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

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

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3 **Review article: HIV transmission risk through anal intercourse: systematic**  
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10  
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## Abstract

**Background:** The 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 HAART.

**Results:** 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%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 amongst heterosexuals suggests 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

**Key messages**

- Unprotected anal intercourse (AI) is a high risk practice for HIV transmission (higher risk than vaginal (VI) or orogenital 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 unprotected AI with an infected partner. Prevention messages must emphasise the high risk associated with AI and that control measures such as condoms must be used for both VI and AI.

## Introduction

Studies systematically reviewing much-needed estimates of 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 worldwide.(1, 2) However, none have specifically focused on anal intercourse (AI), despite its role driving HIV epidemics among men who have 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 United States (US) practising unprotected receptive AI (URAI) is approximately seven-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 randomised controlled trials for mother-to-child transmission(8) 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 reported(13) (details provided in Supplementary Information).

**Selection criteria and data extraction:** Empirical per-act and per-partner (irrespective of partnership duration and frequency of sex acts) estimates were extracted. Abstracts pre-1990, studies using sample sizes <10 and estimates derived from dynamical modelling studies fitted to empirical HIV prevalence curves were excluded. Estimates where infection of partners was ascertained clinically(14) 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 practiced 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 which 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:

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

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3 where  $\beta_{p,all}$  is risk per-partner for VI and AI;  $\beta_{c,v}$  and  $\beta_{c,a}$  are per-act transmission probabilities for VI  
4 (v) and receptive AI (a), respectively; and  $d$  is the proportion of  $n$  sex acts which are AI rather than  
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8 VI.  
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### 10 11 *Intervention impact: HAART*

12 We assessed the potential reduction in HIV infectivity caused by HAART reducing viral load, using two  
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14 published functions of infectivity by viral load.(17-21) In brief the difference between the two functions is  
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16 that Function 1 was based on results from the Rakai study of HIV transmission in heterosexual couples  
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18 (presumed through vaginal intercourse (VI) transmission)(22) and assumes a linear relationship  
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20 between infectiousness and log serum viral load; function 2 was based on data from a Zambian cohort  
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22 of discordant couples(23) and assumed a logistic function between infectivity and plasma viral load,  
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24 which provides better fits to the low number of transmissions observed for low viral loads of index  
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26 individuals.(21)We assume that successful HAART reduces blood viral load from an average, baseline  
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28  $V_0$  to  $V_1$  copies/ml. Further details are provided in Supplementary Information.  
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## 38 **Results**

### 39 *Search results*

40 62,643 titles were searched and 27 potentially appropriate publications identified, three of which were  
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42 identified through bibliographies of searched articles. Four publications reporting per-act(24-27) and 12  
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44 reporting per-partner(28-39) estimates were included. These were from MSM (n=12(24, 25, 28, 30-37,  
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46 39)), heterosexual (n=3(26, 27, 29)) or mixed (n=1(34)) study populations. Per-partner estimates from  
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48 Nicolosi et al's study of heterosexuals, where AI was practiced "often or always" ( $\geq 50\%$  of all  
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50 intercourse) within the partnership were included; those with less frequent practice were excluded.(29)  
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52 Figure S1, Supplementary Information, summarises the search strategy. All identified studies were from  
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54 industrialised countries. Figure 1 summarises study estimates for per-act and per-partner AI  
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56 transmission probabilities as forest plots, including summary estimates from the meta-analyses. Details  
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58 of included and excluded studies are in Tables S1 and S2 of Supplementary Information, respectively.  
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3 Table S3 summarises heterosexual per-partner estimates which have been stratified by frequency of AI  
4 practice. Table S4 summaries AI study estimates stratified by different risk factors.  
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9 The only per-act estimates included were for URAI. Vittinghoff et al's estimates for protected receptive  
10 AI (0.18%, 95%CI 0.10-0.28), unprotected insertive AI (UIAI) (0.06%, 95%CI 0.02-0.19) and protected  
11 insertive AI (0.04%, 95%CI 0.01-0.11), based on partners of index cases who were "HIV infected or of  
12 unknown serostatus" were excluded because no attempt was made to estimate the unknown HIV status  
13 of index cases by using HIV prevalence as a proxy for exposure to an HIV infected partner.(25)  
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### 20 21 *Study design and estimate type*

22 The included studies employed three study designs: retrospective-partner (n=11(24, 26-34, 37)),  
23 prospective discordant-couple (n=1(36)) and simple-prospective (longitudinal cohort, n=4(25, 35, 38,  
24 39)) studies. In retrospective-partner studies, the infection status of each partner becomes known only  
25 at the time of the study. The index case and time of infection are determined based on exposure to a  
26 salient risk factor. In prospective discordant-couple studies, stable (preferably monogamous) HIV-  
27 serodiscordant couples are followed up after diagnosis of the index partner. These studies also provide  
28 per-partner HIV transmission rates but, with only one included study (and only 10 couples(36)), we  
29 report and use cross-sectional results at the end of follow-up for the meta-analysis. With simple-  
30 prospective studies, individuals (not necessarily monogamous) are recruited following sexual contact  
31 with potentially infected, high-risk partners and serostatus monitored. As index cases are not recruited,  
32 HIV exposure is estimated using HIV prevalence in the pool of potential partners and the reported coital  
33 frequency. Therefore prospective studies suffer from problems of selection bias (prospective  
34 discordant-couple) and uncertainty estimating numbers of HIV exposures (simple-prospective) and are  
35 not necessarily superior to the retrospective-partner study design.  
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52 Per-act estimates were derived from retrospective-partner (n=3(24, 26, 27)) and simple-prospective  
53 (n=1(25)) studies. Per-partner estimates were derived from retrospective-partner (n=8(28-34, 37)),  
54 prospective-discordant couple (n=1(36)) and simple-prospective (n=3(35, 38, 39)) studies. For both  
55 URAI-only and UIAI-only per-partner estimates, three were derived from retrospective-partner(29, 31,  
56 34) and one from simple-prospective(39) study data.  
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5 We categorised study estimates into “crude” and “adjusted”. “Crude” estimates are based on the HIV  
6 status of partners of index cases and assume that the index case was the only source of exposure. In  
7 high-risk populations, multiple exposures to HIV through sexual contact with other partners and through  
8 other types of sexual practice may lead to overestimation of infectivity. Thus “Adjusted” estimates are  
9 based on statistical models to control for multiple exposures. One study also adjusted for multiple  
10 modes of sexual transmission: from URAI, UIAI, protected AI and oro-genital intercourse.(25) No study  
11 provided both crude and adjusted estimates. Brief details on adjusted estimates are provided in Table  
12 S1, Supplementary Information. Numbers of per-act and per-partner estimate by adjustment type and  
13 study design are given in Table 1. For per-partner transmission probabilities, retrospective-partner  
14 studies reported crude estimates, while prospective studies tended to report adjusted estimates. This  
15 made it difficult to disentangle the effect of study design from adjustment for multiple exposures. In  
16 addition, all estimates where the standard error had to be approximated using an uncertainty range  
17 quoted by authors, were adjusted estimates.  
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### 33 *Infectiousness of anal intercourse for heterosexuals and MSM*

34 Table 1 shows the per-act and per-partner summary estimates by exposure (combined URAI-UIAI,  
35 URAI-only and UIAI-only). Two per-act URAI estimates were based on studies among MSM(24, 25) and  
36 two among heterosexual couples.(26, 27) The per-act summary estimate was 1.4% (95%CI 0.2-2.5) (or  
37 1.8% [95%CI 0.3-3.2] if Halperin et al's abstract estimate is excluded due to lack of further detail on  
38 methods(26)). No significant differences in per-act URAI estimates between heterosexual couples and  
39 MSM was found ( $p=0.674$ ). However, while MSM estimates(24, 25) were similar to each other ( $Q=0.2$ ,  
40  $p=0.635$ ,  $I^2=0\%$ ), heterosexual estimates(26, 27) were heterogeneous ( $Q=10.5$ ,  $p=0.001$ ,  $I^2=90\%$ ,  
41 Figure 1, Table 1). Most per-partner estimates were derived from studies on MSM. Exceptions were  
42 Nicolosi et al, studying heterosexual couples,(29) and Giesecke et al, who enrolled a small proportion of  
43 heterosexual participants.(34) Cheingsong-Popov et al did not describe study participants but it appears  
44 likely, given the 1984 publication date, that the AIDS and AIDS-related complex patients reporting AI  
45 were MSM.(28) There was no evidence that the heterosexual combined URAI-UIAI crude per-partner  
46 estimate(29) was significantly different from the eight crude estimates from MSM ( $p=0.821$ ).  
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### *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% monogamy(29) (Figure 1).

For combined URAI-UIAI, the summary estimate based on crude estimates only is 48.1% (95%CI 35.3-60.8); for URAI only is 51.4% (95%CI 28.1-74.7); and for UIAI only is 29.4% (95%CI 16.0-42.9) (Table 1). The forest plot (Figure 1) and Q and I<sup>2</sup> statistics (Table 1) highlight significant residual heterogeneity across estimates, even after excluding adjusted estimates. Nicolosi et al study participants reported 100% monogamy,(29) 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, while 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 discussed variability of infectiousness between individuals and suggested that 10-20% of infected MSM may have far greater infectiousness (~≥10% per-act).(24) Table S4, Supplementary Information, summarises 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 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

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3 infection.(24-27) Leynaert et al was a retrospective-partner study where the exposure period was only  
4 crudely estimated.(27) Although some transmissions in Vittinghoff et al's prospective study may have  
5 occurred as a result of acute infection exposure, the study estimate only included study participants  
6 reporting partners known to be HIV-infected. Therefore, the index cases were unlikely to be in the highly  
7 infectious acute HIV stage because of the time lag between infection and HIV diagnosis and disclosure  
8 of their status to their partners included in the study. Therefore the true average per-act infectivity  
9 across all infection stages may be higher than our 1.4% summary estimate because retrospective-  
10 partner studies may miss the acute infection stage, or may be lower because Vittinghoff's prospective  
11 study may have misattributed some transmission events from unidentified HIV exposures.  
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### 23 *Relationship between per-act and per-partner infectivity for anal intercourse*

24 Figure 2 illustrates the relationship between per-act and cumulative HIV risk over a partnership through  
25 URAI (by number of sexual acts), compared to per-partner combined URAI-UIAI summary estimates  
26 from our meta-analysis (drawn as horizontal lines). The figure indicates, for example, that only 36 URAI  
27 acts would be required to produce the per-partner Combined URAI-UIAI summary estimate of 39.9% if  
28 we assume per-act URAI HIV transmission probability is 1.4%. If 50% of acts are receptive and 50%  
29 insertive, 60 unprotected AI acts are required if we assume UIAI per-act risk is 0.3% (same as for VI;  
30 see Figure 2 legend for details) and 51 acts if the UIAI per-act risk is 0.6%. Competing risk from UIAI  
31 increases the total number of unprotected acts necessary for transmission per partnership only by  
32 relatively modest amounts, especially when the increase in transmission probability of UIAI compared to  
33 VI is large, because UIAI infectiousness becomes closer to that of URAI. As suggested previously,(24)  
34 under the model assumptions, it is difficult to explain per-partner risk estimates as a function of per-act  
35 estimates. The results imply relatively few UAI acts per relationship among the partnerships included in  
36 the per-partner studies. As too few MSM per-partner studies reported length of partnership or number of  
37 sex acts per partnership (Table S1), it is difficult to test this hypothesis. While some of the partnerships  
38 in the per-partner studies may have been relatively short with few sexual acts, this is unlikely to be the  
39 case for all partnerships and all studies. For example, Nicolosi et al reported a median partnership  
40 duration of 2.9 years,(29) implying a relatively large number of acts. Figure S2 shows how empirical  
41 per-partner study estimates do not show the expected increase in infectivity with increasing number of  
42 sexual exposures to the index partner predicted by the Bernoulli process (equation (1)) in absence of  
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3 heterogeneity. The discrepancies between per-act and per-partner estimates (Figures 2, S2) may partly  
4 be explained by condom use, competing risks from exposure to HIV outside the main partnership, or  
5 some degree of heterogeneity in transmission probability per-act between individuals and within  
6 individuals over time, implying that our assumption of independence of risk per-act within a partnership  
7 is invalid. If there is heterogeneity in infectiousness or susceptibility between individuals, this may  
8 explain the saturation of per-partner risk at lower levels than predicted using our per-act summary  
9 estimate. The four per-act estimates represent exposure without condoms: DeGruttola and Leynaert et  
10 al reported <1% condom use(24, 27) and Vittinghoff and Halperin et al adjusted for it.(25, 26) In  
11 contrast, many per-partner studies reported “some condom use” but generally did not quantify  
12 frequency (although it appears that condom use was generally very inconsistent within partnerships).  
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25 If we assume the 18.35% per-act URAI estimate of Leynaert et al associated with primary infection,(27)  
26 only 3 URAI acts are necessary for per-partner HIV risk to exceed 40.4% (per-partner URAI-only  
27 summary estimate, results not shown). Therefore high infectiousness associated with primary infection  
28 may account for the high per-partner estimates observed for some partnerships consisting of few acts.  
29 However, relatively few short duration partnerships are likely to occur while infected individuals  
30 experience primary infection, because this period is very short (approximately three months(40)),  
31 although this will depend on the sexual network structure. Late-stage infection is also associated with  
32 high infectiousness,(27) so the same argument could apply, although sexual activity of AIDS patients is  
33 likely to be much lower.  
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#### 45 *Implications for the effectiveness of interventions: HAART*

