

Rethinking the heterosexual infectivity of HIV-1: a systematic review and meta-analysis



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Studies of cumulative HIV incidence suggest that cofactors such as genital ulcer disease, HIV disease stage, and male circumcision influence HIV transmission; however, the heterosexual infectivity of HIV-1 is commonly cited as a fixed value (approximately 0.001, or one transmission per 1000 contacts). We sought to estimate transmission cofactor effects on the heterosexual infectivity of HIV-1 and to quantify the extent to which study methods have affected infectivity estimates. We undertook a systematic search (up to April 27, 2008) of PubMed, Web of Science, and relevant bibliographies to identify articles estimating the heterosexual infectivity of HIV-1. We used meta-regression and stratified random-effects meta-analysis to assess differences in infectivity associated with cofactors and study methods. Infectivity estimates were very heterogeneous, ranging from zero transmissions after more than 100 penile-vaginal contacts in some serodiscordant couples to one transmission for every 3.1 episodes of heterosexual anal intercourse. Estimates were only weakly associated with study methods. Infectivity differences, expressed as number of transmissions per 1000 contacts, were 8.1 (95% CI 0.4–15.8) when comparing uncircumcised to circumcised susceptible men, 6.0 (3.3–8.8) comparing susceptible individuals with and without genital ulcer disease, 1.9 (0.9–2.8) comparing late-stage to mid-stage index cases, and 2.5 (0.2–4.9) comparing early-stage to mid-stage index cases. A single value for the heterosexual infectivity of HIV-1 fails to reflect the variation associated with important cofactors. The commonly cited value of 0.001 was estimated among stable couples with low prevalences of high-risk cofactors, and represents a lower bound. Cofactor effects are important to include in epidemic models, policy considerations, and prevention messages.

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Introduction

More than 33 million people are infected with HIV worldwide, with 2.5 million new infections arising in the past year alone.¹ Every HIV infection results from a transmission event, and one of the fundamental parameters driving the spread of HIV is its infectivity, defined as the probability of transmission during a single potentially infectious contact between an infected and an uninfected individual. A commonly cited^{2–6} value of approximately 0.001 for the heterosexual infectivity of HIV-1 has led to claims in biomedical reports, prevention education materials, policy recommendations, and the popular press that HIV cannot be transmitted efficiently through heterosexual contact. These claims are difficult to reconcile with the large numbers of HIV infections that have been acquired through heterosexual contact since the epidemic began.^{1,7–9}

Infectivity estimation requires an accurate count of the transmission events resulting from a defined number of potentially infectious exposures experienced by a specified population of susceptible individuals. Reliable counts of potentially infectious sexual exposures are very difficult to obtain. Often, it is possible to estimate only an approximate number of unprotected sex acts occurring between one individual who is presumed to be infectious and another who is presumed to be susceptible over some specified interval of time. Overestimation of the number of potentially infectious exposures will deflate infectivity estimates; underestimation will have the opposite effect.

Infectiousness and susceptibility could be influenced by multiple factors, such as direction of transmission (male-to-female versus female-to-male),¹⁰ type of sexual act,^{11,12} viral load,^{13,14} male circumcision,^{15–18} vaginal flora,¹⁹ age,²⁰ and sexually transmitted infections (STIs).^{21–23} The

effects of these transmission cofactors on cumulative HIV incidence have been characterised; however, efforts to quantify their effects at the per-contact level have been rare, and practical applications of infectivity estimates often ignore the possibility of cofactor influence.

Accurate, detailed estimates of the heterosexual infectivity of HIV are essential for understanding the epidemic, evaluating potential interventions, and communicating risk. We undertook a systematic review and meta-analysis of observational studies estimating the heterosexual infectivity of HIV-1 to (1) summarise existing infectivity estimates, (2) relate these estimates to methodological features of the studies producing them, (3) quantify cofactor effects on infectivity, and (4) identify gaps in understanding.

