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Heterosexual risk of HIV-1 infection per sexual act: a systematic review and meta-analysis of observational studies

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Abstract

We conducted a systematic review and meta-analysis of observational studies of the risk of HIV-1 transmission per heterosexual contact. The search to September 2008 identified 43 publications based on 25 different study populations. Pooled female-to-male (0·0004,95%CI=0·0001-0·0014) and male-to-female (0·0008,CI=0·0006-0·0011) transmission estimates in developed countries reflected a low risk of infection in the absence of antiretrovirals. Developing country female-to-male (0·0038,CI=0·0013-0·0110) and male-to-female (0·0030,CI=0·0014-0·0063) estimates in absence of commercial sex(CS) work were higher. In meta-regression analysis, the infectivity across estimates in absence of CS work was significantly associated with gender, setting, the interaction between setting and gender and HIV prevalence. The pooled receptive anal intercourse estimate was much higher (0·017,CI=0·003-0·089). Estimates for the early and late phase of HIV infection were 9·2(CI=4·5-18·8) and 7·3(CI=4·5-11·9)-fold larger than for the asymptomatic phase, respectively. After adjusting for CS exposure, presence or history of genital ulcers in either couple member increased per-act infectivity 5·3(CI=1·4-19·5)-fold compared to no sexually transmitted infection. Study estimates among non-circumcised men were at least twice those among circumcised men. Developing country estimates were more heterogeneous than developed country

Conflicts of interest

None

estimates, which indicates poorer study quality, greater heterogeneity in risk factors or under-reporting of high-risk behaviour. Efforts are needed to better understand these differences and quantify infectivity in developing countries.

INTRODUCTION

Since the beginning of the HIV epidemic, mother-to-child transmission and iatrogenic transmission through contaminated blood products and unsafe injections have decreased due to improved health procedures and treatment options, especially in developed countries[1-5]. However, the notion that different patterns of sexual behaviours and/or biological factors such as male circumcision and genital ulcer disease (GUD) can explain worldwide differences in heterosexual epidemic size has recently been questioned[6-9]. Some believe that sexual transmission has been overestimated, while iatrogenic transmission has been underestimated[10-12]. Quantifying the risk of HIV infection following sexual intercourse with an infected partner is important to better understand the epidemiology of HIV infection worldwide and to take appropriate public health decisions.

Sexual transmission estimates fall broadly into two categories: per-act transmission probabilities[13-23], which quantify the risk of infection per sexual contact, and per-partner transmission probabilities[13,24-27], which measure the cumulative risk of infection over many sex acts during a partnership. In both cases, transmission probabilities depend upon the infectiousness of the HIV-infected partner and the susceptibility of the HIV-uninfected partner. Infectiousness and susceptibility depend on behavioural, biological, genetic and immunological risk factors of the host and/or the virus[5-6,21-24,28-42]. Per-act transmission probabilities are methodologically difficult to measure[43]. The time of seroconversion of the index case and the transmission to his/her partner, the number of unprotected sex acts, duration of exposure to HIV and potential HIV cofactors among the index cases and the susceptible partners at the time of transmission are rarely known precisely, especially for time-varying cofactors such as recurrent sexually transmitted infections (STI)[5,16,43-45].

Early narrative or methodological reviews have reported a limited selection of per-act estimates[10-12,42,46-48]. More recently, Powers et al[49] published a systematic review of per-act HIV-1 transmission probabilities of 27 articles based on 15 unique study populations. Our systematic review extends this work by including 43 publications based on 25 different study populations. Our objectives were to provide summary estimates of HIV-1 transmission probabilities per heterosexual contact, to perform in-depth univariate and multivariate meta-regression analyses to explore the variation across study estimates, and to estimate the influence of key risk factors on infectivity. The review focuses on HIV-1 which is more pathogenic and prevalent than HIV-2[50-51].

METHODS

Search strategy

The literature search to September 6th 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 29th 2007, and again to September 6th 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))). Bibliographies of relevant articles were examined for additional references. Four of six authors contacted provided complementary information.

Selection criteria and data extraction

Publications reporting empirical per-act heterosexual HIV-1 transmission probability estimates, or sufficient information to derive one were included. Indirect estimates from mathematical modelling studies, reviews, pre-1990 abstracts, and studies with sample sizes fewer than ten were excluded. No other restrictions were put on language, location, study design or type of exposure. Each publication was examined by two reviewers(RFB,MCB) to extract information on per-act estimates (denoted p_i for the i^{th} study), 95%CI, as well as study and participant characteristics, which were used to define covariates. M-to-F and F-to-M estimates were extracted preferably to estimates combining gender(C). Per-act estimates stratified by anal intercourse, genital ulcers, disease stage of the index cases, male circumcision status, and viral load were also extracted.

Meta-analysis

Pooled transmission probability estimates and 95%CI were derived using a random effects model based on the inverse variance method[52-54]. Natural log (ln)-transformed study estimates were used to avoid problems associated with heteroscedasticity[55]. If not explicitly stated in the publication, per-act transmission probabilities were derived using reports of total or frequency of sexual contacts. To improve consistency across studies, infectivity estimates reported as rates were converted into per-act transmission probabilities[56]. Heterogeneity across study estimates was explored using the Q-statistic, sub-group and sensitivity analyses and meta-regression techniques[52-54]. Random-effects meta-regression models were fitted on ln-transformed study estimates using the procedure “proc Mixed” in SAS 9·13. Pooled estimates were exponentiated to obtain estimates on the original scale. Forest plots were produced in R 2.7.0[57].

Analysis plan

First, we conducted a principal meta-analysis using the crude gender-specific estimates from each publication. Where multiple publications reported estimates based on the same study population, the estimate from the largest or most recent sample was included. We then conducted sensitivity analyses by calculating pooled estimates for different sub-groups of studies (e.g. for females only, with and without CS exposure). We also used univariate and

multivariate meta-regression techniques to explore potential sources of heterogeneity across estimates using the following covariates: study design, setting, year of publication, gender, exposure, condom, STI, contamination and ANC HIV prevalence. Finally, we conducted a series of secondary analyses using transmission estimates stratified by risk factors.

Covariates were defined using available information from each study. The covariate setting was used as a marker of unmeasured risk-factors (e.g. viral subtype, co-infection)[49]. The covariate "Exposure" differentiated between studies conducted among partners following commercial sex(CS) work, as clients or FSWs, or among partners of index cases infected following blood transfusion, or exposed to various sources(including intravenous drug use(IDU), or infected heterosexually. "Contamination" was defined to reflect the likelihood of exposure to HIV via sources (sexual or blood) other than sex with the main index partner. "Condom" characterised studies where its use was rare or somewhat controlled for. "STI" was defined to capture the level of ulcerative STI reported in each study. HIV prevalence from antenatal clinics(ANC) at the time and study location reported from independent sources(e.g. www.who.int/globalatlas), was used as a marker of potential unmeasured parenteral or extramarital exposure, assuming that the risk would increase with HIV prevalence. Further details are provided in Webonly Methods.