46 Figure 3a illustrates the relationship between per-partner HIV risk and total sex acts involving exposure  
47 to HIV-infected partners not on HAART, considering both VI/UIAI and URAI exposure (see legend for  
48 details). Using function 1 (Figure 3b), the predicted HIV transmission probabilities per-act for VI/UIAI  
49 and URAI with successful HAART are 0.013% and 0.061% respectively i.e. 96% lower than without  
50 therapy. Under these assumptions, 1000 sex acts leads to a male-to-female per-partner HIV risk of  
51 12.2% if no AI is practised (i.e. only VI is practiced) and 12.6%, 14.3%, 16.3% and 20.2% if AI is  
52 practised for 1%, 5%, 10% and 20% of all sex acts, respectively. For MSM, 1000 acts leads to per-  
53 partner risk of 30.9% if partners alternate URAI and UIAI, and 45.6% if the initially uninfected partner is  
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3 always receptive. As expected, our per-partner HIV risk estimates with HAART, even assuming  
4 continuous viral suppression, are larger than Wilson et al's(17) estimates using the same function,  
5 because we used recent and higher baseline per-act VI infectivity estimates from developing country  
6 studies only (due to the lack of AI infectivity studies from developing countries, per-act URAI was  
7 informed by developed country studies only) .(13) Using function 2 (Figures 3c-e), the predicted per-act  
8 VI/UIAI and URAI estimates with successful HAART are 0.0002% and 0.0011% respectively i.e. 99.9%  
9 lower than without therapy. Under these assumptions, 1000 sex acts leads to a male-to-female per-  
10 partner HIV risk of <0.5% even where AI constitutes 20% of all sex acts, <1% for MSM practising URAI  
11 and UIAI with equal frequency and 1.1% for MSM solely practising URAI (Figure 3c). However, if viral  
12 rebound occurs due to treatment failure, per-partner transmission risks become much larger (Figures  
13 3d-e).  
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## 29 Discussion

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31 Four per-act URAI estimates produced a summary estimate of 1.4% (95%CI 0.2-2.5) and per-partner  
32 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-  
33 43.3) for combined URAI-UIAI, URAI and UIAI transmission respectively. Competing risk from UIAI only  
34 marginally increases HIV transmission per partnership (39.9% for combined, 40.4% for URAI only)  
35 which supports the hypothesis that UIAI is substantially less infectious than URAI. However, the  
36 significant heterogeneity between per-partner estimates led to wide confidence intervals, primarily due  
37 to differences in analytic methods and study design. Thus these "average" AI transmission probabilities  
38 should be used with caution.  
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49 The large discrepancy between crude and adjusted per-partner estimates (Table 1) makes  
50 interpretation of the results particularly difficult, especially because similar adjustments used to quantify  
51 per-act VI estimates were found to have little impact.(13, 41) The combined URAI-UIAI summary  
52 estimate using adjusted per-partner estimates was approximately six times lower than for the summary  
53 of crude estimates. As many MSM study subjects may have multiple partners, adjusted estimates may  
54 be more reliable. However, the 42.9% (95%CI 29.1-57.8%) crude per-partner estimate reported by  
55 Nicolosi et al for heterosexual relationships with high levels of monogamy,(29) together with the high  
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3 per-act estimates identified, are difficult to reconcile with the low summary estimate for adjusted per-  
4 partner infectiousness. Most studies did not collect the necessary sexual activity information required to  
5 gain a better understanding of the relationship between per-act and per-partner risk. Variation across  
6 study estimates may also partly be explained by differences in distributions of risk factors in sampled  
7 populations, study designs and various (time-varying) characteristics of the type of sexual behaviour,  
8 characteristics of the infected partner and those of the uninfected partner. For example, duration of  
9 exposure to an infected partner, frequency of unprotected acts per-partner and presence of various  
10 cofactors for transmission, such as condom use, will differ (Table S1). While HIV transmission for  
11 heterosexual men engaging in AI will predominantly occur by insertive intercourse, MSM experience  
12 risk through both insertive and/or receptive AI.  
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25 As suggested previously,(24) the difficulty in reconciling per-act and per-partner estimates highlights the  
26 difficulty in specifying a unique estimate of AI and supports that there is considerable heterogeneity in  
27 infectivity between individuals, over the course of infection and/or that our assumption of independence  
28 of risk per-act within a partnership is invalid.(42) DeGruttola et al in 1989 suggested that such  
29 heterogeneity leads to underestimation of the number of partners who would be infected after few acts  
30 and overestimation of numbers who would be infected after many acts. Heterogeneity in per-act or per-  
31 partner HIV infectiousness has also been reported in other studies for VI(13, 41) and intercourse for  
32 MSM.(27, 33, 34) Additional evidence of heterogeneity in per-partner estimates by potential risk factors  
33 such as STI history are summarised in Table S4, but the number of studies is limited. Estimates  
34 stratified by risk categories (Tables S3 and S4) may suffer from publication bias, as they are more likely  
35 to be reported if differences are significant.  
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50 URAI per-act estimates are substantially higher than for male-to-female VI (0.08%, 95%CI 0.06-0.11%  
51 developed countries; 0.30%, 95%CI 0.14-0.63% developing countries).(13) Most studies of  
52 heterosexual couples have found an increased male-to-female transmission risk among couples  
53 practising AI, even if only occasionally.(13, 41, 43-50) Rectal mucosa lacks the protective humoral  
54 immune barrier present in cervicovaginal secretions(51) and is more susceptible to traumatic abrasions  
55 which may facilitate transmission.(52) We found no evidence of a difference in per-act AI infectivity  
56 between heterosexual and MSM couples, possibly because they are biologically similar practices, yet  
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3 per-partner infectivities may differ due to dissimilar frequencies of practising AI within heterosexual and  
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5 MSM relationships. However, the only heterosexual per-partner study consisted of couples with high  
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7 frequency of AI ( $\geq 50\%$  of sexual acts)(29) and therefore, given the much higher risk of transmission  
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9 during AI than VI, estimates should be comparable to those from MSM studies. Our review extends  
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11 previous HIV infectivity research because we investigated per-act and per-partner AI infectivity among  
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13 MSM and heterosexuals. However, we found no AI estimates from developing countries and, given the  
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15 different distributions in risk factors such as STI prevalences and HIV subtypes between settings, we  
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17 may underestimate overall AI infectiousness for developing countries, as has been suggested for per-  
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19 act VI infectiousness.(13, 41)

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23 Our AI transmission probability estimates are considerably higher than oro-genital risks, which were  
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25 found to be very low, but non-zero.(53) For example, our per-act URAI summary estimate is 35-fold  
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27 larger than the highest per-act oro-genital estimate (0.04% for unprotected receptive oro-genital  
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29 intercourse, 95%CI 0.01-0.17%(25)). Thus, practicing oral sex with an HIV-infected individual  
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31 considerably reduces the risk of HIV acquisition compared to that for URAI and UIAI, but does not  
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33 reduce it to zero. Individuals often make sophisticated choices regarding the balance of risk and  
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35 pleasure;(54, 55) this difference in risk should be appropriately communicated to relevant populations.

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

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3 frequency of protected and unprotected AI are required from populations in developing countries to  
4 explore the influence of AI on generalised epidemics.(65)  
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9 Our analysis of how the impact of HAART on HIV transmission may be mitigated by AI suffers from  
10 several limitations due to its simplicity and the difficulty in quantifying AI infectiousness highlighted in  
11 this review (for example, per-act VI risk was taken from a meta-analysis for male-to-female transmission  
12 in developing countries,(13) but our per-act URAI summary estimate represents industrialised countries  
13 only because no relevant studies from developing countries were identified; we assume that  
14 infectiousness varies with viral load similarly for AI and VI and that coital frequency remains constant  
15 over time; and again we stress the need for caution in utilising our quantitative pooled estimates).  
16 Nevertheless, it serves to vividly illustrate the large excess in HIV risk that individuals may experience  
17 over time if they occasionally engage in UAI with an infected partner. Thus prevention messages must  
18 emphasise the high risk associated with AI and that control measures such as condoms must be used  
19 for both VI and AI.  
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33 Drawing conclusions on the use of HAART for HIV prevention is beyond the scope of this paper.  
34 However, the contrasting quantitative results obtained regarding the impact of HAART on per-partner  
35 transmission risk using the two functions (Figures 3b-e) highlight that caution is required when relying  
36 on viral load data to predict the potential impact of HAART on transmission and the importance of  
37 clearly describing the model assumptions. Different viral load functions produce different predictions  
38 (Figure 3). Figures 3d-e demonstrate the sensitivity of results to frequency of viral rebound and to the  
39 infectiousness associated with these rebounds. Further work in this area is necessary given the  
40 increasing interest in HAART use as a prevention tool.(66, 67) Modelling cannot be used as a substitute  
41 for empirical evidence, and data are starting to become available.(68)  
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52 In terms of product development, oral pre-exposure prophylaxis may be more appropriate for use  
53 among populations where there is a high frequency of AI if adherence to condom use or rectal  
54 microbicide use is poor, or if microbicide efficacy is lower for AI than VI. All microbicide trials potentially  
55 suffer from bias from AI.(69-71) There must be greater understanding of the role that AI plays in  
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heterosexual as well as MSM sex lives, particularly in regions with high HIV incidence, so that we can design and implement measures to minimise the role that it plays in HIV transmission.

## Conflicts of interest

We declare that we have no commercial or other association that might pose a conflict of interest.

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## Figure legends and Tables

**Figure 1** Forest plot of studies estimating HIV transmission probabilities for anal intercourse expressing risk as a) per-act and b) per-partner. For crude estimates (unfilled boxes), the size of box represents relative study sample size.

**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 unprotected receptive anal intercourse (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 and unprotected insertive AI (UIAI) summary estimates (plotted as horizontal lines), predicts the required average number of acts per partnership (x-axis), under our model assumptions (see Methods). 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 per-act UIAI has the same HIV transmission probability as penile-vaginal intercourse (summary estimate of per-act penile-vaginal intercourse (VI), male-to-female transmission for developing countries: 0.3%<sup>(13)</sup>) 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 to VI is large, because UIAI infectiousness becomes closer to that of URAI.

**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 unprotected receptive anal intercourse (URAI) within the partnership (if in a monogamous HIV discordant relationship) or amongst 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

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3 to be penile-vaginal; 50% represents MSM partnerships where each partner practises URAI and  
4 UIAI equally often; 100% represents MSM where the seronegative partner is always receptive.  
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6 Scenario a) represents the impact of URAI on per-partner HIV risk assuming a constant per-act  
7 probability for URAI (1.4%, Table 1) and for penile-vaginal intercourse (summary estimate of per-  
8 act penile-vaginal intercourse, male-to-female transmission for developing countries: 0.3%;(13)  
9 we assume, in the absence of per-act HIV estimates for UIAI identified by our review, that HIV  
10 transmission probability is the same as for female-to-male penile-vaginal intercourse). Scenario  
11 b) uses function 1 to investigate impact of HAART, predicting per-partner HIV risk within a  
12 discordant couple where the index male has successful viral suppression due to highly active  
13 antiretroviral therapy (HAART); scenario c) investigates the same, by using function 2 (note  
14 change of y-axis scale). Scenarios d) and e) use function 2 (separating graphs for women and  
15 MSM for clarity), additionally including viral rebound as a result of treatment failure for a  
16 proportion of the duration of exposure. The derived relationship between URAI infectiousness and  
17 plasma viral load calculated in function 2 is illustrated in Figure S3.  
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**Table 1 Summary transmission probability estimates for anal intercourse: meta-analyses results**

Estimate type		Median	Min	Max	Summary random	Q*	p*	I <sup>2</sup> †	N	References and study design
		(%)	(%)	(%)	effects estimate, %					
					(95%CI)					
Per-act	URAI	1.0	0.4	3.4	1.4 (0.2-2.5)	10.8	.013	72%	4	3 R-P(24, 26, 27) 1 S-P(25)
	Retrospective	1.3	0.4	3.4	1.6 (0.0-3.2)	10.5	.005	81%	3	3 R-P(24, 26, 27)
	Prospective	0.8	-	-	0.8 (0.2-2.8)	-	-	-	1	1-S-P(25)
Per-partner	Combined URAI-UIAI	42.9	0.0	72.6	39.9 (22.5-57.4)	497.1	<.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	<.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	.063	71%	2	2 S-P(35, 38)
	Retrospective	51.1	30.5	72.6	52.3 (39.7-64.9)	78.1	<.001	91%	8	8 R-P(28-34, 37)
	Prospective	5.1	0.0	12.0	7.3 (1.8-12.8)	3.7	.161	46%	3	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	<.001	98%	4	3 R-P(29, 31, 34) 1 S-P(39)
	Crude	46.4	36.2	69.5	51.4 (28.1-74.7)	20.5	<.001	90%	3	3 R-P(29, 31, 34)
	Adjusted	10.0	-	-	10.0 (4.2-15.8)	-	-	-	1	1-S-P(39)
Per-partner	UIAI	27.1	0.7	36.6	21.7 (0.2-43.3)	60.6	<.001	95%	4	3 R-P(29, 31, 34) 1 S-P(39)
	Crude	35.7	18.4	36.6	29.4 (16.0-42.9)	5.1	.077	61%	3	3 R-P(29, 31, 34)
	Adjusted	0.7	-	-	0.7 (0.0-1.3)	-	-	-	1	1 S-P(39)