Methods

Search strategy and selection criteria

We conducted a literature search in four steps. First, we searched the PubMed/Medline and Web of Science databases through April 27, 2008, with the following terms: (“HIV” OR “human immunodeficiency virus”) AND ([“transmission” AND (“probability” OR “efficiency” OR “rate”)] OR [“transmission” AND “risk” AND (“per” AND “contact”) OR [“per” AND “act”]]) OR “infectivity” OR “infectiousness” OR “transmissibility”) AND (“sexual” OR “heterosexual” OR “coital”). There were no language restrictions to the search. Second, we examined the resulting abstracts (or titles if the abstract was unavailable) to identify articles that (1) mentioned any type of transmission probability estimate, (2) described mathematical models that could have used transmission probability estimates as inputs, (3) related frequency of heterosexual contact to HIV transmission, or (4) referred

See Online for webappendices 1 and 2

generally to heterosexual transmission in the title (if the abstract was unavailable). Third, we undertook a detailed, manual review of the text and bibliographies of articles meeting these criteria to identify articles that produced estimates of the heterosexual infectivity of HIV. Finally, we excluded articles that provided only (1) graphical displays of continuous infectivity functions produced with data that were used in other articles to generate point estimates, or (2) upper and lower infectivity limits (but no point estimates) produced with data that were used in other articles to generate point estimates.

Data extraction

For each study population in each article, one investigator (KAP) extracted two types of estimates (where available): (1) the most precise overall (whole-sample) infectivity estimate, and (2) the most precise stratified estimate within each cofactor category. The cofactors of interest were genital ulcer disease, any (non-specific) STI, male circumcision, female bacterial vaginosis, age, HIV-1 subtype, disease stage, viral load, antiretroviral use, contact type, geographic region, and transmission direction. In articles with all male or all female index cases, the “overall” estimate and the estimate stratified by transmission direction were one and the same.

We included estimates produced specifically for HIV-1, as well as type-non-specific estimates derived outside of west Africa, since HIV-1 predominates outside of that

region.²⁴ If an estimate was not reported but could be calculated from the available data, we used equation 1 (webappendix 1) to calculate the estimate. For each infectivity estimate that we extracted or calculated, we also recorded the corresponding standard error. If the standard error was not reported, we calculated an approximate value with the methods described in webappendix 2. We applied a half-integer continuity correction when no transmission events were reported.

Multiple articles could share (partly or wholly) a single study population. To avoid duplication, we included from each study population only the most precise overall estimate and most precise stratified estimate within each cofactor category. For each population's most precise overall estimate, we also extracted information about the following methodological features of the corresponding study: (1) partnership status of susceptible individuals (independent individual versus partner of a person known to be HIV infected); (2) timing of exposure and outcome assessment (cross-sectional versus longitudinal); (3) method for defining the index case's infection date (if used to determine the start of HIV exposure); (4) exclusion or inclusion of susceptible individuals reporting sexual contacts outside the defined index case set; (5) exclusion or inclusion of susceptible individuals reporting possible blood exposures to HIV; (6) length of the interval between HIV tests in longitudinal analyses; (7) exclusion or inclusion of condom-protected acts; (8) exclusion or inclusion of adjustment for self-report error; and (9) type of analytical model.

Statistical analyses

Assessing heterogeneity

To assess the consistency of the overall (whole-sample) estimates, we examined the p value for Cochran's Q , a standard homogeneity test statistic.

We did two main types of analyses to relate the overall infectivity estimates to the study methods of interest. First, we calculated a pooled, random-effects estimate of infectivity within each study design or analysis category, using stratified homogeneity tests to examine the consistency of estimates within categories. Second, we did a series of univariable random-effects meta-regression analyses, each with overall infectivity as the dependent variable and a particular study design or analysis feature as the independent variable. As a form of influence analysis, we did a series of repeat meta-regression analyses, excluding one estimate from the analyses in each series.

We used a similar approach to examine differences in infectivity according to transmission cofactors. For each cofactor, we undertook stratified meta-analyses and univariable meta-regression analyses (this time with stratified estimates) with the same methods we used for the study design and analysis characteristics. Additionally, to assess the independent effect of each transmission cofactor, we created one multiple meta-regression model

