higher prevalence of bacterial STI<sup>31</sup>.

PrEP users are at high risk for the incidence of STI due to their high sexual vulnerability; however, they are also more likely to undergo STI testing, detection and treatment, since the clinical follow-up of PrEP users also requires more frequent screening and counseling. Although the first PrEP randomized clinical trials revealed no statically significant rise in the number of sexual partners or condomless sexual exposure<sup>1,2,4</sup>, more recent publications have suggested that there may be an increase in condomless sex and in the incidence of STI among PrEP users<sup>6-12</sup>.

The 12-months cumulative incidence of syphilis, Ct and Ng in our study were 13.4%, 11.4% and 8.9%, respectively. The incidence of STI seems to be higher in the later stages after the PrEP initiation, suggesting that risky behaviors may increase several months after the beginning of PrEP. More importantly, molecular screening tests for Ct and Ng in multiple sites yielded a higher detection of infections, mainly in asymptomatic individuals and in the oropharynx and anal swabs. A systematic review and meta-analysis evaluated the occurrence of STI including recent syphilis, Ct and Ng among PrEP users<sup>17</sup>, demonstrating that one in four patients (23.9%) had at least one STI at the moment of PrEP onset. In our study, 11.9% (95% CI 8.9-15.4) of the participants had at least one STI at baseline; however, multisite screening for Ct and Ng had not been implemented in the first months of activities in our PrEP clinic, and as a consequence, a few Ct/Ng cases may have been missed. The meta-analysis published by Ong *et al.* showed a prevalence of Ct/Ng in genital, anorectal and oropharynx of 4.0%/2.1%, 8.5%/9.3% and 2.4%/4.9%, respectively<sup>17</sup>. These results are similar to the ones found in our study, with higher percentages of positive results in the oropharynx and anal sites.

Although testing of asymptomatic patients and of extra-urinary sites is still uncommon in Brazil, the importance of

anal screening for the diagnosis of Ct and Ng among PrEP users should receive further attention. Studies in Europe, North America and Asia have described 7.2-9.5% of Ct prevalence in anorectal specimens among MSM populations seeking medical care and/or who had a history of receptive anal intercourse<sup>18-20,32-34</sup>, and up to 95% of these infections may be asymptomatic<sup>18,20,34</sup>. Molecular biology testing of multisites enables the detection and prompt management of asymptomatic extragenital infections. Supporting this strategy, Jenness *et al.*<sup>35</sup> showed in a mathematical model that the expansion of PrEP coverage and the increase in testing and treatment of STI (including rectal and urogenital infections) among vulnerable individuals may reduce the incidence of Ct and Ng even in the presence of the risk compensation. An important limitation for the implementation of the multisite screening is the financial burden of using multiple PCR collection kits per person/visit. An alternative strategy that has been evaluated to reduce costs and increase the feasibility of molecular tests in health services is the use of pooled sites sampling. Some studies suggested that this method allows a substantial reduction of costs with a minimum impact on the sensitivity of tests<sup>36,37</sup>.

The estimated global prevalence of syphilis in men and women is approximately 0.5%<sup>14</sup>. In our study, one quarter of PrEP users had been exposed to Tp as documented by a positive treponemal test, and 7% had active infection at baseline. Our results were similar to those found by Ong and colleagues in a systematic review of PrEP users<sup>17</sup> and those described in the Brazilian national report that analyzed PrEP dispensations and outcomes in 2018<sup>27</sup>. Of note, the incidence of sexually-acquired syphilis is increasing in Brazil, from 34.1 cases per 100 thousand inhabitants in 2015 to the peak of 76.2 cases per 100 thousand inhabitants in 2018. In 2019, the reported incidence was 72.8/100.000, but the decrease may be due to a delay in data input during the COVID-19 pandemic<sup>38</sup>. While the cumulative incidence of syphilis at 12 months in our study was 13.4%, the incidence among PrEP users in the Brazilian national surveillance was 4%<sup>27</sup>. This difference could be partially explained by the rising incidence of syphilis over the last years, a high frequency of testing in our medical facility, or an increased risk profile in our study sample.

The incidence rates for Ct, Ng and syphilis described by Ong and colleagues were 21.5 (95% CI 17.9-25.8), 37.1 (95% CI 18.3-25.5) and 11.6 (95% CI 9.2-14.6) cases per 100 person-years, respectively<sup>17</sup>. In our study, the rates were 11.1 (95% CI 7.2-17.2), 9.1 (95% CI 5.5-15.0) and 15.4 (95% CI 11.2-21.0) cases per 100 person-years, respectively. Possible reasons for the lower incidence of Ct and Ng in our study include the characteristics of our study population, with a higher percentage of educated, white/

Caucasian, cisgender MSM, a low compliance with Ct/Ng test, or the relatively short follow-up period.

Our study had a few limitations. We retrieved data collected in routine clinical care, with some amount of missing data. Molecular testing for Ct and Ng had not been implemented when the PrEP use started in our institution, and even after its implementation, the uptake was not homogeneous due to refusals in some cases. In addition, we were restricted to a single healthcare facility in an affluent area of Sao Paulo, the largest city in Brazil. Therefore, our outcomes may not be reliably extrapolated to other facilities with different patterns of social interactions and distinct epidemiological contexts.

Despite these limitations, our findings clearly demonstrate the utility of a periodic testing for Ct and Ng among asymptomatic PrEP users in multiple anatomic sites with the aim of breaking the chain of STI transmission. The Centers for Disease Control (CDC) recommends testing every 3-6 months, in all anatomic sites<sup>39</sup>, while the Brazilian guideline still recommends urine or genital fluid testing every 6 months<sup>21</sup>. Shorter intervals have been shown to further increase the number of asymptomatic cases that are detected and treated<sup>35</sup>.

Our institution maintained the use of multisite screening after observing the high positivity rate in the current study, and encourages the frequent testing of patients coupled with educational initiatives focusing on breaking the chain of STI transmission. PrEP programs should be used as tools to promote HIV and STI awareness and to implement timely and effective diagnosis and treatment of STI at a populational level.

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## CONFLICT OF INTERESTS

The authors declare no conflicts of interests.

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