

**The presence or absence of symptoms among cases of urethral gonorrhoea occurring in a cohort
of men taking HIV pre-exposure prophylaxis in the PrEPX Study**

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Abstract

We aimed to estimate how often urethral gonorrhoea is symptomatic among men in the Pre-Exposure Prophylaxis Expanded Victoria study. Eighty seven percent of 213 cases of urethral gonorrhoea were symptomatic. Ensuring men with urethral gonorrhoea both recognise and present early for treatment is critical to reduce transmission.

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Introduction

Studies that have attempted to determine the proportion of men who develop symptoms following infection of the urethra with *Neisseria gonorrhoeae* have been subject to considerable potential bias. Apart from one cohort analysis undertaken nearly 50 years ago, these cross-sectional studies have either been retrospective descriptions from sexual health clinics or studies screening large numbers of men [1-7]. Studies in sexual health clinics are biased towards overestimating the proportion of patients with symptoms because men who develop symptoms preferentially attend these services [8]. These clinic-based studies have estimated that 89-94% of men with urethral *N. gonorrhoeae* develop symptoms [1-3]. One cohort analysis among service men in 1974 found that 98% of men with urethral gonorrhoea developed symptoms [7]. In contrast, screening studies are biased towards underestimating the proportion of patients with symptoms because cases with symptoms have a much shorter duration and therefore are less likely to be present in cross sectional studies. Furthermore, these screening studies have primarily screened asymptomatic men (i.e. reporting that between 0-58% of men have symptoms) [4-6].

Estimating the proportion of men who have symptoms from urethral gonorrhoea is important because the recognition of symptoms prompt individuals to access health care and treatment. This allows for other important steps, such as contract tracing, which can put substantial downward pressure on transmission within populations. However, if symptoms are uncommon among men with urethral gonorrhoea, then strategies that increase symptom recognition will be less effective in reducing transmission while strategies that promote regular asymptomatic screening of men at risk may be preferred.

We recently undertook a large cohort study of participants taking pre-exposure prophylaxis (PrEP) for HIV in which 233 cases of urethral gonorrhoea occurred [9]. Data from this cohort study should provide a less biased method of determining the proportion of symptomatic cases than previous studies because participants were required to attend PrEP appointments every three months and STI screening was required of all participants regardless of the presence of symptoms. Participants were

also asked to attend their study enrolment clinic for testing and treatment should they develop STI symptoms between quarterly visits. The present study aimed to determine the proportion of men with symptomatic urethral gonorrhoea from the cohort study.

Materials and Methods

The Pre-Exposure Prophylaxis Expanded (PrEPX) Victoria study was a multisite, single-armed, open-label intervention study of tenofovir disoproxil fumarate and emtricitabine for HIV PrEP among 4,275 participants in Victoria, Australia, between July 2016 and May 2018 [9]. Men were followed up every three months. We conducted a retrospective analysis of the clinical records of men with linked STI testing data who developed incident urethral gonorrhoea and urethral chlamydia during the 3185 person years of follow up in the PrEPX study. A detailed description of the PrEPX study is published elsewhere [10]. 2981 PrEPX participants enrolled through one of five recruitment sites which also participate in the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance (ACCESS) project, an existing sentinel surveillance network [11], and were monitored for STI outcomes during study follow-up.

Patient Consent Statement

Ethics approval was obtained from the Alfred Hospital Human Research Ethics Committee for the PrEPX study (projects 100/16 and 248/17) [10]. All participants provided written consent to have their medical records reviewed as part of this project when they consented to the PrEPX study. Participants who had a positive test result from a urethral swab or first pass urine specimen for *N. gonorrhoeae* by nucleic acid amplification (NAAT) at one of the five recruitment sites were included in this analysis. As previously described [10], the ACCESS system uses specialised data extraction software to routinely extract clinical data from patient management systems. These data identified each case of urethral gonorrhoea among participants in the PrEPX study. Chart review for all urethral gonorrhoea cases was performed by LCD and ETA.

We reported the frequency, proportion and corresponding 95% confidence intervals (CI) of urethral symptoms and other clinical characteristics.

Results

Between July-2016 and May-2018, 233 cases of urethral gonorrhoea were diagnosed among 191 individual men. Table 1 shows the characteristics of the 191 men. Of the 191 men, 160 individuals were diagnosed with a single infection, 24 with two infections, 5 with three infections, 1 with four infections and 1 with six infections during the study period (Table 2).

A total of eight cases were excluded from this analysis because two cases (one participant) had been excluded from the PrEPX study at enrolment after HIV was diagnosed and six cases did not have information on urethral symptoms in their clinical notes.

Of the 225 cases included, 176 reported urethral symptoms on the day of testing and 49 reported an absence of symptoms. Of the 176 cases who had urethral symptoms, 139 had typical urethral discharge (yellow, green or pus like) and 30 had other urethral symptoms such as urethral discomfort, dysuria or a non-purulent discharge.