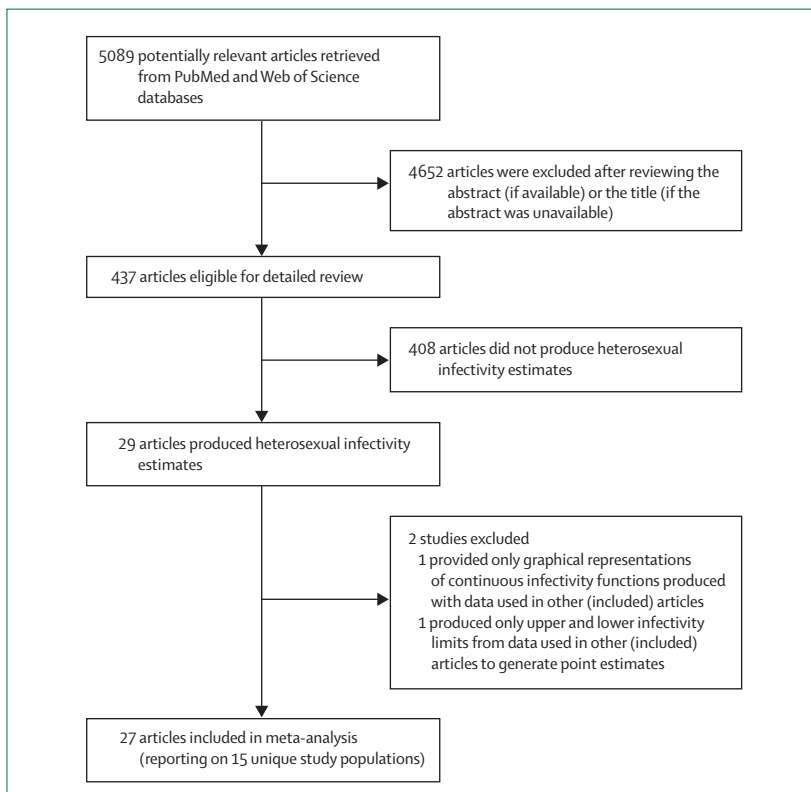


Figure 1: Flow diagram for study selection

Study population, setting, and susceptible type	Number of susceptible individuals*	Most precise overall infectivity estimate (transmission events per 1000 exposures)†	Standard error (transmission events per 1000 exposures)‡
Cameron,¹⁸ Kenya, female sex workers' clients			
Cameron (1989) ¹⁸	73	96.69‡§	37.55‡¶
Fischl,³³ USA, partners of known HIV-positive individuals			
Longini (1989) ³⁷	45	1.0‡	0.2‡
Peterman,⁵⁴ USA, partners of known HIV-positive individuals			
Wiley (1989) ³⁸	53	1.39	0.44
Kaplan (1990) ²⁹	53	1.4	0.41
Kim (1990) ³⁰	80	1.02‡	0.3‡
Kramer (1990) ³¹	55	1.3	0.41¶
Shiboski (1998) ³²	51	0.8	0.41
Thai military conscripts,⁵⁵ Thailand, female sex workers' clients			
Mastro (1994) ³³	673	31‡	3.83‡
Satten (1994) ³⁴	673	31	3.83
European Study Group,⁵⁶ Europe, partners of known HIV-positive individuals			
de Vincenzi (1994) ³⁵	121	1.0	0.31
Downs (1996) ³⁶	525	0.5‡	0.08‡
Leynaert (1998) ³⁷	499	0.9	0.1
Kramer (2002) ³⁸	525	0.5‡	0.08¶
Hira,³⁹ Zambia, partners of known HIV-positive individuals			
Hira (1997) ³⁹	110	3.85‡§	1.03‡¶
Saracco,⁴⁰ Italy, partners of known HIV-positive individuals			
Saracco (1997) ⁴⁰	627	0.6‡	0.13‡
California Partners' Study,⁵⁷ USA, partners of known HIV-positive individuals			
Wiley (1989) ³⁸	59	0.78	0.25
Jewell (1990) ⁴¹	159	1	0.16¶
Jewell (1994) ⁴²	88	1.29	0.34
Padian (1997) ⁴³	360	0.9	0.13
Shiboski (1998) ³²	302	0.6‡	0.10‡
O'Brien,⁵⁸ USA, partners of known HIV-positive individuals			
Shiboski (1998) ³²	31	0.9‡	0.41‡
Ragni,⁵⁹ USA, partners of known HIV-positive individuals			
Kramer (2002) ³⁸	45	0.55‡§	0.23‡¶
Senegal cohort,⁴⁴ Senegal, female sex workers			
Donnelly (1993) ⁴⁴	780	0.27	0.08¶
Gilbert (2003) ⁴⁵	1948	0.56‡	0.05‡¶
Marincovich,⁴⁶ Spain, partners of known HIV-positive individuals			
Marincovich (2003) ⁴⁶	74	0.17‡	0.17‡¶
Baeten,⁴⁷ Kenya, male truck drivers			
Baeten (2005) ⁴⁷	745	6.3‡	1.43‡
Rakai study,⁶⁰ Uganda, partners of known HIV-positive individuals			
Gray (2001) ⁴⁸	174	1.1	0.18
Corey (2004) ⁴⁹	174	1.1	0.18
Wawer (2005) ⁵⁰	235	1.2‡	0.15‡
Nairobi cohort,⁶¹ Kenya, female sex workers			
Hayes (1995) ⁵¹	117	2.62‡§	0.30¶
Kramer (2002) ³⁸	232	1.54‡§	0.14¶
Kimani (2008) ⁵²	687	0.63‡	0.04‡¶

