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

Marie-Claude Boily, Rebecca F Baggaley, Lei Wang, Benoit Masse, Richard G White, Richard J Hayes, Michel Alary

Lancet Infect Dis 2009; 9: 118–29

Department of Infectious Disease Epidemiology, Faculty of Medicine, Imperial College, London, UK (M-C Boily PhD, R F Baggaley PhD)**; Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK** (R G White PhD, Prof R J Hayes DSc)**; Population Health Research Unit, Hôpital du Saint-Sacrement, Centre Hospitalier, University of Quebec, and Department of Social and Preventive Medicine, Faculty of Medicine, Laval University, Quebec City, Quebec, Canada** (M-C Boily, Prof M Alary PhD)**; and Statistical Center for HIV/AIDS Research and Prevention, Fred Hutchinson Cancer Research Center, Seattle, WA, USA** (L Wang PhD, B Masse PhD)

Correspondence to: Dr Marie-Claude Boily, Department of Infectious Disease Epidemiology, Imperial College, Norfolk Place, London N1 3LG, UK
mc.boily@imperial.ac.uk

We did a systematic review and meta-analysis of observational studies of the risk of HIV-1 transmission per heterosexual contact. 43 publications comprising 25 different study populations were identified. Pooled female-to-male (0·04% per act [95% CI 0·01–0·14]) and male-to-female (0·08% per act [95% CI 0·06–0·11]) transmission estimates in high-income countries indicated a low risk of infection in the absence of antiretrovirals. Low-income country female-to-male (0·38% per act [95% CI 0·13–1·10]) and male-to-female (0·30% per act [95% CI 0·14–0·63]) estimates in the absence of commercial sex exposure (CSE) were higher. In meta-regression analysis, the infectivity across estimates in the absence of CSE was significantly associated with sex, setting, the interaction between setting and sex, and antenatal HIV prevalence. The pooled receptive anal intercourse estimate was much higher (1·7% per act [95% CI 0·3–8·9]). Estimates for the early and late phases of HIV infection were 9·2 (95% CI 4·5–18·8) and 7·3 (95% CI 4·5–11·9) times larger, respectively, than for the asymptomatic phase. After adjusting for CSE, presence or history of genital ulcers in either couple member increased per-act infectivity 5·3 (95% CI 1·4–19·5) times versus no sexually transmitted infection. Study estimates among non-circumcised men were at least twice those among circumcised men. Low-income country estimates were more heterogeneous than high-income country estimates, which indicates poorer study quality, greater heterogeneity of risk factors, or under-reporting of high-risk behaviour. Efforts are needed to better understand these differences and to quantify infectivity in low-income 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 because of improved health procedures and treatment options, particularly in high-income 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 been questioned.[6–9] Some believe that sexual transmission has been overestimated, whereas iatrogenic transmission has been underestimated.[10–12] Quantification of the risk of HIV infection after sexual intercourse with an infected partner is needed to better understand the epidemiology of HIV infection worldwide and to enable appropriate public-health decisions to be taken.

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 on 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 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 or 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 (STIs).[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 and colleagues[49] published a systematic review of per-act HIV-1 transmission probabilities of 27 studies 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 do 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 (up to Sept 6, 2008) was done in three stages. First, PubMed, Science Direct, and NLM Gateway online databases were searched to September, 2006, by use of the following 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, 2007, and

again to Sept 6, 2008) by use of 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 that reported empirical per-act heterosexual HIV-1 transmission probability estimates, or sufficient information to derive these estimates, 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, 95% CIs, and study and participant characteristics, which were used to define covariates. Male-to-female and female-to-male estimates were extracted in preference to combined estimates. 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] To deal with zero values a small value of 0·000001 was used. 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 (see webappendix for details).[56] Heterogeneity across study estimates was explored by use of the Q statistic, subgroup and sensitivity analyses, and meta-regression techniques.[52–54] Random-effects meta-regression models were fitted on ln-transformed study estimates with the procedure "proc Mixed" in SAS version 9.13. Pooled estimates were exponentiated to obtain estimates on the original scale.

The main meta-analysis was done using the crude sex-specific estimates from each publication. If multiple publications reported estimates based on the same study population, the estimate from the largest or most recent sample was included—of these estimates, the largest took precedence. We then did sensitivity analyses by calculating pooled estimates for different subgroups of studies (eg, for women only, with and without commercial-sex exposure [CSE]). We also used univariate and multivariate meta-regression techniques to explore potential sources of heterogeneity across estimates with the following

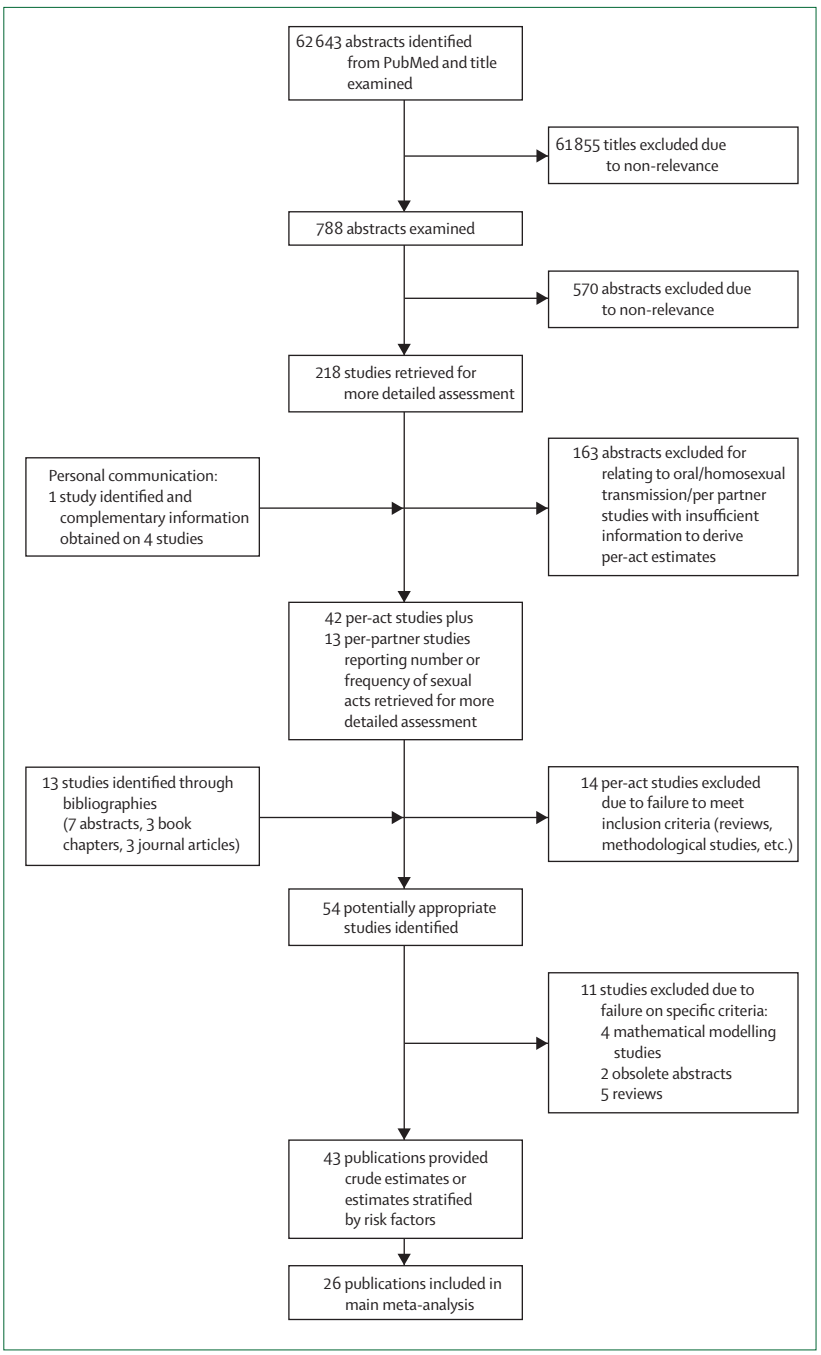

***Figure 1*: Selection of studies on heterosexual per-act HIV-1 transmission probabilities**
The 43 publications included 26 articles that were included in the main meta-analysis and seven articles only included in the sub-analyses by risk factor.[17,20,46,57–60] The remaining articles were duplicates and were not included in any analysis, but are shown in webtable 1 for completeness.

See **Online** for webappendix and webtable 1

For more on **WHO's Global Health Atlas** see http://www.who.int/globalatlas

covariates: study design, setting, year of publication, sex, exposure, condom use, STI, contamination, and antenatal HIV prevalence. Finally, we did a series of secondary analyses using transmission estimates stratified by risk factors.

