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High incidence of syphilis in HIV-positive homosexual men: data from two community-based cohort studies

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Abstract. ***Background*:** Syphilis has re-emerged and become established in gay communities in most developed countries since the late 1990s. HIV infected men have been disproportionately affected by this endemic, but it is unclear whether this is due to behavioural or biological reasons. We report incidence and risk factors for syphilis in two community-based cohorts of HIV-negative and HIV-positive homosexual men in Sydney, Australia. ***Methods*:** Participants were recruited using similar community-based strategies in both cohorts and underwent annual face-to-face interviews. Syphilis screening was offered to all consenting participants at annual visits. ***Results*:** In the HIV-negative cohort, 21 men seroconverted to syphilis and one man had a syphilis re-infection during 2001–07, an incidence of 0.49 per 100 person-years (95% CI: 0.31–0.74). In the HIV-positive cohort during 2005–07, eight men seroconverted and one man had a syphilis re-infection, giving an incidence of 3.62 per 100 person-years (95% CI: 1.67–6.48). All nine reported a recent CD4 count of more than 350 cells μL^{-1}. Syphilis incidence was significantly higher in the HIV-positive cohort after adjustment for age (hazard ratio (HR) = 9.20, 95% CI: 3.63–23.31). Unprotected anal intercourse (UAI) with HIV-positive partners was significantly associated with incident syphilis in both cohorts (HR = 4.45, 95% CI: 1.37–14.45 in HIV-negative; HR = 8.67, 95% CI: 1.03–72.76 in HIV-positive). ***Conclusion*:** Syphilis incidence was almost 10-fold higher in HIV-positive than in HIV-negative homosexual men, and it was not related to a CD4 count below 350 μL^{-1}. UAI with HIV positive partners was of particular importance in the transmission of syphilis.

Additional keywords: homosexuality, incidence, male, risk factor.

Introduction

The incidence of syphilis in homosexual men has undergone dramatic changes in recent years. Before the HIV epidemic, syphilis was extremely common in this population,[1–3] but the 1980s saw a remarkable decline in its incidence and it was virtually eliminated in many settings.[4,5] In the late 1990s, syphilis re-emerged and it has since become endemic in gay communities in most developed countries.[6–12]

A consistently described feature of re-emergent syphilis in homosexual men has been a disproportionate representation of HIV infected men who make up more than half of the cases of syphilis reported among homosexual men in most locations.[13,14] The reasons for this over-representation are unclear. They may be behavioural, reflecting higher levels of risky sexual activity among gay men with HIV infection,[15] or they may be biological, possibly mediated by some form of immunological susceptibility due to HIV infection.

We examined incidence and risk factors for syphilis in two community-based cohort studies in Sydney, Australia: (i) the Health in Men (HIM) cohort of HIV-negative homosexual men and (ii) the Positive Health (pH) cohort of HIV-positive cohort homosexual men.

Methods

Both studies recruited participants using similar community-based methods and the only sexual behaviour entry criterion was that participants had to report having sex with at least one man during the previous 5 years.[15,16] In each study, the men were interviewed face-to-face annually.

In the HIV-negative cohort, syphilis testing was offered to consenting participants annually from 2001. The same testing was made available to participants in the HIV-positive cohort from 2005. In both cohorts, a positive screening enzyme immunoassay (EIA; ICE syphilis, Murex Biotech Ltd,

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Dartford, UK) was confirmed with the *Treponema pallidum* particle agglutination assay and/or the fluorescent treponemal antibody absorption test. The rapid plasma reagin (RPR) test was used to assist clinical staging and to detect re-infection (defined as an increase of four-fold or greater from the previous test).

Data analyses were performed using STATA 10.1 (STATA Corporation, College Station, TX, USA). The exact binomial method was used to calculate 95% confidence intervals (CIs). Univariate Cox regression was used for risk analyses, and hazard ratio (HR) and their corresponding 95% CI were calculated for these associations. For ordinal variables, *P* tests for trend were performed for variables which had data in at least three categories. *P*-values for homogeneity were calculated when there were data in only two strata. Due to the small numbers of incident cases, multivariate analyses were not attempted for risk factors.

Results

There were 1427 men enrolled in the HIV-negative cohort. Enrolment occurred during 2001–2004 and follow up ceased in 2007. There were 308 men who were offered sexual health screening in the HIV-positive cohort. Enrolment occurred in 1998–2006 and follow up ceased in 2007. The median age at baseline participants was 35 years (range: 18–75) in the HIV-negative cohort, and 45 years in the HIV-positive cohort (range: 22–71) at their initial test.