*Total included in overall infectivity calculation. Stratified analyses were done in subsets containing fewer individuals. †To allow readers to see how we selected the most precise estimate within each population, for infectivity estimates and/or standard errors taken directly from an article, we report the provided value(s) to the number of decimal places provided in the article. For infectivity estimates and/or standard errors that we calculated ourselves, we report the values to two decimal places. ‡The most precise estimate and corresponding standard error within each study population. §Calculated from reported data using equation 1 (webappendix 1). ¶Calculated using method 1 in webappendix 2. ||Calculated from reported CIs (see webappendix 2).

Table 1: Overall (whole-sample) estimates of heterosexual infectivity of HIV-1 by study population

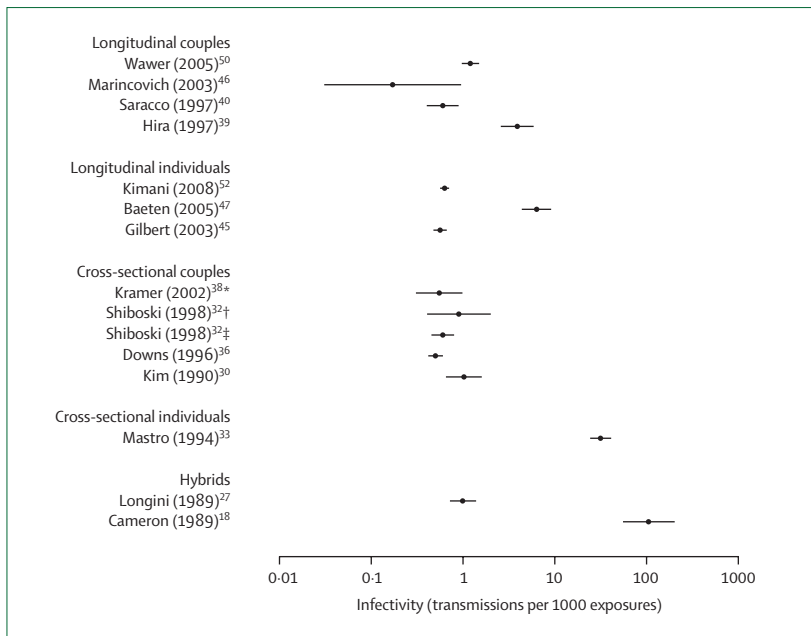


Figure 2: Forest plot of overall (whole-sample) estimates by study design

Study-specific infectivity estimates and 95% CIs. For symmetry of CIs on the log axis, the plotted values were calculated from logit-transformed transmission probabilities and their corresponding CIs. Untransformed values were used in all meta-analyses. *Ragni³⁹ data. †O'Brien³⁸ data. ‡California Partners' Study²⁷ data.

for each combination of cofactors with at least one infectivity estimate available for each stratum. Because of the limited number of stratified estimates, we did not perform influence analyses around transmission cofactor results.

We used Stata software (StataCorp, College Station, TX, USA), version 9.2, for all meta-analyses, using restricted maximum-likelihood to estimate the among-population variance in each meta-regression.