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5 \* Q statistic calculated using Cochran's Q test for heterogeneity, summing the squared deviations of each study's estimate from the overall pooled estimate,  
6 weighting the contribution of each study by its inverse variance.(72) Under the hypothesis of homogeneity among the transmission probability estimates, the Q  
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8 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.  
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10 †  $I^2$  calculated as described in Higgins et al.(73)  $I^2$  lies between 0% and 100%; 0% indicates no observed heterogeneity and larger values show increasing  
11 heterogeneity.  
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14 N – number of study estimates; p – p-value; P-DC – prospective discordant-couple study design; Q – heterogeneity statistic; R-P – retrospective-partner study  
15 design; S-P – simple prospective study design; UIAI – unprotected insertive anal intercourse; URAI – unprotected receptive anal intercourse. Crude estimates:  
16 estimates calculated through simple derivation as number of seroconversions out of number of sexual acts involving exposure.  
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18 Adjusted estimates: estimates derived using more sophisticated calculation of transmission probability.  
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20 Fixed effects summary estimates can be found in Table S5, Supplementary Information.  
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**Table 2 Summary of selected epidemiological studies investigating practice of anal intercourse amongst heterosexual populations published in the last 10 years.**

Study	Population	Age (years)	Sample size	% reporting AI	Exposure period
<b>Industrialised countries</b>					
Pollack, unpublished data 1999, from 1992 National AIDS Behavioral Methodology Study <sup>4,5</sup>	US population survey, women	18-49	1071	6.1%	Past 6 months
Laumann et al 1994 (74) <sup>4</sup>	US population survey	18-59	3432	23%	Ever
				10% men	Past year
				9% women	Past year
				2.3% men	Last sex
				1.2% women	Last sex
		50-54		3% men	Past year
				2% women	Past year
		25-29		2.4% women	Last sex
Gross et al 2000 (60)	US HIV negative women "at high risk of HIV infection"	11% 18-25 38% 26-35 51% ≥36	1268	32%	Past 6 months
Baldwin et al 2000 (57)	US random sample of sexually experienced university students (oversampling ethnic groups)	Mean 21, all <30	647	23%	Ever

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Study	Population	Age (years)	Sample size	% reporting AI	Exposure period
Johnson et al 2001 (64)	UK population-based survey (NATSAL)	16-44	11,161 <sup>3</sup>	7.0% men 6.5% women	Past year (1990)
				12.3% men 11.3% women	Past year (2000)
Friedman et al 2001 (58)	US women, inner city minority neighbourhood	18-24	202	14%	Past year
Flannery et al 2003 (75)	US sexually experienced female college students 1993-2000	NR	761	32%	Ever
Leichliter et al 2007 (61)	US general population survey	15-44	12,571	30% women 34% men	Ever
Houston et al 2007 (76)	US inner city adolescent, sexually experienced females	12-18	350	16% main partners 12% casual partners	Past 3 months
Tian et al 2008 (77)	US STD clinic attendees	15-39	2357	18.3% 39.3%	Past 3 months Past year
<b>Developing countries</b>					
Karim & Ramjee 1998 (78)	South Africa FSW surveyed at truck stops	Mean 24	145	43% with clients	Ever
Matasha et al 1998 (79)	Tanzania cohort of sexually experienced male and female school pupils	Median 15, 12-20	661	6%	First sexual experience <sup>1</sup>
Sallah et al 1999 (80)	Togo female college students	20-29	817	9% 37.8%	Likely currently <sup>2</sup> Likely ever <sup>2</sup>
Fonck et al 2000 (81)	Kenya FSW cohort	Mean 32	318	14%	Likely ever <sup>2</sup>

Study	Population	Age (years)	Sample size	% reporting AI	Exposure period
Ramjee & Gouws 2002 (82)	South Africa truck drivers	Mean 37, 18-71	184	42%	Likely ever <sup>2</sup>
Ferguson & Morris 2003 (83)	Kenya FSW cohort	NR	339	20%	Ever
Lane et al 2006 (84)	South Africa national survey of adolescent sexual behaviours, sexually active respondents	15-24	~7976	5.3% women 5.5% men	Ever
Schwant et al 2006 (85)	Kenya FSW cohort	Mean 35, 15-63	147	40.8%	Ever
Skoler-Karpoff et al 2008 (70)	South Africa, baseline characteristics from a microbicide RCT, sexually active, HIV-negative women	≥16 (4% 16-17, 33% 18-24, 63% ≥25)	6202	2% <sup>6</sup>	Past 3 months
Subramanian et al 2008 (86)	India, survey of clients of FSW	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
Munro et al 2008 (87)	India, community based survey	Mean 30, 15-49	4653	2.6% <sup>7,8</sup> men 0.3% <sup>8</sup> women	Ever
Kalichman et al 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

Abbreviations: aOR – adjusted odds ratio; FSW – female sex worker; NATSAL – National Survey of Sexual Attitudes and Lifestyles; NR – not recorded; STD – sexually transmitted disease.

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<sup>1</sup> Authors 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 orogenital and anal sex".

<sup>2</sup> Not specified in the publication.

<sup>3</sup> Total completing NATSAL 2000 questionnaire, including non-heterosexuals (% reporting AI is for heterosexual practices only).

<sup>4</sup> Results taken from review by Halperin 1999 (6).

<sup>5</sup> Lance M. Pollack personal communication, September 1999 to D. Halperin (6).

<sup>6</sup> Unprotected AI only.

<sup>7</sup> A further 0.6% of men reported ever having had AI with another man.

<sup>8</sup> Seventeen (0.8%) of men and 68 (2.3%) of women reported not knowing if they had ever experienced AI. None of these men were HIV positive, but among women, 'not knowing' was significantly associated with HIV infection, compared to the group of women reporting no AI experience.

For Review Only

## HIV infectiousness through anal intercourse: Supplementary Information

*Baggaley et al.*

### Supplementary methods

#### Search strategy

The literature search to September 6<sup>th</sup> 2008 was conducted in three stages. First, PubMed, Science Direct and NLM Gateway online databases were searched to September 2006 using search terms: "HIV transmission probability" OR "HIV transmission probabilities" OR "HIV infectivity" OR "HIV infectiousness" NOT "perinatal" NOT "mother to child" NOT "mother-to-child" and by replacing "HIV" by the terms, "LAV", "HTLV-III" and "HTLV III". PubMed was searched by titles. Science Direct and NLM Gateway were searched by abstracts, titles, keywords and authors. The PubMed search was updated twice (to June 29<sup>th</sup> 2007, and again to September 6<sup>th</sup> 2008) using more efficient search terms and Boolean operators, for matches under any field: (HIV OR LAV OR HTLV III OR HTLV-III OR AIDS OR human immunodeficiency virus OR human T-lymphotropic virus III OR acquired immunodeficiency) AND (infectiousness OR infectivity OR probability OR contact OR contacts OR partner OR partners OR wives OR spouses OR husbands OR couples OR discordant OR (transmission AND (heterosexual OR homosexual OR risk OR female OR male OR anal))). Titles were evaluated and obviously irrelevant publications discarded. Potentially relevant publications' abstracts were evaluated, where they were available on the online database. Obviously irrelevant publications were again discarded and all other manuscripts were retrieved as pdfs or paper copies for evaluation. Bibliographies of relevant articles were checked and experts in the field were contacted in order to identify additional relevant publications. One contacted author provided additional information.

#### Intervention impact: HAART

We assessed the potential reduction in HIV infectivity caused by HAART reducing viral load, using two published functions of infectivity by viral load.(17-21) We assume that successful HAART reduces blood viral load from an average, baseline  $V_0$  to  $V_1$  copies/ml.

Function 1 was based on results from the Rakai study of HIV transmission in heterosexual couples (presumed through vaginal intercourse (VI) transmission)(22) and assumes a linear relationship

between infectiousness and log serum viral load (17-20): each ten-fold increment in viral load is associated with a 2.45-fold increase in the risk of HIV transmission per-act.

$$\beta_{c,v,1} = 2.45^{\log_{10}(V_1/V_0)} \beta_{c,v,0} \quad (3)$$

where  $\beta_{c,v,0}$  and  $\beta_{c,v,1}$  are the probabilities of VI HIV transmission with viral loads  $V_0$  and  $V_1$ , respectively.

Function 2 was based on data from a Zambian cohort of discordant couples(23) 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) The rate of HIV VI transmission (per-partner per year),  $\beta_{rate,v}(V)$ , is a function of viral load  $V$  and is defined as follows:(21)

$$\beta_{rate,v}(V) = \beta_{rate,v,max} V^k / [V^k + (V_{50})^k] \quad (4)$$

where  $\beta_{rate,v,max}$ , the maximum infection rate per annum, is 0.317 per year;  $V_{50}$ , the viral load at which infectiousness is half its maximum, is 13,938 copies/mL and  $k$ , the steepness of increase in infectiousness as a function of viral load, is 1.02.(21)

We translated transmission rates  $\beta_{rate,v}(V)$  to per-act  $\beta_{c,v}(V)$  using equation (1) from main text re-written as:

$$\beta_{c,v}(V) = 1 - (1 - \beta_{rate,v}(V))^{1/n} \quad (5)$$

where  $n$  represents unprotected sex acts/year for the Zambian population.

In the absence of data for anal intercourse (AI) transmission by viral load, we assumed that the relationships between infectiousness and viral load defined in equations (3) and (4) hold for AI as well as VI.(17) The increased infectiousness of AI relative to VI,  $g$ , can be defined as

$$g = \frac{\beta_{c,a}}{\beta_{c,v}}$$

where we assumed  $\beta_{c,v}$  is 0.3% (male-to-female estimate for developing countries from Boily et al(13))

and  $\beta_{c,a}$  from our meta-analysis (see Findings).

To estimate reduction in infectiousness with HAART we first estimate a “typical” infectiousness for untreated individuals by assuming a baseline viral load for index cases  $V_0$  of  $10^{4.5}$  HIV RNA copies/ml which falls to  $V_1$ , 10 copies/ml, with effective HAART, with treatment initiated before formation of the partnership (following Wilson et al(17)). For function 1, we assume that our meta-analysis  $\beta_{c,a}$  estimate represents infectiousness at  $10^{4.5}$  HIV RNA copies/ml and use this to derive  $\beta_{c,a}$  at 10 copies/ml using equation (3). For function 2, we derive  $n$  as 83 unprotected acts/year (7 acts/month) by using equation (5) and assuming  $\beta_{c,v}(10^{4.5})$  is 0.3%. Then, we can derive  $\beta_{c,v}(V)$  for all  $V$  and estimate  $\beta_{c,a}(V)$  as  $g\beta_{c,v}(V)$ . Therefore per-act URAI for viral load  $V_1$  is:  $\beta_{c,a}(V_1) = g \left( 1 - \left( 1 - \beta_{c,v}(V_1) \right)^{1/n} \right)$ .

To explore the impact of treatment failure (failure to suppress viral load) on cumulative HIV risk, we modify equation (2) as follows:

$$\beta_{p,all} = 1 - \left( 1 - \beta_{c,v}(V_1) \right)^{(1-h)(1-d)n} \left( 1 - \beta_{c,v}(V_1) \right)^{h(1-d)n} \left( 1 - \beta_{c,a}(V_r) \right)^{(1-h)dn} \left( 1 - \beta_{c,a}(V_r) \right)^{hdn} \quad (6)$$

where  $h$  is the proportion of time (or the proportion of sex acts if frequency of sex is constant over time) that an individual experiences treatment failure and  $V_r$  is the level of viral rebound.

## Figure legends

**Figure S1** Flowchart summarising the results of the search on HIV-1 transmission probabilities relating to anal intercourse sex up to September 6th 2008. UIAI – unprotected insertive anal intercourse; URAI – unprotected receptive anal intercourse.