Incidence

Among HIV-negative participants, 1397 men (97.9%) were tested for syphilis at baseline and 42 (3.0%) were positive. Among them, 33 (78.6%) reported being previously diagnosed with syphilis. By the end of study, 1261 men had at least one follow up syphilis test and 21 men seroconverted. One man had a syphilis re-infection. Thus, the overall syphilis incidence was 0.49 per 100 person-years (95% CI: 0.31–0.74).

Among HIV-positive men who were offered sexual health screening, a total of 248 participants (80.5%) were tested for syphilis and 47 (19.0%) were seropositive at their initial test. Among them, 43 responded to whether they had been diagnosed with syphilis and 41 (95.3%) reported such a diagnosis. By the end of the study, 173 men had at least one follow up syphilis test, and eight men seroconverted. In addition, one man had a syphilis re-infection. Therefore, the overall syphilis incidence was 3.62 per 100 person-years (95% CI: 1.67–6.48).

Syphilis incidence in the HIV-positive cohort was significantly higher than that of HIV-negative cohort and this remained significant after adjustment for age (HR = 9.20, 95% CI: 3.63–23.31).

Risk factors

In the HIV-negative cohort, compared with those who reported no unprotected anal intercourse (UAI), men who had incident syphilis were more likely to report UAI with both regular and casual partners (HR = 3.71, 95% CI: 1.32–10.45) and to report UAI with HIV-positive partners (HR = 4.45, 95% CI: 1.37–14.45; Table 1). Men with incident syphilis were also non-significantly more likely to report more frequent receptive oral sex with casual partners, regardless of whether ejaculation occurred (no ejaculation: *P* trend = 0.079; with ejaculation: *P* trend = 0.075). Syphilis incidence was 0.77 per 100 person-years (95% CI: 0.42–1.28) in those who reported more than five casual sexual partners in the past 6 months and it was significantly higher than in those who reported five or less casual partners (HR = 2.48, 95% CI: 1.04–5.93).

In the HIV-positive cohort, men who acquired incident syphilis were significantly more likely to report multiple other HIV-positive sexual partners (HR = 9.60, 95% CI: 1.31–81.22). Engaging in UAI with HIV-positive partners also put these men at significantly elevated risk (HR = 8.67, 95% CI: 1.03–72.76). There was no association between lower CD4 count and incident syphilis (*P* trend = 0.711). All men with incident syphilis reported a recent CD4 count greater than 350 cells μL^{-1}. All men with incident syphilis reported more than five casual sexual partners in the past 6 months, an incidence of 6.16 per 100 person-years (95% CI: 2.86–11.38).

Discussion

Syphilis incidence was almost 10-fold higher in HIV-positive than in HIV-negative homosexual men. The higher incidence of syphilis in HIV positive men did not appear to be related to lower immunity due to HIV infection with all those acquiring syphilis having a recent CD4 count of 350 cells μL^{-1} or higher. In both HIV-negative and HIV-positive men, reporting HIV-positive sexual partners was associated with increased syphilis risk. Syphilis incidence was significantly associated with reporting UAI. While there were positive associations with oral sexual practices, these did not reach statistical significance. Thus, unprotected anal sex with HIV-positive partners appeared particularly important in the transmission of syphilis for both HIV-negative and HIV-positive men.

The increasing practice of serosorting in Australia and elsewhere,[17,18] and the association of syphilis with unprotected anal sex that we have reported here, may help explain why syphilis has continued to affect mainly HIV-positive men. Serosorting among HIV-positive men will lead to the formation of a network of highly sexually active HIV-positive men who practice unprotected anal sex with each other. Given the incidence data and risk factors for syphilis that we have described, this would appear to be a highly effective positive feedback loop to increase syphilis incidence.

Both the HIV-negative and the HIV-positive cohorts were community-based, thus we believe the syphilis incidence can be viewed as being reasonably representative of gay community attached homosexual men in Sydney. The participation rate for syphilis testing was substantially lower in the HIV-positive cohort than in the HIV-negative cohort. This was likely related to the fact that annual venepuncture was required in the HIV-negative cohort, but not in the HIV-positive cohort. However, there was no difference in number of HIV-positive partners reported in the past 6 months and recent CD4 counts in the HIV-positive cohort between those who tested for syphilis and those who did not.