Effect measures

The coefficients produced by the meta-regression analyses represent average “infectivity differences” associated with study methods or transmission cofactors. In the analysis of study methods, the infectivity difference is the absolute difference in (weighted) average infectivity contrasting studies using one type of method (eg, longitudinal measurements) with studies at a reference level (eg, cross-sectional measurement). In the cofactor analysis, the infectivity difference compares infectivity for populations at one cofactor level (eg, 100% genital ulcer disease) with infectivity for populations at a reference level (eg, 0% genital ulcer disease). For example, a weighted average infectivity of 15 transmission events per 1000 contacts among those with a cofactor, compared with a value of ten transmission events per 1000 contacts among those without the cofactor, corresponds to an infectivity difference of five (ie, 15–10) transmission events per 1000 contacts. In other words, an average of five more transmission events per 1000 contacts occurred in the group with the cofactor than in the group without the cofactor.

Results

Literature search

Figure 1 shows the results of the literature search. The search produced 5089 articles. Of these, 4652 did not meet the eligibility criteria for detailed review. The abstracts or titles of these ineligible articles addressed various topics—including HIV prevalence, risk behaviours, and risk factors—but did not indicate production or use of per-contact transmission probability estimates. Of the 437 articles that were eligible for detailed review, 29 produced heterosexual infectivity estimates. One article provided only graphical representations of continuous infectivity functions produced with data used in other (included) articles to generate point estimates,²⁵ and one article produced only upper and lower infectivity limits from data used in other (included) articles to generate point estimates,²⁶ so our final set contained 27 articles.^{18,27–52} The 27 articles reported on 15 unique study populations.^{18,39,40,44,46,47,53–61}

Data extraction

Overall estimates

We identified 32 overall (whole-sample) estimates (table 1), but included in our analyses only the single most precise overall estimate from each of the 15 study populations.

Study design and analysis features

Studies based infectivity calculations on two types of events experienced by susceptible individuals: transmission events and heterosexual HIV exposures. The number of transmission events was defined by the number of susceptible individuals found (cross-sectionally or longitudinally) to be HIV infected. Counts of heterosexual HIV exposures were estimated from the reported number of sexual contacts occurring between susceptible individuals and index cases over a period (retrospective or prospective) when susceptible individuals were assumed or known to be HIV uninfected and index cases were assumed or known to be HIV infected. In contexts where index cases were not specifically identifiable (eg, studies in which the susceptible individuals were sex workers or their clients), infectivity calculations included an additional term for the probability of HIV exposure in a contact, estimated as the HIV prevalence among the population with which susceptible individuals had contact.

13 of the 15 overall estimates were generated by one of four basic study designs (figure 2). Four estimates were generated by “discordant couples studies”—that is, longitudinal studies of susceptible individuals who were partners of a known HIV-positive index case.^{39,40,46,50} Three were produced by longitudinal studies of susceptible and presumptively HIV-exposed individuals (eg, sex workers or their clients) recruited without specific index cases.^{45,47,52} In each of the longitudinal study types, susceptible individuals were HIV seronegative at

enrolment, and exposures and transmission events were measured prospectively. Five estimates (including two from different study populations described in reference 32) were from cross-sectional studies of susceptible individuals who were partners of a known HIV-positive index case.^{30,32,36,38} One estimate was produced by a cross-sectional study of susceptible and presumptively HIV-exposed individuals recruited without specific index cases.³³ In each of the cross-sectional study types, HIV exposures were assessed retrospectively and the number of transmission events was assessed as the number of prevalent cases.

The two estimates not from basic study designs were from “hybrid” designs. One study measured HIV outcomes longitudinally among seronegative individuals reporting (retrospectively) a single sex worker contact just before enrolment.¹⁸ The other study measured exposures and transmission events both cross-sectionally and longitudinally among partners of known HIV-infected individuals, and provided only an aggregate infectivity estimate across time periods.²⁷

Of the six studies that calculated the start of infectious contacts as the index case’s infection date, two (including the estimate using O’Brien data in reference 32) were able to determine the index infection date as the date of blood transfusion.^{30,32} The remaining four (including the estimate using California Partners’ Study data in reference 32) used roughly estimated index infection dates based on epidemic curves or incubation periods from previous studies.^{27,32,36,38} In longitudinal analyses, the length of the interval between HIV tests ranged from 2 weeks to 10 months. Nine of the 15 estimates were from studies that specified some exclusion criteria based on possible outside exposures to HIV (including two from different populations in reference 32),^{18,27,30,32,36,40,46,50} but only eight (including two from different populations in reference 32) accounted for condom-protected acts or noted that condom use was rare,^{30,32,39,40,46,47,52} and only three overall estimates were adjusted for self-report error.^{36,39,50} Seven of the estimates were calculated as the number of transmission events divided by the total number of exposures,^{18,38–40,46,50,52} five were calculated with a Bernoulli

