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INFECTIOUS DISEASE

HIV transmission risk through anal intercourse: systematic review, meta-analysis and implications for HIV prevention

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Background The human immunodeficiency virus (HIV) infectiousness of anal intercourse (AI) has not been systematically reviewed, despite its role driving HIV epidemics among men who have sex with men (MSM) and its potential contribution to heterosexual spread. We assessed the per-act and per-partner HIV transmission risk from AI exposure for heterosexuals and MSM and its implications for HIV prevention.

Methods Systematic review and meta-analysis of the literature on HIV-1 infectiousness through AI was conducted. PubMed was searched to September 2008. A binomial model explored the individual risk of HIV infection with and without highly active antiretroviral therapy (HAART).

Results A total of 62 643 titles were searched; four publications reporting per-act and 12 reporting per-partner transmission estimates were included. Overall, random effects model summary estimates were 1.4% [95% confidence interval (CI) 0.2–2.5] and 40.4% (95% CI 6.0–74.9) for per-act and per-partner unprotected receptive AI (URAI), respectively. There was no significant difference between per-act risks of URAI for heterosexuals and MSM. Per-partner unprotected insertive AI (UIAI) and combined URAI–UIAI risk were 21.7% (95% CI 0.2–43.3) and 39.9% (95% CI 22.5–57.4), respectively, with no available per-act estimates. Per-partner combined URAI–UIAI summary estimates, which adjusted for additional exposures other than AI with a ‘main’ partner [7.9% (95% CI 1.2–14.5)], were lower than crude (unadjusted) estimates [48.1% (95% CI 35.3–60.8)]. Our modelling demonstrated that it would require unreasonably low numbers of AI HIV exposures per partnership to reconcile the summary per-act and per-partner estimates, suggesting considerable variability in AI infectiousness between and within partnerships over time. AI may substantially increase HIV transmission risk even if the infected partner is receiving HAART; however,

predictions are highly sensitive to infectiousness assumptions based on viral load.

Conclusions Unprotected AI is a high-risk practice for HIV transmission, probably with substantial variation in infectiousness. The significant heterogeneity between infectiousness estimates means that pooled AI HIV transmission probabilities should be used with caution. Recent reported rises in AI among heterosexuals suggest a greater understanding of the role AI plays in heterosexual sex lives may be increasingly important for HIV prevention.

Keywords HIV, anal intercourse, infectivity, transmission probability, review, meta-analysis, HAART

Introduction

Studies systematically reviewing much-needed estimates of human immunodeficiency virus (HIV) infectiousness for various modes of transmission have recently been published,¹⁻⁴ partly in response to discussions regarding the relative importance of each mode for HIV epidemics world wide.^{1,2} However, none has specifically focused on anal intercourse (AI), despite its role driving HIV epidemics among men who has sex with men (MSM). AI may also contribute substantially to heterosexual epidemics in sub-Saharan Africa and elsewhere.³

AI within heterosexual relationships is not an uncommon practice but is often underreported.^{4,5} It is estimated that the absolute number of women in the USA practising unprotected receptive AI (URAI) is ~7-fold higher than the number of MSM practising URAI,⁶ while 75% of study participants in the South African site of a multi-centre microbicides trial reported URAI during follow-up.⁷

Highly active antiretroviral therapy (HAART) is likely to substantially reduce risk from AI, as demonstrated by randomized controlled trials for mother-to-child transmission⁸ and observational studies for heterosexual partnerships.^{9,10} Although some ecological evidence suggests a reduction in AI infectiousness due to HAART may have occurred,¹¹ no direct empirical evidence is yet available. However, the high infectiousness associated with AI, as reviewed here, indicates that even with a substantial reduction due to HAART, the residual infectiousness could still present a high risk to partners, especially if coupled with risk compensation.¹¹

Our aims were systematically to review the literature on estimates of unprotected AI (UAI) per-act and per-partner transmission probabilities for heterosexuals and MSM, to investigate the relationship between per-act and per-partner summary estimates and to explore the implications of practising URAI for prevention of HIV transmission in the presence of HAART.

Methods

The systematic review was undertaken following MOOSE guidelines for reviews of observational studies.¹²

Search strategy

As previously reported¹³ (details provided in Supplementary data available at *IJE* online).

Selection criteria and data extraction

Empirical per-act and per-partner (irrespective of partnership duration and frequency of sex acts) estimates were extracted. Abstracts of pre-1990, studies using sample sizes of less than 10 and estimates derived from dynamic modelling studies fitted to empirical HIV prevalence curves were excluded. Estimates where infection of partners was ascertained clinically¹⁴ or only through questioning the index,¹⁵ rather than by laboratory HIV diagnosis were excluded. Per-partner estimates from studies of heterosexuals were restricted to including only those sexual partners where AI was practised for $\geq 50\%$ of all sex acts within the partnership. There was no other restriction by study design or language of publication. Each relevant publication was examined by two investigators for data extraction.

Quantitative data synthesis and statistical methods

Meta-analysis

Stata 10.0 produced random effects model summary estimates. For studies not providing a point estimate, the arithmetic midpoint of the confidence bounds or estimate range was used. For studies reporting estimates with an uncertainty range (reflecting uncertainty to model assumptions) rather than a 95% confidence interval (95% CI), a standard error or sufficient information to derive these directly, we approximated the standard error from symmetric and asymmetric intervals as $1/1.96$ the largest absolute value (to account for asymmetric intervals) of the

widths between the point estimate and the sensitivity bounds.

Relationship between per-act and per-partner transmission probability

We investigated the relationship between per-act and per-partner AI transmission probabilities over n sex acts using the following Bernoulli process that assumes independence of risk for each sex act within a partnership^{16,17}:

$$\beta_{p,a} = 1 - (1 - \beta_{c,a})^n \quad (1)$$

where $\beta_{p,a}$ and $\beta_{c,a}$ are the per-partner (p) and per-act (c) transmission probability for AI (a), respectively. For heterosexual populations practising both vaginal intercourse (VI) and AI, Equation (1) becomes:

$$\beta_{p,\text{all}} = 1 - (1 - \beta_{c,v})^{(1-d)n} (1 - \beta_{c,a})^{dn} \quad (2)$$

where $\beta_{p,\text{all}}$ is risk per-partner for VI and AI; $\beta_{c,v}$ and $\beta_{c,a}$ are per-act transmission probabilities for VI (v) and receptive AI (a), respectively; and d is the proportion of n sex acts which are AI rather than VI.