**Figure S2** Relation between per-partner HIV risk estimates (cumulative probability of HIV transmission) stratified by number of sexual acts per partnership and the number of sexual acts with an HIV infected partner (assuming a per-act unprotected receptive anal intercourse risk of 1.4% (95%CI 0.2,2.5), the random effects summary estimate from our meta-analysis). Per-partner estimates from Seage et al (37) and Coates et al (31) are plotted as horizontal lines. Grey lines show the per-partner HIV risk by number of sexual acts predicted using the Bernoulli model (equation 1, main text) using the URAI per-act summary estimate (solid line) and 95%CI (dotted lines). The graph illustrates the discrepancy

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3 between per-act and per-partner estimates: per-act estimates underestimate HIV transmission risk for  
4 partnerships involving only a few sex acts, compared with per-partner estimates. They are likely to  
5 overestimate the risk for partnerships involving many (>100) sex acts.  
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11 **Figure S3** Penile-anal and penile-vaginal transmission probabilities by plasma viral load: a) HIV  
12 transmission rates per year and b) HIV transmission per-act. Penile-vaginal transmission rate estimates  
13 derived from Fraser et al(21) and penile-vaginal per-act and penile-anal estimates inferred using the  
14 functions described in the Methods section, main text.  
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21 **Figure S4** Comparison of functions 1 and 2 to derive infectiousness by viral load. Graphs show derived  
22 relationships for penile-vaginal HIV transmission rate per year. Function 2 uses the function given in  
23 equation (4), main text. Function 1 uses the function given in equation (3) main text but using rate rather  
24 than per-act of HIV transmission, where the HIV transmission rate at  $10^{4.5}$  log<sub>10</sub> copies/ml is set to be  
25 the same as that predicted using function 2. The observed transmission rates for viral load strata  
26 reported in Quinn et al(22) are also plotted. a) shows the deviation in predicted transmission rates at  
27 high viral loads; b) is the same graph on a smaller scale, showing the deviation in predicted  
28 transmission rates at low viral loads.  
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Table S1 Details of studies estimating transmission probabilities for anal intercourse

Study	Setting/Study design/Population/Date	Stage of HIV infection/other risk factors, uncontrolled cofactors	Transmission probability, % (x/n, 95% CI)
<b>PER ACT ESTIMATES</b>			
<b>URAI</b>			
DeGruttola et al 1989 (24)	US retrospective-partner (132 MSM – some infected, some uninfected – and 155 sexual partners from the previous 30 months). Binomial model fitted to data, assuming a constant risk of transmission throughout infection, but authors explored models allowing different infectivity levels across index cases. Uninfected as well as infected individuals were included as index cases in order to account within the model for HIV transmission events occurring outside the primary relationship.	<100% monogamy, 15% AIDS and 20% ARC amongst index cases, <1% condom use	<b>0.5-3.0</b> <sup>1</sup>
Leynaert et al 1998 (27)	European retrospective-partner (part of a prospective multi-centre study). 499 heterosexual couples; 359 with male index, of whom 20% engaged in AI. All data used to inform a probabilistic model to estimate per act infectivity for multiple types of intercourse at different stages of infection of index (but only URAI, no UIAI). 1987-1992, M-to-F transmission.	Contact partner had no other "risk factors for HIV other than sexual contacts with the index case"; 0% systematic condom use, history of STI in index or partner since 1980 among some couples.	<b>3.38</b> (NR/359, 1.85,4.91) <sup>2</sup>
Vittinghoff et al 1999 (25) <sup>3</sup>	US simple-prospective multi-centre study (1583 high risk MSM, followed for up to 18 months (total 2633 person-years) with at least one sexual contact with an HIV positive or unknown serostatus partner), 1992-1994. Modified Bernoulli regression model using data from men with complex patterns of exposure [multiple types of exposure (URAI, protected insertive AI, etc.)]. Regression of participants with multiple exposures with multiple partners.	No IDU exposure. STI (NG, CT, urethritis) considered as covariates within the model. Information on index cases limited: partner reported sexual contacts as HIV positive, negative or unknown serostatus. Frequency of condom use reported and estimates adjusted accordingly.	<b>0.82</b> (0.24, 2.76) <sup>4</sup>
Halperin et al 2002 (abstract) (26) and S.C. Shiboski, personal communication 2003	US California Partner Study, recruited 1985-1986, M-to-F transmission, retrospective-partner study. Described in Padian et al 1987 (89): 59 male index cases and their female partners. Abstract does not report absolute transmission probabilities but the ratio of URAI to M-to-F penile-vaginal intercourse transmission probabilities: 10.3 (2.1, 51.3); further information provided through personal communication.	Adjusted for condom use, history of STI, IDU in males <sup>5</sup>	<b>0.4</b> (0.08,2.0)
<b>PER PARTNERSHIP ESTIMATES</b>			
<b>Combined URAI AND UIAI</b>			
Cheingsong-Popov et al 1984 (28)	UK retrospective-partner ,regular or casual sexual partners of AIDS or ARC patients (likely MSM but not explicitly stated) 1983-1984	AIDS and ARC No further information	<b>41.7</b> (15/36, 27.1-57.8)

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Study	Setting/Study design/Population/Date	Stage of HIV infection/other risk factors, uncontrolled cofactors	Transmission probability, % (x/n, 95% CI)	
Weller et al 1987 (30)	UK retrospective-partner, MSM, regular (≥6 months) sexual partners of AIDS patients, no date	51% AIDS, 49% ARC Partners of index cases were not monogamous Partnership duration: median 26 months and 30 months for seroconcordant and serodiscordant couples, respectively Cumulative incidence over 6 months: 0.0	60.0	(21/35, 43.6-74.4)
Goldsmith et al 1987 (32)	US retrospective-partner, MSM with sexual contact with HIV infected MSM <sup>6</sup> , 1981-1983	AIDS or ARC Partners of index cases were not monogamous (mean 396 and 278 lifetime male sexual partners for seroconverters and non-seroconverters, respectively) Partnership duration: 15 of 20 were long-term partnerships (2 months – 12 years); 5 were only 1 or 2 exposures, 9-13 months prior to study recruitment STI history (mean 4.5 and 2.5 episodes for seroconverters and non-seroconverters, respectively)	70.0	(14/20, 48.1-85.5)
Osmond et al 1988 (90)	US retrospective-partner (recruitment for a case-control study), sexual partners of MSM AIDS patients (at least 10 sexual contacts within 2 years of index case's AIDS diagnosis), 1983-1984	100% AIDS Partners of index cases were not monogamous Partnership duration: median 29 months (range: 2-221 months); 11% any condom use with index (0% had consistent condom use)	72.6	(85/117, 63.9-79.9)
Coates et al 1988 (31)	Canada retrospective-partner, healthy sexual contacts of MSM with AIDS or ARC (≥1 contact within 1 year of index's diagnosis), 1984-1985	51% AIDS and 49% ARC Partners were not monogamous Cumulative incidence over 3 months: 0.0	58.5	(144/246, 52.3-64.5)
Kaplan 1990 (35)	Using data from Grant et al 1987, simple-prospective (91) (see Table S2, excluded studies, for details)	Bernoulli model (alternative non-parametric model gave an estimate of 5.3, no 95% CI provided)	5.1	(2.2-8.0)
Giesecke et al 1992 (34) <sup>7</sup>	Sweden retrospective-partner, partner notification of all patients diagnosed in Sweden (heterosexuals and MSM) 1989-1990	MSM only	43.6	(17/39, 29.3-59.0)
Palenicek et al 1992 (36)	US prospective discordant-couple, sexual partners of MSM practicing URAI and/or UIAI during follow-up 1988-1990	0% AIDS at enrolment Not all partners were monogamous; duration of partnership ≥3 months (75% ≥3 years) UC: STI history, ART (20% ZDV) 20% URAI (without ejaculation), 70% UIAI Duration of follow-up: 1 year	0.0	(0/10, 0.0-27.8)
Seage et al 1993 (92)	US retrospective-partner, sexual partners of MSM 1985-1990	Partners of index cases were not monogamous	30.5	(57/187, 24.3-37.4)
Nicolosi et al 1994 (29)	Italy retrospective-partner, sexual partners of IDU, transfusion recipients, MSM, recruited from health clinics 1987-1991, combined male and female index cases	No IDU, transfusion or needle exposure, CSW contact, MSM, 100% monogamous. Some condom use, STI history. AI as frequency of sexual practice: often or always (≥50% intercourse)	42.9	(18/42, 29.1-57.8)
Porco et al 2004 (93)	US San Francisco Men's Health Study: simple-prospective, MSM 1994-1999	Used probabilistic risk model. Assumed constant HIV prevalence in MSM population in San Francisco between 1994 and 1999. Study participants had multiple partners and serostatus of partners was inferred using prevalence data. Aim of study is to prove a significant difference between infectivity in pre- and post-HAART eras, rather than obtain infectivity estimates per se. Estimate is infectiousness in absence of ART.	12.0	(5.3-18.7) <sup>8</sup>

Study	Setting/Study design/Population/Date	Stage of HIV infection/other risk factors, uncontrolled cofactors	Transmission probability, % (x/n, 95% CI)
<b>URAI</b>			
Coates et al 1988 (31) <sup>9</sup>	Canada retrospective-partner, healthy sexual contacts of MSM with AIDS or ARC ( $\geq 1$ contact within 1 year of index's diagnosis), 1984-1985	Not stated	<b>69.5</b> (114/164, 62.1-76.0)
Giesecke et al 1992 (34) <sup>7</sup>	Sweden retrospective-partner, partner notification of all patients diagnosed in Sweden (heterosexuals and MSM), 1989-1990	All (heterosexuals and MSM)	<b>36.2</b> (17/47, 24.0-50.5)
Samuel et al 1994 (39)	Using data from Grant et al 1987, simple-prospective (91) (see Table S2, excluded studies, for details)	Estimates based on a series of models with varying assumptions, including: timescale used, inclusion or exclusion of condom use and ejaculation, and whether the model type includes additional transmission risk from other routes i.e. UIAI and oro-genital sex. Model assumptions include: choice of partner is not affected by their infection status and infectivity is constant over time.	<b>~10</b> (range: 4.2-12.0)
Nicolosi et al 1994 (29)	Italy retrospective-partner, sexual partners of IDU, transfusion recipients, MSM, recruited from health clinics 1987-1991, male index cases	No IDU, transfusion or needle exposure, CSW contact, MSM, 100% monogamous. Some condom use, STI history. AI as frequency of sexual practice: often or always ( $\geq 50\%$ intercourse)	<b>46.4</b> (13/28, 29.5-64.2)
<b>UIAI</b>			
Coates et al 1988 (31) <sup>10</sup>	Canada retrospective-partner, healthy sexual contacts of MSM with AIDS or ARC ( $\geq 1$ contact within 1 year of index's diagnosis), 1984-1985	Not stated	<b>36.6</b> (30/82, 27.0-47.4)
Giesecke et al 1992 (34) <sup>7</sup>	Sweden retrospective-partner, partner notification of all patients diagnosed in Sweden (heterosexuals and MSM), 1989-1990	All (heterosexuals and MSM)	<b>18.4</b> (7/38, 9.2-33.4)
Samuel et al 1994 (39)	Using data from Grant et al 1987, simple-prospective (91) (see Table S2, excluded studies, for details)	Estimates based on a series of models with varying assumptions, including: timescale used, inclusion or exclusion of condom use and ejaculation, and whether the model type includes additional transmission risk from other routes i.e. UIAI and oro-genital sex. Model assumptions include: choice of partner is not affected by their infection status and infectivity is constant over time.	<b>0.15-1.5</b>
Nicolosi et al 1994 (29)	Italy retrospective-partner, sexual partners of IDU, transfusion recipients, MSM, recruited from health clinics 1987-1991, female index cases	No IDU, transfusion or needle exposure, CSW contact, MSM, 100% monogamous. Some condom use, STI history. AI as frequency of sexual practice: often or always ( $\geq 50\%$ intercourse)	<b>35.7</b> (5/14, 16.3-61.2)

ARC – AIDS-related complex; ART – antiretroviral therapy; CT – Chlamydia trachomatis; HAART – highly active antiretroviral therapy; MSM – men who have sex with men; M-to-F – male-to-female; NG – Neisseria gonorrhoea; NR – not recorded; PIAI – protected insertive anal intercourse; STI – sexually transmitted infection; UIAI – unprotected insertive anal intercourse; URAI – unprotected receptive anal intercourse; ZDV – zidovudine (AZT).

<sup>1</sup> Authors reported in the Discussion section that results of their model allowing the per act risk to vary between individuals implied an even broader range of risk of transmission than the 0.5-3.0% main result reported in the abstract: they state that, "50% of the partners of infected men have a sero-conversion risk per exposure of less than 0.02 [2%]; 10-20% of infected partners have a great than 0.10 [10%] risk of seroconversion per sexual exposure."

<sup>2</sup> 95%CI were derived from available information because it was not reported in the publication.

<sup>3</sup> Publication additionally provides estimates for protected receptive anal intercourse (0.18%, 95%CI 0.10-0.28) and unprotected (0.06%, 95%CI 0.02-0.19) and protected (0.04%, 95%CI 0.01-0.11) insertive anal intercourse, but these outcomes are per exposure "with an HIV infected or unknown serostatus partner" because there were too few such contacts with known infected partners to provide stable per act estimates and have therefore been excluded from the analysis.

<sup>4</sup> There were 7 seroconverters who had practised URA with a known HIV infected partner, with 564 URAI contacts. However the per act estimate was calculated using the entire dataset (which included 49 seroconverters) which took into account exposures of all types.

<sup>5</sup> Unadjusted per act URAI estimate reported as 0.6% (95%CI 0.1-2.0).

<sup>6</sup> The 20 partners were from only six index cases recruited for the study.

<sup>7</sup> Probabilities were independent of the duration of relationship.

<sup>8</sup> Derived from 3.4% standard error reported in the publication.

<sup>9</sup> Defined as sexual contacts that involve URAI.

<sup>10</sup> Defined as sexual contacts that do not involve URAI.