Category	Number of estimates	Stratified meta-analysis results		Univariable meta-regression results		References	
		Homogeneity p value	Infectivity*† (95% CI)	Infectivity*‡ (95% CI)	Infectivity* difference (95% CI)		
Partnership status	Partner of known HIV-positive individual	10	<0.0001	0.73 (0.51–0.96)	0.63 (0.54–0.73)	0	27,30,32,36,38–40, 46,50§¶
	Independent individual	5	<0.0001	0.96 (0.42–1.50)	0.61 (0.54–0.68)	–0.02 (–0.14 to 0.10)	18,33,45,47,52
Outcome ascertainment	Any cross-sectional	8	<0.0001	0.88 (0.38–1.38)	0.61 (0.49–0.72)	0	18,27,30,32,33, 36,38§¶
	All longitudinal	7	<0.0001	0.71 (0.48–0.94)	0.62 (0.56–0.69)	0.01 (–0.11 to 0.14)	39,40,45–47,50,52
Index infection date	Crude estimate	4	0.1	0.61 (0.44–0.79)	0.59 (0.46–0.71)	0	27,32,36,38¶¶**
	Transfusion date	2	0.8	0.98 (0.50–1.45)	0.98 (0.50–1.46)	0.39 (–0.10 to 0.89)	30,32††
External sex exposures‡‡	Some exclusions	8	0.0001	0.71 (0.49–0.92)	0.68 (0.52–0.85)	0	27,30,32,36,40, 46,50§
	No exclusions	2	0.002	2.05 (0.00–5.27)	0.78 (0.24–1.31)	0.10 (–0.47 to 0.65)	38,39¶¶
Blood exposures	Some exclusions	9	<0.0001	0.71 (0.48–0.95)	0.63 (0.53–0.73)	0	18,27,30,32,36, 40,46,50§
	No exclusions	6	<0.0001	0.97 (0.52–1.42)	0.61 (0.54–0.68)	–0.02 (–0.14 to 0.10)	33,38,39,45,47,52¶¶
HIV testing interval§§	>3 months	6	0.0001	0.67 (0.50–0.84)	0.63 (0.56–0.69)	0	27,40,45,46,50,52
	≤3 months	3	0.02	5.36 (0.84–9.89)	4.73 (3.10–6.37)	4.10 (2.47 to 5.74)	18,39,47
Condom-protected acts	Some protection	5	<0.0001	1.11 (0.35–1.88)	0.70 (0.57–0.83)	0	27,33,36,38,50¶¶
	Protection rare or adjusted for	8	<0.0001	0.70 (0.44–0.97)	0.62 (0.53–0.70)	–0.08 (–0.24 to 0.08)	30,32,39,40,46, 47,52§
Self-report error	Not corrected or mentioned	12	<0.0001	0.71 (0.47–0.95)	0.61 (0.54–0.67)	0	18,27,30,32,33, 38,40,45–47,52§¶¶
	Corrected	3	<0.0001	1.19 (0.40–1.97)	0.67 (0.53–0.82)	0.06 (–0.09 to 0.22)	36,39,50
Analytical model¶¶¶	Bernoulli model	5	<0.0001	1.13 (0.50–1.77)	0.56 (0.48–0.64)	0	30,33,36,45,47
	Transmissions/acts	7	<0.0001	0.71 (0.39–1.03)	0.64 (0.57–0.70)	0.08 (–0.03 to 0.18)	18,38–40,46,50, 52¶¶
	Failure probability	3	0.2	0.76 (0.47–1.06)	0.69 (0.52–0.87)	0.13 (–0.06 to 0.32)	27,32§

*Transmissions per 1000 exposures. †Random-effects estimate pooled within a given stratum of study characteristic. ‡From random-effects models with overall infectivity as dependent variable and study feature as independent variable. §Two estimates from reference 32 (O’Brien and California Partners’ Study). ¶Estimate from reference 38 uses Ragni data. ||Applies only to studies basing exposure period start on index infection date. **Estimate from reference 32 uses California Partners’ Study data. ††Estimate from reference 32 uses O’Brien data. ‡‡Applies only to studies of couples. §§Applies only to studies with any longitudinal HIV testing to detect incident cases among susceptible individuals. ¶¶¶See webappendix 1.