RESULTS

Search results

Titles of 62,643 articles from the search were examined. Abstracts of 788 articles were read and 218 papers retrieved for more detailed examination. Most studies were excluded because they were risk factor analyses, reported non-sexual or homosexual transmission, per partner estimates, or did not provide enough information to derive an estimate. Forty-two studies reporting at least one per-act heterosexual HIV-1 transmission estimate and thirteen studies reporting sufficient information to derive one were identified from the PubMed search and in one case by personal communication. Fourteen publications, mainly reviews or methodological studies, were rejected. Thirteen additional publications were identified by perusing the bibliographies of relevant articles. Eleven publications were rejected based on our pre-defined criteria. Forty-three publications reporting crude per-act estimates and/or estimates stratified by risk factors were found[14-21,56,58-60,62-70,72-73,75-89,91-94], based on 25 study populations[6,24-28,30,58-59,61,64,68-71,74,77-79,81-82,86,90,93-94](Figure 1, Webonly table 1).

Data extraction and study characteristics

Many publications reported results from the same study population (e.g. five publications[14,16,83-85] were based on the US-CDC study[25]) and estimates from the most recent or largest sample were included. Roth and Allen reported on two samples of the same study population that we assumed independent[59,60].

Essentially four study designs have been used: retrospective-partner, prospective-discordant-couple, and simple prospective and retrospective 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[15-16,43,87,92]. However, in transfusion studies, the infection time of index cases can be determined more precisely from the date of the transfusion[16,25, 27,43,77,81-82]. Otherwise, it is estimated by exploring possible dates of infection or by defining a distribution of possible infection times using information from questionnaires and local epidemic curves or CD4+ cell counts[15-16,45,83-84,87,92]. In prospective-discordant-couple studies, stable (preferably monogamous) HIV serodiscordant couples are followed-up after diagnosis of the index partner[19-20,68,70]. The sexual history and seroconversion of the partner are assessed prospectively. With simple prospective or retrospective studies, susceptible or infected and susceptible individuals (not necessarily monogamous) are recruited respectively, following sexual contact with potentially infected, high-risk partners. As index cases are not recruited, exposure to HIV is estimated using HIV prevalence in the pool of potential partners and the reported coital frequency[21,62-63,72,73].

To avoid duplication, 26 of the 43 publications were included in the principal meta-analysis of crude estimates(Webonly table 1). All but one[75] of these 26 publications reported on data collected pre-2001 from developed (Europe, North America) or developing (Africa, Asia, Haiti) country settings. Seven[19,59,60,64,68-70] developing country publications were from prospective-discordant couple studies, five[21,58,62,72,75] were simple retrospective or prospective studies and one[65] was a retrospective-partner study. Developed country estimates were all derived from prospective-discordant-couple[18,77,82,86,91,93-94] or retrospective-partner studies[15-16,78,80,81,83,91].

Study quality

The reported information on study quality and potential sources of biases varied across studies. For example, in retrospective-partner studies, the identification of index cases and time of infection may be more precise when index cases have been infected through contaminated blood products rather than IDU, bisexual or casual sex. Partners of index cases infected through high-risk behaviour (IDU, sexual promiscuity) may also have higher-risk activities, and therefore higher rates of STIs and/or additional sources of exposure other than sex with the index. Six retrospective-partner studies included index cases who were transfusion recipients[16,77-78,81-83]; seven included index cases infected through various sources[15,18,80,86,91,93-94], including mainly IDU[93-94]; and eight included index cases probably infected heterosexually[19,59-60,64-65,68-70]. All five non-partner (i.e. simple prospective or retrospective) studies were conducted in developing country among participants following CS exposure, as FSW clients[58,62], FSWs[72,75] or men with multiple partners (including sex with FSWs)[21], also with high rates of STIs[21,58,62].

Many retrospective partner or discordant couple studies attempted to exclude partners with additional sources of HIV exposure other than sex with the index partner using various exclusion criteria[15, 27,30-31,78,90,93,94]. For example, Marincovich[94] excluded partners who reported parenteral exposure, blood transfusion, tattooing and multiple partners, whereas Pedraza[93] excluded IDU and promiscuous participants. Infrequent exposure of partners to blood through injections from traditional healers or multiple sexual partners was reported by a few participants in studies by Allen[59] and Roth[60]. Based on reported information, we

judged that contamination was possible in ten publications due to occasional reports of extramarital sex[15,21,59,60,62,80,83,86] and/or potential exposure to blood[58,60,62,72]. Due to the high-risk associated with CS exposure, it was generally assumed to be the source of infection, which may not always be the case[58,71]. "Contamination" was considered unlikely for Wawer[20] and Fideli[70] since HIV transmissions within couples were matched by molecular linkage. Failure to control for condom use may lead to over-estimation of unprotected sex acts and underestimation of infectivity. Only three publications did not report any attempt to control for condom use or did not provide sufficient information[58,62,80](Webonly table 1).

Principal meta-analysis

The meta-analysis included 35 crude gender-specific (M-to-F, F-to-M, C) transmission risk estimates(Webonly table 1). One publication reported independent estimates from both the prospective-discordant and retrospective partner study components, which were both included[91]. Per-act estimates ranged from 0·000[77,86,94] to 0·082[58] and displayed considerable heterogeneity (Q=1591,p-value<0·0001)(Table 1, Figure 2). The highest and less precise estimates were mostly from developing countries. The heterogeneity across estimates remained significant even after stratification by gender(Table 1). With further stratification by setting (developed versus developing countries), the heterogeneity across gender-specific study estimates was no longer significant for developed countries only. The pooled C, F-to-M and M-to-F developed country estimates were 0·0008(95%CI 0·0004-0·0016), 0·0004(0·0001-0·0014) and 0·0008(0·0006-0·0011) respectively. In contrast, the pooled F-to-M and M-to-F estimates for developing countries were 0·0087(0·0028-0·0270) and 0·0019 (0·0009-0·0043), respectively. The pooled M-to-F estimate with CS exposure only was much lower than the F-to-M estimates, reflecting the relatively lower Senegalese[72] and recent Kenyan estimates[75](Webonly table 1). Interestingly, after excluding estimates following CS exposure, which were the only ones from simple prospective and retrospective studies and were exclusively from developing countries, the pooled M-to-F estimates increased, whereas the F-to-M estimates decreased(Table 1). The heterogeneity between developing country estimates remained.

In univariate meta-regression analyses, a statistically significant fraction of the variability across all 35 study estimates could be explained by either exposure, setting, STI level, condom, design, or ANC prevalence(Table 2). Greater infectivity was associated with CS exposure, developing country setting, studies that did not control for condom use, non-partner studies, and higher STI or higher ANC HIV prevalence. The covariates condom and STI (borderline) were no longer significant after excluding estimates with CS exposure(Table 2). Among all developing country estimates, only gender, condom and year of publication (negative association) were significantly associated with infectivity; no association were found after removing the estimates with CS exposure (details not shown).