Covariates were defined by available information from each study. The covariate setting was used as a marker of unmeasured risk factors (eg, viral subtype, co-infection).[49] The exposure covariate differentiated between studies done among partners after commercial sex, as clients or female sex workers (FSWs), or among partners of index cases infected after blood transfusion, or those exposed to various other sources of HIV (including intravenous drug use or those infected heterosexually). The contamination covariate was defined to indicate the likelihood of exposure to HIV via sources (sexual or blood) other than sex with the main index partner. The condom-use covariate characterised studies in which condom use was rare or somewhat controlled for. The STI covariate was defined to capture the prevalence of ulcerative STI reported in each study. HIV prevalence from antenatal clinics (ANC) at the time and study location reported from independent sources (eg, WHO's Global Health Atlas) 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 the webappendix.

	Study estimates (N)	Per-act HIV-1 transmission probability* (95% CI)	Heterogeneity	
			Q†	p value
All study estimates[15,16,18,19,21,61–64,66,67,70–73,75–81,84,87,88,89]	35	0·182% (0·110–0·299)	1590·5	<0·0001
Stratified by sex				
Combined[66,76,78,84,88]	5	0·179% (0·020–1·572)	91·4	<0·0001
Female-to-male[19,21,61–64, 70,72,81,87]	11	0·377% (0·114–1·251)	426·9	<0·0001
Male-to-female[15–16,18–19,62–63,67,70–73,75,77,79–81,87,89]	19	0·124% (0·078–0·199)	559·0	<0·0001
Stratified by sex and CSE				
No CSE‡				
Female-to-male[19,62–63,70,72,81,87]	8	0·164% (0·056–0·481)	147·5	<0·0001
Male-to-female[15–16,18–19,62–63,67,70–72,77,79–81,87,89]	17	0·143% (0·088–0·233)	356·9	<0·0001
CSE only§				
Female-to-male[21,61,64]	3	2·442% (0·690–8·658)	48·1	<0·0001
Male-to-female[73,75]	2	0·051% (0·020–0·131)	36·3	<0·0001
Stratified by sex and setting				
High-income countries				
Combined[76,78,84,88]	4	0·077% (0·037–0·161)	3·7	0·30
Female-to-male[81,87]	3	0·042% (0·013–0·141)	3·9	0·1411
Male-to-female[15–16,18,77,79–81,87,89]	10	0·081% (0·060–0·109)	14·8	0·0976
Low-income countries				
Combined[66]	1	1·179%	..	..
Female-to-male[19,21,61–64,70,72]	8	0·867% (0·279–2·701)	218·4	<0·0001
Male-to-female[19,62–63,67,70–73,75]	9	0·193% (0·086–0·433)	519·5	<0·0001
Female-to-male without CSE‡[19,62–63,70,72]	5	0·380% (0·131–1·099)	40·9	<0·0001
Male-to-female without CSE‡[19,62–63,67,70–72]	7	0·300% (0·144–0·626)	109·2	<0·0001

*Random-effects models. †Calculated on the ln scale. ‡Studies that included CSE were removed to assess their influence. §Estimates of CSE were all from low-income countries and were the only non-partner studies.

Table 1: **Pooled estimates for subsets of crude study estimates stratified by setting, sex, and commercial-sex exposure (CSE)**

Results

Study selection

Figure 1 shows details of the study selection procedure. 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. 42 studies reporting at least one per-act heterosexual HIV-1 transmission estimate and 13 studies reporting sufficient information to derive an estimate were identified from the PubMed search and in one case by personal communication. 14 publications, mainly reviews or methodological studies, were rejected. 13 additional publications were identified by perusing the bibliographies of relevant articles. 11 publications were rejected based on our pre-defined criteria. 43 publications that reported crude per-act estimates or estimates stratified by risk factors were found,[14–21,56–89] based on 25 study populations (webtable 1).[6,24–28,30,58,61,62,66,70–72,76,77,79,80,84,88–93]

Many studies reported results from the same study population (eg, five studies[14,16,81–83] were based on a US Centers for Disease Control and Prevention [CDC] study[25]) and estimates from the most recent or largest sample were included. Two studies reported on the same study population,[62,63] although we assumed them to be independent because they analysed different subpopulations over a different period.

Study characteristics

Overall, four study designs were used by the included studies: retrospective partner, prospective discordant-couple, and simple prospective (longitudinal cohort) and retrospective (cross-sectional) 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 on the basis of exposure to a salient risk factor.[15,16,43,60,85] For example, in transfusion studies, the infection time of index cases can be determined more precisely from the date of the transfusion.[16,25,27,43,76,79,80] Otherwise, infection time is estimated by exploring possible dates of infection or by defining a distribution of possible infection times by use of information from questionnaires and local epidemic curves or CD4-cell counts.[15,16,45,60,81,82,85] In prospective discordant-couple studies, stable (preferably monogamous) HIV-serodiscordant couples are followed up after diagnosis of the index partner,[19,20,70,72] and 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), respectively,

are recruited after sexual contact with potentially infected, high-risk partners. Because index cases are not recruited, exposure to HIV is estimated by use of HIV prevalence in the pool of potential partners and the reported coital frequency.[21,64,65,73,74]

To avoid duplication, 26 of 43 studies were included in the main meta-analysis of crude (unstratified by risk factors) estimates (webtable 1). We included male-to-female and female-to-male estimates were in preference to combined estimateds where possible. All but one[75] of these 26 studies reported on data collected before 2001 from high-income (Europe, North America) or low-income (Africa, Asia, Haiti) country settings. Seven studies from low-income countries were prospective discordant-couple studies,[19,62,63,66,70–72] five were simple retrospective or prospective studies,[21,61,64,73,75] and one was a retrospective partner study.[67] High-income country estimates were all derived from prospective discordant-couple studies[18,76,80,84,87–89] or retrospective partner studies.[15,16,77–79,81,87]

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 if index cases have been infected through contaminated blood products rather than intravenous drug use, or bisexual or casual sex. Partners of index cases infected through high-risk behaviour (drug use, 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 case. Six retrospective-partner studies included index cases who were transfusion recipients;[16,76,77,79–81] seven studies included index cases infected through various sources,[15,18,78,84,87–89] including mainly intravenous drug use;[88,89] and eight studies included index cases probably infected heterosexually.[19,62,63,66,67,70–72] All five non-partner (ie, simple prospective or retrospective) studies were done in low-income countries among participants after CSE, as clients,[61,64] FSWs,[73,75] or men with multiple partners (including sex with FSWs),[21] also with high rates of STIs.[21,61,64]

Many retrospective partner or discordant couple studies attempted to exclude partners with additional sources of HIV exposure other than sex with the index partner by use of various exclusion criteria.[15,27,30,31,77,88,89,93] For example, Marincovich and collegues[89] excluded partners who reported parenteral exposure, blood transfusion, tattooing, and multiple partners, whereas Pedraza and colleagues[88] excluded intravenous drug users 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 two studies.[62,63] Based on reported information, we judged that contamination was possible in ten studies because of occasional reports of extramarital sex[15,21,62–64,78,81,84] and/or potential exposure to blood.[61,63,64,73]

