Per-contact probability of HIV transmission in homosexual men in Sydney in the era of HAART

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Objective: The objective of this study is to estimate per-contact probability of HIV transmission in homosexual men due to unprotected anal intercourse (UAI) in the era of HAART.

Design: Data were collected from a longitudinal cohort study of community-based HIV-negative homosexual men in Sydney, Australia.

Methods: A total of 1427 participants were recruited from June 2001 to December 2004. They were followed up with 6-monthly detailed behavioral interviews and annual testing for HIV till June 2007. Data were used in a bootstrapping method, coupled with a statistical analysis that optimized a likelihood function for estimating the per-exposure risks of HIV transmission due to various forms of UAI.

Results: During the study, 53 HIV seroconversion cases were identified. The estimated per-contact probability of HIV transmission for receptive UAI was 1.43% [95% confidence interval (CI) 0.48–2.85] if ejaculation occurred inside the rectum, and it was 0.65% (95% CI 0.15–1.53) if withdrawal prior to ejaculation was involved. The estimated transmission rate for insertive UAI in participants who were circumcised was 0.11% (95% CI 0.02–0.24), and it was 0.62% (95% CI 0.07–1.68) in uncircumcised men. Thus, receptive UAI with ejaculation was found to be approximately twice as risky as receptive UAI with withdrawal or insertive UAI for uncircumcised men and over 10 times as risky as insertive UAI for circumcised men.

Conclusion: Despite the fact that a high proportion of HIV-infected men are on antiretroviral treatment and have undetectable viral load, the per-contact probability of HIV transmission due to UAI is similar to estimates reported from developed country settings in the pre-HAART era.

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Introduction

Most studies of per-contact probability of sexual HIV transmission have been in heterosexual people [1–4], and few estimates have been made for sex between homosexual men [5,6]. The estimation of per-contact risk in homosexual men is more complex than that of heterosexual transmission. First, sexual monogamy is more common in heterosexuals, and thus serodiscordant monogamous couples are more readily available for study

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[1,7]. Among homosexual men, regular relationships are frequently nonmonogamous, and the HIV status of the other partners is often unknown [8]. Second, in contrast to heterosexual transmission, in which men always take the insertive role and women the receptive role in penetrative sex, homosexual men can take either the insertive or receptive role.

It has long been demonstrated that receptive unprotected anal intercourse (UAI) with an HIV-positive man is the major behavioral risk factor for HIV transmission among gay and other homosexual men [9]. However, the role of insertive UAI cannot be ignored [10]. The phenomenon of 'strategic positioning', in which an HIV-negative man takes the insertive role while engaging in UAI with a nonseroconcordant partner in order to reduce his risk of HIV infection, has been increasingly reported [11]. Yet, the relative risk of insertive UAI in homosexual men has not been fully examined. Emerging evidence that circumcised men may have a lower risk of acquiring HIV during insertive anal intercourse [12], consistent with heterosexual studies demonstrating reduced risk during insertive vaginal intercourse [13–15], also suggests that the effect of circumcision on per-contact probability requires exploration.

It has been a decade since the last attempt to estimate the per-contact risk of HIV transmission in homosexual men [6], during which the landscape of HIV management has changed substantially. The majority of people with HIV in resource-rich countries now receive HAART. In Australia, it has been estimated that about 70% of people with diagnosed HIV are currently receiving HAART, and consequently, most people with HIV have undetectable viral load [16]. Despite these average decreases in viral load across populations of HIV-infected people, HIV incidence has been increasing since the late 1990s in homosexual men in most developed countries including Australia [17]. There is a paucity of data on HIV transmission risk at low viral loads [18–20], and no studies have reported HIV transmission risk in the era of HAART among homosexual men with high treatment rates [18]. In this study, we calculate the per-contact risk of HIV seroconversion in a prospective cohort of initially HIV-negative homosexual men in Sydney, Australia, in an environment in which most men with HIV are diagnosed and most are receiving HAART.

Methods

Participants

The Health in Men (HIM) cohort study recruited participants from a range of community-based settings in Sydney between June 2001 and December 2004, as described elsewhere [21]. Men recruited to the study met the following inclusion criteria: [1] reported having sex with other men within the previous 5 years, [2] lived in Sydney or participated regularly in its gay community and [3] tested HIV negative at baseline. They were followed to the end of June 2007. Signed informed consent was obtained from all participants. Ethics approval was granted by the Human Research Ethics Committee at the University of New South Wales.