Table 1. Risk factors for incident syphilis in cohorts of HIV-positive and HIV-negative homosexual men in Sydney, Australia

	HIV-negative cohort (HIM)						HIV-positive cohort (pH)					
	Person-years	*n*	Incidence (per 100 person-years)	Hazard ratio	95% CI	*P*-value	Person-years	*n*	Incidence (per 100 person-years)	Hazard ratio	95% CI	*P*-value
Age						0.264[A]						0.622[A]
<35	1536.9	9	0.59	1	–		25.5	2	7.85	1	–	
35–44	1723.2	11	0.64	1.23	0.51–3.00		58.8	1	1.70	0.18	0.02–2.10	
>44	1223.1	2	0.16	0.34	0.07–1.58		164.2	6	3.66	0.42	0.07–2.47	
Number of HIV-positive partners past 6 months						0.221[A]						0.032[B]
0	3822.7	17	0.44	1	–		111.3	1	0.90	1	–	
1	438.3	3	0.68	1.59	0.46–5.41		31.8	0	0.00	–	–	
>1	222.2	2	0.90	2.21	0.51–9.56		105.2	8	7.60	9.60	1.13–81.22	
Unprotected anal intercourse past 6 months												
No unprotected anal intercourse	1788.3	9	0.50	1	–		110.7	1	0.90	1	–	
By partner type						0.010[B]						0.166[A]
Regular only	1741.8	4	0.23	0.47	0.15–1.53		23.4	1	4.27	5.03	0.31–82.50	
Casual only	561.6	3	0.53	1.07	0.29–3.98		70.6	3	4.25	5.04	0.51–49.56	
Both	382.7	6	1.56	3.71	1.32–10.45		40.8	4	9.80	13.89	1.33–144.66	
By sexual positioning						0.660[A]						0.130[A]
Insertive only	693.4	2	0.29	0.60	0.13–2.76		20.1	2	9.94	8.97	0.78–103.93	
Receptive withdrawal	577.7	3	0.52	1.08	0.29–3.98		22.2	1	4.50	4.78	0.29–78.14	
Receptive ejaculation	1417.6	8	0.56	1.18	0.46–3.07		94.5	5	5.29	6.39	0.70–58.37	
By partner's HIV status						0.046[A]						0.042[B]
Negative only	1687.3	3	0.18	0.38	0.10–1.39		9.5	0	0.00	–	–	
HIV status unknown	803.1	6	0.75	1.48	0.52–4.17		18.5	0	0.00	–	–	
HIV-positive	201.3	4	1.99	4.45	1.37–14.45		108.8	8	7.35	8.67	1.03–72.76	
Oral sex with casual partners in the past 6 months												
Insertive withdrawal						0.261[A]						0.075[B]
No	1245.3	4	0.32	1	–		70.5	0	0.00	–	–	
Occasional	1062.6	5	0.47	1.43	0.38–5.30		71.0	3	4.22	1	–	
Frequent	2106.4	13	0.62	1.87	0.61–5.73		106.8	6	5.62	1.33	0.32–5.63	
Insertive to ejaculation						0.203[B]						0.808[B]
No	3192.0	12	0.38	1	–		161.9	5	3.09	1	–	
Occasional	1097.9	10	0.91	2.36	1.02–5.47		75.2	4	5.32	1.69	0.43–6.56	
Frequent	124.4	0	0.00	–	–		11.3	0	0.00	–	—	
Receptive withdrawal						0.079[A]						0.215[B]
No	1273.2	3	0.24	1	–		68.7	0	0.00	–	–	
Occasional	982.2	4	0.41	1.71	0.38–7.62		59.6	4	6.71	1	–	
Frequent	2159.0	15	0.69	2.84	0.82–9.81		120.1	5	4.16	0.66	0.17–2.57	
Receptive to ejaculation						0.075[A]						0.263[A]
No	3591.5	14	0.39	1	–		138.7	3	2.16	1	–	
Occasional	700.0	7	1.00	2.56	1.03–6.34		82.8	5	6.04	2.61	0.60–11.42	
Frequent	123.1	1	0.81	1.85	0.24–14.08		26.9	1	3.72	2.20	0.21–22.46	

[A]*P*-value for trend.
[B]*P*-value for homogeneity.

To date, conventional means to curb the outbreaks of syphilis in homosexual men, such as increased partner notification and expanded syphilis screening coupled with treatment of asymptomatic disease, have shown inconsistent results.[19,20] New, innovative approaches to syphilis control are desperately needed to control this epidemic. This study suggests that interventions targeted towards highly sexually active HIV-positive men are likely to be most effective.

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Conflicts of interest

None declared.

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References

1 Centers for Disease Control and Prevention. Syphilis–United States, 1983. *MMWR Morb Mortal Wkly Rep* 1984; 33: 433–6.

2 Fichtner RR, Aral SO, Blount JH, Zaidi AA, Reynolds GH, Darrow WW. Syphilis in the United States: 1967–1979. *Sex Transm Dis* 1983; 10: 77–80. doi: 10.1097/00007435-198304000-00006

3 Sydney AIDS Study Group. The Sydney AIDS project. Sydney AIDS study group. *Med J Aust* 1984; 141: 569–73.

4 Mulhall BP, Hart G, Harcourt C. Sexually transmitted diseases in Australia: a decade of change. Epidemiology and surveillance. *Ann Acad Med Singapore* 1995; 24: 569–78.

