High rate of repeat sexually transmitted diseases among men who have sex with men in South Africa: a prospective cohort study

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SHORT SUMMARY

There is high incidence of urethral and rectal STDs among symptomatic South African MSM, highlighting the need to strengthen STD prevention and control strategies.

ABSTRACT

We observed a high rate of incident STDs within 55 days(median) of follow up(78% retention) among symptomatic MSM(n=78) in South Africa (188 per 100 person-years 95%CI 1.2-2.7)); 16 newly acquired and 10 with persistent positivity. This highlights the need to strengthen prevention efforts, whereas introduction of diagnostics is urgently warranted.

KEY WORDS

Incidence; MSM; Africa; syndromic management; STD

INTRODUCTION

In Sub-Saharan Africa, management of STDs in men who have sex with men (MSM) is generally syndromic with urethritis as the most common clinical presentation (1, 2). In the absence of routine diagnostics, the aetiological profile of urethritis in African MSM is not well documented and limited to studies assessing *N. gonorrhoeae* and *C. trachomatis* prevalence. In South Africa, only two studies have reported on STDs among MSM that were recruited regardless of presence of symptoms with a point prevalence of 10% and 24% for *C. trachomatis* at any anatomic site and 3% and 16% for *N. gonorrhoeae* at any anatomic site (3, 4). The prevalence of *M. genitalium* and *T. vaginalis* infection, two important causes of urethritis in the male population, is undocumented among African MSM (5, 6).

Syndromic management of STDs has several challenges. First, many STDs remain untreated as a large proportion is asymptomatic, in particular rectal and oropharyngeal infections (3, 6). This is especially important as STD infection enhances HIV transmission when exposed (7). Unlike urethritis , rectal discharge is not included in any syndromic management guidelines which in practice likely results in undertreated infections due to provision of inadequate treatment that targets other infections than STDs. In the absence of diagnostics, presumptive treatment of high-risk men could provide a solution to address the burden of symptomatic and asymptomatic infections in MSM. The WHO algorithm for presumptive STD treatment based on risk assessment could theoretically cover cases of asymptomatic infection (8). However, Sanders and colleagues evaluated this algorithm and found a sensitivity of 74% and a specificity of 46% (9).

To address the burden of STDs among MSM in Africa it is imperative to not only understand the prevalence and aetiological profile of STDs, but also to have insight in the incidence of symptomatic and asymptomatic infections. This study determines the incidence of both symptomatic and asymptomatic STDs in a population of symptomatic MSM visiting public healthcare facilities in Johannesburg, South Africa. All MSM were routinely universally tested for urethral and rectal STDs at

baseline and follow-up. At follow-up, we distinguish between incident and repeat/persistent positivity.

METHODS

Study setting

This prospective cohort study was conducted at two primary healthcare facilities that offer free sexual health services for MSM in Johannesburg in 2015-2016. The facilities are situated in socio-economically deprived areas; one in the city centre and the other in Soweto, Johannesburg's largest township (2). This study was approved by the Human Research Ethics Committee of the University of the Witwatersrand, Johannesburg, South Africa (Ref: M150352).

Study population and study design

MSM presenting with urethral and/or rectal discharge were included in the study. Socio-demographic data were collected through a questionnaire. Urine and rectal swabs from all participants were tested for *C. trachomatis*, *N. gonorrhoeae*, *T. vaginalis* and *M. genitalium*. *C. trachomatis* and *N. gonorrhoeae* were detected using the High Pure PCR Template Preparation Kit (Roche Diagnostics, Switzerland) and the Presto CT/NG assay (Microbiome Ltd). *M. genitalium* and *T. vaginalis* were detected using an in-house real-time PCR assay and the LightCycler 480 Instrument (Roche Diagnostics). Upon recruitment, MSM were provided with standard syndromic management (single dose of 100 mg azithromycin and 250 mg ceftriaxone); metronidazole 2 g single dose was provided when *T. vaginalis* was detected or in case of reported female partner with vaginal discharge (1). Follow-up visits were scheduled after 6 weeks of initial treatment, or earlier in case of symptoms. At follow-up, all diagnostic tests were repeated at the two anatomic sites, regardless of symptoms. All MSM tested positive at follow up were recalled for targeted treatment.

Definitions

A repeat syndromic episode was defined as occurrence of symptoms at follow-up, regardless of a documented STI at either visit. Incident infection was defined as detection of a different pathogen at any anatomic site, or detection of the same pathogen at a different anatomic site. Persistent positivity was defined as detection of the same pathogen at the same anatomic site. STD incidence of MSM testing positive for any organism at any anatomic site was determined from baseline to date of testing at follow up.

RESULTS

Characteristics of the study population

A total of 78 MSM participated in the study, 37 in the township clinic and 41 in the city center clinic. Urethral discharge was reported by 63 MSM, rectal discharge by 14 MSM, and 1 MSM reported both. The median age was 28 years (inter quartile range (IQR) 24-32). Two thirds identified as gay (71%, n=55) and one third as bisexual (29%, n=23). Half of the MSM reported a history of urethritis , 25 (32%) less than a year ago and 11 (14%) more than one year ago. At baseline, 36 men (46%) were HIV positive of whom 24 men (67%) were already on antiretroviral therapy; 39/42 participants were tested for HIV of whom 7 (18%) tested newly positive.