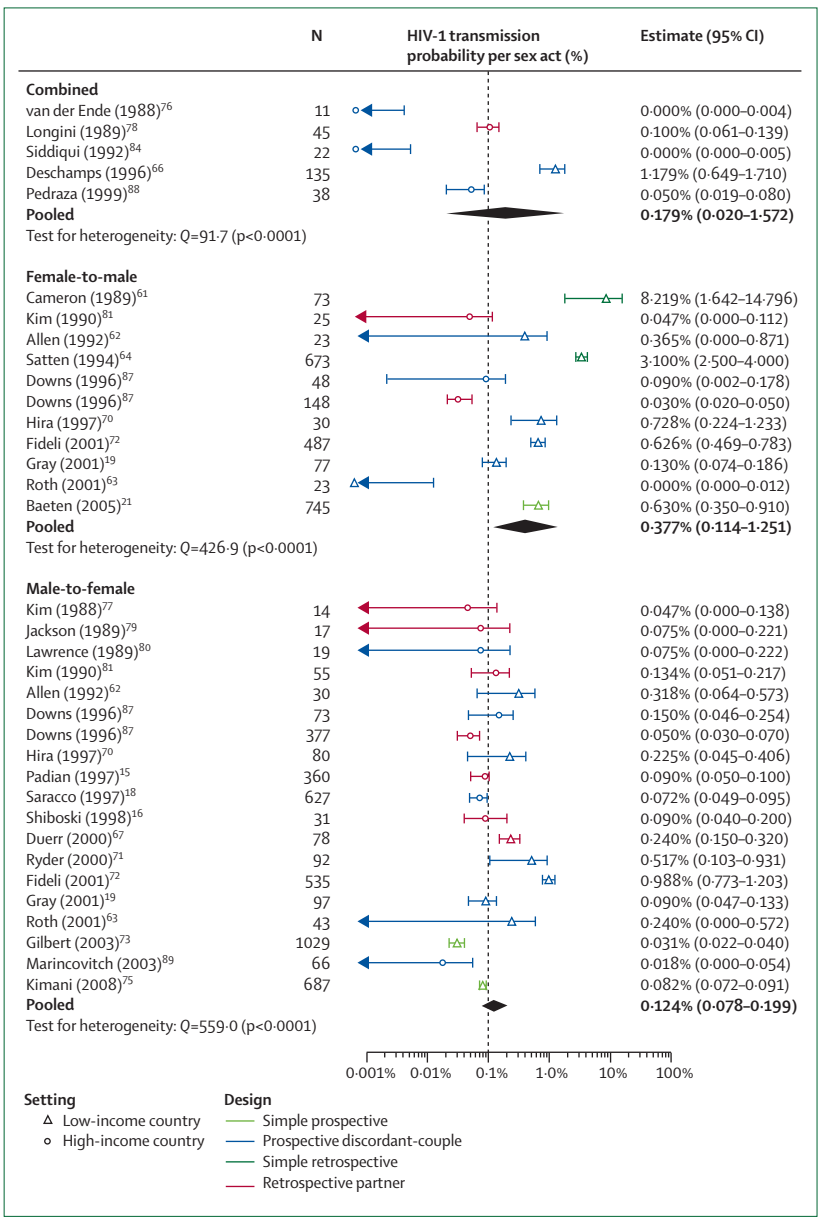

***Figure 2*: Crude sex specific per-act study estimates**
For reference, a vertical dotted line is shown at 0·1% because this has previously been a commonly cited value for HIV-1 per-act transmission probability.[49] Pooled data estimates were calculated by random-effects meta-analyses. Heterogeneity statistics were calculated on the ln scale. Arrow indicates zero value of estimate and/or lower confidence limit. See webtable 1 and webappendix for details of individual estimate derivation.

Because of the high risk associated with CSE, it was generally assumed to be the source of infection, which may not always be the case.[61,91,73] Contamination was thought unlikely in two studies,[20,72] because HIV transmissions within couples were matched by epidemiological linkage. Failure to control for condom use may lead to over-estimation of unprotected sex acts and underestimation of infectivity. Only three studies did not report any attempt to control for condom use or did not provide sufficient information (webtable 1).[61,64,78]

See Online for webtable 2

	RR (95% CI)	p value
High-income country		
Female-to-male	1 (reference)	..
Male-to-female	1·81 (0·83–3·95)	0·136
Combined	1·63 (0·62–4·29)	0·319
Low-income country		
Female-to-male	1 (reference)	..
Male-to-female	1·02 (0·53–2·00)	0·933
Combined*	5·61 (1·80–17·55)	0·003
Male-to-female transmission		
High-income country	1 (reference)	..
Low-income country	1·85 (0·88–3·92)	0·107
Female-to-male transmission		
High-income country	1 (reference)	.
Low-income country	3·25 (1·09–9·74)	0·035
ANC HIV prevalence†	1·05 (1·01–1·08)	0·007

Fraction of the variance explained=82% (calculated on the ln scale). Final model: sex (p=0·014)+setting (p=0·0001)+setting×sex (p=0·021)+antenatal clinic (ANC) HIV prevalence (p=0·007). *Includes only one study.[66] †The natural logarithm of the infectivity estimate was increased linearly by 0·046 times for each 1% increase in ANC HIV prevalence. The covariates explored in the different multi-regression models included sex, design, setting, exposure, condom, sexually transmitted infections, contamination, ANC HIV prevalence.

***Table 2*: Main multivariate analysis: final meta-regression model for the subset of crude study estimates from partner studies (n=30) without commercial-sex exposure**

Main meta-analyses

The meta-analysis included 35 crude sex-specific (male-to-female, female-to-male, combined) transmission probability estimates (webtable 1, figure 2). One publication reported independent estimates from both the prospective discordant and retrospective partner study components, which were both included.[87] Per-act estimates ranged from zero[76,84,89] to 8·2%,[61] and showed highly significant heterogeneity (table 1, figure 2). The highest (>0·1%) estimates were mostly from low-income countries. The heterogeneity across estimates remained significant even after stratification by sex (table 1). With further stratification by setting (high-income *vs* low-income countries), the heterogeneity across sex-specific study estimates was no longer significant for high-income countries only. The pooled combined, female-to-male, and male-to-female high-income country estimates were 0·08% per act (95% CI 0·04–0·16), 0·04% per act (95% CI 0·01–0·14), and 0·08% per act (95% CI 0·06–0·11), respectively. By contrast, the pooled female-to-male and male-to-female estimates for low-income countries were 0·867% per act (95% CI 0·279–2·601) and 0·193% per act (95% CI 0·086–0·433), respectively. The pooled male-to-female estimate with CSE only was much lower than the female-to-male estimates, indicating the relatively lower Senegalese and recent Kenyan estimates (webtable 1).[73,75] Interestingly, by excluding estimates after CSE, which were the only estimates from simple prospective and retrospective studies and were exclusively from low-income countries, the pooled male-to-female estimates increased, whereas the female-to-male estimates decreased (table 1). The heterogeneity between low-income country estimates remained.

In univariate meta-regression analyses, a substantial fraction of the variability across all 35 study estimates could be explained by either exposure, setting, STI prevalence, condom use, design, or ANC prevalence (webtable 2). Greater infectivity was associated with CSE, low-income 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 CSE (webtable 2). Among all low-income country estimates, only sex, condom use, and year of publication (negative association) were significantly associated with infectivity; no association was found after removing the estimates with CSE (webtable 2).

The multivariate meta-regression analyses aimed to explain the heterogeneity across the 30 high-income and low-income country estimates without CSE, which were all based on discordant-couple or retrospective partner studies. In models that controlled for sex (p>0·23) and study design (p>0·49), only setting, ANC prevalence or exposure were independently associated with infectivity (p<0·0001) and explained 62–68% of the variability (not shown). In models that included design (p>0·10), sex (p<0·015), setting (p<0·0001), and the interaction between setting and sex (p<0·036), only contamination (p=0·009) or ANC prevalence (p=0·006) remained significant and together explained 83–85% of the variability (not shown). Lower infectivity estimates were associated with the contamination category "no information" compared with the categories "possible" or "unlikely", which were not statistically different (p=0·45). Thus, our final model excluded design and included ANC prevalence (table 2).

Secondary analyses

Only two studies reported male-to-female estimates for receptive anal intercourse (pooled estimate 1·69% per act [95% CI 0·32–8·91]),[59,60] and five studies explicitly reported male-to-female estimates for vaginal sex only (pooled estimate 0·076% per act [95% CI 0·052–0·111]).[16,18,60,70,79] Additional information on these estimates is available from the authors on request.

Six publications reported low-income country estimates stratified by GUD status of HIV-1-susceptible partners,[21,57,61,65,69] which indicated increased HIV susceptibility caused by GUD, or by GUD status of the index case,[19] which indicated increased HIV infectivity. One study was excluded because the confidence interval could not be derived.[69] The only study[19] among stable couples, reported lower infectivity in the presence of GUD than those reported in the presence of CSE.[21,57,61,65] An additional eight study estimates in the absence of STI were also included.[18,59,65,71,77,80,81,87] Because of the small number of

estimates, simple explanatory meta-regression analyses were done. We classified the estimates into three categories: study participants without STI; without GUD but potentially other STI; and with GUD and potentially other STI (figure 3). The covariate GUD status alone explained 57% of the variability across study estimates. The meta-regression model with the covariates CSE and GUD status explained a larger fraction of the variability (81%) than GUD status with either covariates setting (77%) or sex (70%; details not shown). Estimates in the presence of GUD were five times larger than estimates in absence of STI, whereas CSE was associated with an 11-times increase in infectivity compared to estimates without CSE (table 3).

Seven studies reported estimates by disease stage of index partners from partner studies (figure 4).[17,20,56,58,60,78,81] We only included one[20] of the two studies reporting on the same low income country population.[20,56] Wawer and colleagues[20] reported many estimates from different subsamples of discordant couples in which index cases had been infected for different lengths of time. We used the pooled estimate from couples for which index cases had seroconverted for less than 5 months (1·07% per act), which was larger than from couples 6–15 months (0·17% per act) and 16–35 months (0·10% per act) after the index cases had seroconverted (figure 4). The study estimate from all couples with prevalent index cases (0·08% per act) was used for the asymptomatic stage. The late-stage estimate used corresponded to 6–15 months before death of index cases (0·49% per act).[20] Per-act estimates were 0·29–1·07%, 0·04–0·093%, and 0·13–5·67% for the early, asymptomatic, and late-stage disease, respectively. Disease stage alone explained 95% of the variability across estimates. After adjusting for disease stages, the addition of the setting covariate was not significant (table 3). The impact of mode of sexual transmission could not be explored owing to lack of data. The risk in the early (risk ratio [RR] 9·2 [95% CI 4·5–18·8]) and late (RR 7·3 [95% CI 4·5–11·9]) disease stages, adjusted for setting, were significantly larger than for the asymptomatic phase (table 3).