Data collection

All eligible men willing to participate were interviewed annually face-to-face, with 6-monthly telephonic interview between these visits. At baseline, participants reported whether they had been circumcised, and self-report was almost perfectly correlated with examination findings by the study nurse in a subset of participants [22]. At each interview, detailed quantitative data on the number of episodes of insertive and receptive UAI in the last 6 months were collected for regular and for casual partners, by HIV status of these partners (negative, positive or unknown), and, for receptive UAI, by whether or not ejaculation occurred. Episodes of protected anal intercourse involving condom failures, including condom breakage and slippage, were included as episodes of UAI of each relevant mode and were not separately recorded. In very few instances (less than 10 occasions during the study), participants reported that they 'do not know' or 'refused' to indicate the number of episodes of UAI types; in such circumstances, the number of episodes was recorded as zero.

Ascertainment of HIV seroconversion

Methods of ascertainment of HIV seroconversion have been described elsewhere [23]. Briefly, incident HIV infections were identified through annual HIV testing at follow-up visits ($n = 31$) and by matching against the national HIV registry to identify infections in people who tested outside the study ($n = 22$).

Among HIV seroconverters for whom we had data on HIV seroconversion symptoms ($n = 17$), the date of HIV infection was estimated according to the following decision process: if a western blot was complete ($n = 8$), then the date was chosen as the earlier of the midpoint between the last HIV-negative test and first HIV-positive test or 2 weeks prior to the onset of symptom; if a western blot was incomplete ($n = 9$), then the date was chosen as the latest of the midpoint between the last HIV-negative test and first HIV-positive test or 2 weeks prior to the onset of symptom. Among HIV seroconverters for whom we had no data on HIV seroconversion symptoms ($n = 36$), the midpoint between periodic HIV tests was used to estimate the date of HIV infection.

Our analysis included all episodes of UAI reported to take place between the first follow-up interview and the end of study for those who remained HIV negative, and to the estimated date of HIV seroconversion for those who became HIV infected during the study. All episodes of UAI reported at baseline were excluded from the per-contact risk calculation.

In 13 participants whose HIV seroconversions were identified through matching with Australia's national HIV registry, the estimated date of HIV infection was later than their last interview due to loss to follow-up. In these individuals, there were no behavioral data available at the time of estimated infection. Information obtained from the last interview was carried forward for per-contact risk calculation in seven patients in whom the estimated date of infection was less than 12 months after the last interview. Those whose estimated date of infection was more than 12 months after the last interview were excluded ($n = 6$).

Statistical analysis

Statistical analyses were performed using STATA version 10.0 (STATA Corporation, College Station, Texas, USA). Total numbers of episodes of UAI by sexual position (insertive, receptive with withdrawal and receptive with ejaculation) were tabulated according to partners' HIV status. Proportions of HIV seroconverters and nonseroconverters who engaged in UAI by sexual positioning and partners' HIV status were also compared using a chi-squared test.

A bootstrapping technique was performed to obtain a simulation-based probability distribution for estimates of the per-contact probability of HIV transmission for insertive (with or without circumcision) or receptive (with or without ejaculation) UAI. Ten thousand simulations were executed with Matlab (Mathworks, Maryland, USA); for each simulation, 'n' individuals were randomly sampled (with replacement) from the pool of 'n' people. The algorithm determined the optimal transmission probabilities that maximized the likelihood function:

$$L(\beta_I, \beta_{IC}, \beta_R, \beta_{RW} | n^I, n^R, n^{RW}, c, y) = \prod_{i=1}^{N} f_i^{y_i}(1 - f_i)^{1-y_i},$$

where $y_i = 1$ if seroconversion took place and $y_i = 0$ if man i remained uninfected, and

$$f_i(\beta_I, \beta_{IC}, \beta_R, \beta_{RW}) = 1 - (1 - \beta_R)^{n_i^R}(1 - \beta_{RW})^{n_i^{RW}}(1 - \beta_I)^{(1-c_i)n_i^I}(1 - \beta_{IC})^{c_i n_i^I}$$

is the probability that man i remains uninfected after n_i^I, n_i^R and n_i^{RW} acts of insertive, receptive with ejaculation and receptive with withdrawal/no ejaculation, respectively, and β_I, β_{IC}, β_R and $\beta_{RW}$are the probabilities of HIV transmission per unprotected insertive (uncircumcised), insertive (circumcised), receptive with ejaculation and receptive with withdrawal act of UAI, respectively. The symbol c_i represents each man's circumcision status ($c_i = 1$ for circumcised and $c_i = 0$ for uncircumcised). The number of UAI exposures with HIV-infected partners was determined by the sum of the number of UAI exposures reported with HIV-positive partners, the number of UAI events with partners of unknown status multiplied by the assumed HIV prevalence in the population and the number with partners that were assumed to be negative multiplied by the assumed HIV prevalence in the population who have not been diagnosed with HIV.