Intervention impact: HAART

We assessed the potential reduction in HIV infectivity caused by HAART reducing viral load, using two published^{17–21} functions of infectivity by viral load. In brief, the difference between the two functions is that Function 1 was based on results from the Rakai study of HIV transmission in heterosexual couples (presumed through VI transmission)²² and assumes a linear relationship between infectiousness and log serum viral load; Function 2 was based on data from a Zambian cohort of discordant couples²³ and assumed a logistic function between infectivity and plasma viral load, which provides better fits to the low number of transmissions observed for low viral loads of index individuals.²¹ We assume that successful HAART reduces blood viral load from an average, baseline V_0 to V_1 copies/ml. Further details are provided in the Supplementary data available at *IJE* online.

Results

Search results

A total of 62 643 titles were searched and 27 potentially appropriate publications were identified, three of which were identified through bibliographies of searched articles. Four publications reporting per-act^{24–27} and 12 reporting per-partner^{28–39} estimates were included. These were from MSM ($n=12$ ^{24,25,28,30–37,39}), heterosexual ($n=3$ ^{26,27,29}) or mixed ($n=1$ ³⁴) study populations. Per-partner estimates from Nicolosi *et al.*'s study²⁹ of heterosexuals, where AI was practised 'often or always' ($\geq 50\%$ of all intercourse) within the partnership were included;

those with less frequent practise were excluded. Supplementary Figure S1 (available as Supplementary data at *IJE* online) summarizes the search strategy. All identified studies were from industrialized countries. Figure 1 summarizes study estimates for per-act and per-partner AI transmission probabilities as forest plots, including summary estimates from the meta-analyses. Details of included and excluded studies are in Supplementary Tables S1 and S2 (available as Supplementary data at *IJE* online), respectively. Supplementary Table S3 (available as Supplementary data at *IJE* online) summarizes heterosexual per-partner estimates that have been stratified by frequency of AI practice. Supplementary Table S4 (available as Supplementary data at *IJE* online) summarizes AI study estimates stratified by different risk factors.

The only per-act estimates included were for URAI. Vittinghoff *et al.*'s²⁵ estimates for protected receptive AI (0.18%, 95% CI 0.10–0.28), unprotected insertive AI (UIAI) (0.06%, 95% CI 0.02–0.19) and protected insertive AI (0.04%, 95% CI 0.01–0.11), based on partners of index cases who were "HIV infected or of unknown serostatus", were excluded because no attempt was made to estimate the unknown HIV status of index cases by using HIV prevalence as a proxy for exposure to an HIV-infected partner.

Study design and estimate type

The included studies employed three study designs: retrospective-partner ($n=11$ ^{24,26–34,37}), prospective discordant-couple ($n=1$ ³⁶) and simple-prospective (longitudinal cohort, $n=4$ ^{25,35,38,39}) studies. In retrospective-partner studies, the infection status of each partner becomes known only at the time of the study. The index case and time of infection are determined based on exposure to a salient risk factor. In prospective discordant-couple studies, stable (preferably monogamous) HIV-serodiscordant couples are followed up after diagnosis of the index partner. These studies also provide per-partner HIV transmission rates but, with only one included study (and only 10 couples³⁶), we report and use cross-sectional results at the end of follow-up for the meta-analysis. With simple-prospective studies, individuals (not necessarily monogamous) are recruited following sexual contact with potentially infected, high-risk partners and serostatus monitored. As index cases are not recruited, HIV exposure is estimated using HIV prevalence in the pool of potential partners and the reported coital frequency. Therefore, prospective studies suffer from problems of selection bias (prospective discordant-couple) and uncertainty in estimating the numbers of HIV exposures (simple-prospective) and are not necessarily superior to the retrospective-partner study design.

Per-act estimates were derived from retrospective-partner ($n=3$ ^{24,26,27}) and simple-prospective ($n=1$ ²⁵) studies. Per-partner estimates were derived