Only two studies reported empirical estimates stratified by level of either semen or serum viral load on the same study population (not shown).[19,20] Partners of index cases who had a median serum viral load of approximately 30 000 HIV RNA copies per mL (range <400–3·1×10^6 copies per mL <5 months after seroconversion) had a higher infectivity (1·07% per act) than those with a median serum viral load of approximately 2600 copies/mL by 15 months,[20] and even higher than Gray's estimate (0·23% per act) if viral load exceeded 38 500 copies per mL.[19] Wawer and colleagues'[20] estimate from couples for which prevalent index cases were followed up for 0–10 months was higher (0·09% per act at a median of ~10 300 copies per mL), albeit not significantly, than when followed up for more than 30 months (0·04% per act at a median of ~15 000 copies per mL). Gray and colleagues'[19] combined per-act estimates at high (>38 500 serum viral load copies per mL), medium (~1700–12 499 or 12 500–38 499 copies per mL), and low (<1700 copies per mL) viral loads were 0·23%, 0·13% or 0·14%, and 0·01%, respectively. Two studies 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.[22,23]

Only two studies reported female-to-male estimates by circumcision status (not shown).[21,61] Baeten and colleagues'[21] study female-to-male transmission estimate among uncircumcised men was approximately 2·6 times that among circumcised men (1·3% per act [95% CI 0·5–2·0] *vs* 0·5% per act [95% CI 0·3–0·7]) and 4·5 times larger in non-circumcised than circumcised men in the presence of GUD (1·8% per act [95% CI 0·0–3·7] *vs* 0·4% per act [95% CI 0·0–0·9]). In Cameron and

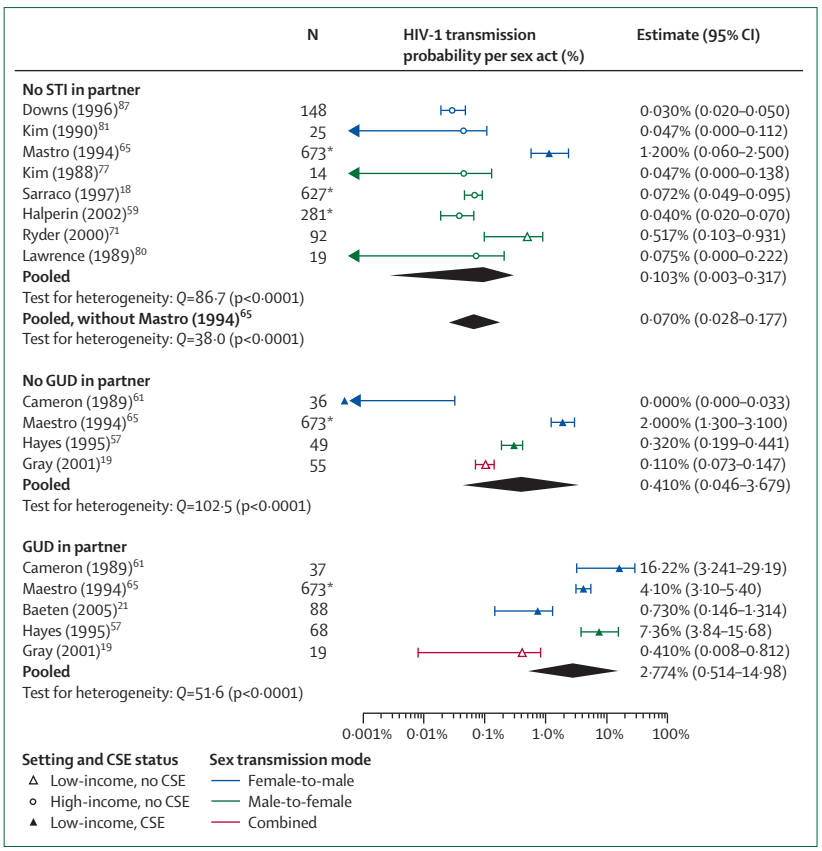

***Figure 3*: Per-act and pooled estimates for sub-analyses of estimates stratified by genital ulcer disease (GUD) status in HIV-1 susceptible partner†**

Pooled data estimates were calculated by random-effects meta-analyses. Heterogeneity statistics were calculated on the ln scale. Number (N) of participants in the subgroup sample (*total sample size). Arrow indicates zero value of estimate and/or lower confidence limit. See webappendix for details of individual estimate derivation. †Only one study[19] reported GUD status for the index cases rather than for HIV-susceptible partners. Estimate for Halperin et al[59] was adjusted for anal intercourse, condom use, and history of sexually transmitted infection. Hayes et al's[57] estimate was obtained during episodes of GUD, rather than during follow-up (which included periods with and without GUD episodes). Details for this analysis are available from the authors on request.

	RR (95%CI)	p value
Analysis by GUD status (17 study estimates)*		
GUD status	..	0·0162
No STI	1 (reference)	..
No GUD	1·11 (0·30–4·14)	..
GUD	5·29 (1·43–19·58)	..
Commercial-sex exposure	..	<0·0001
No	1 (reference)	..
Yes	11·08 (3·47–35·35)	..
Analysis by disease stage (14 study estimates)†		
Disease stage	..	<0·0001
Asymptomatic	1 (reference)	..
Early	9·17 (4·47–18·81)	..
Late	7·27 (4·45–11·88)	..
Setting	..	0·347
Low-income countries	1 (reference)	..
High-income countries	0·79 (0·49–1·29)	..

*Fraction of the total variance explained=81% (calculated on ln scale). †Fraction of the total variance explained=96% (calculated on ln scale).

Table 3: **Multivariate meta-regression models for sub-analysis by genital ulcer disease (GUD) status and disease stage**

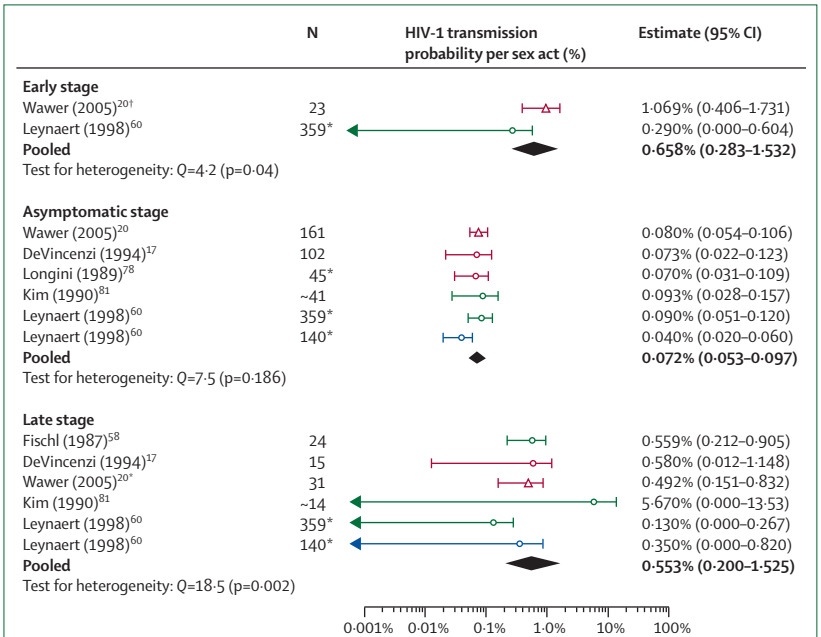

Figure 4: **Per-act and pooled estimates for sub-analyses of study estimates stratified by HIV-1 disease stage**
Pooled data estimates were calculated by random-effects meta-analyses. Heterogeneity statistics were calculated on the ln scale. Number (N) of participants in the subgroup sample (*total sample size). Arrow indicates zero value of estimate and/or lower confidence limit. See webappendix for details of individual estimate derivation. †For early-stage disease, we used the data from Wawer et al[20] at <5 months since seroconversion of the index case, in preference to the data provided by Pinkerton et al[56] (not shown). *For late-stage disease, we used the estimates obtained 6–15 months before death for Wawer et al's[20] study. Details on selection of estimates for this analysis is available from the authors on request.

colleagues' study,[61] study estimates were higher among uncircumcised men (18·5% per act [95% CI 2·3–34·8]) than among circumcised men (2·2% per act [95% CI 0·0–6·4]). Among those with GUD, estimates were six times higher among uncircumcised men (42·8% per act [95% CI 1·26–73·0]) than among circumcised men (6·7% per act [95% CI 0·0–19·2]). In the absence of GUD, no HIV transmission occurred in circumcised or uncircumcised men.[61]