The bootstrapping algorithm maximized the log-likelihood function using a random walk minimization to estimate the transmission risk parameters under a number of conditions, including men who only reported having UAI with HIV-positive partners, only reported UAI with HIV-positive partners or partners of unknown HIV status, reported any UAI, or reported insertive or receptive UAI. For simulations in which UAI acts with men of unknown status or men presumed to be HIV negative are included, a variety of assumptions were made about the HIV prevalence in the pool of such partners: HIV prevalence of 5, 10 or 15% in partners of unknown serostatus and HIV prevalence of 0.5, 1, 1.5 or 2% in partners presumed to be HIV negative. The reported estimates were based on the Sydney studies [23,24] that have estimated the HIV prevalence in partners of unknown HIV status of 10% and of reported HIV-negative partners of 0.5%.

Results

The HIM study enrolled 1427 men from June 2001 to December 2004. The median age at enrollment was 35 years (range 18−75 years). The vast majority (95.2%) of participants were self-identified as gay or homosexual. Nearly two-thirds of men (65.7%) were reported being circumcised at baseline.

A total of 1381 men had at least one follow-up interview by the end of the study in June 2007 and 53 seroconverted with HIV. The overall follow-up time was 5160 person-years, with a median of 3.9 years per participant. The estimation of per-contact risk was based on 1136 men, including 46 HIV seroconverters, who reported at least one episode of UAI during the study.

Over time, these 1136 men reported a total of 228 056 episodes of UAI (Table 1). There were slightly more episodes of insertive UAI than receptive (56.1 vs. 43.9%). The majority (87.0%) of episodes of UAI, regardless of sexual positioning, were with partners reported to be HIV negative. Very few participants ($n = 93$, 8.2%) reported receptive UAI with HIV-positive partners, and the majority of episodes (76.8%) in this situation involved the HIV-positive partner withdrawing prior to ejaculation.

Table 1. Number of episodes of unprotected anal intercourse by participants' reported HIV status of partner in the Health in Men study.

	HIV-negative partners			HIV-positive partners			HIV status of unknown partners			Total	
UAI by sexual positioning	Number of men	Number of episodes	%	Number of men	Number of episodes	%	Number of men	Number of episodes	%	Number of episodes	%
Insertive UAI	887	108 379	47.5	153	8042	3.5	563	11 583	5.1	128 004	56.1
Receptive UAI with withdrawal	769	33 520	14.7	84	2009	0.9	390	3853	1.7	39 382	17.3
Receptive UAI with ejaculation	663	56 514	24.8	33	608	0.3	194	3548	1.6	60 670	26.6
Total										228 056	100.0

UAI, unprotected anal intercourse. Number of men who reported at least one episode of such act. Percentages are of the total number of episodes of UAI (228 056).

HIV seroconverters were significantly more likely to report insertive UAI with HIV-positive partners and receptive UAI with withdrawal with partners who were HIV positive or of unknown HIV status (Table 2). An unexpected finding, based on small numbers of men, was that HIV seroconverters reported significantly fewer episodes of receptive UAI with ejaculation with HIV-positive partners than nonseroconverters. However, this result was skewed by six men who did not seroconvert, despite reporting a total of 502 episodes of this behavior.

Estimates under various assumptions of HIV prevalence in partners who were reported to be HIV negative or of unknown HIV status are shown in Fig. 1. Similar transmission risk estimates were obtained across different assumptions (Fig. 1). In the scenario that HIV prevalence was 10% in partners of unknown HIV status and 0.5% in partners thought to be HIV negative, the estimated per-contact probability of HIV transmission for insertive UAI in participants who were circumcised was 0.11% [95% confidence interval (CI) 0.02–0.24] (Table 3), and it was 0.62% (95% CI 0.07–1.68) in those who were uncircumcised. For receptive UAI, the per-contact probability was 1.43% (95% CI 0.48–2.85) if ejaculation inside the rectum occurred, and it was 0.65% (95% CI 0.15–1.53) if withdrawal occurred prior to ejaculation. Thus, receptive UAI with ejaculation was approximately twice as risky as receptive UAI with withdrawal or insertive UAI for uncircumcised men, and over 10 times as risky as insertive UAI for circumcised men. Regardless of circumcision status, the pooled data estimates of the per-contact probability for insertive UAI was 0.16% (95% CI 0.05–0.31), for receptive UAI with ejaculation was 1.47% (95% CI 0.51–2.93) and for receptive UAI with withdrawal was 0.74% (95% CI 0.18–1.68).