The multivariate meta-regression analyses aimed to explain the heterogeneity across the 30 developed and developing country estimates without CS exposure, which were all based on discordant-couple or retrospective-partner studies. When controlling for gender(p-value>0.23) and study design(p-value>0.49), only setting, ANC prevalence and exposure

were independently associated with infectivity(p-value<0·0001) and explained 62-68% of the variability(details not shown). In models including design(p-value>0.10), gender(p-value<0.015), setting(p-value<0.0001), the interaction term between setting and gender(p-value<0.036), only contamination(p-value=0.009) or ANC prevalence(p-value=0.006) remained statistically significant and together explained 82-85% of the variance(details not shown). Lower infectivity estimates were associated with the contamination category "no information" compared to the categories "possible" or "unlikely", which were not statistically different(p-value =0·45). Thus, our final model excluded design and included ANC prevalence(Webonly table 2). Combined and M-to-F developed country estimates, adjusted for prevalence, were ~1·6(0·6-4·3)- and ~1·8-(0·8-3·9)-fold larger than F-to-M estimate, respectively, but the difference did not reach statistical significance. F-to-M and M-to-F developing country estimates were of similar magnitude(RR 1·0,p-value=0·93). M-to-F and F-to-M developing country estimates were 1·8(0·9-3·9)-fold and 3·3(1·1-9·7)-fold larger than developed country estimates, respectively. The natural logarithm of the infectivity estimate was increased by an average 0·046-fold for each 1% increase in ANC HIV prevalence(Webonly table 2).

Secondary analysis by risk factors

Only two publications[89,92] reported M-to-F estimates for receptive anal intercourse (RAI) (pooled=0·017, CI:0·003-0·089,Q=4·2) and five[16,18,68,81,92] explicitly reported M-to-F estimates for vaginal sex only (pooled=0·0008,CI:0·0005-0·0009,Q=9·5)(Additional information available from the authors)).

Six publications reported developing country estimates stratified by GUD status of the HIV-1 susceptible partners[19,21,58,63,67,76](reflecting increased HIV susceptibility due to GUD or by GUD status of the index case[19] (reflecting increased HIV infectivity). Gray reported a lower infectivity in presence of GUD than the other study estimates in presence of CS exposure[21,58,63,76]. An additional eight study estimates in absence of STI were also included[18,63,69,78,82-83,89,91]. Due to the small number of estimates, simple explanatory meta-regression analyses were undertaken. We classified the estimates into three categories: study participants without STI; without GU but potentially other STI; and with GU and potentially other STI as well(Table 3). The covariate GU status alone explained 57% of the variability across study estimates. The meta-regression model with the covariates CS exposure and GU status explained a larger fraction of the variability(81%) than GU status with either covariates setting(77%) or gender (70%)(details not shown). Estimates in the presence of GU were 5-fold larger than estimates in absence of STI, whereas CS exposure was associated with an 11-fold increase in infectivity compared to estimates without CS exposure(Table 4).

Seven publications, two on the same developing country population[20,56], reported estimates by disease stage of index partners from partner studies(Table 5)[17,20,56,79-80,83,92]. Estimates ranged from 0·0010 to 0·0107, 0·0004 to 0·0010 and 0·0013 to 0·0567 for the early, asymptomatic and late stage, respectively. Wawer[20] reported many estimates from different sub-samples of discordant couples where index cases had been infected for different lengths of time. We used the estimate from couples where index cases had seroconverted for less

than five months(p_i=0·0107), which was larger than from couples 6-15 months and 16-35 months after the index cases had seroconverted(Table 5). The estimate from all couples with prevalent index cases(p_i=0·0008) was used for the asymptomatic stage. The late stage estimate used corresponded to 6-15 months before death of index cases (p_i=0·0049). Disease stage alone explained 95% of the variability across estimates. After adjusting for disease stages, the addition of the covariate "Setting" was not significant(Table 4). The impact of gender could not be explored due to lack of data. The risk in the early(RR=9·2,CI:4·5-18·8) and late stage (RR=7·3,CI:4·5-11·9) adjusted for setting were significantly larger than for the asymptomatic phase(Table 4).

Only two publications reported empirical estimates stratified by level of either semen or serum viral load on the same study population[19,20](additional information available from the authors). Partners of index cases who had a median serum viral load ~30,000 HIV RNA copies/ml(range<400-3,100,000 copies/ml <5 months after seroconversion) had a higher infectivity (p_i=0·0107) than those with a median serum viral load ~2600 copies/ml by 15 months[20], and even higher than Gray's estimate(p_i=0·0023) when viral load exceeded 38,500 copies/ml[19]. Wawer's[20] estimate from couples where prevalent index cases were followed-up for 0-10 months was higher(p_i=0·0009,~10,300 copies/ml), albeit not significantly, than when followed-up for more than 30 months(p_i=0·0004,~15,000 copies/ml). Gray's[19] combined estimates at high(>38,500 serum copies /ml); medium(~1700-12,499 or 12,500-38,499 copies/ml), and low(<1700 copies/ml) viral loads were p_i=0·0023, p_i=0·0013 or p_i=0·0014, and p_i=0·0001, respectively. Pilcher[22] and Chakraborty[23] also reported higher infectivity at higher viral load but their estimates were not directly comparable because they were derived from theoretical studies based on measurement of HIV-1 viral load by volume of semen.

Only two publications reported F-to-M estimates by circumcision status[21,58](additional information available from the authors). Baeten's[21] crude F-to-M transmission estimate among uncircumcised men was approximately 2·6 times that among circumcised men(p_i=0·013,CI:0·005-0·020 vs p_i=0·005,CI:0·003-0·007) and 4·5 times larger in non-circumcised than circumcised men in the presence of GUD (p_i=0·018,CI:0·000-0·037 vs p_i=0·004,CI:0·000-0·009)[21]. In Cameron's study[58], crude estimates were higher among uncircucmsied(p_i=0·185,CI:0·023-0·348) than circumcised(p_i=0·022,CI:0·000-0·064) men. Amongst those with GU, estimates were six-fold higher among uncircumcised(p_i= 0·428,CI: 0·0126-0·730) than circumcised men(p_i=0·067,CI:0·000-0·192). In the absence of GU, no HIV transmission occurred in circumcised or uncircumcised men[58].

DISCUSSION

Summary of the results

Our systematic review and meta-analysis of HIV-1 transmission probabilities per heterosexual act comprehensively updates and extends the findings of a recent similar review[49]. We confirmed the earlier observation of considerable heterogeneity in per-act estimates[49], provided gender-specific transmission estimates and identified additional sources of heterogeneity by exploring interactions between covariates. We also reported the influence of key risk factors on infectivity in terms of relative risk, instead of risk difference,

which is easier to interpret. Heterogeneity across crude study estimates could be mostly explained by commercial sex exposure as FSWs or clients, setting, gender and the ANC HIV prevalence at the time and study location. Although a previous review only found a weak association between gender and infectivity [49], our results suggested that this may vary by settings. In the subset of estimates without CS exposure, the pooled F-to-M transmission estimate for developed countries, adjusted for HIV prevalence, was about half the M-to-F or Combined estimates(RR~0·5), although the difference failed to reach statistical significance. In contrast, the adjusted developing country F-to-M and M-to-F estimates were very similar(RR~1·0), and the F-to-M developing country estimate(RR~3·3) significantly larger than the F-to-M developed country estimate. The M-to-F or Combined pooled estimates in our sub-analyses in absence of RAI, GU, CS exposure, or for the asymptomatic phase were of similar magnitude(~0·0007) to the M-to-F and Combined pooled estimates from developed countries(~0·0008), which would suggest that they represent the average per-vaginal-sex-act transmission in absence of cofactors, during the asymptomatic phase.