Discussion

Our systematic review and meta-analysis of HIV-1 transmission probabilities per heterosexual act updates and extends the findings of a recent similar review.[49] We confirmed the earlier observation of substantial heterogeneity in per-act estimates,[49] provided sex-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 (risk ratios), instead of risk difference, which is easier to interpret. Heterogeneity across crude study estimates could be mostly explained by CSE as FSWs or clients, setting, sex, and ANC HIV prevalence at the time and location of the study. Although a previous review only found a weak association between sex and infectivity,[49] our results suggested that this may vary by settings. In the subset of estimates without CSE, the pooled female-to-male transmission estimate for high-income countries, adjusted for HIV prevalence, was about half the male-to-female or combined estimates (RR about 0·5), although the difference failed to reach significance. By contrast, the adjusted low-income country female-to-male and male-to-female estimates were very similar (RR about 1·0), and the female-to-male low-income country estimate (RR about 3·3) was significantly larger than the female-to-male high-income country estimate. The male-to-female or combined pooled estimates in our sub-analyses in the absence of receptive anal intercourse, GUD, CSE, or for the asymptomatic phase were of similar magnitude (about 0·07% per act) to the male-to-female and combined pooled estimates from high-income countries (about 0·08% per act), 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 on infectivity.[16,39,42,49,69,94] In agreement with studies among homosexual men,[5,95–97] our pooled estimate by receptive anal intercourse supports evidence that it is a more risky practice than receptive vaginal sex. Two studies reporting per-act estimates by circumcision status suggested a three to eight times increase in HIV infection among uncircumcised men overall or in presence of GUD.[21,61] This is consistent, yet somewhat higher, with the results

of two previous meta-analyses,[94,98] and three recent randomised controlled trials of male circumcision.[99–101] We found that the presence of GUD and CSE were independently associated with increased infectivity. Our GUD cofactor estimate (RR 5·3) was intermediate between previous study estimates for high-risk groups (10–50 and 50–300 for male-to-female and female-to-male transmission per act, respectively),[57] and those from a meta-analysis of observational studies that reported a 2·8 times (95% CI 2·0–4·0) and 4·4 times (95% CI 2·9–6·6) increase in female and male susceptibility caused by GUD, respectively.[102]

Our RRs and estimates from observational studies may be biased because of misclassification, undiagnosed STI, or misreporting of symptoms. Additionally, the intermittent nature of GUD means that it is unlikely to have been present throughout the at-risk period, and per-contact cofactor effects may therefore be underestimated.[44,57] Our cofactor estimate predominantly captured the increased HIV susceptibility caused by GUD (only one study reported estimates stratified by GUD status of index cases[19]). Thus, the increased risk associated with CSE may partly indicate increases in HIV infectivity because high-risk index cases (FSW, clients) would probably have also been infected with GUD or other STIs. Baeten and colleagues'[21] female-to-male study estimate from men with multiple partners (31% monogamous, 57% sex with FSW) was higher than from the subsample of men who only reported sex with their wives (0·63% [0·35–0·91] *vs* 0·38% [<0·01–69·73] per act, p>0·10).

Interestingly, the early Kenyan[61] and Thai[64] FSW-to-client estimates were substantially larger than the Senegalese and the recent Kenyan client-to-FSW estimates.[73–75] Although these estimates are probably imprecise because they were based on simple retrospective or cross-sectional study design, the large difference (>35 times) could also be caused by other cofactors. STI prevalence 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.[103,104] By contrast, the client studies were done in east Africa (early in the epidemic) and Thailand, where male circumcision prevalence is lower than in west Africa,[105] and at a time when STI and GUD were virtually ubiquitous, FSW were experiencing an explosive HIV epidemic, and index partners were more likely to be in the primary phase of HIV infection.[46,61,90,106] For example, one group reported prevalences of 21% *Haemophilus ducreyi*, 80% herpes simplex virus 2, and 9% GUD among Thai FSWs.[65,106] Additionally, Kimani and colleagues[75] suggested that the decline in per-act infectivity observed over calendar time in their study correlated with a decline in STI prevalence among FSWs.

Previous individual-based studies showed an association between HIV infectivity and viral load or time since infection.[22,24,28,107–110] Our risk-factor analysis also suggested increased infectivity for index cases in the early and late phase of infection compared with the asymptomatic phase. The difference between estimates for the early and late stages was not significant, which may indicate 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 lack of statistical power. A recent re-analysis of Wawer and colleagues' data[20] suggested that primary infection and late-stage infection were 26 and seven times higher than asymptomatic infection, respectively, and that the high infectiousness during primary infection lasted approximately 3 months.[111]

We initially did not impose any inclusion criteria based on study design because 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 so-called "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 such studies. Frailty selection would result in under-estimation of infectivity. Shiboski and colleagues[16,45] have also suggested that heterogeneity in infectivity was not well shown by the US CDC data[25] and CDC Heterosexual AIDS Transmission Study[27] retrospective-partner studies because the duration of many relationships was too short compared with the time since infection of index cases.

Results from our risk-factor analyses are mainly explanatory. The estimates of the magnitude of the cofactor effects may not be very precise because of 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 subgroups of the study sample. Publication biases may also be present because 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 CSE is difficult to interpret, but is unlikely to be caused by study design or analytic methods. As reported previously,[49] study design was only weakly associated with infectivity. Additionally, we converted estimates reported as rates into probabilities (webappendix), which improved comparability across studies. Larger transmission probabilities may lead to higher HIV prevalence in the general population, as estimated in low-income countries. Alternatively, higher HIV prevalence may increase the likelihood of contamination resulting from exposure to additional sources of infection other than sex with the main index

partner and thus bias estimates upward. Low-income country estimates displayed greater heterogeneity than high-income country estimates. Sex, date of publication, or the covariate condom (confounded with CSE) only explained a significant fraction of the variation across low-income country estimates (if estimates with CSE 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 indicate uncaptured contamination or variation in the prevalence of key risk factors. For example, the larger female-to-male than male-to-female estimates in three discordant-partner studies[19,62,70] in low-income countries may indicate contamination, because men are more likely than women to report extramarital sex before or during the study period.[28,62,63,66,71,112] Interestingly, in Fideli and colleagues' study,[72] in which transmission events within couples could be epidemiologically linked, female-to-male transmission was lower than male-to-female transmission. However, their estimates were larger than Wawer and colleagues' study,[20] whereby infections within couples were also confirmed by epidemiological linkage, which reduces the risk of misclassification, but does not reduce biases caused by misreporting of number of unprotected sex acts or unmeasured risk factors.[113]

Because many studies in low-income countries were done within the context of interventions involving an important counselling component,[19,20,62,70,71] 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.[19,70] Other studies tried to minimise misreporting biases on sexual behaviour by checking for concordance between both members in the couple or using sexual diaries.[19,66] In Roth and colleagues' study,[63] because men reported more protected sex acts then women, we used the sexual activity reported by women to minimise over-estimation of infectivity. Conflicting evidence remains about unmeasured exposure to contaminated equipment or blood transfusion that may have increased low-income country estimates.[7,8,10–12,114–116] 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.[73,74,91,103,104]

We cannot exclude the possibility that our high and heterogeneous low-income country estimates are a result of unmeasured heterogeneity in the prevalence of risk factors. To assert that a 3·5-times difference in female-to-male pooled estimates between low-income and high-income countries is solely caused by contamination would imply that approximately 70% of infections are acquired outside the main relationship. Although this seems inconsistent with the relatively low proportion of unlinked infections reported in at least two studies,[20,72,112] this remains a subject of debate.[114–117] Powers and colleagues[49] reported a weak association between region and infectivity, which they assumed was a proxy for viral subtypes. However, they also found greater heterogeneity across estimates from Africa. The reason for the differences by setting is likely to be multifactorial. Lack of male circumcision may be more important in low-income countries than in Europe (where circumcision is rare) because of interacting cofactors such as ulcerative STI.[39,118–121] Between-settings differences may never be completely understood because risk factors such as STI prevalences may have changed since the beginning of the epidemic.[75,122] Greater heterogeneity in risk factors or median viral loads in low-income countries may exacerbate frailty selection over time. Median plasma viral loads as high as $1{\cdot}26\times10^6$ copies per mL have been observed among acutely infected men in Malawi, and presence of STI was the stronger risk factor associated with high viral load.[42,121] 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.[42,121] This possibility may also explain why estimates tended to be lower (albeit not significantly) for couples with prevalent index cases with 31–40 months of follow-up (0·04% per act), compared with 0–10 months (0·09% per act), despite the higher median viral load reported after 30 months.[20] However, unmeasured reduction in prevalence of risk factors resulting from longer exposure to the study or other intervention is also possible.

Heterogeneity across estimates may also be caused by population-level declines in infectivity over calendar time as the fraction of recent seroconverters is expected to decrease in maturing epidemics.[57,62,63,75] Nonoxinol 9 spermicide, which has been associated with increased susceptibility to GUD and HIV infection,[36,123,124] was also reported in at least four early African studies.[62,63,70,72] However, in the study by Allen and colleagues,[62] only 12% of women reported the use of nonoxinol 9 without condoms, 6% and 19% reported a history of STI in the past year and past 2 years, respectively, which were similar to estimates reported in the Rakai study.[19] Most studies were done before wide-scale use of antiretroviral therapy and is therefore unlikely to have influenced results.[29,32]

Conclusions

Our results indicated higher transmission probabilities for low-income than for high-income country studies. The greater heterogeneity of low-income 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 caused by differential infectivity of the different viral subtypes, mutation of chemokine-receptor genes, contraception method, genetic, biological, and virological host factors, and interaction with other

Search strategy and selection criteria

These are described in detail in the Methods section.

infectious diseases,[5,33–41,50,108–111,118,123–125] 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 to design appropriate prevention strategies. The methodology of discordant-partner studies could be improved by designing and powering them for carefully planned risk-factor analyses, including epidemiological linkage, by use of data collection methods to reduce social desirability biases, cross-validating sexual history in couples, and carefully documenting non-sexual potential sources of contamination.