For Review Only

Table S2 Details of transmission probabilities for anal intercourse: excluded study estimates

Study	Setting	Transmission probability, %	Reason for exclusion
<b>Per act</b>			
May & Anderson 1987 (94)	-	~5	Inferred from data on doubling times of the HIV epidemic in various countries, duration of infection and sexual activity.
DeGruttola et al (abstract) 1988 (95)	33 couples	<b>2.01 – 5.37</b>	Abstract pre-1990; likely superseded by DeGruttola et al 1989 (24).
Ahlgren et al 1990 (96)	Model fitted to observed seroconversion curves using San Francisco hepatitis B vaccine trial cohort samples, 1978-1986. Ranges for estimates reflect the fitting of several models with different assumptions (e.g. for sexual behaviour) to the data. Models with heterogeneous infectivity by stage of infection were insensitive to changes in infectiousness during AIDS because of the relatively small proportion infected who had developed AIDS during 1978-1986; therefore the value 4.0% was chosen relatively arbitrarily.	<b>1.09-1.29</b> (all stages) <b>3.23-5.06</b> (early, pre-seroconversion) <b>0.00237-0.0578</b> (asymptomatic) <b>4.0</b> (AIDS)	HIV transmission mathematical modelling study which estimates per act infectivity by fitting the model to observed seroconversion curves, rather than an empirical study.
Eisenberg 1991 (97)	Not stated	<b>1.0</b>	Estimates were reported but not estimated in this study.
Jacquez et al 1994 (98)	Calculations of infectiousness by stage of HIV infection for use as input parameters for an HIV transmission model to investigate the contribution of primary HIV infection within MSM cohorts	<b>10-30</b> (primary stage) <b>0.01-0.1</b> (asymptomatic stage) <b>0.1-1.0</b> (symptomatic stage)	Based on a literature review of transmission probabilities together with estimates of the basic reproductive number for HIV and numbers of sexual contacts for various settings (US and Thailand)
Rapatski et al 2005 (99)	US retrospective cohort, M-to-F transmission through URAI; analysis of San Francisco City Clinics Cohort (SFCCC) data	<b>2.4</b> (primary stage) <b>0.2</b> (asymptomatic stage) <b>29.9</b> (symptomatic stage)	HIV transmission mathematical modelling study which estimates per act infectivity by fitting the model to the epidemic curve, rather than an empirical study.
<b>Per partner</b>			
Gazzard et al 1984 (14)	UK cross-sectional (MSM, sexual partners of AIDS/ARC patients) 1980-1984	<b>60.7</b> (17/28, 42.4-76.4)	Description of a clustering of cases; HIV positive patients identified by clinical symptoms only rather than laboratory test.
Weber et al 1986 (100)	UK cross-sectional (MSM, sexual (AI) partners of AIDS patients – ≥4 contacts in the 2 years preceding AIDS diagnosis of index, casual partners excluded)	<b>59.3</b> (32/54, 46.0-71.3)	Matched case-control study – recruitment bias by serostatus of partner.
Grant et al 1987 (91)	US San Francisco Men's Health Study: simple-prospective, MSM 1984-1986 Estimates calculated using mathematical modelling, with a number of assumptions including constant infectiousness over duration of infection.	<b>10.2</b> (4.3-16.0, assuming proportionate (random) mixing) <b>8.0</b> (3.4-12.6, assuming assortative mixing by sexual activity class)	Analysis superseded by other model analyses for Combined URAI and UIAI (35) and separate URAI and UIAI (39) estimates.

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Study	Setting	Transmission probability, %	Reason for exclusion
Ozturk et al 1987 (101)	US cross-sectional (MSM, sexual partners of AIDS patients)	75.0 (6/8, 40.9-92.9)	Sample size <10.
Flateby et al 1996 (15)	Norway, cross-sectional, MSM attending HIV clinics, asked about HIV status of steady partner 1988-1992	58.3 (14/24, 95% CI 38.8-75.5)	No follow-up of partner – data on serostatus ascertained from questionnaire of "index" only.

MSM – Men who have sex with men; M-to-F – male-to-female HIV transmission.

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**Table S3 Heterosexual per-partner transmission probabilities: stratified by unprotected anal intercourse exposure**

Study	Study design/Direction of transmission	Risk categories	Transmission probability, % (x/n, 95% CI)	
Goedert et al 1987 (102)	Cross-sectional, M-to-F	Ever	<b>0.0</b>	(0/4, 0.0-49.0)
		Never	<b>20.0</b>	(4/20, 8.1-41.6)
Johnson et al 1989 (103)	Cross-sectional, M-to-F	Ever	<b>31.3</b>	(5/16, 14.2-55.6)
		Never	<b>16.1</b>	(10/62, 9.0-27.2)
European Study Group 1992 (46)	Cross-sectional, combined M-to-F and F-to-M	At least once (M-to-F)	<b>45.7</b>	(42/92, 35.9-55.8)
		At least once (F-to-M)	<b>14.6</b>	(7/48, 7.2-27.2)
		At least once (combined)	<b>35.0</b>	(49/140, 27.6-43.2)
		Never (M-to-F)	<b>13.6</b>	(40/295, 10.1-17.9)
		Never (F-to-M)	<b>11.8</b>	(12/102, 6.9-19.4)
		Never (combined)	<b>13.1</b>	(52/397, 10.1-16.8)
Seidlin et al 1993 (48)	Cross-sectional, combined M-to-F and F-to-M	Ever (M-to-F)	<b>66.0</b>	(33/50, 52.2-77.6)
		Ever (F-to-M)	<b>66.7</b>	(4/6, 30.0-90.3)
		Ever <sup>1</sup> (combined)	<b>66.1</b>	(37/56, 53.0-77.1)
		Never (M-to-F)	<b>43.5</b>	(40/92, 33.8-53.7)
		Never (F-to-M)	<b>60.0</b>	(3/5, 23.1-88.2)
		Never (combined)	<b>44.3</b>	(43/97, 34.8-54.2)
Nicolosi et al 1994 (29)	Cross-sectional, combined M-to-F and F-to-M	Often or always (≥50% intercourse) (M-to-F)	<b>46.4</b>	(13/28, 29.5-64.2)
		Often or always (≥50% intercourse) (F-to-M)	<b>35.7</b>	(5/14, 16.3-61.2)
		Often or always (≥50% intercourse) (combined)	<b>42.9</b>	(18/42, 29.1-57.8)
		Sometimes (<50% intercourse) (M-to-F)	<b>48.9</b>	(45/92, 38.9-59.0)
		Sometimes (<50% intercourse) (F-to-M)	<b>13.2</b>	(5/38, 5.8-27.3)
		Sometimes (<50% intercourse) (combined)	<b>38.5</b>	(50/130, 30.5-47.0)
		Never (M-to-F)	<b>27.1</b>	(82/303, 22.4-32.3)
		Never (F-to-M)	<b>7.6</b>	(11/144, 4.3-13.2)
De Vincenzi 1994 (104)	Prospective, M-to-F (cumulative risk estimates)	Ever during follow-up	<b>25.0</b>	(2/8, 7.1-59.1)
		Never during follow-up	<b>9.2</b>	(6/65, 4.3-18.7)
Guimaraes et al 1995 (105)	Cross-sectional, M-to-F	Ever	<b>69.8</b>	(44/63, 57.6-79.8)
		Never	<b>34.0</b>	(48/141, 26.7-42.2)
Nagachinta et al 1997 (106)	Cross-sectional, M-to-F	Past 2 years: yes	<b>26.7</b>	(4/15, 10.9-52.0)
		no	<b>47.0</b>	(182/387, 42.1-52.0)
Padian et al 1997 (107)	Cross-sectional, M-to-F	Yes <sup>2</sup>	<b>30.4</b>	(35/115, 22.8-39.4)
Panda et al 2000 (108)	Cross-sectional, M-to-F	Yes <sup>2</sup>	<b>60.0</b>	(6/10, 31.3-83.2)
		No	<b>43.7</b>	(66/151, 36.1-51.7)

F-to-M – female-to-male HIV transmission; M-to-F – male-to-female HIV transmission.

<sup>1</sup> Median number of episodes of anal intercourse = 17 (range: 1-1650).

<sup>2</sup> Frequency of this practice within the partnership not specified.

**Table S4 Details of transmission probabilities for anal intercourse: stratified by different risk categories**

Study	Risk categories	Transmission probability, % (x/n, 95% CI)	
<b>PER ACT ESTIMATES</b>			
Leynaert et al 1998 (27)	Primary Infection (first 3 months)	18.35	(2.08,34.6)
	Incubation (CD4 $\geq$ 200/mm <sup>3</sup> )	1.38	(0.00,3.38)
	AIDS (CD4 <200/mm <sup>3</sup> )	18.35	(2.08,34.6)
<b>PER PARTNER ESTIMATES</b>			
<b>HIV disease stage</b>			
Osmond et al 1988 (90)	Sexual contact ended before index's AIDS diagnosis	66.7	(46/69, 54.9-76.6)
	Sexual contact continued after index's AIDS diagnosis	81.3	(39/48, 68.1-89.8)
	Sexual contact ended before index's AIDS diagnosis:		
	RAI usual with index: no	59.4	(19/32, 42.3-74.5)
	yes	73.0	(27/37, 57.0-84.6)
	Sexual contact continued after index's AIDS diagnosis:		
	RAI usual with index: no	62.5	(15/24, 42.7-78.8)
	yes	100.0	(24/24, 86.2-100.0)
Giesecke et al 1992 (34)	Combined: asymptomatic	35.7	(10/28, 20.7-54.2)
	symptomatic	63.6	(7/11, 35.4-84.8)
	URAI: asymptomatic	34.9	(15/43, 22.4-49.8)
	symptomatic	50.0	(2/4, 15.0-85.0)
	UIAI: asymptomatic	13.3	(4/30, 5.3-29.7)
	symptomatic	37.5	(3/8, 13.7-69.4)
<b>Contact frequency</b>			
Weller et al 1987 (30)	Transmission by frequency of RAI: < once/month	26.7	(4/15, 10.9-52.0)
	> once/month	80.0	(16/20, 58.4-91.9)
Osmond et al 1988 (90)	RAI usual with index: no	73.9	(34/46, 59.7-84.4)
	yes	83.6	(51/61, 72.4-90.8)
<b>STI history</b>			
Seage et al 1993 (92)	History of NG or TP	51.2	(22/43, 36.8-65.4)
	No history	24.3	(35/144, 18.0-31.9)
<b>Number of sexual contacts</b>			
Seage et al 1993 (92)	Frequency of URAI with index:		
	1-4	25.0	(3/12, 8.9-53.2)
	5-50	28.0	(14/50, 17.5-41.7)
	$\geq$ 51	32.0	(40/125, 24.5-40.6)
Coates et al 1988 (31)	Number of "sexual encounters" with index:		
	1	47.4	(18/38, 32.5-62.7)
	2-4	54.9	(39/71, 43.4-66.0)
	5-50	61.1	(33/54, 47.8-73.0)
	$\geq$ 51	65.1	(54/83, 54.3-74.4)
<b>Duration of partnership</b>			
Seage et al 1993 (92)	1 month	22.9	(11/48, 13.3-36.5)
	2-6 months	29.6	(8/27, 15.9-48.5)
	7-12 months	33.3	(12/36, 20.2-49.7)
	13-24 months	42.9	(6/14, 21.4-67.4)
	25-36 months	20.0	(5/25, 8.9-39.1)
	$\geq$ 37 months	38.9	(14/36, 24.8-55.1)
<b>Age of partner</b>			
Seage et al 1993 (92)	Age of partner: 18-24 years	28.6	(4/14, 11.7-54.6)
	25-29 years	33.3	(15/45, 21.4-47.9)
	30-34 years	38.0	(19/50, 25.9-51.8)
	$\geq$ 35 years	23.4	(18/77, 15.3-34.0)

MSM – men who have sex with men; NG – Neisseria gonorrhoea; RAI – receptive anal intercourse; TP – Treponema pallidum (syphilis); UIAI – unprotected insertive anal intercourse; URAI – unprotected receptive anal intercourse.

**Table S5 Summary transmission probability estimates for anal intercourse: meta-analyses results**

Estimate type		Median (%)	Min (%)	Max (%)	Summary estimate		Q	p	N	References
					Fixed effects estimate, % (95%CI)	Random effects estimate, % (95%CI)				
Per-act	URAI	1.0	0.4	3.4	1.1 (0.5-1.7)	1.4 (0.2-2.5)	10.8	.013	4	(24-27)
Per-partner	Combined URAI UIAI	42.9	0.0	72.6	22.9 (20.8-25.0)	39.9 (22.5-57.4)	497.1	<.001	11	(28-38)
	Crude	43.6	0.0	72.6	50.7 (47.2-54.1)	48.1 (35.3-60.8)	91.0	<.001	9	(28-34, 36, 37)
	Adjusted	8.6	5.1	12.0	6.2 (3.5-8.9)	7.9 (1.2-14.5)	3.5	.063	2	(35, 38)
Per-partner	URAI	41.3	10.0	69.5	34.9 (30.7-39.0)	40.4 (6.0-74.9)	164.9	<.001	4	(29, 31, 34, 39)
	Crude	46.4	36.2	69.5	60.9 (55.0-66.8)	51.4 (28.1-74.7)	20.5	<.001	3	(29, 31, 34)
	Adjusted	10.0	-	-	10.0 (4.2-15.8)	10.0 (4.2-15.8)	-	-	1	(39)
Per-partner	UIAI	27.1	0.7	36.6	0.9 (0.2-1.6)	21.7 (0.2-43.3)	60.6	<.001	4	(29, 31, 34, 39)
	Crude	35.7	18.4	36.6	29.6 (22.0-37.2)	29.4 (16.0-42.9)	5.1	.077	3	(29, 31, 34)
	Adjusted	0.7	-	-	0.7 (0.0-1.3)	0.7 (0.0-1.3)	-	-	1	(39)

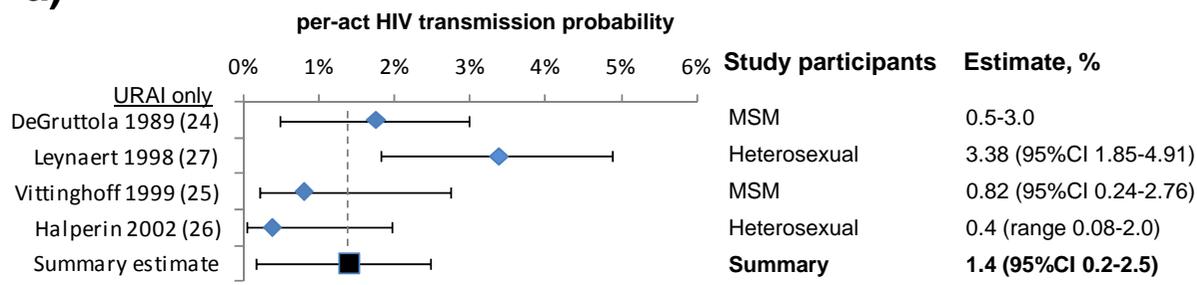
N – number of study estimates; p – p-value; Q – heterogeneity statistic; UIAI – unprotected insertive anal intercourse; URAI – unprotected receptive anal intercourse.