Despite differences in some selection criteria and the strategy adopted for the analysis, we confirmed the findings of previous reviews on the weak influence of study quality[49] and the importance of key risk factors[16,39,42,49,67,105] on infectivity. In agreement with studies among homosexuals[5,101-103] our pooled estimate by RAI supports that it is a more risky practice than receptive vaginal sex. Two studies reporting per-act estimates by circumcision status[21,58] suggested a ~3 to 8-fold increase in HIV infection among uncircumcised males overall or in presence of GUD. This is consistent, yet somewhat higher, with the results of two meta-analyses[104-105] and three recent randomised controlled trials of male circumcision[106-108]. We found that the presence of GU and CS exposure were independently associated with increased infectivity. Our GU cofactor estimate(RR 5·3) was intermediate between previous estimates for high-risk groups (10-50 and 50-300 for M-to-F and F-to-M transmission per act respectively)[76] and those from a meta-analysis of observational studies which reported a 2·8-fold(2·0-4·0) and 4·4-fold (2·9-6·6) increase in female and male susceptibility due to GUD[109], respectively. Both our RR and estimates from observational studies may be biased due to misclassification, undiagnosed STI, misreporting of symptoms. In addition, the intermittent nature of GU means that it is unlikely to have been present throughout the at-risk period and per-contact cofactor effects may therefore be underestimated[44,76]. Our cofactor estimate predominantly captured the increased HIV susceptibility due to GU (as only one study[19] reported estimates stratified by GU status of index cases). Thus, the increased risk associated with CS exposure may partly reflect increases in HIV infectivity since high-risk index cases (FSW, clients) would likely have also been infected with GU or other STIs. Baeten's F-to-M study estimate from men with multiple partners (31% monogamous, 57% sex with FSW) was higher than from the sub-sample of men who only reported sex with their wives (p_i=0·0068 vs 0·0038, p-value>0·10)[21].

Interestingly, the early Kenyan and Thai FSW-to-client estimates[58,62] were considerably larger than the Senegalese and the recent Kenyan client-to-FSW estimates[72-73,75]. Although these estimates are likely imprecise since they were based on simple retrospective or cross-sectional study design, the large difference (>35-fold) could also be due to cofactors. STI rates may have been lower among Senegalese FSWs because of an early governmental

public health programme, whereby self-identified FSW regularly attended health clinics providing free STI treatment[110-111]. In contrast, the client studies were conducted in East Africa (early in the epidemic) and Thailand, where circumcision prevalence is lower than in West Africa[112] and at a time when STI and GUD were virtually ubiquitous and when FSW were experiencing an explosive HIV epidemic, and index partners were more likely to be in the primary phase of HIV infection[46,61,113]. For example, Limpakarnjanarat reported 21% Haemophilus ducreyi, 80% Herpes Simplex Virus-2, and 9% GUD among Thai FSWs[63,113]. Kimani also suggested that the decline in per-act infectivity observed over calendar time in their study correlated with a decline in STI prevalence among FSWs[75].

Previous individual-based studies showed an association between HIV infectivity and viral load or time since infection[22,24,28,114-117]. Our risk factor analysis also suggested increased infectivity for index cases in the early and late phase of infection compared to the asymptomatic phase. The difference between estimates for the early and late stages was not statistically significant, which may reflect similar infectivity, under-sampling of couples with most recently infected and highly infectious index cases, imprecise definition of the duration of the early phase or a lack of statistical power. A recent re-analysis of Wawer's data suggested that primary infection and late-stage infection were 26 and 7 times higher than asymptomatic infection and that the high infectiousness during primary infection lasted ~ 3 months[118].

Study limitations

We initially did not impose any inclusion criteria based on study design since each design has intrinsic biases, even prospective discordant-partner studies, which are seen as the most appropriate design to estimate transmission probabilities. Although discordant partner studies are likely to reduce recall biases regarding type and frequency of unprotected contacts and HIV cofactors, the reporting of sensitive behaviour is still subject to social desirability biases. Frailty selection, whereby the most vulnerable couples of "high and fast transmitters" rapidly become seroconcordant[16,45], may also result in over-sampling of less susceptible partners and/or less infective index cases who remain uninfected longer and become more likely to be enrolled in discordant couples studies. Frailty selection would result in under-estimation of infectivity. Shiboski also suggested that heterogeneity in infectivity was not well reflected in the US-CDC[25], CDC-HATS[27] retrospective-partner studies because the duration of many relationships was too short compared to the time since infection of index cases[16,45].

Results from our risk factor analyses are mainly explanatory. The estimates of the magnitude of the cofactor effects may not be very precise due to the small number of studies and covariates that could be explored, the heterogeneity across study estimates, differences in risk factor exposure definitions across studies and because study estimates were based on sub-groups of the study sample. Publication biases may also be present since estimates by risk factor may not be reported from studies that did not find a significant association.

The independent positive association between infectivity and setting or ANC HIV prevalence for studies without CS exposure is difficult to interpret but is unlikely to be due to study design or analytic methods. As reported previously[49], study design was only weakly

associated with infectivity. In addition, we converted estimates reported as rates into probabilities which improved comparability across studies. Larger transmission probabilities may lead to higher HIV prevalence in the general population, as estimated in developing countries. Alternatively, higher HIV prevalence may increase the likelihood of "contamination" due to exposure to additional sources of infection other than sex with the main index partner and bias estimates upward. Developing country estimates displayed greater heterogeneity than developed country estimates. Gender, date of publication, or the covariate condom (confounded with CS exposure) only explained a significant fraction of the variation across developing country estimates (when estimates with CS were included). This is not entirely surprising given the limited number of studies and that the STI, contamination, and condom use covariates could only be defined broadly, leading to potential misclassification. Thus, the heterogeneity may reflect un-captured "contamination" or variation in the prevalence of key risk factors. For example, the larger F-to-M than M-to-F estimates in three[19,59,68] discordant couples studies in developing countries may indicate contamination since men often report more extramarital sex than females prior or during the study period[28,59,60,64,69,119]. Interestingly, in Fideli's study[70], where transmission events within couples could be epidemiologically linked, F-to-M transmission was lower than M-to-F transmission. However, Fideli's estimates were larger than Wawer's estimates, where infections within couples were also confirmed by molecular linkage, which reduces the risk of misclassification, but does not reduce biases due to misreporting of number of unprotected sex acts or unmeasured risk factors[120]. As many studies in developing countries were carried out within the context of interventions involving an important counselling component[19-20,59,68-69], condom use may have been over-reported by study participants, leading to higher infectivity estimates. Nevertheless, reported condom use remained low or even decreased in some studies[19,68]. Other studies tried to minimise misreporting biases on sexual behaviour by checking for concordance between both members in the couple or using sexual diaries[19,64]. In Roth's study, because men reported more protected sex acts then women, we used the sexual activity reported females to minimise biases in our estimates[60]. Conflicting evidence remains regarding unmeasured exposure to contaminated equipment or blood transfusion that may have increased developing country estimates[7,8,10-12,121-123]. An early cohort study of registered Senegalese FSWs reported high prevalence of transfusion, scarification, excision or tattoos, yet HIV prevalence in West Africa and the reported transmission probability estimate for this population are low[71-73,110-111].