Conflicts of interest

We declare that we have no conflicts of interest. RFB was supported during part of the research by an unrestricted educational grant from GlaxoSmithKline.

Acknowledgments

This work was supported by the Wellcome Trust (RFB [GR082623MA] and RGW [GR078499MA]), GlaxoSmithKline (RFB), and the UK Medical Research Council (RGW). Part of this work was supported by the National Institute of Allergy Infectious Diseases of the US National Institutes of Health (BM and LW: 5U01AI068615). MA is a National Researcher of the Fonds de la Recherche en Santé du Québec, Canada (grant #8722). Support for this study was partly provided by the Bill and Melinda Gates Foundation (M-CB). The views expressed herein are those of the authors and do not necessarily reflect the official policy or position of the Bill & Melinda Gates Foundation. We thank Elizabeth Baggaley and Kamal Desai for language translations, and Peter Gilbert and Stephen Shiboski for personal communication. We would also like to thank the anonymous reviewers for very useful comments.

References

1 Brewer TH, Hasbun J, Ryan CA, et al. Migration, ethnicity and environment: HIV risk factors for women on the sugar cane plantations of the Dominican Republic. *AIDS* 1998; **12:** 1879–87.

2 Fiscus SA, Adimora AA, Schoenbach VJ, et al. Perinatal HIV infection and the effect of zidovudine therapy on transmission in rural and urban counties. *JAMA* 1996; **275:** 1483–88.

3 Harris NS, Thomson SJ, Call R, et al. Zidovudine and perinatal human immunodeficiency virus type 1 transmission: a population-based approach. *Pediatrics* 2002; **109:** e60.

4 Thaithumyanon P, Thisyakorn U, Limpongsanurak S, et al. Intrapartum and neonatal zidovudine treatment in reduction of perinatal HIV-1 transmission in Bangkok. *J Med Assoc Thai* 2001; **84:** 1229–34.

5 Baggaley RF, Boily MC, White RG, Alary M. Systematic review of HIV-1 transmission probabilities: In absence of antiretroviral therapy. Geneva: UNAIDS Reference Group on Estimates, Modelling and Projection, 2004.

6 Plummer FA, Simonsen JN, Cameron DW, et al. Cofactors in male-female sexual transmission of human immunodeficiency virus type 1. *J Infect Dis* 1991; **163:** 233–39.

7 Schmid GP, Buve A, Mugyenyi P, et al. Transmission of HIV-1 infection in sub-Saharan Africa and effect of elimination of unsafe injections. *Lancet* 2004; **363:** 482–88.

8 Buve A, Bishikwabo-Nsarhaza K, Mutangadura G. The spread and effect of HIV-1 infection in sub-Saharan Africa. *Lancet* 2002; **359:** 2011–17.

9 Nyindo M. Complementary factors contributing to the rapid spread of HIV-1 in sub-Saharan Africa: a review. *East Afr Med J* 2005; **82:** 40–46.

10 Deuchert E, Brody S. Plausible and implausible parameters for mathematical modeling of nominal heterosexual HIV transmission. *Ann Epidemiol* 2007; **17:** 237–44.

11 Gisselquist D, Potterat JJ, Brody S, Vachon F. Let it be sexual: how health care transmission of AIDS in Africa was ignored. *Int J STD AIDS* 2003; **14:** 148–61.

12 Gisselquist D, Potterat JJ, Brody S. Running on empty: sexual co-factors are insufficient to fuel Africa's turbocharged HIV epidemic. *Int J STD AIDS* 2004; **15:** 442–52.

13 Garnett GP, Rottingen JA. Measuring the risk of HIV transmission. *AIDS* 2001; **15:** 641–43.

14 Kaplan EH. Modeling HIV infectivity: must sex acts be counted? *J Acquir Immune Defic Syndr* 1990; **3:** 55–61.

15 Padian NS, Shiboski SC, Glass SO, Vittinghoff E. Heterosexual transmission of human immunodeficiency virus (HIV) in northern California: results from a ten-year study. *Am J Epidemiol* 1997; **146:** 350–57.

16 Shiboski SC, Padian NS. Epidemiologic evidence for time variation in HIV infectivity. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998; **19:** 527–35.

17 de Vincenzi IA, European Study Group on Heterosexual Transmission of HIV. Longitudinal study of human immunodeficiency virus transmission by heterosexual partners. *N Engl J Med* 1994; **331:** 341–46.

18 Saracco A, Veglia F, Lazzarin A. Risk of HIV-1 transmission in heterosexual stable and random couples. The Italian Partner Study. *J Biol Regul Homeost Agents* 1997; **11:** 3–6.

19 Gray RH, Wawer MJ, Brookmeyer R, et al. Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda. *Lancet* 2001; **357:** 1149–53.

20 Wawer MJ, Gray RH, Sewankambo NK, et al. Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. *J Infect Dis* 2005; **191:** 1403–09.

21 Baeten JM, Richardson BA, Lavreys L, et al. Female-to-male infectivity of HIV-1 among circumcised and uncircumcised Kenyan men. *J Infect Dis* 2005; **191:** 546–53.

22 Pilcher CD, Tien HC, Eron JJ Jr, et al. Brief but efficient: acute HIV infection and the sexual transmission of HIV. *J Infect Dis* 2004; **189:** 1785–92.

23 Chakraborty H, Sen PK, Helms RW, et al. Viral burden in genital secretions determines male-to-female sexual transmission of HIV-1: a probabilistic empiric model. *AIDS* 2001; **15:** 621–27.

24 Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. *N Engl J Med* 2000; **342:** 921–29.

25 Peterman TA, Stoneburner RL, Allen JR, et al. Risk of human immunodeficiency virus transmission from heterosexual adults with transfusion associated infections. *JAMA* 1988; **259:** 55–58.

26 Padian N, Marquis L, Francis DP, et al. Male-to-female transmission of human immunodeficiency virus. *JAMA* 1987; **258:** 788–90.

27 O'Brien TR, Busch MP, Donegan E, et al. Heterosexual transmission of human immunodeficiency virus type 1 from transfusion recipients to their sex partners. *J Acquir Immune Defic Syndr* 1994; **7:** 705–10.

28 Tovanabutra S, Robison V, Wongtrakul J, et al. Male viral load and heterosexual transmission of HIV-1 subtype E in northern Thailand. *J Acquir Immune Defic Syndr* 2002; **29:** 275–83.

29 Porco TC, Martin JN, Page-Shafer KA, et al. Decline in HIV infectivity following the introduction of highly active antiretroviral therapy. *AIDS* 2004; **18:** 81–88.

30 European Study Group on Heterosexual Transmission of HIV. Comparison of female to male and male to female transmission of HIV in 563 stable couples. *BMJ* 1992; **304:** 809–13.

31 European Study Group on Heterosexual Transmission of HIV. Risk factors for male to female transmission of HIV. *BMJ* 1989; **298:** 411–15.

32 Wilson DP, Law MG, Grulich AE, Cooper DA, Kaldor JM. Relation between HIV viral load and infectiousness: a model-based analysis. *Lancet* 2008; **372:** 314–20.

33 Holmberg SD, Horsburgh CR Jr, Ward JW, Jaffe HW. Biologic factors in the sexual transmission of human immunodeficiency virus. *J Infect Dis* 1989; **160:** 116–25.

34 Buchacz KA, Wilkinson DA, Krowka JF, et al. Genetic and immunological host factors associated with susceptibility to HIV-1 infection. *AIDS* 1998; **12** (suppl A)**:** S87–94.

35 Samson M, Libert F, Doranz BJ, et al. Resistance to HIV-1 infection in caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene. *Nature* 1996; **382:** 722–25.

36 Van Damme L, Ramjee G, Alary M, et al. Effectiveness of COL-1492, a nonoxynol-9 vaginal gel, on HIV-1 transmission in female sex workers: a randomised controlled trial. *Lancet* 2002; **360:** 971–77.

37 Hudgens, MG, Longini IM, Vanichseni S, et al. Subtype-specific transmission probabilities for human immunodeficiency virus type 1 among injecting drug users in Bangkok, Thailand. *Am J Epidemiol* 2002; **155:** 159–68.

38 Soto-Ramirez LE, Renjifo B, McLane MF, et al. HIV-1 Langerhans' cell tropism associated with heterosexual transmission of HIV. *Science* 1996; **271:** 1291–93.

39 Wasserheit JN. Epidemiological synergy. Interrelationships between human immunodeficiency virus infection and other sexually transmitted diseases. *Sex Transm Dis* 1992; **19:** 61–77.

40 Laga M, Alary M, Nzila N, et al. Condom promotion, sexually transmitted diseases treatment, and declining incidence of HIV-1 infection in female Zairian sex workers. *Lancet* 1994; **344:** 246–48.