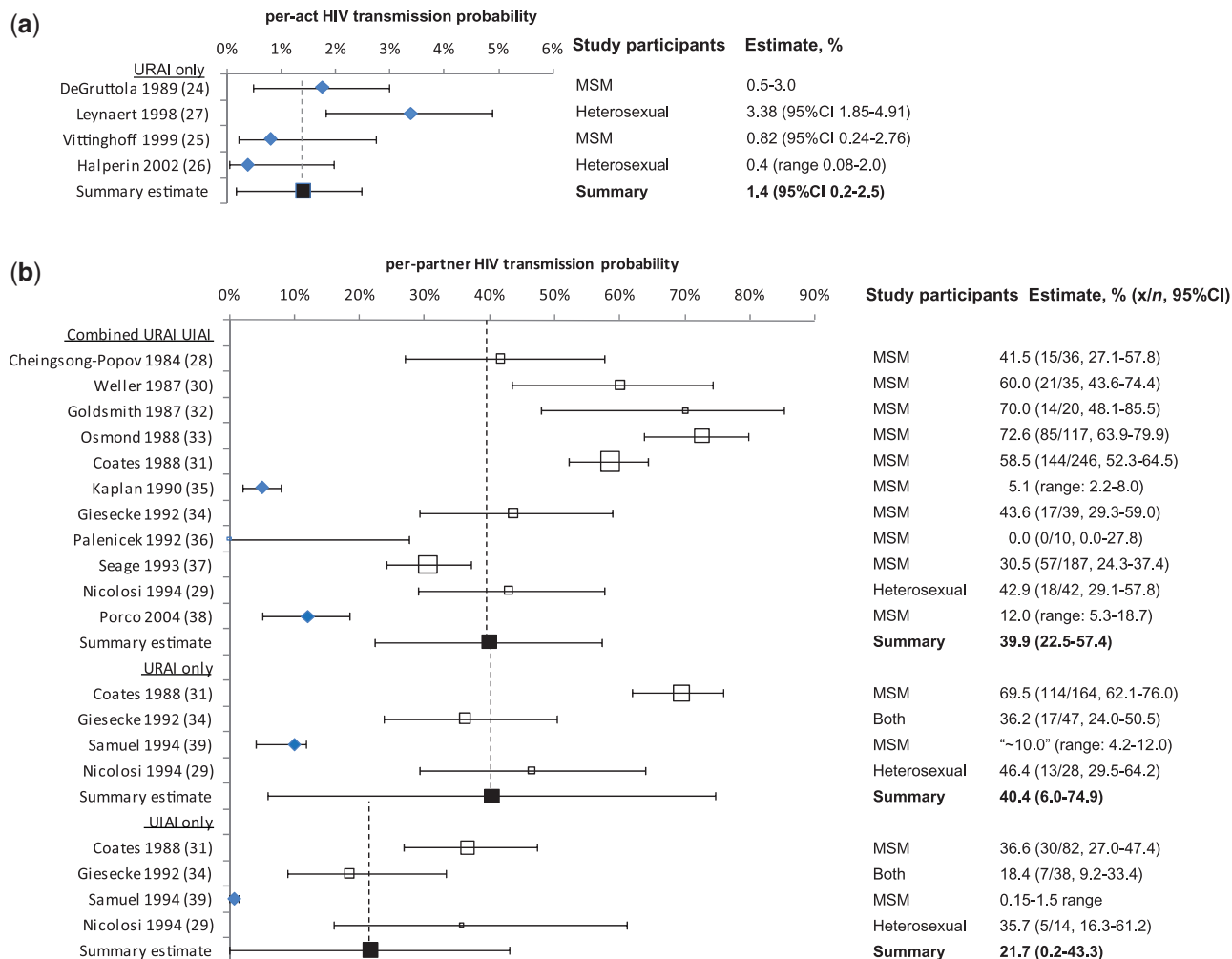


Figure 1 Forest plot of studies estimating HIV transmission probabilities for AI expressing risk as (a) per-act and (b) per-partner. For crude estimates (unfilled boxes), the size of box represents relative study sample size. Adjusted estimate (filled Rhombus), Crude estimate based on x number of seroconverting partners among n couples with an infected index partner (open square), Summary estimate (filled square)

from retrospective-partner ($n = 8^{28-34,37}$), prospective-discordant couple ($n = 1^{36}$) and simple-prospective ($n = 3^{35,38,39}$) studies. For both URAI-only and UIAI-only per-partner estimates, three were derived from retrospective-partner^{29,31,34} and one from simple-prospective³⁹ study data.

We categorized study estimates into ‘crude’ and ‘adjusted’. ‘Crude’ estimates are based on the HIV status of partners of index cases and assume that the index case was the only source of exposure. In high-risk populations, multiple exposures to HIV through sexual contact with other partners and through other types of sexual practice may lead to overestimation of infectivity. Thus, ‘adjusted’ estimates are based on statistical models to control for multiple exposures. One study also adjusted for multiple modes

of sexual transmission: URAI, UIAI, protected AI and oro-genital intercourse.²⁵ No study provided both crude and adjusted estimates. Brief details on adjusted estimates are provided in Supplementary Table S1 (available as Supplementary data at *IJE* online). Numbers of per-act and per-partner estimate by adjustment type and study design are given in Table 1. For per-partner transmission probabilities, retrospective-partner studies reported crude estimates, whereas prospective studies tended to report adjusted estimates, which made it difficult to disentangle the effect of study design from adjustment for multiple exposures. In addition, all estimates where the standard error had to be approximated using an uncertainty range quoted by authors were adjusted estimates.

Table 1 Summary transmission probability estimates for AI: meta-analyses results

Estimate type	Median (%)	Min. (%)	Max. (%)	Summary random effects estimate, % (95% CI)	Q ^a	P ^a	I ^{2b} (%)	N	References and study design
Per-act URAI	1.0	0.4	3.4	1.4 (0.2–2.5)	10.8	0.013	72	4	3 R-P ^{24,26,27} 1 S-P ²⁵
Retrospective Prospective	1.3 0.8	0.4 –	3.4 –	1.6 (0.0–3.2) 0.8 (0.2–2.8)	10.5	0.005	81	3	3 R-P ^{24,26,27} 1 S-P ²⁵
Per-partner Combined URAI–UIAI	42.9	0.0	72.6	39.9 (22.5–57.4)	497.1	<0.001	98	11	8 R-P ^{28–34,37} 1 P-DC ³⁶ 2 S-P ^{35,38}
Crude	43.6	0.0	72.6	48.1 (35.3–60.8)	91.0	<0.001	91	9	8 R-P ^{28–34,37} 1 P-DC ³⁶
Adjusted	8.6	5.1	12.0	7.9 (1.2–14.5)	3.5	0.063	71	2	2 S-P ^{35,38}
Retrospective Prospective	51.1 5.1	30.5 0.0	72.6 12.0	52.3 (39.7–64.9) 7.3 (1.8–12.8)	78.1 3.7	<0.001 0.161	91 46	8 3	8 R-P ^{28–34,37} 2 S-P ^{35,38} 1 P-DC ³⁶
Per-partner URAI	41.3	10.0	69.5	40.4 (6.0–74.9)	164.9	<0.001	98	4	3 R-P ^{29,31,34} 1 S-P ³⁹
Crude Adjusted	46.4 10.0	36.2 –	69.5 –	51.4 (28.1–74.7) 10.0 (4.2–15.8)	20.5	<0.001	90	3	3 R-P ^{29,31,34} 1 S-P ³⁹
Per-partner UIAI	27.1	0.7	36.6	21.7 (0.2–43.3)	60.6	<0.001	95	4	3 R-P ^{29,31,34} 1 S-P ³⁹
Crude Adjusted	35.7 0.7	18.4 –	36.6 –	29.4 (16.0–42.9) 0.7 (0.0–1.3)	5.1	0.077	61	3	3 R-P ^{29,31,34} 1 S-P ³⁹

^aQ-statistic calculated using Cochran's Q-test for heterogeneity, summing the squared deviations of each study's estimate from the overall pooled estimate, weighting the contribution of each study by its inverse variance.⁷² Under the hypothesis of homogeneity among the transmission probability estimates, the Q-statistic follows a chi-square distribution with $k - 1$ degrees of freedom, with k being the number of studies. From this, the P-value for heterogeneity can be derived.

^bI² is calculated as described in Higgins *et al.*⁷³ I² lies between 0 and 100%; 0% indicates no observed heterogeneity and larger values show increasing heterogeneity. N, number of study estimates; P, P-value; P-DC, prospective discordant-couple study design; R-P, retrospective-partner study design; S-P, simple-prospective study design; crude estimates, estimates calculated through simple derivation as number of seroconversions out of number of sexual acts involving exposure; adjusted estimates, estimates derived using more sophisticated calculation of transmission probability. Fixed effects summary estimates can be found in Supplementary Table S5 (available as Supplementary data at *IJE* online).

Infectiousness of AI for heterosexuals and MSM

Table 1 shows the per-act and per-partner summary estimates by exposure (combined URAI–UIAI, URAI-only and UIAI-only). Two per-act URAI estimates were based on studies among MSM^{24,25} and two among heterosexual couples.^{26,27} The per-act summary estimate was 1.4% (95% CI 0.2–2.5) (or 1.8% (95% CI 0.3–3.2) if Halperin *et al.*'s²⁶ abstract estimate is excluded due to lack of further detail on methods). No significant differences in per-act URAI estimates between heterosexual couples and MSM were found ($P=0.674$). However, while MSM estimates^{24,25} were similar to each other ($Q=0.2$; $P=0.635$; $I^2=0\%$), heterosexual estimates^{26,27} were heterogeneous ($Q=10.5$; $P=0.001$; $I^2=90\%$; Figure 1; Table 1). Most per-partner estimates were derived from studies on MSM. Exceptions were the studies by Nicolosi *et al.*²⁹ studying heterosexual couples, and Giesecke *et al.*³⁴ who enrolled a small proportion of heterosexual participants. Cheingsong-Popov *et al.*²⁸ did not describe study participants but it appears likely, given the 1984 publication date, that the acquired immunodeficiency syndrome (AIDS) and AIDS-related complex patients reporting AI were MSM. There was no evidence that the heterosexual combined URAI–UIAI crude per-partner estimate²⁹ was significantly different from the eight crude estimates from MSM ($P=0.821$).