Potential role of risk factors

We cannot exclude the possibility that our high and heterogeneous developing country estimates are due to unmeasured heterogeneity in the prevalence of risk factors. To assert that a 3·5-fold difference in F-to-M pooled estimates between developing and developed countries is solely due to contamination would imply that ~70% of infections are acquired outside the main relationship. While this seems inconsistent with the relatively low proportion of unlinked infections reported in at least two studies[19,70,119], this remains a subject of debate[121-124]. Powers et al reported a weak association between region and infectivity, which they assumed was a proxy for viral subtypes[49]. However, they also found greater heterogeneity across estimates from Africa. The reason for the differences by setting is likely to be multi-factorial. Lack of male circumcision may be more important in

developing countries than in Europe, where circumcision is rare, due to interacting cofactors such as ulcerative STI[39,125-128]. It is possible that between-settings differences may never be completely understood because risk factors such as STI prevalences may have changed since the beginning of the epidemic[75,129]. Greater heterogeneity in risk factors or median viral loads in developing countries may exacerbate frailty selection over time. Median plasma viral load as high as 6·1 $\log_{10}$ copies/ml has been observed among acutely infected men in Malawi and presence of STI was the stronger risk factor associated with high viral load[42,128]. Thus, intermittent interaction between risk factors may result in very high peaks of infectivity during the incubation period and results in frailty selection at the population level[42,128]. This may also explain why estimates tended to be lower (albeit not significantly) for couples with prevalent index cases with 31-40 months follow-up(p_i=0·0004), compared to 0-10 months(p_i=0·0009), despite the higher median viral load reported after 30 months[20]. However, unmeasured reduction in prevalence of risk factors due to longer exposure to the study or other intervention is also possible.

Heterogeneity across estimates may also be due to population-level declines in infectivity over calendar time[59-60,75-76] as the fraction of recent seroconverters is expected to decrease in maturing epidemics. Nonoxynol-9 spermicide, which has been associated with increased susceptibility to GU and HIV infection[36,130-131], was also reported in at least four early African studies[59-60,68,70]. However, in Allen's study[59], only 12% of females reported the use of Nonoxynol-9 without condoms, 6% and 19% reported a history of STI in the past year and past two years, respectively, which were comparable to rates reported in the Rakai study[19]. Most studies were carried out before wide-scale use of antiretroviral therapy and which is therefore unlikely to have influenced results[29,32].

Implications of findings

Our results indicated higher transmission probabilities for developing than for developed country studies. The greater heterogeneity of developing country estimates is itself interesting and may suggest poorer study quality, greater heterogeneity in risk factors or greater under-reporting of high-risk behaviour in these studies. More research is needed to better understand these differences, and particularly the low estimates from Rakai[19-20]. Greater heterogeneity may also be due to differential infectivity of the different viral subtypes, mutation of chemokine-receptor genes, contraception method, genetic, biological and virologic host factors, and interaction with other infectious diseases[5,33--41,50,115-118,125,130-132]. A better quantification of per-act infectivity is important to improve understanding of the epidemiology of HIV/AIDS worldwide, to predict the future HIV/AIDS pandemic and when designing appropriate prevention strategies. The design of discordant-partner studies could be improved by designing and powering them for carefully planned risk factor analyses, including epidemiological linkage, using data collection methods to reduce social desirability biases, cross validating sexual history in couples and carefully documenting non-sexual potential sources of contamination.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ANC	Antenatal clinic
C	Gender combined HIV-1 transmission probability estimate
CS	Commercial sex
FSW	Female sex worker
F-to-M	Female-to-male HIV-1 transmission probability estimate
GUD	Genital ulcer disease
IDU	Intravenous drug use(r)
M-to-F	Male-to-female HIV-1 transmission probability estimate
RAI	Receptive anal intercourse
RR	Relative risk
STI	Sexually transmitted infections

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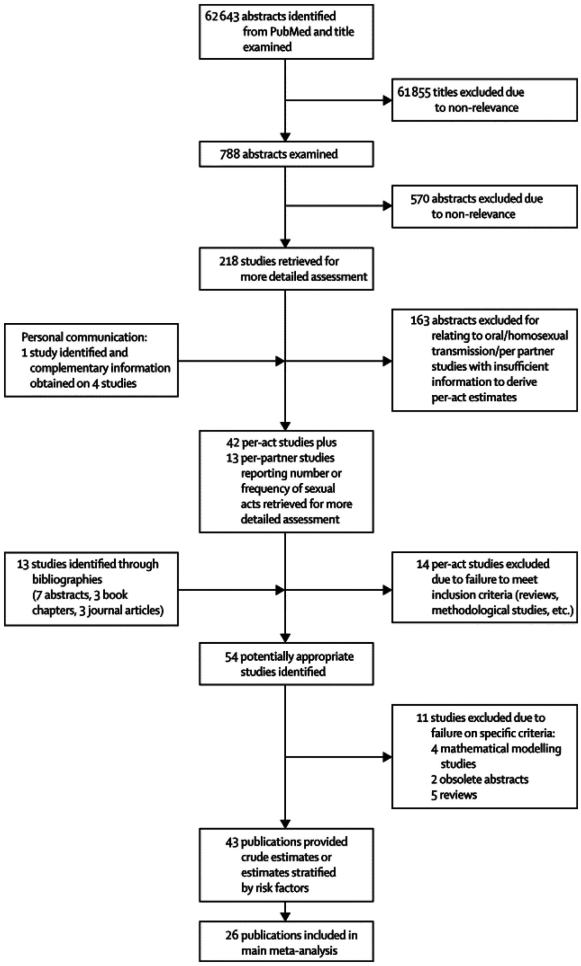
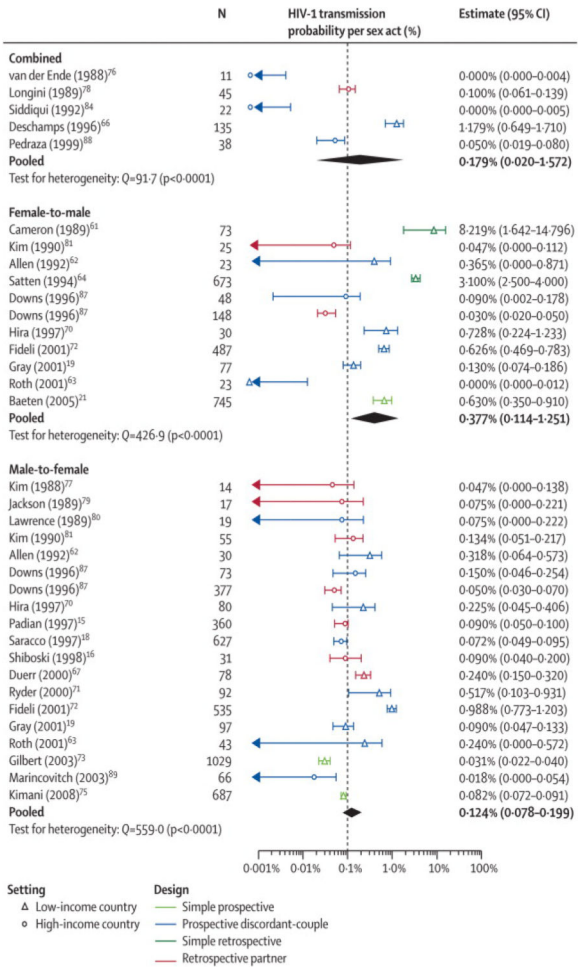
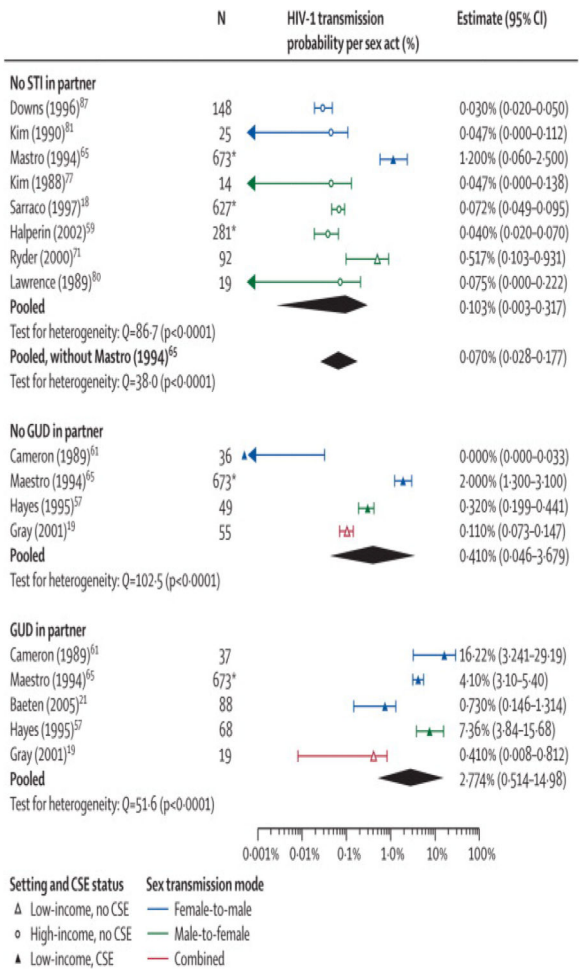