41 Sewankambo N, Gray RH, Wawer MJ, et al. HIV-1 infection associated with abnormal vaginal flora morphology and bacterial vaginosis. *Lancet* 1997; **350:** 546–50.

42 Cohen MS, Pilcher CD. Amplified HIV transmission and new approaches to HIV prevention. *J Infect Dis* 2005; **191:** 1391–93.

43 Shiboski S, Padian NS. Population- and individual-based approaches to the design and analysis of epidemiologic studies of sexually transmitted disease transmission. *J Infect Dis* 1996; **174** (suppl 2)**:** S188–200.

44 Boily MC, Anderson RM. Measure human immunodeficiency virus transmission and the role of other sexually transmitted diseases. Measures of association and study design. *Sex Transm Dis* 1996; **23:** 312–32.

45 Shiboski SC, Jewell NP. Statistical analysis of the time dependence of HIV infectivity based on partner study data. *J Am Stat Assoc* 1992; **87:** 360–72.

46 Mastro TD, de Vincenzi I. Probabilities of sexual HIV-1 transmission. *AIDS* 1996; **10** (suppl A)**:** S75–82.

47 May RM, Anderson RM. Transmission dynamics of HIV infection. *Nature* 1987; **326:** 137–42.

48 Gisselquist D, Potterat JJ. Heterosexual transmission of HIV in Africa: an empiric estimate. *Int J STD AIDS* 2003; **14:** 162–73.

49 Powers KA, Poole C, Pettifor AE, Cohen MS. Rethinking the heterosexual infectivity of HIV-1: systematic review and meta-analysis. *Lancet Infect Dis* 2008; **8:** 553–63.

50 Poulsen AG, Kvinesdal BB, Aaby P, et al. Lack of evidence of vertical transmission of human immunodeficiency virus type 2 in a sample of the general population in Bissau. *J Acquir Immune Defic Syndr* 1992; **5:** 25–30.

51 De Cock KM, Adjorlolo G, Ekpini E, et al. Epidemiology and transmission of HIV-2: why there is no HIV-2 pandemic. *JAMA* 1993; **270:** 2083–86.

52 Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger M, Davey Smith G, Altman DG, eds. Systematic reviews in health care: meta-analysis in context, 2nd edn. London: BMJ Publishing Group, 2001: 285–313.

53 Hartung J, Knapp G. An alternative test procedure for meta-analysis. In: Schulze R, Holling H, Bohning D, eds. Meta-analysis. New developments and applications in medical and social sciences. Cambridge, MA: Hogrefe & Huber, 2003.

54 van Houwelingen, HC, Arends LR, Stijnen T. Tutorial in biostatistics. Advanced methods in meta-analysis: multivariate apporach and meta-regression. *Stat Med* 2002; **21:** 589–624.

55 Baggaley RF, Boily MC, White RG, Alary M. Risk of HIV-1 transmission for parenteral exposure and blood transfusion: a systematic review and meta-analysis. *AIDS* 2006; **20:** 805–12.

56 Pinkerton SD. Probability of HIV transmission during acute infection in Rakai, Uganda. *AIDS Behav* 2008; **12:** 677–84.

57 Hayes RJ, Schulz KF, Plummer FA. The cofactor effect of genital ulcers on the per-exposure risk of HIV transmission in sub-Saharan Africa. *J Trop Med Hyg* 1995; **98:** 1–8.

58 Fischl MA, Dickinson GM, Scott GB, et al. Evaluation of heterosexual partners, children, and household contacts of adults with AIDS. *JAMA* 1987; **257:** 640–44.

59 Halperin DT, Shiboski SC, Palefsky JM, Padian NS. High level of HIV-1 infection from anal intercourse: a neglected risk factor in heterosexual AIDS prevention. Proceedings of the XIV International Conference on AIDS, Barcelona, Spain; July 7–12, 2002 [abstract ThPeC7438].

60 Leynaert B, Downs AM, de Vincenzi I. Heterosexual transmission of human immunodeficiency virus: variability of infectivity throughout the course of infection. *Am J Epidemiol* 1998; **148:** 88–96.

61 Cameron DW, Simonsen JN, D'Costa LJ, et al. Female to male transmission of human immunodeficiency virus type 1: risk factors for seroconversion in men. *Lancet* 1989; **2:** 403–07.

62 Allen S, Tice J, Van de Perre P, et al. Effect of serotesting with counselling on condom use and seroconversion among HIV discordant couples in Africa. *BMJ* 1992; **304:** 1605–09.

63 Roth DL, Stewart KE, Clay OJ, et al. Sexual practices of HIV discordant and concordant couples in Rwanda: effects of a testing and counselling programme for men. *Int J STD AIDS* 2001; **12:** 181–88.

64 Satten, GA, Mastro TD, Longini IM Jr. Modelling the female-to-male per-act HIV transmission probability in an emerging epidemic in Asia. *Stat Med* 1994; **13:** 2097–106.

65 Mastro TD, Satten GA, Nopkesorn T, et al. Probability of female-to-male transmission of HIV-1 in Thailand. *Lancet* 1994; **343:** 204–07.

66 Deschamps MM, Pape JW, Hafner A, Johnson WD Jr. Heterosexual transmission of HIV in Haiti. *Ann Intern Med* 1996; **125:** 324–30.

67 Duerr A, Hsia J, Nicolosi A, et al. Probability of male-to-female HIV transmission among couples with HIV subtype E and B. Proceedings of the XIII International Conference on AIDS, Durban, South Africa; Jul 9–14, 2000 [abstract WePpC1319].

68 Duerr A, Xia Z, Nagachinta T, Tovanabutra S, Tansuhaj A, Nelson K. Probability of male-to-female HIV transmission among married couples in Chiang Mai, Thailand. Proceedings of the X International Conference on AIDS, Yokahama, Japan; Aug 7–12, 1994 [abstract 105C].

69 Corey L, Wald A, Celum CL, Quinn TC. The effects of herpes simplex virus-2 on HIV-1 acquisition and transmission: a review of two overlapping epidemics. *J Acquir Immune Defic Syndr* 2004; **35:** 435–45.

70 Hira SK, Feldblum PJ, Kamanga J, et al. Condom and nonoxynol-9 use and the incidence of HIV infection in serodiscordant couples in Zambia. *Int J STD AIDS* 1997; **8:** 243–50.

71 Ryder RW, Kamenga C, Jingu M, et al. Pregnancy and HIV-1 incidence in 178 married couples with discordant HIV-1 serostatus: additional experience at an HIV-1 counselling centre in the Democratic Republic of the Congo. *Trop Med Int Health* 2000; **5:** 482–87.

72 Fideli US, Allen SA, Musonda R, et al. Virologic and immunologic determinants of heterosexual transmission of human immunodeficiency virus type 1 in Africa. *AIDS Res Hum Retroviruses* 2001; **17:** 901–10.

73 Gilbert PB, McKeague IW, Eisen G, et al. Comparison of HIV-1 and HIV-2 infectivity from a prospective cohort study in Senegal. *Stat Med* 2003; **22:** 573–93.

74 Donnelly C, Leisenring W, Kanki P, Awerbuch T, Sandberg S. Comparison of transmission rates of HIV-1 and HIV-2 in a cohort of prostitutes in Senegal. *Bull Math Biol* 1993; **55:** 731–43.

75 Kimani J, Kaul R, Nagelkerke NJ, et al. Reduced rates of HIV acquisition during unprotected sex by Kenyan female sex workers predating population declines in HIV prevalence. *AIDS* 2008; **22:** 131–37.

76 van der Ende ME, Rothbarth P, Stibbe J. Heterosexual transmission of HIV by haemophiliacs. *BMJ* 1988; **297:** 1102–03.

77 Kim HC, Raska K, Clemow L, et al. Human immunodeficiency virus infection in sexually active wives of infected hemophilic men. *Am J Med* 1988; **85:** 472–76.

78 Longini IM, Scott Clark W, Haber M, Horsburgh R Jr. The stages of HIV infection: waiting times and infection transmission probabilities. In: Castillo-Chavez C, ed. Mathematical and statistical approaches to AIDS epidemiology. Berlin: Springer-Verlag, 1989: 111–37.

79 Jackson JB, Kwork SY, Hopsicker JS, et al. Absence of HIV-1 infection in antibody negative sexual partners of HIV-1 infected hemophiliacs. *Transfusion* 1989; **29:** 265–67.

80 Lawrence DN, Jason JM, Holman RC, Heine P, Evatt BL. Sex practice correlates of human immunodeficiency virus transmission and acquired immunodeficiency syndrome incidence in heterosexual partners and offspring of U.S. hemophilic men. *Am J Hematol* 1989; **30:** 68–76.

81 Kim MY, Lagakos SW. Estimating the infecivity of HIV from partner studies. *Ann Epidemiol* 1990; **1:** 117–28.

82 Wiley JA, Herschkorn SJ, Padian NS. Heterogeneity in the probability of HIV transmission per sexual contact: the case of male-to-female transmission in penile-vaginal intercourse. *Stat Med* 1989; **8:** 93–102.