Reliability of estimates

All per-partner summary estimates displayed considerable heterogeneity. Summary estimates calculated using adjusted estimates were considerably lower than those using crude estimates (Figure 1; Table 1). However, the reliability of summary adjusted estimates is questionable because only the crude combined URAI–UIAI summary estimate was based on more than five estimates. Interestingly, while crude per-partner estimates from MSM populations may overestimate per-partner infectivity because of competing exposures due to frequent lack of monogamy,^{28,30–34,36,37,39} they were in good agreement with crude per-partner estimates from heterosexual couples reporting high frequency of AI and 100% monogamy²⁹ (Figure 1).

For combined URAI–UIAI, the summary estimate based on crude estimates only was 48.1% (95% CI 35.3–60.8), for URAI-only 51.4% (95% CI 28.1–74.7) and for UIAI-only 29.4% (95% CI 16.0–42.9) (Table 1). The forest plot (Figure 1) and Q - and I^2 -statistics (Table 1) highlight significant residual heterogeneity across estimates, even after excluding adjusted estimates. Nicolosi *et al.*'s²⁹ study participants reported 100% monogamy, yet the 42.9% (95% CI 29.1–57.8) combined URAI–UIAI risk is more consistent with the crude MSM study estimates despite potential contamination from competing HIV exposures, than the adjusted MSM estimates. Separating

combined URAI–UIAI estimates by study design (prospective^{35,36,38} versus retrospective^{28–34,37}) gave similar findings because both adjusted estimates were derived from simple-prospective studies and the remaining prospective study, of serodiscordant couples, was small ($n=10^{36}$).

Heterogeneity of infectiousness

Despite providing a single per-act URAI estimate, DeGruttola *et al.*²⁴ discussed variability of infectiousness between individuals and suggested that 10–20% of infected MSM may have far greater infectiousness (about $\geq 10\%$ per-act). Supplementary Table S4 (available as Supplementary data at *IJE* online) summarizes the few per-act and per-partner estimates stratified by risk factors. The only per-act estimate stratified by infection stage [primary infection and AIDS stages each separately estimated as 18.35% (95% CI 2.08–34.6); asymptomatic incubation stage 1.38% (95% CI 0.0–3.38)]²⁷ reflects the variability in infectiousness within an individual over time. However, it is likely that none of the four average per-act AI infectivity estimates adequately captures the contribution of high infectiousness during acute, pre-seroconversion infection.^{24–27} The study by Leynaert *et al.*²⁷ was a retrospective-partner study where the exposure period was only crudely estimated. Although some transmissions in Vittinghoff *et al.*'s prospective study might have occurred as a result of acute infection exposure, the study estimate included only study participants reporting partners known to be HIV infected. Therefore, the index cases were unlikely to be in the highly infectious acute HIV stage because of the time lag between infection and HIV diagnosis and disclosure of their status to their partners included in the study. Therefore, the true average per-act infectivity across all infection stages may be higher than our 1.4% summary estimate because retrospective-partner studies may miss the acute infection stage, or may be lower because Vittinghoff's prospective study may have misattributed some transmission events from unidentified HIV exposures.

Relationship between per-act and per-partner infectivity for AI

Figure 2 illustrates the relationship between per-act and cumulative HIV risk over a partnership through URAI (by number of sexual acts), compared with per-partner combined URAI–UIAI summary estimates from our meta-analysis (drawn as horizontal lines). The figure indicates, for example, that only 36 URAI acts would be required to produce the per-partner combined URAI–UIAI summary estimate of 39.9% if we assume that per-act URAI HIV transmission probability is 1.4%. If 50% of acts are receptive and 50% insertive, 60 UAI acts are required if we assume that UIAI per-act risk is 0.3% (same as for VI; see Figure 2 legend for details) and 51 acts if the UIAI per-act risk