Table 2: Results of stratified meta-analysis and meta-regression based on study design and analysis characteristics

	Category	Number of estimates	Stratified meta-analysis results		Univariable meta-regression results		References
			Homogeneity p value	Infectivity*† (95% CI)	Infectivity*‡ (95% CI)	Infectivity* difference (95% CI)	
Region	USA/Europe	8	0.05	0.59 (0.44–0.75)	0.56 (0.46–0.66)	0	27,30,32,36,38,40,46§
	Africa	6	<0.0001	0.91 (0.59–1.22)	0.64 (0.57–0.71)	0.08 (–0.04 to 0.20)	18,39,45,47,50,52
	Asia	1	n/a	31.00 (25.00–40.00)¶	n/a	n/a	33
Type of act	Penile-vaginal	5	0.0002	0.84 (0.51–1.17)	n/a	n/a	32,37,39,40,50
	Penile-anal	1	n/a	33.80 (18.51–49.09)¶	n/a	n/a	37
Transmission direction	Male-to-female	10	0.001	0.66 (0.54–0.79)	0.64 (0.57–0.72)	0	29,32,37,38,40,45,46,48,52§**
	Female-to-male	6	<0.0001	2.76 (1.19–4.33)	0.64 (0.45–0.84)	–0.002 (–0.21 to 0.21)	18,30,33,37,47,48
Genital ulcer disease status of susceptible individual††	No genital ulcer disease	4	<0.0001	3.72 (0.70–6.75)	1.46 (0.94–1.97)	0	18,33,49,51
	Genital ulcer disease	5	<0.0001	30.55 (11.27–49.84)	7.46 (4.75–10.17)	6.00 (3.25 to 8.76)	18,33,47,49,51
STI status of susceptible individual††	No STI	1	n/a	12.00 (6.00–25.00)¶	n/a	n/a	33
	STI	2	0.1	55.86 (4.43–107.29)	n/a	n/a	18,33
Circumcision status of susceptible male individual	Circumcised	2	0.4	5.13 (3.37–6.89)	5.13 (3.36–6.89)	0	18,47
	Not circumcised	2	0.02	97.33 (0.00–295.16)	13.21 (5.70–20.72)	8.08 (0.37 to 15.80)	18,47
Mean age of susceptible individual	≥30 years	6	<0.0001	1.06 (0.56–1.56)	0.94 (0.71–1.16)	0	27,32,38,39,45††§§
	<30 years	2	<0.0001	15.71 (0.00–45.20)	0.99 (0.58–1.40)	0.05 (–0.41 to 0.52)	33,37
Index disease stage	Mid	4	0.9	0.71 (0.57–0.85)	0.71 (0.57–0.85)	0	27,30,37,50
	Early	2	0.05	4.67 (0.00–10.46)	3.25 (0.93–5.56)	2.54 (0.22 to 4.86)	37,50
	Late	4	0.02	3.18 (0.94–5.42)	2.56 (1.58–3.53)	1.85 (0.86 to 2.83)	27,30,37,50
Mean index age	<30 years	1	n/a	0.90 (0.70–1.10)¶	n/a	n/a	37
	≥30 years	3	0.02	1.31 (0.66–1.96)	n/a	n/a	27,39,48

n/a=not applicable. STI=sexually transmitted infection. *Transmissions per 1000 exposures. †Random-effects estimate pooled within a given stratum of transmission cofactor. ‡From random-effects models with infectivity as dependent variable and transmission cofactor as independent variable. §Two estimates from reference 32 (O'Brien and California Partners' Study). ¶Estimate based on single study only. ||Meta-regression results computed only when the number of estimates exceeded 1 in the comparison group and in the referent stratum. **Estimate from reference 38 uses Ragni data. ††Before or during study period. †††Estimate from reference 32 uses O'Brien data. §§Two estimates from reference 38 (Ragni and Nairobi cohort data).