5 Rolfs RT, Nakashima AK. Epidemiology of primary and secondary syphilis in the United States, 1981 through 1989. *JAMA* 1990; 264: 1432–7. doi: 10.1001/jama.264.11.1432

6 Centers for Disease Control and Prevention. Resurgent bacterial sexually transmitted disease among men who have sex with men – King County, Washington, 1997–1999. *MMWR Morb Mortal Wkly Rep* 1999; 48: 773–7.

7 Centers for Disease Control and Prevention. Primary and secondary syphilis among men who have sex with men – New York City, 2001. *MMWR Morb Mortal Wkly Rep* 2002; 51: 853–6.

8 D'Souza G, Lee JH, Paffel JM. Outbreak of syphilis among men who have sex with men in Houston, Texas. *Sex Transm Dis* 2003; 30: 872–3. doi: 10.1097/01.OLQ.0000091144.72555.13

9 Dupin N, Jdid R, N'Guyen YT, Gorin I, Franck N, Escande JP. Syphilis and gonorrhoea in Paris: the return. *AIDS* 2001; 15: 814–5. doi: 10.1097/00002030-200104130-00026

10 Hopkins S, Lyons F, Coleman C, Courtney G, Bergin C, Mulcahy F. Resurgence in infectious syphilis in Ireland: an epidemiological study. *Sex Transm Dis* 2004; 31: 317–21. doi: 10.1097/01.OLQ.0000123653.84940.59

11 Jayaraman GC, Read RR, Singh A. Characteristics of individuals with male-to-male and heterosexually acquired infectious syphilis during an outbreak in Calgary, Alberta, Canada. *Sex Transm Dis* 2003; 30: 315–9. doi: 10.1097/00007435-200304000-00008

12 Lacey HB, Higgins SP, Graham D. An outbreak of early syphilis: cases from North Manchester General Hospital. *Sex Transm Infect* 2001; 77: 311–3. doi: 10.1136/sti.77.5.311

13 Brown AE, Sadler KE, Tomkins SE, McGarrigle CA, LaMontagne DS, Goldberg D, *et al*. Recent trends in HIV and other STIs in the United Kingdom: data to the end of 2002. *Sex Transm Infect* 2004; 80: 159–66. doi: 10.1136/sti.2004.009571

14 Kahn RH, Heffelfinger JD, Berman SM. Syphilis outbreaks among men who have sex with men: a public health trend of concern *Sex Transm Dis* 2002; 29: 285–7. doi: 10.1097/00007435-200205000-00006

15 Prestage G, Mao L, Fogarty A, Van de Ven P, Kippax S, Crawford J, *et al*. How has the sexual behaviour of gay men changed since the onset of AIDS: 1986–2003. *Aust N Z J Public Health* 2005; 29: 530–5. doi: 10.1111/j.1467-842X.2005.tb00245.x

16 Jin F, Prestage GP, Mao L, Kippax SC, Pell CM, Donovan B, *et al*. Transmission of herpes simplex virus types 1 and 2 in a prospective cohort of HIV-negative gay men: the Health in Men study. *J Infect Dis* 2006; 194: 561–70. doi: 10.1086/506455

17 Mao L, Crawford JM, Hospers HJ, Prestage GP, Grulich AE, Kaldor JM, *et al*. 'Serosorting' in casual anal sex of HIV-negative gay men is noteworthy and is increasing in Sydney, Australia. *AIDS* 2006; 20: 1204–6. doi: 10.1097/01.aids.0000226964.17966.75

18 Xia Q, Molitor F, Osmond DH, Tholandi M, Pollack LM, Ruiz JD, *et al*. Knowledge of sexual partner's HIV serostatus and serosorting practices in a California population-based sample of men who have sex with men. *AIDS* 2006; 20: 2081–9. doi: 10.1097/01.aids.0000247566.57762.b2

19 Ciesielski C, Kahn RH, Taylor M, Gallagher K, Prescott LJ, Arrowsmith S. Control of syphilis outbreaks in men who have sex with men: the role of screening in nonmedical settings. *Sex Transm Dis* 2005; 32: S37–42. doi: 10.1097/01.olq.0000181148.80193.91

20 Hogben M, Paffel J, Broussard D, Wolf W, Kenney K, Rubin S, *et al*. Syphilis partner notification with men who have sex with men: a review and commentary. *Sex Transm Dis* 2005; 32: S43–7. doi: 10.1097/01.olq.0000180565.54023.bf

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