83 Kramer I, Yorke JA, Yorke ED. Modelling non-monogamous heterosexual transmission of AIDS. *Math Comput Model* 1990; **13:** 99–107.

84 Siddiqui NS, Brown LS Jr, Phillips RY, Vargas O, Makuch RW. No seroconversions among steady sex partners of methadone-maintained HIV-1-seropositive injecting drug users in New York City. *AIDS* 1992; **6:** 1529–33.

85 Jewell NP, Shiboski SC. Statistical analysis of HIV infectivity based on partner studies. *Biometrics* 1990; **46:** 1133–50.

86 Jewell NP, Malani HM, Vittinghoff E. Non parametric estimation for a form of doubly censored-data, with application to two problems in AIDS. *J Am Stat Assoc* 1994; **89:** 7–19.

87 Downs AM, De Vincenzi I. Probability of heterosexual transmission of HIV: relationship to the number of unprotected sexual contacts. *J Acquir Immune Defic Syndr Hum Retrovirol* 1996; **11:** 388–95.

88 Pedraza MA, del Romero J, Fernando R, et al. Heterosexual transmission of HIV-1 associated with high plasma viral load levels and a positive viral isolation in the infected partner. *J Acquir Immune Defic Syndr Hum Retrovirol* 1999; **21:** 120–25.

89 Marincovich B, Castilla J, del Romero J, et al. Absence of hepatitis C virus transmission in a prospective cohort of heterosexual serodiscordant couples. *Sex Transm Infect* 2003; **79:** 160–62.

90 Nopkesorn T, Mastro TD, Sangkharomya S, et al. HIV-1 infection in young men in Northern Thailand. *AIDS* 1993; **7:** 1233–39.

91 Kanki P, M'Boup S, Marlink K, et al. Prevalence and risk determinants of human immunodeficiency virus type-2 (HIV-2) and human immunodeficiency virus type-1 (HIV-1) in west African female prostitutes. *Am J Epidemiol* 1992; **36:** 895–907.

92 Rakwar J, Lavreys L, Thompson ML, et al. Cofactors for the acquisition of HIV-1 among heterosexual men: prospective cohort study of trucking company workers in Kenya. *AIDS* 1999; **13:** 607–14.

93 Nicolosi A, Corrêa Leite ML, Musicco M, et al. The efficiency of male-to-female and female-to-male sexual transmission of the human immunodeficiency virus: a study of 730 stable couples. *Epidemiology* 1994; **5:** 570–75.

94 Weiss HA, Quigley MA, Hayes RJ. Male circumcision and risk of HIV infection in sub-Saharan Africa: a systematic review and meta-analysis. *AIDS* 2000; **14:** 2361–70.

95 DeGruttola V, Seage GR 3rd, Mayer KH, Horsburgh CR Jr. Infectiousness of HIV between male homosexual partners. *J Clin Epidemiol* 1989; **42:** 849–56.

96 Vittinghoff E, Douglas J, Judson F, et al. Per-contact risk of human immunodeficiency virus transmission between male sexual partners. *Am J Epidemiol* 1999; **150:** 306–11.

97 Seage GR, Mayer KH, Horsburgh CJR. Risk of human immunodeficiency virus infection from unprotected receptive anal intercourse increases with decline in immunologic status of infected partners. *Am J Epidemiol* 1993; **137:** 899–908.

98 Siegfried N, Muller M, Volmink J, et al. Male circumcision for prevention of heterosexual acquisition of HIV in men. *Cochrane Database Syst Rev* 2003; **3:** CD003362.

99 Auvert B, Taljaard D, Lagarde E, et al. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 trial. *PLoS Med* 2005; **2:** e298.

100 Gray RH, Kigozi G, Serwadda D, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. *Lancet* 2007; **369:** 657–66.

101 Bailey RC, Moses S, Parker CB, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. *Lancet* 2007; **369:** 643–56.

102 Rottingen JA, Cameron DW, Garnett GP. A systematic review of the epidemiologic interactions between classic sexually transmitted diseases and HIV: how much really is known? *Sex Transm Dis* 2001; **28:** 579–97.

103 Laurent C, Seck K, Coumba N, et al. Prevalence of HIV and other sexually transmitted infections, and risk beahviours in unregistered sex workers in Dakar, Senegal. *AIDS* 2003; **17:** 1811–16.

104 Meda N, Ndoye I, M'Boup S, et al. Low and stable HIV infection rates in Senegal: natural course of the epidemic or evidence for success of prevention? *AIDS* 1999; **13:** 1397–405.

105 Drain PK, Halperin DT, Hughes JP, et al. Male circumcision, religion, and infectious diseases: an ecologic analysis of 118 developing countries. *BMC Infect Dis* 2006; **6:** 172.

106 Limpakarnjanarat K, Mastro TD, Yindeeyoungyeon W, et al. STDs in female prostitues in northern Thailand. Proceedings of the IX International Conference on AIDS, Berlin, Gernany; June 6–11, 1993 [abstract PO-C10-2820].

107 Ragni MV, Faruki H, Kingsley LA. Heterosexual HIV-1 transmission and viral load in hemophilic patients. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998; **17:** 42–45.

108 Lee TH, Sakahara N, Fiebig E, et al. Correlation of HIV-1 RNA levels in plasma and heterosexual transmission of HIV-1 from infected transfusion recipients. *J Acquir Immune Defic Syndr Hum Retrovirol* 1996; **12:** 427–28.

109 Pedraza MA, del Romero J, Roldán F, et al. Heterosexual transmission of HIV-1 is associated with high plasma viral load levels and a positive viral isolation in an infected partner. *J Acquir Immune Defic Syndr Hum Retrovirol* 1999; **21:** 120–25.

110 Osmond D, Bacchetti P, Chaisson RE, et al. Time of exposure and risk of HIV infection in homosexual partners of men with AIDS. *Am J Public Health* 1988; **78:** 944–48.

111 Hollingsworth TD, Anderson RM, Fraser C. HIV-1 transmission, by stage of infection. *J Infect Dis* 2008; **198:** 687–93.

112 Allen S, Meinzen-Derr J, Kautzman M, et al. Sexual behaviour of HIV discordant couples after HIV counselling and testing. *AIDS* 2003; **17:** 733–40.

113 Guest G, Bunce A, Johnson L, et al. Fear, hope and social desirability bias among women at high risk for HIV in West Africa. *J Fam Plann Reprod Health Care* 2005; **31:** 285–87.

114 White RG, Cooper BS, Kedhar A, et al. Quantifying HIV-1 transmission due to contaminated injections. *Proc Natl Acad Sci USA* 2007; **104:** 9794–99.

115 Gisselquist D. How much do blood exposures contribute to HIV prevalence in female sex workers in sub-Saharan Africa, Thailand and India? *Int J STD AIDS* 2007; **18:** 581–88.

116 Gisselquist D, Potterat J. Questioning Wawer et al's estimated rate of sexual transmission from persons with early HIV infection. *J Infect Dis* 2005; **192:** 1497–98.

117 Wawer M, Serwadda D, Quinn TC, et al. Questioning Wawer et al's estimated rate of sexual transmission from persons with early HIV infection. Reply to Gisselquist and Potterat. *J Infect Dis* 2005; **192:** 1497–98.

118 Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. *Sex Transm Infect* 1999; **75:** 3–17.

119 Weiss HA. Male circumcision as a preventive measure against HIV and other sexually transmitted diseases. *Curr Opin Infect Dis* 2007; **20:** 66–72.

120 Seed J, Allen S, Mertens T, et al. Male circumcision, sexually transmitted disease, and risk of HIV. *J Acquir Immune Defic Syndr Hum Retrovirol* 1995; **8:** 83–90.

121 Pilcher CD, Price MA, Hoffman IF, et al. Amplified transmission of HIV-1: comparison of HIV-1 concentrations in semen and blood during acute and chronic infection. *AIDS* 2007; **21:** 1723–30.

122 Paz-Bailey G, Rahman M, Chen C, et al. Changes in the etiology of sexually transmitted diseases in Botswana between 1993 and 2002: implications for the clinical management of genital ulcer disease. *Clin Infect Dis* 2005; **41:** 1304–12.

123 Kreiss J, Ngugi E, Holmes K. Efficacy of nonoxynol 9 contraceptive sponge use in preventing heterosexual acquisition of HIV in Nairobi prostitutes. *JAMA* 1992; **268:** 477–82.

124 Bird KD. The use of spermicide containing nonoxynol-9 in the prevention of HIV infection. *AIDS* 1991; **5:** 791–96.

125 Nielsen NO, Friis H, Magnussen P, et al. Co-infection with subclinical HIV and *Wuchereria bancrofti*, and the role of malaria and hookworms, in adult Tanzanians: infection intensities, CD4/CD8 counts and cytokine responses. *Trans R Soc Trop Med Hyg* 2007; **101:** 602–12.