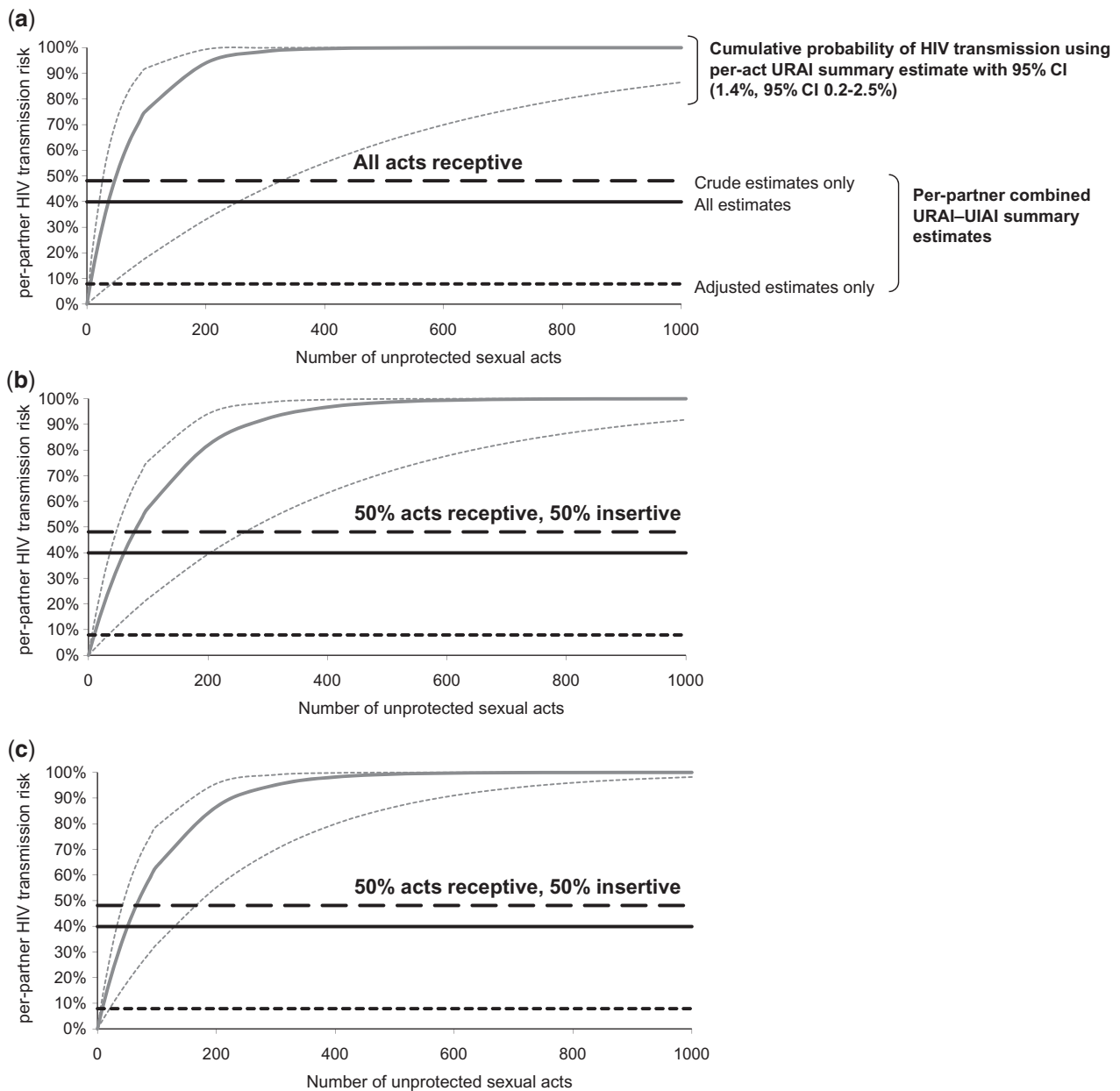


Figure 2 Relation between per-partner HIV transmission risk (cumulative probability of HIV transmission) and the number of sexual acts with an HIV infected partner, using our summary per-act URAI estimate of 1.4% (95% CI 0.2–2.5). The intersection between the modelled per-partner HIV transmission risk (y -axis) and our meta-analytic per-partner combined URAI–UIAI summary estimates (plotted as horizontal lines) predicts the required average number of acts per partnership (x -axis), under our model assumptions (see ‘Methods’ section). Adjusted estimates control for exposures due to multiple partners and crude estimates do not. **(a)** All acts assumed to be URAI; **(b)** 50% acts URAI, 50% acts UIAI, assuming that per-act UIAI has the same HIV transmission probability as penile–vaginal intercourse (summary estimate of per-act penile–vaginal intercourse, male-to-female transmission for developing countries: 0.3%¹³); **(c)** as for **(b)** but UIAI HIV transmission probability is 0.6%. Competing risk from UIAI increases the total number of unprotected acts necessary for transmission per partnership only by relatively modest amounts, especially when the increase in transmission probability of UIAI compared with VI is large, because UIAI infectiousness becomes closer to that of URAI.

is 0.6%. Competing risk from UIAI increases the total number of unprotected acts necessary for transmission per partnership only by relatively modest amounts, especially when the increase in transmission probability of UIAI compared with VI is large, because

UIAI infectiousness becomes closer to that of URAI. As suggested previously,²⁴ under the model assumptions, it is difficult to explain per-partner risk estimates as a function of per-act estimates. The results imply relatively few UAI acts per relationship among

the partnerships included in the per-partner studies. As too few MSM per-partner studies reported length of partnership or number of sex acts per partnership (Supplementary Table S1, available as Supplementary data at *IJE* online), it is difficult to test this hypothesis. Although some of the partnerships in the per-partner studies may have been relatively short with few sexual acts, this is unlikely to be the case for all partnerships and all studies. For example, Nicolosi *et al.*²⁹ reported a median partnership duration of 2.9 years, implying a relatively large number of acts. Supplementary Figure S2 (available as Supplementary data at *IJE* online) shows how empirical per-partner study estimates do not show the expected increase in infectivity with increasing number of sexual exposures to the index partner predicted by the Bernoulli process [Equation (1)] in absence of heterogeneity. The discrepancies between per-act and per-partner estimates (Figure 2; Supplementary Figure S2, available as Supplementary data at *IJE* online) may partly be explained by condom use, competing risks from exposure to HIV outside the main partnership or some degree of heterogeneity in transmission probability per-act between individuals and within individuals over time, implying that our assumption of independence of risk per-act within a partnership is invalid. If there is heterogeneity in infectiousness or susceptibility between individuals, this may explain the saturation of per-partner risk at lower levels than predicted using our per-act summary estimate. The four per-act estimates represent exposure without condoms: DeGruttola *et al.*²⁴ and Leynaert *et al.*²⁷ reported <1% condom use and Vittinghoff *et al.*²⁵ and Halperin *et al.*²⁶ adjusted for it. In contrast, many per-partner studies reported 'some condom use' but generally did not quantify frequency (although it appears that condom use was generally very inconsistent within partnerships).

If we assume the 18.35% per-act URAI estimate of Leynaert *et al.*²⁷ associated with primary infection, only three URAI acts were necessary for per-partner HIV risk to exceed 40.4% (per-partner URAI-only summary estimate, results not shown). Therefore, high infectiousness associated with primary infection may account for the high per-partner estimates observed for some partnerships consisting of few acts. However, relatively few short duration partnerships are likely to occur while infected individuals experience primary infection, because this period is very short [~ 3 months⁴⁰], although this will depend on the sexual network structure. Late-stage infection is also associated with high infectiousness,²⁷ so the same argument could apply, although sexual activity of AIDS patients is likely to be much lower.

Implications for the effectiveness of interventions: HAART

Figure 3a illustrates the relationship between per-partner HIV risk and total sex acts involving

exposure to HIV-infected partners not on HAART, considering both VI/UIAI and URAI exposure (see legend for details). Using Function 1 (Figure 3b), the predicted HIV transmission probabilities per-act for VI/UIAI and URAI with successful HAART are 0.013 and 0.061%, respectively, i.e. 96% lower than without therapy. Under these assumptions, 1000 sex acts leads to a male-to-female per-partner HIV risk of 12.2% if no AI is practised (i.e. only VI is practised) and 12.6, 14.3, 16.3 and 20.2% if AI is practised for 1, 5, 10 and 20% of all sex acts, respectively. For MSM, 1000 acts lead to per-partner risk of 30.9% if partners alternate URAI and UIAI, and 45.6% if the initially uninfected partner is always receptive. As expected, our per-partner HIV risk estimates with HAART, even assuming continuous viral suppression, are larger than Wilson *et al.*'s¹⁷ estimates using the same function, because we used recent and higher baseline per-act VI infectivity estimates from the studies of developing country only (due to the lack of AI infectivity studies from developing countries, per-act URAI was informed by the studies of developed country only).¹³ Using Function 2 (Figure 3c–e), the predicted per-act VI/UIAI and URAI estimates with successful HAART are 0.0002 and 0.0011%, respectively, i.e. 99.9% lower than without therapy. Under these assumptions, 1000 sex acts lead to a male-to-female per-partner HIV risk of <0.5% even where AI constitutes 20% of all sex acts, <1% for MSM practising URAI and UIAI with equal frequency and 1.1% for MSM solely practising URAI (Figure 3c). However, if viral rebound occurs due to treatment failure, per-partner transmission risks become much larger (Figure 3d–e).