Discussion

In contrast to HIV transmission risk in heterosexuals [2,4,7,25,26], data on HIV transmission in homosexual men are limited [5,6]. There have been no publications estimating per-contact probability of HIV transmission between homosexual men in the era of HAART. The participants recruited in the current study came from a setting with high coverage of HAART. Despite this, our estimates of HIV transmission probabilities were found to be similar to those reported from developed settings prior to HAART. For receptive UAI, we estimated the per-contact risk to be 1.43% if ejaculation occurred and 0.65% if withdrawal occurred without ejaculation. We estimated the per-contact risk for insertive UAI to be 0.11% in men who were circumcised and 0.62% in uncircumcised men. Due to differences in sampling and mathematical methods in different studies, it is difficult to directly compare results between studies. Nevertheless, our estimate of the per-contact risk of receptive UAI is

Table 2. Number of episodes of unprotected and anal intercourse reported by seroconverters and nonseroconverters in the Health in Men study.

UAI by sexual positioning and partners' HIV status	Seroconverters ($n=46$)					Nonseroconverters ($n=1090$)					
	Men (n)	%	Episodes	Episodes (median)	Episodes (mean)	Men (n)	%	Episodes	Episodes (median)	Episodes (mean)	P value[1]
Insertive UAI											
With HIV-negative partners	33	71.7	2928	30	88.7	854	78.4	105 451	60	123.5	0.288
With HIV status unknown partners	25	54.3	1498	18	59.9	538	49.4	10 085	4	18.7	0.507
With HIV-positive partners	15	32.6	855	8	57.0	138	12.7	7181	6	52.1	<0.001
Receptive UAI with withdrawal											
With HIV-negative partners	28	60.9	1016	13	36.3	741	68.0	32 504	19	43.9	0.312
With HIV status unknown partners	22	47.8	307	7	14.0	368	33.8	3546	3	9.6	0.049
With HIV-positive partners	10	21.7	334	2.5	33.4	74	6.8	1675	3	22.6	<0.001
Receptive UAI with ejaculation											
With HIV-negative partners	27	58.7	1687	17	62.5	636	58.4	54 827	31	86.2	0.963
With HIV status unknown partners	9	19.6	690	2	76.7	185	17.0	2858	2	15.4	0.647
With HIV-positive partners	7	15.2	39	2	5.6	26	2.4	569	2	21.9	<0.001

UAI, unprotected anal intercourse. $P=1$ for the comparison of percentage of reporting specific modes of UAI between seroconverters and nonseroconverters.

very similar to that from a cohort of homosexual men recruited in the United States in the early 1990s (of 0.82%, which did not differentiate whether or not withdrawal was involved) [6].

Our estimate of the per-contact risk for insertive UAI in uncircumcised men was similar to that for receptive UAI with withdrawal but was 80% lower in those who were circumcised. In comparison, among heterosexual men, per-contact transmission risk was reduced by 50–60% in three randomized controlled trials of circumcision in African settings [13–15]. Our estimate of transmission risk for insertive UAI is approximately twice that of previous estimates [6].

Our finding that the per-contact probability of HIV transmission is similar to that in the pre-HAART era was unexpected, given the close correlation between HIV viral load and its infectiousness in heterosexual and vertical transmission [27]. In Australia, homosexual men have very high rates of recent HIV testing [28]; about 70% of HIV-positive men are receiving HAART, and 75% of those on treatment have undetectable viral load [16]. Thus, it is surprising that our estimates of HIV transmission risk were similar to those in an era when few HIV-positive men would have had undetectable viral load.

There are some potential explanations for this unexpected finding. First, primary HIV infection, which is associated with higher viral load and thus higher infectiousness [29,30], may have a larger role in the dynamics of HIV transmission than expected. In addition, individuals with primary HIV infection are usually unaware of their HIV status. It is likely that some of the partners not identified as HIV positive could have had primary HIV infection. Second, the proportion of undiagnosed HIV infections or prevalence in the population could be higher than we expected [31]. We assumed that the prevalence of HIV among sexual partners thought to be HIV negative and among those with unknown HIV status were 0.5 and 10%, respectively. However, we conducted a sensitivity analysis and found our estimates to be consistent across broad assumptions. Third, it may be possible that HIV transmission by anal intercourse is not as closely related to viral load as it is in vaginal transmission [27]. There is a paucity of data on HIV transmission risk at low viral loads, and there are almost no data on transmission and viral load in homosexual men [18,19]. Fourth, the prevalence of other sexually transmissible infections (STIs) in Sydney, as in many parts of the developed world, was higher during the timeframe of this study than the levels during the pre-HAART era. The presence of other STIs may increase the risk of HIV transmission [32].