Among the 225 cases of urethral gonorrhoea, 222 were also tested for urethral chlamydia on the same day. Of these 222 cases of urethral gonorrhoea, 35 were co-infected with urethral chlamydia. Of the 174 symptomatic cases, 29 (17%) were also co-infected with chlamydia. Of the 48 asymptomatic cases, 6 (13%) were also co-infected with chlamydia.

Among the 49 cases that were asymptomatic, 7 were treated on the day of testing because they were sexual contacts of a known case of gonorrhoea. Of the 42 untreated asymptomatic cases, 37 had a record of them returning for treatment at one of the five recruitment sites and five sought treatment with a local health care provider. Among the 37 asymptomatic cases who returned for treatment, the time between testing and treatment follow up ranged from 2-16 days (mean=6, median=5 days). Nine had documentation that they had since developed some urethral symptoms,

12 cases had no documentation as to whether they were symptomatic or not and 16 remained asymptomatic.

If the proportion of cases with symptoms includes the 176 who initially had symptoms and the 9 who later developed symptoms, then the proportion of cases with symptoms was 87% (185/213) (12 excluded because 7 asymptomatic cases were treated on the day of testing and 5 did not return for treatment at a recruitment site).

Discussion

In this cohort study of men taking PrEP, 87% of men who acquired urethral gonorrhoea developed symptoms. This finding is relatively consistent with the estimates from most of the clinic-based studies where between 89-94% of men were symptomatic [1-3] and the only other cohort study where 98% of infections were symptomatic [7]. However, our findings are substantially greater than the screening studies where between 0-58% were symptomatic [4-6].

One of the strengths of this study is that we have managed to capture participants at 3 monthly intervals and also when symptomatic. Due to the design of this study we have been able to combine the strengths of previous sexual health clinic studies and those of screening studies.

There are several limitations to our study. First, the data on symptoms were collected retrospectively from patient records. Importantly though, only a few cases did not specifically mention either the presence or absence of urethral symptoms. Second, our study may have slightly overestimated the proportion of cases who were asymptomatic because seven asymptomatic cases who were contacts of gonorrhoea were treated on the day and may have developed symptoms if they had not been treated so promptly. We may have also underestimated the proportion of men who would have developed symptoms because some men were recalled and treated within a short

time frame of only a few days (median=5 days). The cases of chlamydia co-infection may have also affected our results. About 17% of the symptomatic cases were co-infected and therefore some of these symptoms may be attributable to the chlamydia infection rather than the gonorrhoea infection.

Previous studies of men attending sexual health clinics have reported slightly higher rates of symptomatic urethral gonorrhoea. Ong's study of 242 MSM attendances at a sexual health clinic in Melbourne found that 89% of urethral gonorrhoea cases were symptomatic [1]. Barbee's case-control study of 1604 MSM attending two sexual health clinics in the U.S., found that 94% of urethral gonorrhoea cases were symptomatic [2]. Martin-Sanchez's study of 116 heterosexual men attending a sexual health clinic in Melbourne found that 94% of cases of urethral gonorrhoea were symptomatic [3]. Most of these sexual health clinics have a standardised reporting form which allows for more complete sets of data. However, the nature of sexual health clinics creates a bias towards more symptomatic cases given individuals with symptoms are prompted to attend these services by the symptoms [12].

The reported proportion of men who are symptomatic with urethral gonorrhoea varies greatly in previous screening studies. In Pack's study of black male adolescents from detention facilities in the U.S, 0/19 cases of urethral gonorrhoea reported symptoms [5]. However, the study also reported 9 cases of dual chlamydia/gonorrhoea urethral infection in which 33% of males were experiencing symptoms so it is possible that 3/28 (11%) had symptoms. A study of 12 young men attending health centres and educational settings in the U.S found that 58% of men with urethral gonorrhoea had symptoms [4]. The study included men with incidental urethral symptoms but actively excluded men who were seeking healthcare with genitourinary symptoms as their primary reason of attendance. A further study by Handsfield of 59 men serving in the US Army reported 32% of men with urethral gonorrhoea had symptoms [6]. These studies have all looked at populations that were

not presenting with symptoms or actively excluded symptomatic presentations, and therefore may have biased the findings to underestimate the numbers of symptomatic infections. They are also limited by their sample sizes which are significantly smaller than the sexual health clinic studies. The study design of these screening studies and low sample sizes may explain why their results have differed so greatly with the results of our study.

The estimate in our cohort analysis was much closer to the previous single cohort study and the clinic studies than it was to the cross-sectional studies. This is likely to be because if most urethral gonorrhoea cases are symptomatic (i.e. finding from our study), then any estimate will be driven mostly by these cases and not the small number of asymptomatic cases. The small number of studies providing asymptomatic cases may reflect how uncommon asymptomatic cases are and therefore pragmatically how difficult it is to undertake studies to identify them.