Discussion

Four per-act URAI estimates produced a summary estimate of 1.4% (95% CI 0.2–2.5) and per-partner summary estimates were 39.9% (95% CI 22.5–57.4), 40.4% (95% CI 6.0–74.9) and 21.7% (95% CI 0.2–43.3) for combined URAI–UIAI, URAI and UIAI transmission, respectively. Competing risk from UIAI only marginally increases HIV transmission per partnership (39.9% for combined, 40.4% for URAI-only), which supports the hypothesis that UIAI is substantially less infectious than URAI. However, the significant heterogeneity between per-partner estimates led to wide CIs, primarily due to differences in analytic methods and study design. Thus, these 'average' AI transmission probabilities should be used with caution.

The large discrepancy between crude and adjusted per-partner estimates (Table 1) makes interpretation of the results particularly difficult, especially because similar adjustments used to quantify per-act VI estimates were found to have little impact.^{13,41} The combined URAI–UIAI summary estimate using adjusted per-partner estimates was approximately six times

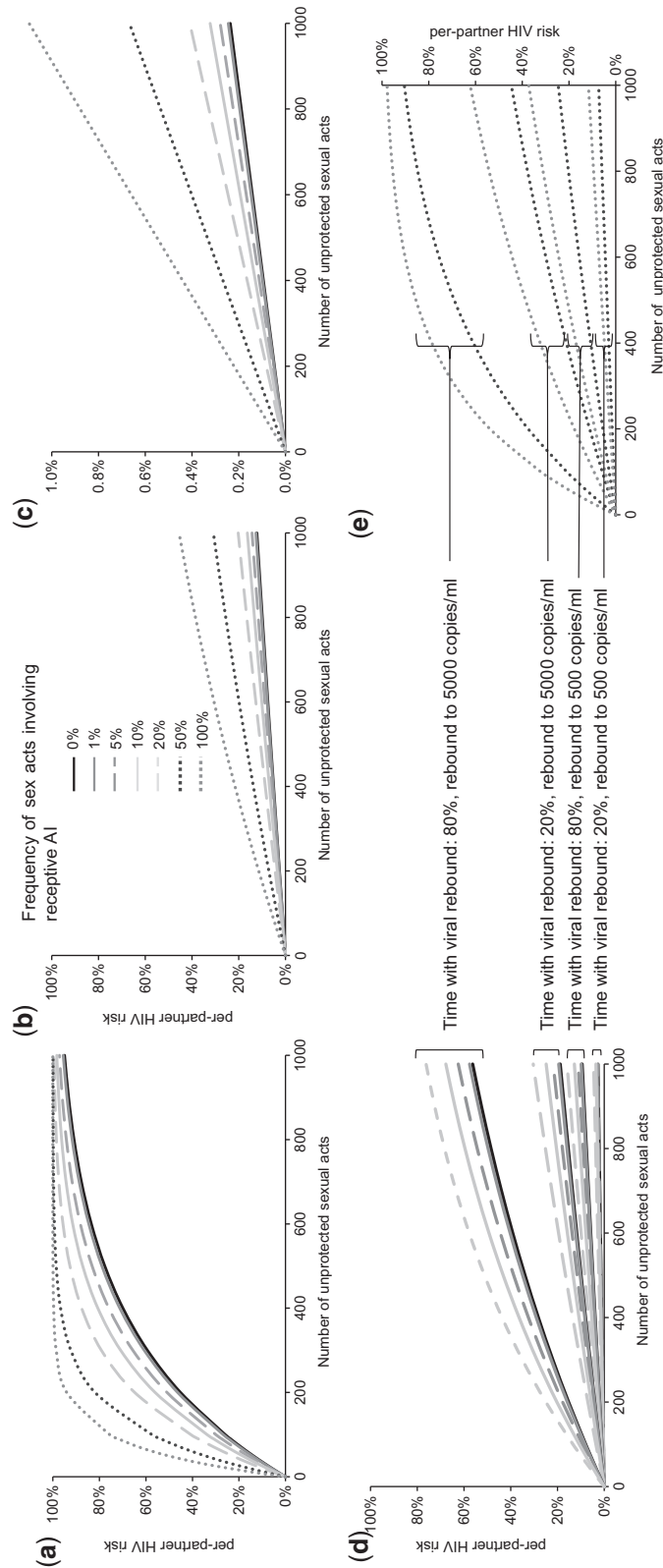


Figure 3 Relation between per-partner HIV risk (cumulative probability of HIV transmission) and the number of all sexual acts (whether penile–vaginal or penile–anal) that uninfected MSM or heterosexual women are exposed to with HIV-infected men, exploring the impact of different frequencies of URAI within the partnership (if in a monogamous HIV discordant relationship) or among all sexual HIV exposures that an uninfected individual encounters. Frequency of sexual acts involving URAI: 0–20% represent ranges for women in heterosexual partnerships, with the remainder of sexual exposures assumed to be penile–vaginal; 50% represents MSM partnerships where each partner practises URAI and UIAI equally often; 100% represents MSM where the seronegative partner is always receptive. Scenario (a) represents the impact of URAI on per-partner HIV risk assuming a constant per-act probability for URAI (1.4%, Table 1) and for penile–vaginal intercourse (summary estimate of per-act penile–vaginal intercourse, male-to-female transmission for developing countries: 0.3%¹³), we assume, in the absence of per-act HIV estimates for UIAI identified by our review, that HIV transmission probability is the same as for female-to-male penile–vaginal intercourse). Scenario (b) uses Function 1 to investigate impact of HAART, predicting per-partner HIV risk within a discordant couple where the index male has successful viral suppression due to HAART. Scenario (c) investigates the same, by using Function 2 (note change of y-axis scale). Scenarios (d) and (e) use Function 2 (separating graphs for women and MSM for clarity), additionally including viral rebound as a result of treatment failure for a proportion of the duration of exposure. The derived relationship between URAI infectiousness and plasma viral load calculated in Function 2 is illustrated in Supplementary Figure S3 (available as Supplementary data at *IJE* online).