Crude estimates: estimates calculated through simple derivation as number of seroconversions out of number of sexual acts involving exposure.

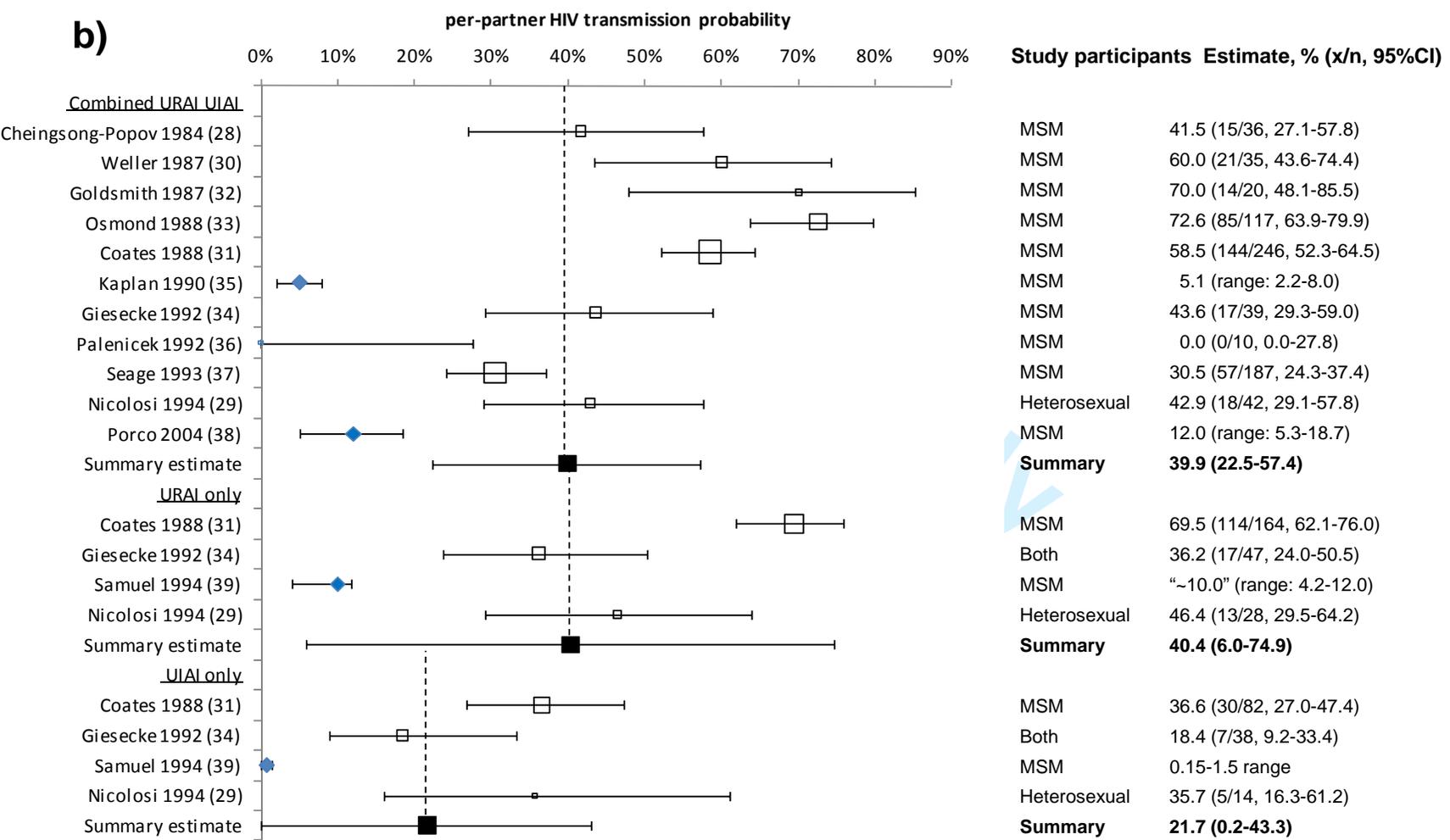
Adjusted estimates: estimates derived using more sophisticated calculation of transmission probability.

# Figure 1

a)

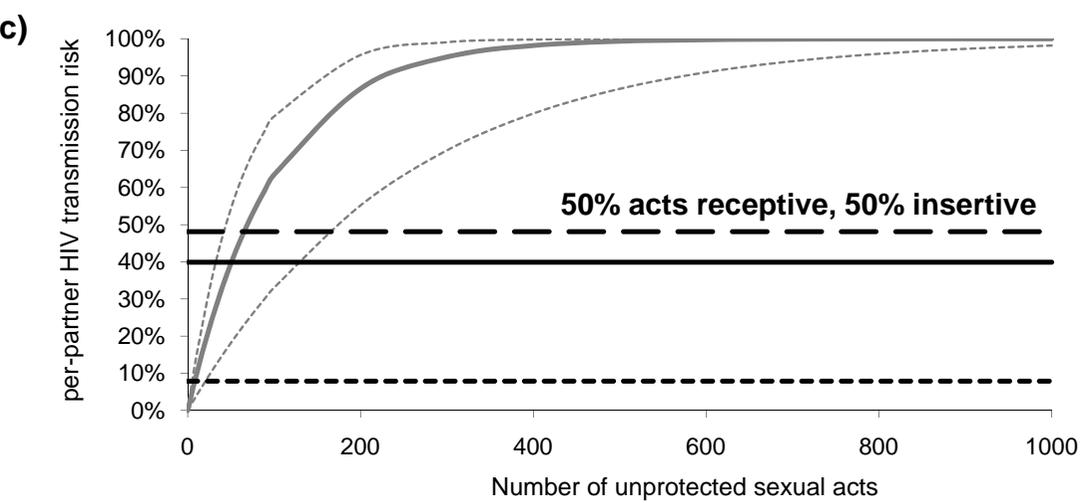
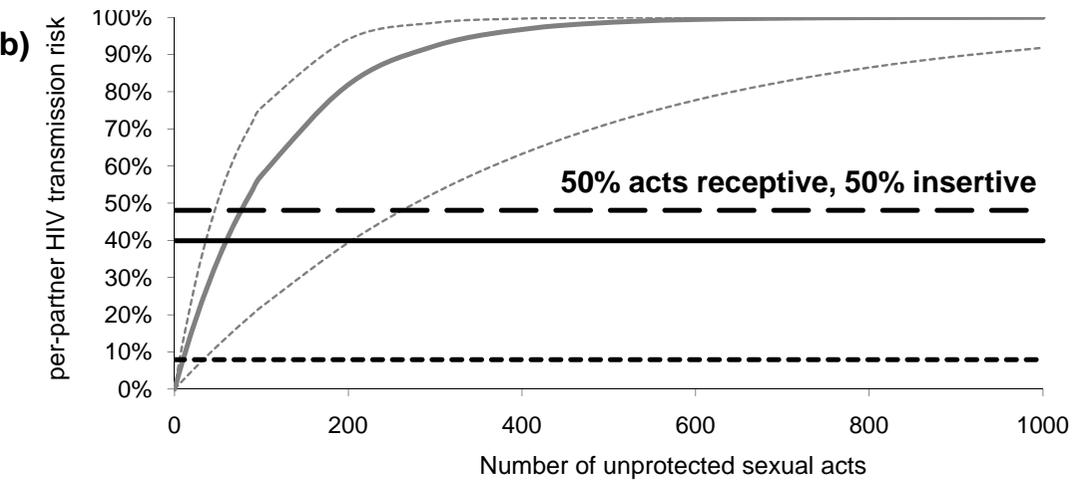
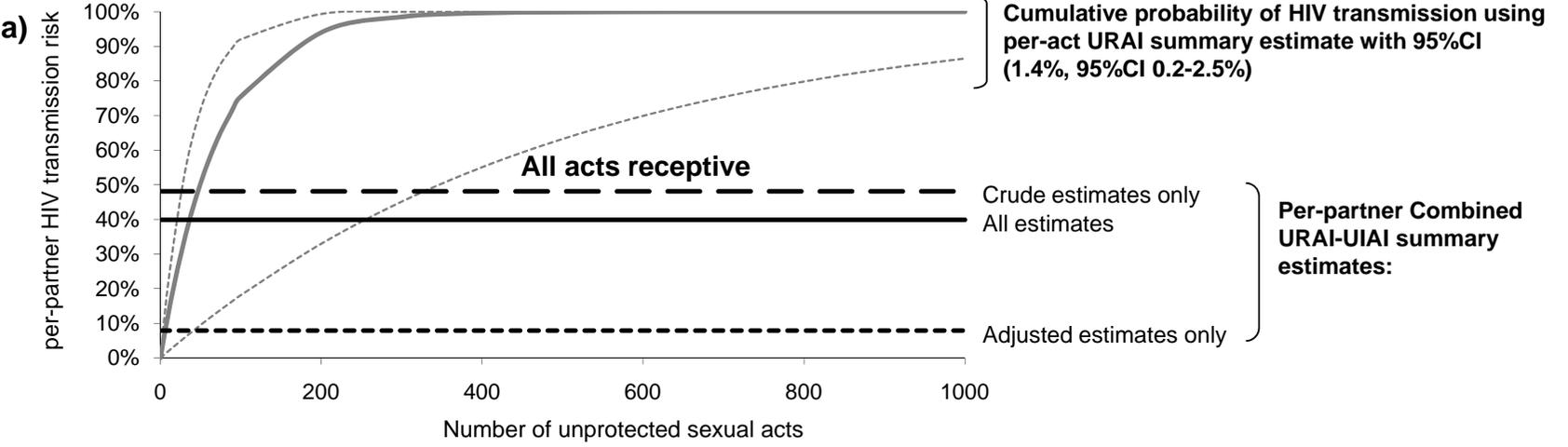