Figure 1.

Flowchart summarising results of the search on heterosexual per-act HIV-1 transmission probabilities. The 11 publications rejected on specific criteria consisted in four mathematical modelling studies[22,23,47,95], two obsolete abstracts,[96-97] and five reviews[10,42,98-100]. The 43 publications included 26 publications included in the principle meta-analysis and seven publications only included in the sub-analyses by risk factor[17,20,46,76,79,89,92]. The remaining publications were duplicates and not included in any analysis but are shown in Webonly table 1 for completion.





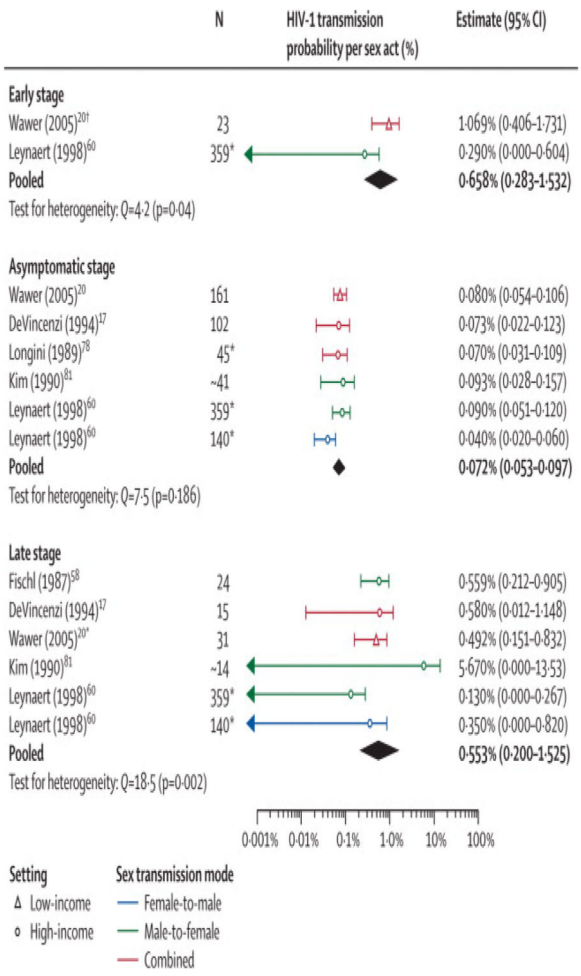


Figure 2.

Forest plots of crude per-act study estimates in the absence of commercial sex exposure for: a) Combined M-to-F and F-to-M estimates; b) F-to-M; and c) M-to-F HIV transmission. The point estimate, sample size (N) and 95%CI for each study are represented. The indice ‘d’ indicates that the 95%CI were derived from available data. The indice “i” indicates that the estimate and CI were derived from information provided in main study; the indice “r” indicates that the original rate estimates and CI were converted into probabilities. For reference, a vertical dotted line is shown at 0·001 because this has previously been a commonly cited value for HIV-1 per-act transmission probability[49]. Light and dark blue lines show estimates from simple prospective and prospective-discordant couple studies, respectively. Green and red lines show estimates from simple retrospective and retrospective-partner studies, respectively. Triangles identify developing country estimates. Circles identify developed country estimates. Note that only the lower bound of the 95%CI of Cameron et al[58] and Satten et al[62] estimates appear on the F-to-M transmission forest plot because they are too large. “L” and “R” denote the prospective-discordant-couple and retrospective-partner-study components of Downs et al[91], respectively.

Table 1

Pooled estimates for subsets of crude study estimates stratified by setting, gender and lack of commercial sex exposure

Subset of studies	Heterogeneity statistic, Q[a]	p-value	p_{random}	95%CI
All (N=35)	1590·5	<0·0001	0·0018	(0·0011-0·0030)
Combined (N=5)	91·4	<0·0001	0·0018	(0·0002-0·0157)
F-to-M (N=11)	426·9	<0·0001	0·0038	(0·0011-0·0125)
M-to-F (N=19)	559·0	<0·0001	0·0012	(0·0008-0·0020)
F-to-M without CS exposure [b] (N=8)	147·5	<0·0001	0·0016	(0·0006-0·0048)
M-to-F without CS exposure [b] (N=17)	356·9	<0·0001	0·0014	(0·0009-0·0023)
F-to-M with CS expsure only [c](N=3)	48·1	<0·0001	0·0244	(0·0069-0·0866)
M-to-F with CS exposure only [c](N=2)	36·3	<0·0001	0·0005	(0·0002-0·0013)
C developed country (N=4)	3·7	0·30	0·0008	(0·0004-0·0016)
C developing country (N=1)*	--	--	0·0118	--
F-to-M developed country (N=3)	3·9	0·1411	0·0004	(0·0001-0·0014)
F-to-M developing country (N=8)	218·4	<0·0001	0·0087	(0·0028-0·0270)
M-to-F developed country (N=10)	14·8	0·0976	0·0008	(0·0006-0·0011)
M-to-F developing country (N=9)	519·5	<0·0001	0·0019	(0·0009-0·0043)
F-to-M developing without CS exposure [b] (N=5)	40·9	<0·0001	0·0038	(0·0013-0·0110)
M-to-F developing country without CS exposure b(N=7)	109·2	<0·0001	0·0030	(0·0014-0·0063)

CI=Confidence interval; M-to-F: male-to-female; F-to-M: female-to-male; C: combining gender; CS: commercial sex; -- not applicable; N= Number of study estimates;

[a] On the ln scale;

[b] Removed to asses their influence:

[c] estimates CS exposure were all from developing countries and the only ones from non-partner studies;