Our samples were recruited from a large variety of community-based sources, and the only behavioral criterion was that participants needed to report having

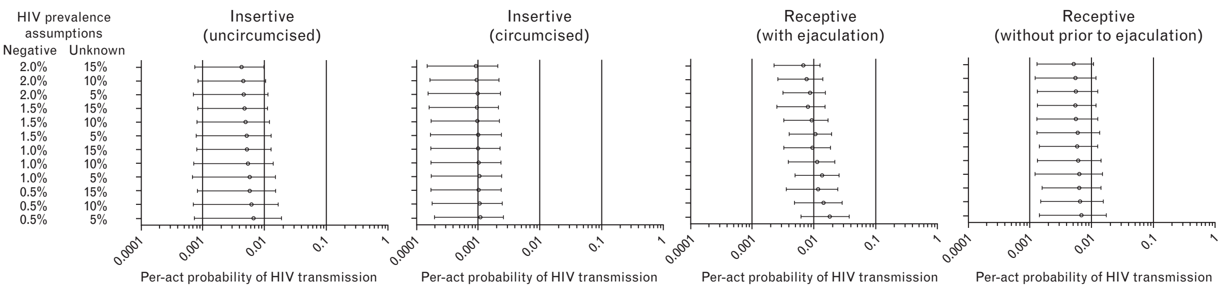

Fig. 1. Estimated per-contact probability of HIV transmission due to unprotected insertive (uncircumcised), insertive (circumcised), receptive (with ejaculation) and receptive (with withdrawal) anal intercourse under various assumptions of HIV prevalence in partners of unknown HIV status and partners presumed to be HIV negative. Open circles represent mean estimates and error bars denote 95% confidence intervals.

sex with another man in the last 5 years. Compared with the previously mentioned US study [6], which required participants to report risky behavior, our estimate could be more representative of gay community-attached men, in general. Being one of the largest cohort studies examining incident HIV infection in homosexual men, only 46 HIV seroconverters who reported at least one episode of UAI were included in the analyses. Almost a quarter of a million episodes of UAI were reported by study participants, although only around 10 000 of these were with partners who were reported to be HIV positive. Due to limited power, covariates, such as STIs and recreational drug use, could not be included in the current estimations.

As with other observational studies relying on participants' self-report, recall bias could influence the accuracy of the results. The study implemented 6-monthly telephonic interviews between annual face-to-face visits to minimize the possible inaccuracy of self-reported sexual behavior due to the long interview interval. The use of face-to-face interviews might have also reduced social desirability bias arising from the studies that collect sensible sexual behaviors.

Despite a more than 10-year gap from the last estimation of HIV transmission risk in homosexual men and the substantially improved treatment availability, the per-contact risk of HIV transmission with an HIV-positive partner does not seem to have reduced. Although these updated estimates are valuable in determining the risk of HIV transmission, caution should be exercised before interpreting the results at the level of individual men. There is considerable heterogeneity between individuals, including various biological and genetic factors associated with HIV infectiousness and susceptibility. This is emphasized by the occurrence of 12 seroconversion cases in the cohort of this study as a result of fewer than 10 episodes of UAI per person and six cases that did not seroconvert, despite extremely large numbers of receptive UAI episodes with HIV-positive partners. However, our estimates are useful for understanding the average magnitude of transmission risk due to different types of sexual exposures among homosexual men in the era of HAART.

Table 3. Estimated per-contact probability of HIV transmission of unprotected anal intercourse in men in the Health in Men study.

	Per-contact probability (%)	95% CI
Insertive UAI		
Among uncircumcised	0.62	0.07–1.68
Among circumcised	0.11	0.02–0.24
Receptive UAI		
With withdrawal	0.65	0.15–1.53
With ejaculation	1.43	0.48–2.85

CI, confidence interval; UAI, unprotected anal intercourse. On the basis of the assumptions that the actual HIV prevalence in HIV status unknown partners and in HIV-negative partners was 10 and 0.5%, respectively.

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