lower than for the summary of crude estimates. As many MSM study subjects may have multiple partners, adjusted estimates may be more reliable. However, the 42.9% (95% CI 29.1–57.8) crude per-partner estimate reported by Nicolosi *et al.*²⁹ for heterosexual relationships with high levels of monogamy, together with the high per-act estimates identified, are difficult to reconcile with the low summary estimate for adjusted per-partner infectiousness. Most studies did not collect the necessary sexual activity information required to gain a better understanding of the relationship between per-act and per-partner risk. Variation across study estimates may also partly be explained by differences in distributions of risk factors in sampled populations, study designs and various (time-varying) characteristics of the type of sexual behaviour, characteristics of the infected partner and those of the uninfected partner. For example, duration of exposure to an infected partner, frequency of unprotected acts per-partner and presence of various cofactors for transmission, such as condom use, will differ (Supplementary Table S1, available as Supplementary data at *IJE* online). While HIV transmission for heterosexual men engaging in AI will predominantly occur by insertive intercourse, MSM experience risk through both insertive and/or receptive AI.

As suggested previously,²⁴ the difficulty in reconciling per-act and per-partner estimates highlights the difficulty in specifying a unique estimate of AI and supports that there is considerable heterogeneity in infectivity between individuals, over the course of infection and/or that our assumption of independence of risk per-act within a partnership is invalid.⁴² DeGruttola *et al.*²⁴ suggested in 1989 that such heterogeneity leads to underestimation of the number of partners who would be infected after few acts and overestimation of numbers who would be infected after many acts. Heterogeneity in per-act or per-partner HIV infectiousness has also been reported in other studies for VI^{13,41} and intercourse for MSM.^{27,33,34} Additional evidence of heterogeneity in per-partner estimates by potential risk factors such as STI history are summarized in Supplementary Table S4 (available as Supplementary data at *IJE* online), but the number of studies is limited. Estimates stratified by risk categories (Supplementary Tables S3 and S4, available as Supplementary data at *IJE* online) may suffer from publication bias, as they are more likely to be reported if differences are significant.

URAI per-act estimates are substantially higher than for male-to-female VI (0.08%, 95% CI 0.06–0.11 in developed countries; 0.30%, 95% CI 0.14–0.63 in developing countries).¹³ Most studies of heterosexual couples have found an increased male-to-female transmission risk among couples practising AI, even if only occasionally.^{13,41,43–50} Rectal mucosa lacks the protective humoral immune barrier present in cervicovaginal secretions⁵¹ and is more susceptible to

traumatic abrasions which may facilitate transmission.⁵² We found no evidence of a difference in per-act AI infectivity between heterosexual and MSM couples, possibly because they are biologically similar practices, yet per-partner infectivities may differ due to dissimilar frequencies of practising AI within heterosexual and MSM relationships. However, the only heterosexual per-partner study consisted of couples with high frequency of AI ($\geq 50\%$ of sexual acts)²⁹ and therefore, given the much higher risk of transmission during AI than VI, estimates should be comparable with those from MSM studies. Our review extends previous HIV infectivity research because we investigated per-act and per-partner AI infectivity among MSM and heterosexuals. However, we found no AI estimates from developing countries, and given the different distributions in risk factors such as STI prevalences and HIV subtypes between settings, we may underestimate overall AI infectiousness for developing countries, as has been suggested for per-act VI infectiousness.^{13,41}

Our AI transmission probability estimates are considerably higher than oro-genital risks, which were found to be very low, but non-zero.⁵³ For example, our per-act URAI summary estimate is 35-fold larger than the highest per-act oro-genital estimate (0.04% for unprotected receptive oro-genital intercourse, 95% CI 0.01–0.17²⁵). Thus, practising oral sex with an HIV-infected individual considerably reduces the risk of HIV acquisition compared with that for URAI and UIAI, but does not reduce it to zero. Individuals often make sophisticated choices regarding the balance of risk and pleasure;^{54,55} this difference in risk should be appropriately communicated to relevant populations.

Studies have demonstrated that a substantial percentage of heterosexuals engage in AI with an opposite-gender partner^{56–60} and that rates of condom use for heterosexual AI are lower than for VI.^{6,61} More recently, research in the USA and the UK has demonstrated an increase in the proportion of heterosexuals reporting practicing AI,^{56,62–64} although this rise may be attributable to social changes affecting reporting bias. The proportion of heterosexually acquired HIV infection attributable to AI depends largely on the frequency of UAI, which varies greatly by population and setting, and the HIV risk profile of the partners of heterosexuals. Table 2 presents a summary of studies identified through a non-exhaustive review of PubMed, documenting the proportion of participants reporting any AI over a defined period for various populations and settings published in the last 10 years. Although these findings may not all be representative of the general population due to small samples and selection biases, the high rates of AI are in line with those investigated with our model. The majority of surveys were conducted in industrialized countries; more and carefully collected data on frequency of protected and unprotected AI are

Table 2 Summary of selected epidemiological studies investigating practice of AI among heterosexual populations published in the last 10 years

Study	Population	Age (years)	Sample size	AI reported (%)	Exposure period
Industrialized countries					
Pollack, 1999, unpublished data; National AIDS Behavioral Methodology Study ^{a,b}	USA population survey, women	18–49	1071	6.10	Past 6 months
Laumann <i>et al.</i> , 1994 ^{74,a}	USA population survey	18–59	3432	23 10 men 9 women 2.3 men	Ever Past year Past year Last sex
		50–54		1.2 women 3 men 2 women 2.4 women	Last sex Past year Past year Last sex
Gross <i>et al.</i> , 2000 ⁶⁰	USA HIV negative women 'at high risk of HIV infection'	11% 18–25 38% 26–35 51% ≥36	1268	32	Past 6 months
Baldwin and Baldwin, 2000 ⁵⁷	USA random sample of sexually experienced university students (oversampling ethnic groups)	Mean 21, all <30	647	23	Ever
Johnson <i>et al.</i> , 2001 ⁶⁴	UK population-based survey (NATSAL)	16–44	111 613 ^c	7.0 men 6.5 women 12.3 men 11.3 women	Past year (1990) Past year (2000)
Friedman <i>et al.</i> , 2001 ⁵⁸	USA women, inner city minority neighbourhood	18–24	202	14	Past year
Flannery <i>et al.</i> , 2003 ⁷⁵	USA sexually experienced female college students 1993–2000	NR	761	32	Ever
Leichliter <i>et al.</i> , 2007 ⁶¹	USA general population survey	15–44	12 571	30 women 34 men	Ever
Houston <i>et al.</i> , 2007 ⁷⁶	USA inner city adolescent, sexually experienced females	12–18	350	16 main partners 12 casual partners	Past 3 months
Tian <i>et al.</i> , 2008 ⁷⁷	USA STD clinic attendees	15–39	2357	18.30 39.30	Past 3 months Past year
Developing countries					
Karim and Ramjee, 1998 ⁷⁸	South Africa FSW surveyed at truck stops	Mean 24	145	43 with clients	Ever
Matasha <i>et al.</i> , 1998 ⁷⁹	Tanzania cohort of sexually experienced male and female school pupils	Median 15, 12–20	661	6	First sexual experience ^d
Sallah <i>et al.</i> , 1999 ⁸⁰	Togo female college students	20–29	817	9 37.80	Likely currently ^e Likely ever ^e
Fonck <i>et al.</i> , 2000 ⁸¹	Kenya FSW cohort	Mean 32	318	14	Likely ever ^e
Ramjee and Gouws, 2002 ⁸²	South Africa truck drivers	Mean 37, 18–71	184	42	Likely ever ^e
Ferguson and Morris, 2003 ⁸³	Kenya FSW cohort	NR	339	20	Ever
Lane <i>et al.</i> , 2006 ⁸⁴	South Africa national survey of adolescent sexual behaviours, sexually active respondents	15–24	~7976	5.3 women 5.5 men	Ever
Schwandt <i>et al.</i> , 2006 ⁸⁵	Kenya FSW cohort	Mean 35, 15–63	147	40.80	Ever
Skoler-Karpoff <i>et al.</i> , 2008 ⁷⁰	South Africa, baseline characteristics from a microbicide RCT,	≥16 (4% 16–17, 33%	6202	2 ^f	Past 3 months