STDs detected at baseline

Eighty percent of MSM had an STD detected (62/78); 50 (64%) had urethral infection and 32 (41%) had rectal infection. An STD was detected in 56/64 (89.1%) of men with urethral discharge. *N. gonorrhoeae* infection was the most common cause of urethral discharge (n=43; 67%), followed by *C. trachomatis* (n=9; 12%), *T. vaginalis* (n=3) and *M. genitalium* (n=1). In 29/64 (45%) of men with urethral discharge an asymptomatic rectal infection was detected (19 *N. gonorrhoeae*, 10 *C. trachomatis* and 3 *T. vaginalis*).

An STD was detected in 6/15 (40%) of men with rectal discharge: all cases of *N. gonorrhoeae*. In 3/15 (20%) of men with rectal discharge an asymptomatic urethral infection was detected (all *N. gonorrhoeae)*.

Repeat syndromic episodes

A total of 61 (78%) MSM men came for a follow- up visit after a median of 55 days (IQR 41-93). MSM lost to follow-up were younger (26 years versus 30 years, P=0.03), all other characteristics were comparable. Repeat symptoms were reported by 8% (5/61) of participants; two reported urethral discharge, two reported rectal discharge and one reported both.

Incidence of STDs

One third of MSM (22/61, 36%) had at least one STD detected at follow-up, 10/61 (16%) had urethral infection, 8/61 had (13%) rectal infection and 4/61 (7%) had both. The total follow-up time for MSM was 11.7 years. As such, the estimated STD incidence was 188 per 100 person-years (95% confidence interval (CI) 118-273 per 100 person-years). Two urethral infections were symptomatic, but none of the rectal infections, resulting in an estimated symptomatic STD incidence of 17 per 100 person-years (95% CI 3-55 per 100 person-years), and 171 per 100 person-years (95% CI 105-253 per 100 person-years) for asymptomatic infection. Among the 22 MSM with STDs at follow-up, infection was considered incident in 16 cases, that is detection of a different pathogen at any anatomic site, or detection of the same pathogen at a different anatomic site (73%; 95% CI 50-89) (Table 1). Persistent positivity was detected in 10 of the cases (46%; 95% CI 24-68), that is detection of the same pathogen at the same anatomic site.

Table 1. Incident and persistent STDs at follow-up in a cohort of high-risk men who have sex with men in Johannesburg, South Africa.

Type	Age	Baseline symptoms	Baseline STD		Follow-up STD	
			Urethral	Rectal	Urethral	Rectal
Incident infection						
	26	Urethral	NG	CT, NG	TV	-
	31	Urethral	NG, TV	TV	-	CT
	27	Urethral	NG, TV	TV	MG	-
	21	Urethral	-	NG	NG	-
	25	Urethral	NG	-	-	CT
	40	Urethral	-	-	-	TV
	32	Rectal	NG	-	-	NG
	28	Rectal	-	NG	NG	-
	32	Rectal	-	-	CT	-
	23	Rectal	-	-	NG	-
	27	Rectal	-	-	NG	-
	29	Both	-	NG	TV	TV
Persistent positivity						
	27	Urethral	NG	-	NG[2]	-
	43	Urethral	-	NG	-	NG
	24	Urethral	-	CT, NG	-	NG
	39	Urethral	NG	-	NG	-
	29	Urethral	NG	NG	-	NG
	35	Urethral	CT	NG	-	NG
Incident infection and persistent positivity						
	30	Urethral	CT, NG	-	NG, TV[2]	-
	36	Urethral	NG	NG	NG, TV, MG	NG, TV
	*	Urethral	CT, NG	-	CT, NG	CT, NG
	32	Rectal	NG	-	NG, TV, MG	TV

[1] The proportion positive for any STD at follow up was comparable between HIV positive and HIV negative MSM (P=0.79), and comparable between MSM on ART and MSM not on ART (P=0.52). [2] Patient reported urethral discharge at follow up. *data is missing. - no STD detected.
We did not observe differences in the proportion baseline STD, follow-up STD, incident infection and persistent positivity between the clinics (P=0.43, P=0.77, P=0.35, P=0.87, respectively).
Abbreviations: NG *Neisseria gonorrhoeae*, CT *Chlamydia trachomatis*, TV *Trichomonas vaginalis* and MG *Mycoplasma genitalium*.

DISCUSSION

This study is among the the first to assess STD incidence among MSM living in an African country using syndromic management. Despite the limited sample size, we show a very high incidence rate of urethral and rectal STDs and highlight the need for more effective prevention and control strategies in this high-risk population.

The aetiological profile of STDs that we observed is in line with that reported for men in the general population (6). This includes infection with *T. vaginalis* and *M. genitalium* which have not been reported in African MSM before and are rarely studied in African men (5). However, these infections are important since metronidazole for *T. vaginalis* is not routinely provided as part of syndromic management, whereas macrolide-resistance may play role in *M. genitalium* (10). Interestingly, only a small proportion of men with rectal discharge had an STD detected but all cases responded to syndromic management. This highlights the need for further research into clinical management of rectal discharge in African MSM.