* reference 64·

Table 2

Univariate meta-regression analyses for different subset of crude study estimates

Covariate	Developed and Developing country estimates			Developing country study estimates only		
	All N=35		Exclude CS exposure estimates N=30	All N=17		Exclude CS exposure estimates N=12
	Pooled [#] estimate (95%CI)	Variance explained [a] *(p-value)*	Variance explained [a] *(p-value)*	Pooled [#] estimate (95%CI)	Variance explained [a] *(p-value)*	Variance explained [a] *(p-value)*
Gender		15·4%	0·6%		34·3%	23·2%
Combined	0·0018 (0·0004-0·0073)	*(0·07)*	*(0·89)*	0·0118 (0·0000-0·0999) [!]	*(0·02)*	*(0·20)*
F-to-M	0·0039 (0·0018-0·0085)			0·0087 (0·0038-0·0198)		
M-to-F	0·0012 (0·0007-0·0022)			0·0019 (0·0009-0·0040)		
Design		*21·6%*	*24·9%*		1·6%	3·6%
P-DC	0·0022 (0·0012-0·0039)	*(0·02)*	*(0·0074)*	0·0038 (0·0017-0·0084)	*(0·85)*	*(0·56)*
R-PS	0·0008 (0·0004-0·0017)			0·0024 (0·0002-0·0314) [*]		
Non-partner	0·0050 (0·0018-0·0141)			0·0050 (0·0016-0·0160)		
Exposure		*40·2%*	*63·1%*		0·9%	
Commercial sex	0·0049 (0·0020-0·0122)	*(0·0001)*	*(<0·0001)*	0·0050 (0·0016-0·0160)	*(0·65)*	*(--)*
TR	0·0008 (0·0003-0·0021)			--		
Various	0·0007 (0·0003-0·0013)			--		
Hetero	0·0037 (0·0020-0·0068) [c]			0·0036 (0·0017-0·0078)		
Setting		*39·8%*	*62·6%*		0%	
Developed	0·0007 (0·0004-0·0012)	*(<0·0001)*	*(<0·0001)*	--	*(--)*	*(--)*
Developing	0·0040 (0·0024-0·0067)			0·0040 (0·0021-0·0076)		
Condom		*23·5%*	1·0%		*46·7%*	
Not controlled	0·0130 (0·0034-0·0498)	*(0·0025)*	*(0·67)*	0·0487 (0·0122-0·1943)	*(0·0002)*	*(--)*
Controlled	0·0015 (0·0010-0·0023)			0·0028 (0·0017-0·0047)		
STI		*30·2%*	28·5%		16·7%	5·2%
L1	0·0008 (0·0003-0·0021)	*(0·01)*	*(0·06)*	0·0052 (0·0004-0·0615)	*(0·37)*	*(0·89)*
L2	0·0010 (0·0003-0·0027)			--		
L3	0·0041 (0·0008-0·0204)			0·0041 (0·0007-0·0232)		
L4	0·0042 (0·0022-0·0082)			0·0059 (0·0027-0·0131)		
Unknown	0·0011 (0·0005-0·0026)			0·0017 (0·0006-0·0053)		
Contamination		9·1%	6·9%		8·8%	10·2%

Covariate	Developed and Developing country estimates			Developing country study estimates only		
Unlikely	0·0011 (0·0005-0·0023)	*(0·17)*	*(0·35)*	0·0053 (0·0013-0·0221)	*(0·47)*	*(0·57)*
Possible	0·0033 (0·0014-0·0077)			0·0061 (0·0021-0·0174)		
No information	0·0019 (0·0009-0·0043)			0·0027 (0·0011-0·0066)		
ANC HIV prevalence[i, u1]	1·06 (1·02-1·11)	*19·6%*	*53·9%*	0·99 (0·94-0·1·07)	0·0%	10·9%
		(0·0063)	*(<0·0001)*		*(0·99)*	*(0·33)*
Year of Publication[i, u2, y]	0·88 (0·53-1·46)	1·2%	6·4%	0·43 (0·26-0·70)	*41·9%*	4·3%
		(0·62)	*(0·23)*	*(0·0009)*	*(0·50)*	
Variance across study estimates in absence of any covariate [a]		1·73	0·97	1·71	0·57	

CS=commercial sex; ANC=Antenatal clinic data; M-to-F=male-to-female; N= number of study estimates; F-to-M= Female-to-male; STI=sexually transmitted infections; IDU= intravenous drug use; --Not applicable because no study had that characteristic. Covariates: Design: P-DC=prospective-discordant-couple; R-PS=retrospective partner study; Non-partner=simple prospective (C-L) or simple retrospective (X-R); TR= transfusion recipient; “Exposure”: partners exposed to CS, index cases infected by transfusion (TR), through IDU, heterosexually, or transfusion (Various) or mainly heterosexually(Hetero). STI is at baseline or during follow-up (for C-L and P-DC studies) or history (for X-R and R-PS studies) among partners or index cases: L1≤ 1%, 1%< L2≤ 5%, 5%<L3≤ 10%; L4: >10% for ulcerative STI or L4: >25% any STI history;

[a] Fraction of the variability across study estimates explained by each covariate on the ln scale;

[b] Estimateswith CS exposure were all from developing countries and the only estimates from non-partner studies;

[#] For categorical variables this corresponds to infectivity estimates;

[i] For continuous variables this corresponds to a linear change in the logarithm of the infectivity estimate of 0.058 per

[u1] 1% prevalence;

[u2] normalised years;

[c] Infectivity estimates are higher because this category includes only developing country study estimates.

[y] year of start of the study was also explored but not significant in any of the subsets(results not shown);

[*] reference 65 only;

[!] reference 64 only.

Table 3

Per-act and pooled estimates for the sub-analysis of study estimates stratified by genital ulcer disease status

Reference	Setting	Exposure	Gender	N[2]	Q[a]	Estimate (95%CI)	Included
No sexually transmitted infection among the HIV-1 susceptible partner							
Downs (1996)[91]	Developed	Non CS	F-to-M	148		0·0003 (0·0002-0·0005)	√
Kim (1990)[83]	Developed	Non CS	F-to-M	25		0·0005 (0·0000-0·0011)[d]	√
Mastro (1994)[63]	Developing	CS	F-to-M	673[t]		0·0120 (0·0006-0·0250)	√
Kim (1988)[78]	Developed	Non CS	M-to-F	14		0·0005 (0·0000-0·0014)[i]	√
Saracco (1997)[18]	Developed	Non CS	M-to-F	627[t]		0·0007 0·0005-0·0010)[r]	√
Halperin (2002)[89]	Developed	Non CS	M-to-F	281[t]		0·0004 (0·0002-0·0007)[adj]	√
Ryder (2000)[69]	Developing	Non CS	M-to-F	92		0·0052 (0·0010-0·0093)[i]	√
Lawrence (1989)[82]	Developed	Non CS	M-to-F	19		0·0008 (0·0000-0·0022)[i]	√
Pooled			**All**	**8**	**86·7**	**0·0010 (0·0003-0·0011)**	
Pooled- without Mastro				**7**	**38·0**	**0·0007 (0·0003-0·0017)**	
No genital ulcer diseases among the HIV-1 susceptible partner[1]							
Cameron (1989)[58]	Developing	CS	F-to-M	36		0·0000 (0·0000-0·0003)[d]	√
Mastro (1994)[63]	Developing	CS	F-to-M	673[t]		0·0200 (0·0130-0·0310)	√
Hayes (1995)[76]	Developing	CS	M-to-F	49		0·0032 (0·0020-0·0044)[d]	√
Gray (2001)[19]	Developing	Non-CS	C	55		0·0011 (0·0007-0·0015)[d]	√
Corey (2004)[67]	Developing	Non-CS	C	nr		0·0004 (nr)[ne]	
			C	nr		0·0019 (nr)[po]	
Pooled			**All**	**4**	**102·5**	**0·0041 (0·0005-0·0368)**	
Presence of genital ulcer diseases in the HIV-1 susceptible partner [1]							
Cameron (1989)[58]	Developing	CS	F-to-M	37		0·1622 (0·0324-0·2919)[d]	√
Mastro (1994)[63]	Developing	CS	F-to-M	673[t]		0·0410 (0·0310-0·0540)	√
Baeten (2005)[21]	Developing	CS	F-to-M	88		0·0073 (0·0015-0·0131)[d]	√
Hayes (1995)[76]	Developing	CS	M-to-F	68		0·0736 (0·0384-0·1568)[d,e]	√
						0·0051 (0·0037-0·0065)[i, f]	
Gray (2001)[19]	Developing	Non-CS	C	19		0·0041 (0·0001-0·0081)[d]	√
Corey (2004)[67]	Developing	Non-CS	C	nr		0·0031 (nr)[po]	
Pooled			**All**	**5**	**51·6**	**0·0277 (0·0051-0·1498)**	