Our results support previous findings that the majority of men with urethral gonorrhoea are symptomatic, however there were a clinically meaningful number of asymptomatic presentations. These findings support health promotion to improve symptom recognition and the provision of accessible sexual health care but also support the need for ongoing screening in asymptomatic high-risk groups. Gonorrhoea infection occurs commonly in other sites (i.e. oropharynx and anorectum) apart from the urethra. Oropharyngeal and anorectal gonorrhoea infections are mostly asymptomatic, while urethral gonorrhoea infections are mostly symptomatic; and therefore, a combination of frequent screening and symptoms awareness are important for gonorrhoea prevention and control.

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POTENTIAL CONFLICTS OF INTERESTS

MT has received speaker's honoraria from Gilead Sciences. MAS has received investigator initiated funding from Gilead Sciences, AbbVie and Bristol Myers Squibb for research unrelated to this work. EJW has received investigator initiated funding from Gilead Sciences and Merck and funding for educational purposes from Gilead Sciences. EPFC has received speaker's honoraria from Gilead Sciences, research grants from Seqirus Australia and Merck in the area of human papillomavirus outside the submitted work.

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AUTHORS' CONTRIBUTIONS

EPFC and CKF conceived and designed the study. EPFC, LCD, ETA, and CKF designed the study materials. LCD and ETA performed the clinical audit. LCD performed the statistical analyses and wrote the first draft of the manuscript. EPFC oversaw the study. MT contributed to data duration. MAS helped lead the quantitative data collections for the PrEPX study and contributed to drafting the manuscript. All authors were involved in revising the manuscript for important intellectual content and approved. EJW was the Principal Investigator of the PrEPX study and contributed to drafting this manuscript.

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Table 1. Characteristics of participants with urethral gonorrhoea (N=191)

Characteristics	No. (%)
Age (years), mean (standard derivation)	36.0 (10.1)
Gender	
<i>Male</i>	189 (99.0)
<i>Transgender – Male</i>	1 (0.5)
<i>Non-binary/Gender Fluid</i>	1 (0.5)
Sex at birth	
<i>Male</i>	189 (99.0)
<i>Female</i>	2 (1.0)
Sexuality	
<i>Gay/Homosexual</i>	180 (94.2)
<i>Bisexual</i>	9 (4.7)
<i>Other</i>	2 (1.0)
Country of birth	
<i>Australia</i>	100 (52.4)
<i>Overseas</i>	68 (35.6)
<i>Missing</i>	23 (12.0)
Injecting drug use at enrolment	
<i>Yes</i>	17 (8.9)
<i>No</i>	174 (91.1)
In the 3 months prior to enrolment:	
<i>Any condomless receptive anal intercourse with a casual male partner with HIV or of unknown HIV status</i>	99 (51.8)
<i>>1 Episode of condomless insertive anal intercourse with a casual male partner with HIV or of unknown HIV status</i>	82 (42.9)
<i>>1 Episode of anal intercourse without correct and consistent condom use (eg, condom slipped off or broke)</i>	59 (30.9)
<i>Used methamphetamines</i>	36 (18.8)
<i>Self-reported diagnosis of rectal gonorrhoea, rectal chlamydia, or syphilis</i>	48 (25.1)

Table 2. Characteristics of 225 cases of urethral *Neisseria gonorrhoeae* in the PrEPX study.

Characteristics	n/N	% (95% CI)
On initial presentation:		
Urethral symptoms present	176/225	78 (72-83)
<i>Co-infected with urethral chlamydia*</i>	29/174	17 (11-23)
<i>Typical Urethral Symptoms</i>	139/176	79 (72-84)
<i>Other Urethral Symptoms†</i>	30/176 ^a	17 (12-23)
Urethral symptoms absent	49/225	22 (17-28)
<i>Co-infected with urethral chlamydia‡</i>	6/48	13 (5-25)
<i>Asymptomatic and treated on day</i>	7/49	14 (7-27)
<i>Asymptomatic and not treated on day</i>	42/49	86 (72-93)
<i>Known contact of gonorrhoea infection</i>	21/225	9 (6-14)
Initially Asymptomatic & Returned for treatment:		
<i>Returned to recruitment site for treatment</i>	37/42	88 (75 – 95)
<i>Urethral symptoms absent</i>	16/37	43 (29 – 59)
<i>Urethral symptoms present</i>	9/37	24 (13 – 40)
<i>Data incomplete to determine symptoms</i>	12/37	32 (20 – 49)
Symptomatic at either presentation§	185/213 ^b	87 (82 – 91)

PrEPX = Pre-exposure Prophylaxis Expanded

* Two men with urethral symptoms were not tested for urethral chlamydia and therefore were excluded for co-infection analysis.

†The data on the nature of the symptoms was missing for seven participants

‡ One man who did not have urethral symptoms was not tested for urethral chlamydia and therefore was excluded for co-infection analysis.

§The denominator excluded seven asymptomatic individuals who were treated on the day of testing (contacts of gonorrhoea) and five who did not return for treatment at the five recruitment sites.