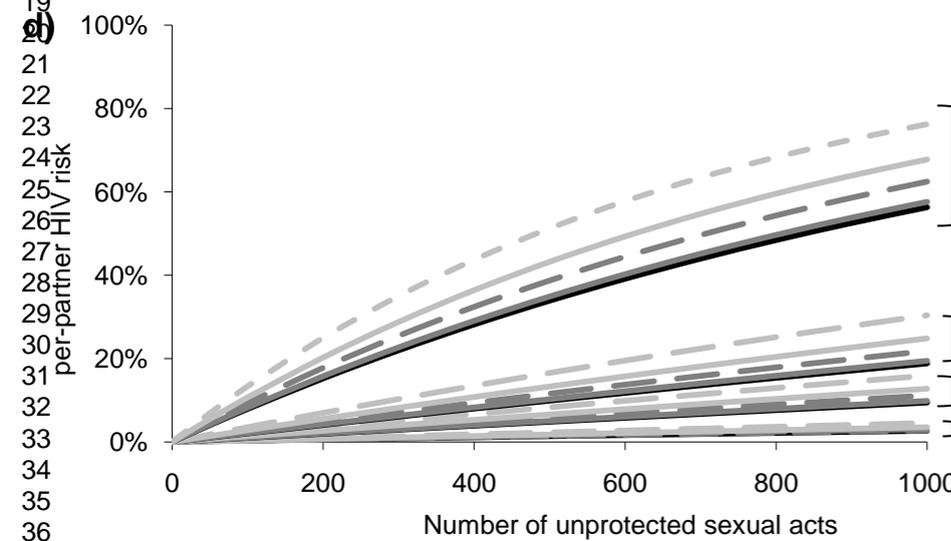
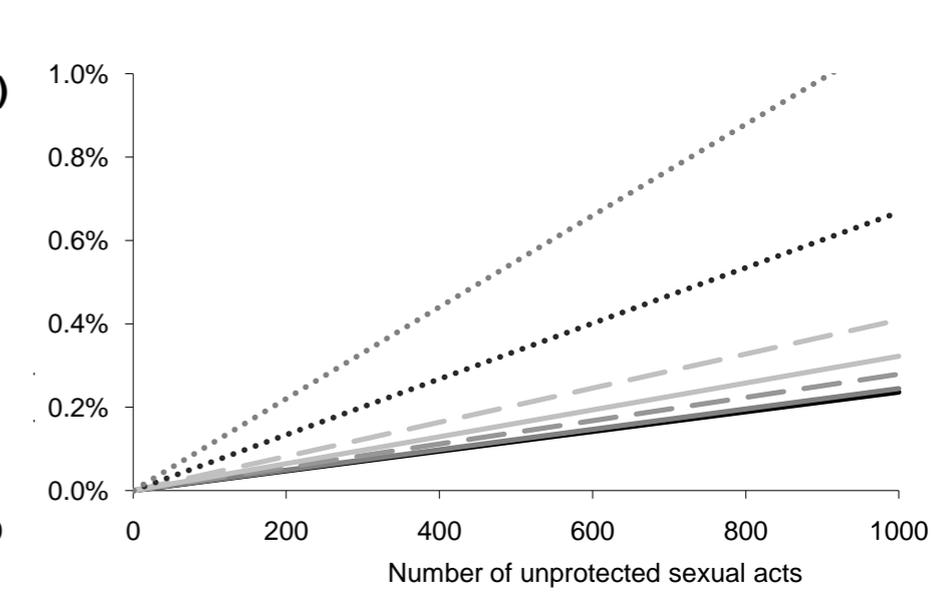
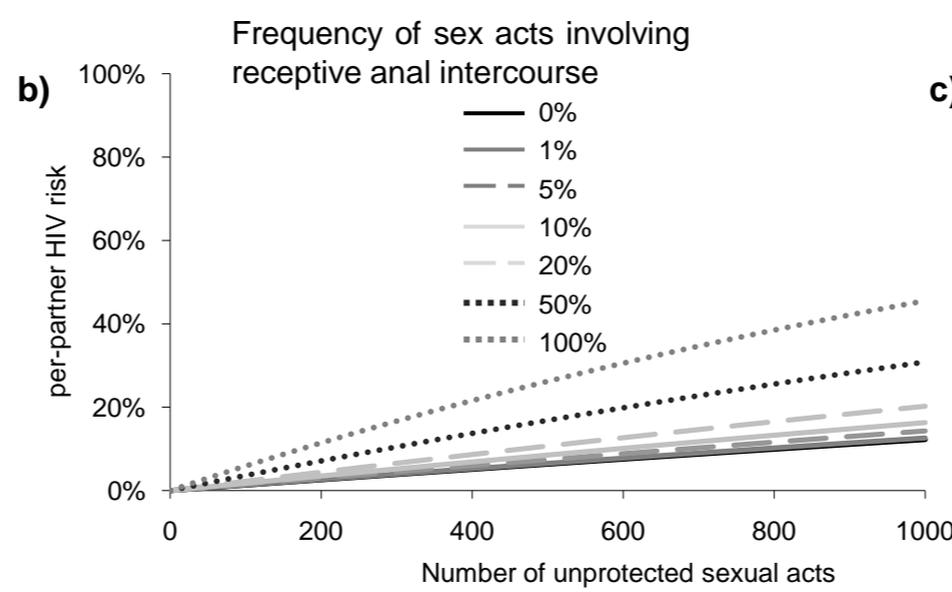
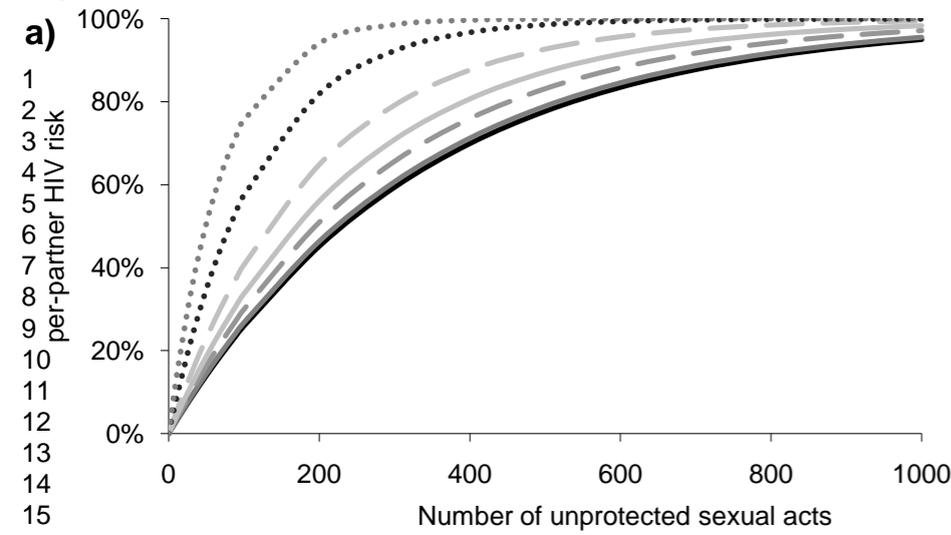
b)



◆ Adjusted estimate  
 □ Crude estimate based on x number of seroconverting partners among n couples with an infected index partner  
 ■ Summary estimate

**Figure 2**



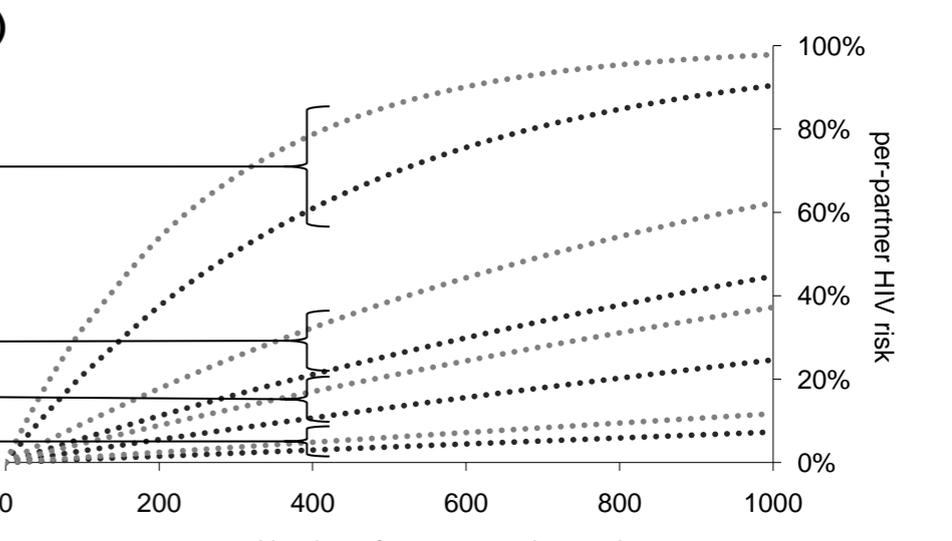


Time with viral rebound: 80%, rebound to 5000 copies/ml

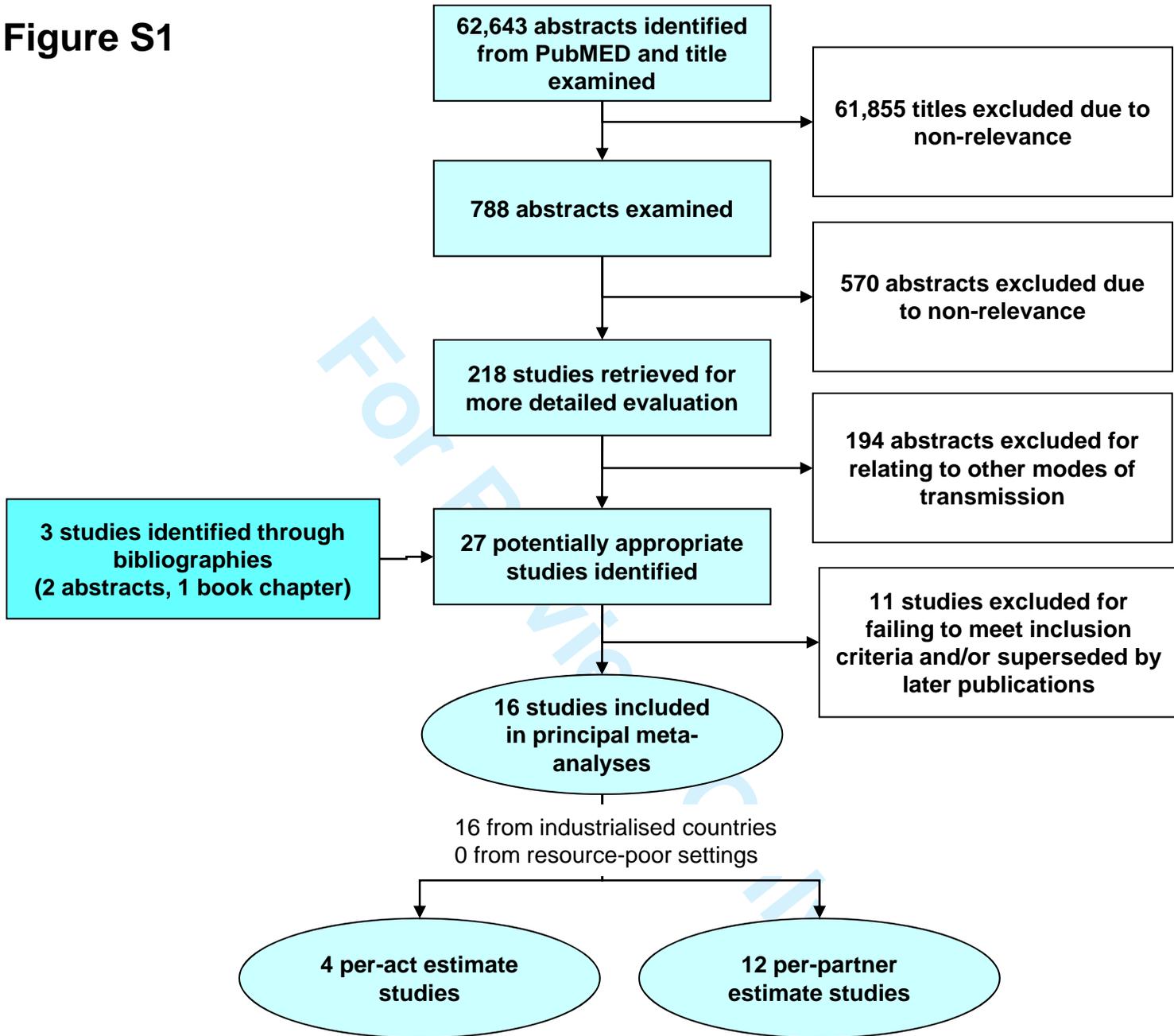
Time with viral rebound: 20%, rebound to 5000 copies/ml

Time with viral rebound: 80%, rebound to 500 copies/ml

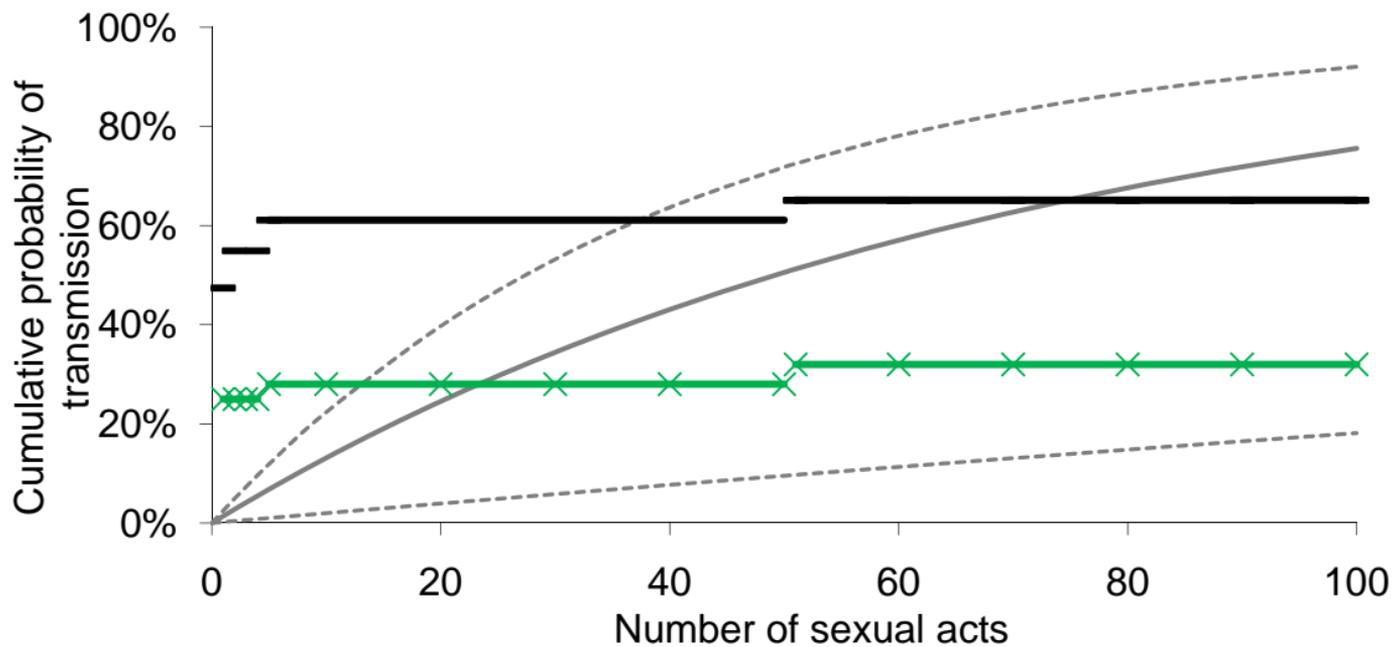
Time with viral rebound: 20%, rebound to 500 copies/ml