[a] Heterogeneity statistics calculated on the ln scale;

[1] Only one publication

[19] reported GU status for the index cases rather than for HIV susceptible; nr: excluded because 95%CI could not be derived from available information;

[adj] estimate adjusted for anal intercourse, condom use, STI history;

[2] N= number of subjects for individual studies or number of estimates included in pooled estimate; C: combined male-to-female and female-to-male transmission; FUP: During follow-up period;

[t] total sample size;

[e] during episodes of GU;

[f] during follow-up period which includes period with and without GU episodes;

[d] The 95%CI was derived;

[i] Estimate and CI derived from information provided in main study;

[r] original rate and CI estimates converted into probabilities;

[po] HSV-2 positive;

[ne] HSV-2 negative; All: include study estimates from any gender.

Table 4

Multivariate meta-regression models for the sub-analysis by GU status and disease stage

GU status (N=17)			
Covariate	RR	95%CI	p-value
GU status			0·0162
No STI	1	--	
No GU	1·11	(0·30, 4·14)	
GU	5·29	(1·43,19·58)	
CS exposure			<0·0001
No	1	--	
Yes	11·08	3·47 (3·47, 35·35)	
Total fraction of the total variance explained = 81% [a]			
Disease stage (N=14)			
Covariate	RR	95%CI	p-value
Disease stage			<0·0001
Asymptomatic	1	--	
Early	9·17	(4·47, 18·81)	
Late	7·27	(4·45, 11·88)	
Setting			0·347
Developing	1	--	
Developed	0·79	(0·49, 1·29)	
Fraction of the total variance explained= 96%[a]			

CI= Confidence interval; N= Number of estimates;

[a]On the ln scale

Table 5

Per-act and pooled estimates for the sub-analysis of study estimates stratified by disease stage

Reference	Setting	Gender	N[2]	Q[a]	Estimate (95%CI)		Included
Early stage							
Wawer (2005)[20]	Developing	C	23		0·0107 (0·0041-0·0173) [r]	< 5months [s]	√
		C	13		0·0017 (0·0002-0·0040) [r]	6-15 months[s]	
		C	7		0·0010 (0·0000-0·0031) [r]	6-35 months[s]	
		C	43[m]		0·0043 (0·0020-0·0067) [r]	All incident index	
Pinkerton (2008)[56]	Developing	C	23		0·0107 (0·0041-0·0173)[d]	< 5 months [s]	
			13		0·0017 (0·0002-0·0040)[d]	6-15 months[s]	
			7		0·0010 (0·0000-0·003 1) [d]	16-35 months[s]	
Leynaert (1998)[92]	Developed	M-to-F	359[t]		0·0029 (0·0000-0·0060)[d]		√
Pooled		**All**	**2**	**4-2**	**0·0066 (0·0028-0·0153)**		
Asymptomatic stage							
Wawer(2005)[20]	Developing	C	161		0·0009 (0·0004-0·0014) [r]	0·10 months FUP	
		C	129		0·0007 (0·0002-0·001 1) [r]	11-20 months FUP	
		C	92		0·0010 (0·0004-0·0016) [r]	21-30 months FUP	
		C	45		0·0004 (0·0000-0·0008) [r]	31-40 months FUP	
		C	161		0·0008 (0·0006-0·001 1) [r]	All prevalent index	√
DeVincenzi (1994)[17]	Developed	C	102		0·0007 (0·0002-0·0012) [r]		√
Longini (1989)[80]	Developed	C	45 [t]		0·0007 (0·0003-0·001 1)[d]		√
Kim (1990)[83]	Developed	M-to-F	~41		0·0009 (0·0003-0·0016)[d]		√
Leynaert (1998)[92]	Developed	M-to-F	359 [t]		0·0009 (0·0005-0·0013)		√
		F-to-M	140 [t]		0·0004 (0·0002-0·0006)		√
Pooled		**All**	**6**	**7-5**	**0-0007 (0·0005-0·0010)**		
Late stage							
Longini (1989)[80]	Developed	C	45[t]		0·0057 (0·0026-0·0088)		
DeVincenzi (1994)[17]		C	15		0·0058 (0·0001-0·0115) [r]		√
Wawer (2005)[20]	Developed	C	22		0·0015 (0·0000-0·0035) [r]	26-35 months before death	
		C	35		0·0037 (0·0013-0·0062) [r]	16-25 months before death	
		C	31		0·0049 (0·0015-0·0083) [r]	6-15 months before death	√
		C	51		0·0039 (0·0021-0·0056) [r]	All late index	

Reference	Setting	Gender	N[2]	Q[a]	Estimate (95%CI)	Included
Kim (1990)[83]	Developed	M-to-F	~14		0·0567 (0·0000-0·1353)[d]	√
Fischl (1987)[79]	Developed	M-to-F	24		0·0056 (0·0021-0·0091)[i]	√
		F-to-M	8		0·0051 (0·0000-0·0109)[i]	
Leynaert (1998)[92]	Developed	M-to-F	359 [t]		0·0013 (0·0000-0·0027)	√
		F-to-M	140 [t]		0·0035 (0·0000-0·0082)	√
Pooled		**All**	**6**	**18-5**	**0-0055 (0·0020-0·0153)**	

C: combined male-to-female and female-to-male transmission; FUP: follow-up period;

~Approximation; All: include study estimates from any gender.

[a] Heterogeneity statistics calculated on the ln scale;

[s] since seroconversion of index case;

[e] used both the retrospective and prospective component of Fischl et al's data[79];

[d] The 95%CI derived;

[i] Estimate and CI derived from information provided in main study;

[r] original rate estimates and CI converted into probabilities;

[t] total sample size;

[m] Different from Table 1 in Wawer et al[20] because there is a mistake in the original paper (denominator reported as 23 when actually 43);