We observed a high incidence of both symptomatic and asymptomatic STDs among MSM. The symptomatic cases were treated successfully with routine syndromic management, however, the asymptomatic infections would normally have remained untreated. This confirms the need to introduce STD diagnostics in clinical management of this high-risk population in order to reduce the burden of infection. Moreover, culture and drug susceptibility testing in repeat *N. gonorrhoeae* positive MSM should be included in such a diagnostic algorithm, since we observed a number of cases with persistent positivity and there is the likelihood of antimicrobial resistance emerging in this population. Although we could not distinguish between repeat infection and treatment failure in these cases the observation is important and warrants further research.

The high incidence rates of syndromic episodes and STDs detected shows that we recruited a population with high-risk sexual behaviour. These findings are in line with a study that revealed a high HIV incidence in a similar MSM population (3). Although we did not measure HIV incidence in our cohort, the number newly diagnosed HIV infections upon recruitment is highly concerning. Innovative prevention, diagnostic and treatment approaches to reduce HIV and STD transmission are warranted in this particular population. In addition to introduction of diagnostics and strengthening partner notification, offering presumptive treatment could be an option. However, the drug(s) of choice would

be complicated, given the already substantial rates of azithromycin and high doxycycline resistance in *N. gonorrhoeae* infection in this population (11).

The relatively small sample size is a limitation of the study. Study recruitment was difficult, despite rigorous efforts by the clinic staff and mobilisation of potential participants through posters. Also, follow-up was not 100%, possibly leading to missed infections at follow-up. Selection due to operational issues and lack of disclosure of same-sex sexual behaviour by men visiting our clinic may have played a role. It is unclear in which direction this bias would have occurred. However, we think such selection would have been random and did not bias our results. The follow-up window to calculate incidence was short and time of acquisition might be different. Also, we did not exclude 'immune-time' for calculating the STD incidence, that is the time participants were taking treatment. Moreover, pharyngeal testing was not done. This all could lead to underestimation of STD incidence.

In conclusion, we observed high incidence rates of symptomatic and asymptomatic STDs in a cohort of MSM living in South Africa. These results indicate a need to strengthen prevention efforts and to introduce diagnostic testing in management of this high-risk population to achieve STD control.

REFERENCES

1. Department of Health, Republic of South Africa. Sexually transmitted infections management guidelines, http://www.kznhealth.gov.za/family/STI-guidelines-2015.pdf (accessed 19-02- 2019).

2. Rees K, Radebe O, Arendse C, et al. Utilization of Sexually Transmitted Infection Services at 2 Health Facilities Targeting Men Who Have Sex With Men in South Africa: A Retrospective Analysis of Operational Data. Sex Transm Dis. 2017; 44(12): 768-73.

3. Rebe K, Lewis D, Myer L, et al. A Cross Sectional Analysis of Gonococcal and Chlamydial Infections among Men-Who-Have-Sex-with-Men in Cape Town, South Africa. PLoS One. 2015; 10(9): e0138315.

4. Zahn RD, K; Sanchez, T; Phaswana-Mafuya, N; Bekker, L.G.; Baral, S; Kearns, R; Yah, C; Sullivan, P. High Prevalence of Sexually Transmitted Infections in a Cohort of Men Who Have Sex with Men and Transgender Women From Port Elizabeth and Cape Town, South Africa. Poster presentation AIDS 2016, Durban South Africa. 2016.

5. Hoffman CM, Fritz L, Radebe O, et al. Rectal Trichomonas vaginalis infection in South African men who have sex with men. Int J STD AIDS. 2018: 956462418788418.

6. Lewis DA, Pillay C, Mohlamonyane O, et al. The burden of asymptomatic sexually transmitted infections among men in Carletonville, South Africa: implications for syndromic management. Sex Transm Infect. 2008; 84(5): 371-6.

7. Kiviat NB, Critchlow CW, Hawes SE, et al. Determinants of human immunodeficiency virus DNA and RNA shedding in the anal-rectal canal of homosexual men. J Infect Dis. 1998; 177(3): 571-8.

8. WHO. Prevention and treatment of HIV and other Sexually Transmitted Infections among Men who have Sex with Men and Transgender People. Switzerland: World Health Organization, 2011:1–86.

9. Sanders EJ, Wahome E, Okuku HS, et al. Evaluation of WHO screening algorithm for the presumptive treatment of asymptomatic rectal gonorrhoea and chlamydia infections in at-risk MSM in Kenya. Sex Transm Infect. 2014; 90(2): 94-9.

10. Maduna LD, Laumen JG, Radebe O, et al. Failure of syndromic management due to drug-resistant *Mycoplasma genitalium* infection in South Africa: a case report. Int J STD AIDS. 2019: 956462418820745.

11. Maduna LD, Kock MM, Radebe O, et al. Rapid emergence of azithromycin resistance in Neisseria gonorrhoeae infection in high risk men in South Africa. Conference abstract, 29th ECCMID, Amsterdam 2019.