# Figure S1



	MSM	Heterosexual	MSM	Heterosexual	Mixed
Combined URAI UIAI	0	0	10	1	0
URAI	2	2	2	1	1
UIAI	0	0	2	1	1
Stratifying by risk factors	0	1	5	0	0



— Per-act URAI summary estimate (1.4%)

--- Per-act URAI 95%CI (0.2-2.5%), two lines on figure

Per-partner estimates stratified by number of sexual contacts:

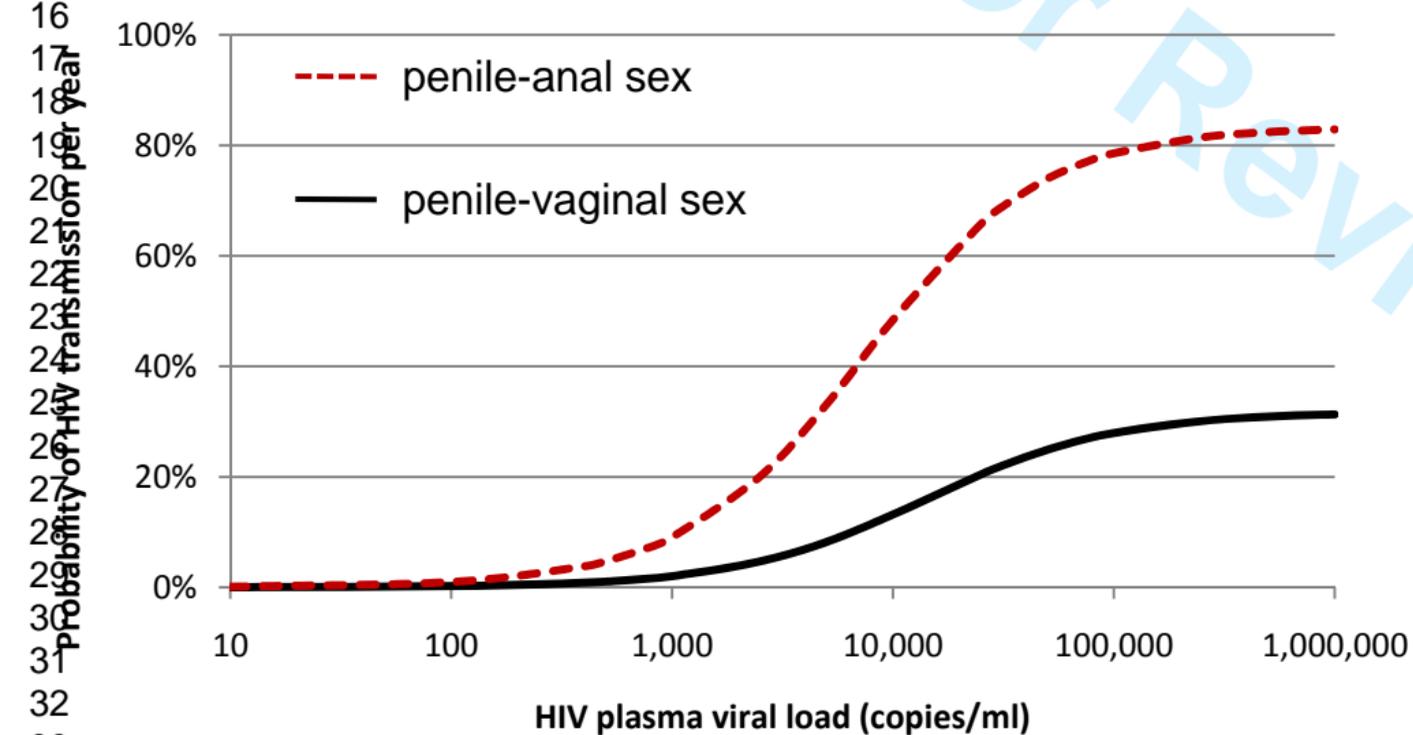
— Coates et al (31)

—\* Seage et al (37)

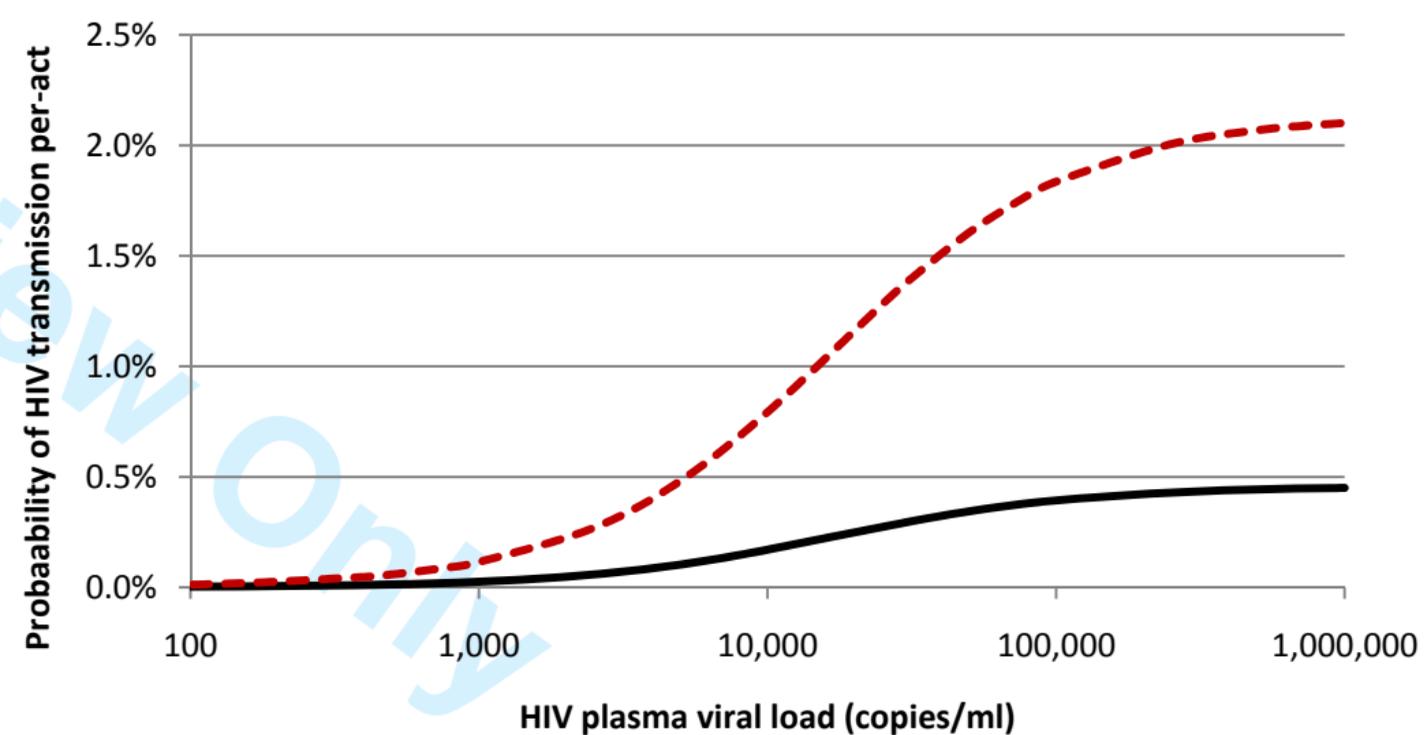
**Figure S2**

11 **Figure S3**

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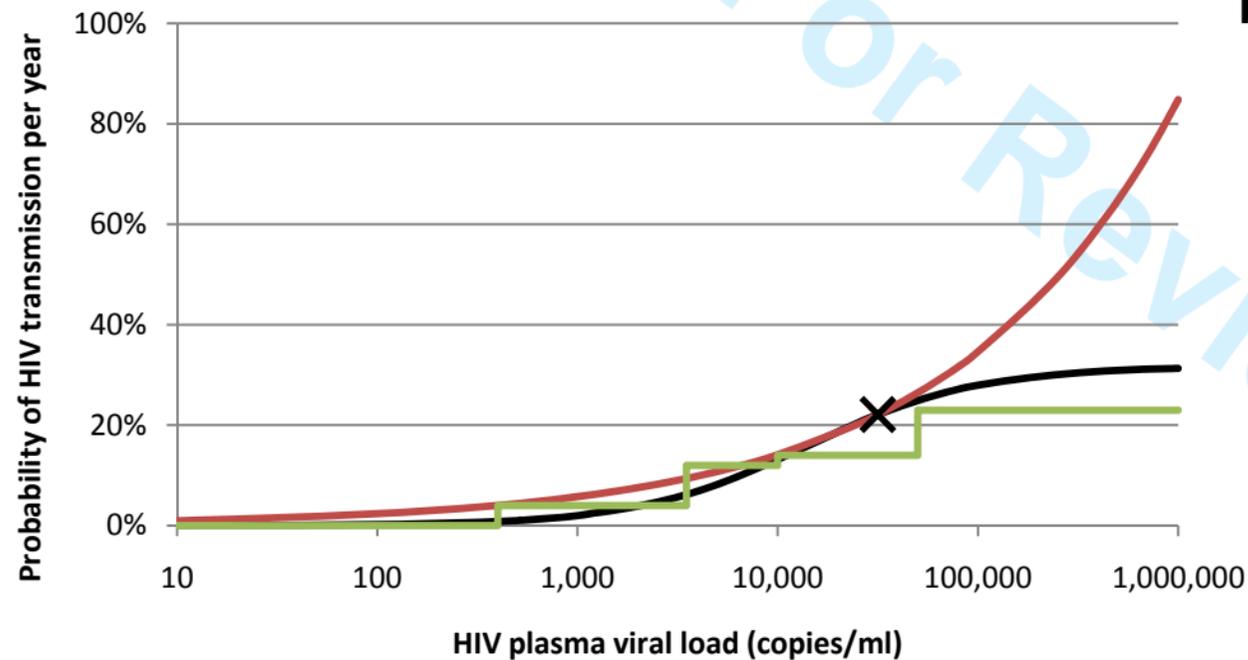


b)

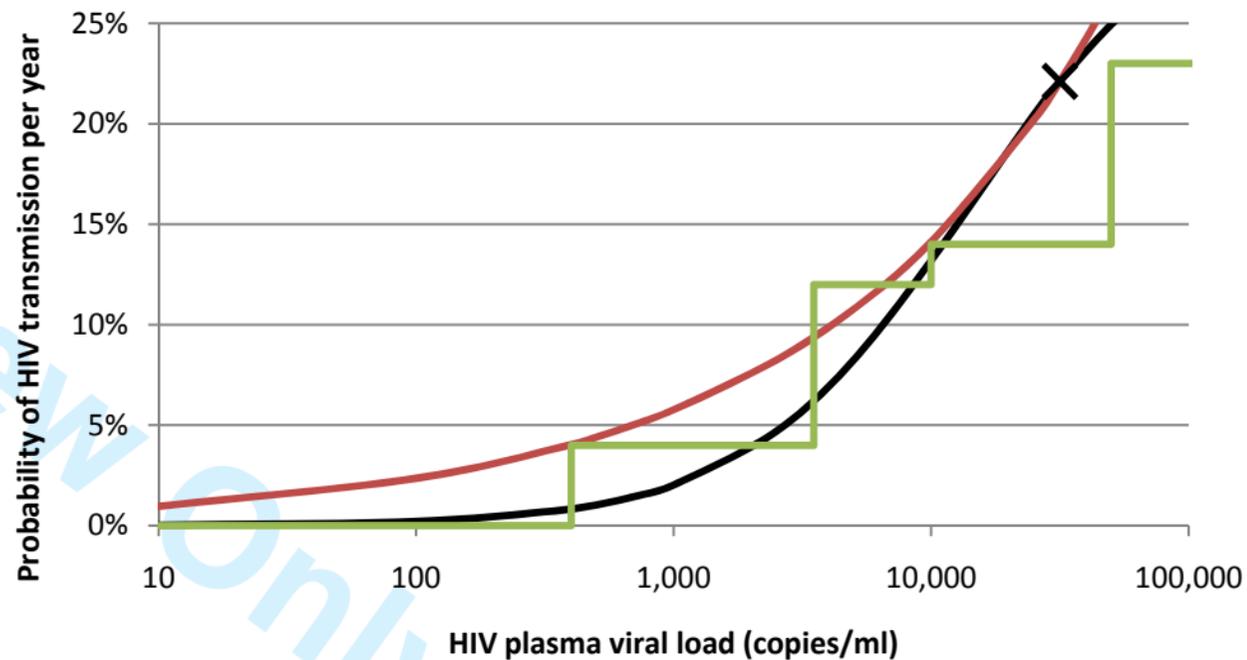


11 **Figure S4**

12  
13  
14 **a)**



14 **b)**



31 — Method 1

32 — Transmission rates reported in Quinn et al (22)

33 — Method 2

34 X  $10^{4.5}$  HIV RNA copies/ml – assumed baseline viral load used for Method 1 calculations

35