(continued)

Table 2 Continued

Study	Population	Age (years)	Sample size	AI reported (%)	Exposure period
Subramanian <i>et al.</i> , 2008 ⁸⁶	sexually active, HIV-negative women India, survey of clients of FSW	18–24, 63% ≥25) Median 30, 18–60	4821	13.3 with FSW 6.2 with main regular female partner 8.3 with male or transgender	Ever Ever Past 6 months Ever
Munro <i>et al.</i> , 2008 ⁸⁷	India, community-based survey	Mean 30, 15–49	4653	2.6 ^{g,h} men 0.3 ^h women	Ever
Kalichman <i>et al.</i> , 2009 ⁸⁸	South Africa, urban township community-based and urban STI clinic surveys	Mean 31, median 30, minimum 18 (men and women combined)	2471 1646	14.6 men 10.4 women	Past 3 months

FSW, female sex worker; NATSAL, National Survey of Sexual Attitudes and Lifestyles; NR, not recorded; RCT, randomized controlled trial; STD, sexually transmitted disease.

^aResults taken from review by Halperin.⁶

^bLance M. Pollack, personal communication, September 1999 to D. Halperin.⁶

^cTotal completing NATSAL 2000 questionnaire, including non-heterosexuals (percentage reporting AI is for heterosexual practices only).

^dAuthors report that results must be interpreted with caution as some younger pupils may have had difficulty in understanding some of the more sensitive questions (questionnaire was self-administered), 'in particular questions on oro-genital and anal sex'.

^eNot specified in the publication.

^fUAI only.

^gA further 0.6% of men reported ever having had AI with another man.

^hSeventeen (0.8%) of men and 68 (2.3%) of women reported not knowing if they had ever experienced AI. None of these men was HIV positive, but among women, 'not knowing' was significantly associated with HIV infection, compared with the group of women reporting no AI experience.

required from populations in developing countries to explore the influence of AI on generalized epidemics.⁶⁵

Our analysis of how the impact of HAART on HIV transmission may be mitigated by AI suffers from several limitations due to its simplicity and the difficulty in quantifying AI infectiousness highlighted in this review (e.g. per-act VI risk was taken from a meta-analysis for male-to-female transmission in developing countries,¹³ but our per-act URAI summary estimate represents industrialized countries only because no relevant studies from developing countries were identified; we assume that infectiousness varies with viral load similarly for AI and VI and that coital frequency remains constant over time; and again we stress the need for caution in utilizing our quantitative pooled estimates). Nevertheless, it serves to vividly illustrate the large excess in HIV risk that individuals may experience over time if they occasionally engage in UAI with an infected partner. Thus, prevention messages must emphasize the high risk associated with AI and that control measures such as condoms must be used for both VI and AI.

Drawing conclusions on the use of HAART for HIV prevention is beyond the scope of this article. However, the contrasting quantitative results obtained regarding the impact of HAART on per-partner transmission risk using the two functions (Figure 3b–e) highlight that caution is required when relying on viral load data to predict the potential impact of HAART on transmission and the importance of clearly describing the model assumptions. Different viral load functions produce different predictions (Figure 3). Figure 3d–e demonstrates the sensitivity of results to frequency of viral rebound and to the infectiousness associated with these rebounds. Further work in this area is necessary given the increasing interest in HAART use as a prevention tool.^{66,67} Modelling cannot be used as a substitute for empirical evidence, and data are starting to become available.⁶⁸

In terms of product development, oral pre-exposure prophylaxis may be more appropriate for use among populations where there is a high frequency of AI if adherence to condom use or rectal microbicide use is poor, or if microbicide efficacy is lower for AI than VI. All microbicide trials potentially suffer from bias from AI.^{69–71} There must be greater understanding of the

role that AI plays in heterosexual as well as MSM sex lives, particularly in regions with high HIV incidence, so that we can design and implement measures to minimize the role that it plays in HIV transmission.

Supplementary data

Supplementary data are available at *IJE* online.

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KEY MESSAGES

- UAI is a high-risk practice for HIV transmission (higher risk than VI or oro-genital intercourse), probably with substantial variation in infectiousness and susceptibility to infection between individuals, and in infectiousness over the duration of infection. The significant heterogeneity between infectiousness estimates means that pooled AI HIV transmission probabilities should be used with caution.
- Most studies did not collect the necessary sexual activity information required to gain a better understanding of the relationship between per-act and per-partner risk. Variation across study estimates may also partly be explained by differences in distributions of risk factors in sampled populations, study designs and various (time-varying) characteristics of the type of sexual behaviour, characteristics of the infected partner and those of the uninfected partner.
- We found no evidence of a difference in per-act AI infectivity between heterosexual and MSM couples.
- Model estimates of the impact of HAART in reducing HIV transmission and the mitigating effect of AI can vary substantially, depending on the assumptions made. Empirical evidence is, therefore, urgently needed in order to inform model estimates, which remain highly uncertain. Nevertheless, our analysis illustrates the large excess in HIV risk that individuals may experience over time if they occasionally engage in UAI with an infected partner. Prevention messages must emphasize the high risk associated with AI and that control measures such as condoms must be used for both VI and AI.

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