Table 3: Results of stratified meta-analysis and meta-regression based on transmission cofactor characteristics

model (webappendix 1),^{30,33,36,45,47} and three (including two in reference 32) were calculated as failure probabilities (webappendix 1).^{27,32}

Transmission cofactors

We included six estimates stratified by type of act, nine by susceptibles' genital ulcer disease status, three by susceptibles' (non-specific) STI status, four by male susceptibles' circumcision status, ten by index disease stage, and 16 by direction of transmission. Eight overall estimates (including two in reference 32) were obtained in the USA or Europe,^{27,30,32,36,38,40,46} six in Africa,^{18,39,45,47,50,52} and one in Asia.³³ Estimates stratified simultaneously by more than one cofactor ranged from approximately 0 among susceptible men without genital ulcer disease, most of whom were circumcised,¹⁸ to 0.32 (one transmission event for every 3.1 contacts) for penile-anal sex between late-stage male index cases and susceptible women (approximately half of whom had an STI).³⁷

Information was available in fewer than two study populations for susceptible bacterial vaginosis and for index STI, genital ulcer disease, bacterial vaginosis, viral load, antiretroviral use, and viral subtype. We were unable to include these cofactors in our analyses, but we included disease stage and geographic region as proxy measures for viral load and subtype, respectively.

Meta-analyses

Overall heterogeneity

As shown in figure 2, the overall infectivity estimates were very heterogeneous ($p < 0.0001$ on homogeneity test).

Study design and analysis features

Our meta-analyses revealed only weak associations between overall infectivity estimates and the design and analysis features of the studies that produced them (table 2). Only one infectivity difference was larger than one transmission event per 1000 contacts: among longitudinal studies, infectivity was inversely associated

with the HIV testing interval. Influence analyses did not show any undue influence of any single study on the meta-regression results.

Transmission cofactors

Several transmission cofactors were associated with increased infectivity (table 3, figure 3). In meta-regression analysis, the cofactors most strongly associated with infectivity were genital ulcer disease in susceptible individuals (infectivity difference *vs* no genital ulcer disease 6.0 transmissions per 1000 exposures, 95% CI 3.3–8.8), lack of circumcision in susceptible men (infectivity difference *vs* circumcised men 8.1 transmissions per 1000 exposures, 0.4–15.8), early-stage infection in index cases (infectivity difference *vs* mid-stage 2.5 transmissions per 1000 exposures, 0.2–4.9), and late-stage infection in index cases (infectivity difference *vs* mid-stage 1.9 transmissions per 1000 exposures, 0.9–2.8). Infectivity was only weakly associated with geographic region (Africa *vs* USA/Europe), direction of transmission, and mean susceptible age. The limited data available for type of contact, susceptible STI status, and mean index age suggest that infectivity is higher for penile-anal (*vs* penile-vaginal) sex, for susceptible individuals with (*vs* without) STI, and for older (*vs* younger) index cases; however, there were insufficient data to undertake meta-regression analyses on these cofactors. The single estimate produced in an Asian setting was substantially higher than estimates produced in the USA or Europe.

We were able to fit only four multiple meta-regression models, because of missing cofactor information, the limited number of studies, and colinearities among variables. Most associations in the multivariable analyses were in the same direction as in univariable meta-regression, with some attenuation or amplification (results not shown).

Discussion

The use of a single, “one-size-fits-all” value for the heterosexual infectivity of HIV-1 obscures important differences associated with transmission cofactors. Perhaps more importantly, the particular value of 0.001 (ie, one infection per 1000 contacts between infected and uninfected individuals) that is commonly used seems to represent a lower bound. As such, this value substantially underestimates the infectivity of HIV-1 in many heterosexual contexts. Of the 11 overall estimates near or below 0.001 identified in this study, nine (including two in reference 32) were produced in analyses of stable couples with low prevalences of high-risk cofactors.^{27,30,32,36,38,40,46,50} In other contexts—particularly if the susceptible partner has an STI or is uncircumcised, if contact is penile-anal, or if the index case is in early-stage or late-stage infection—heterosexual infectivity can exceed 0.1 (one transmission per ten contacts) for penile-vaginal contact or even 0.3 (one transmission per three

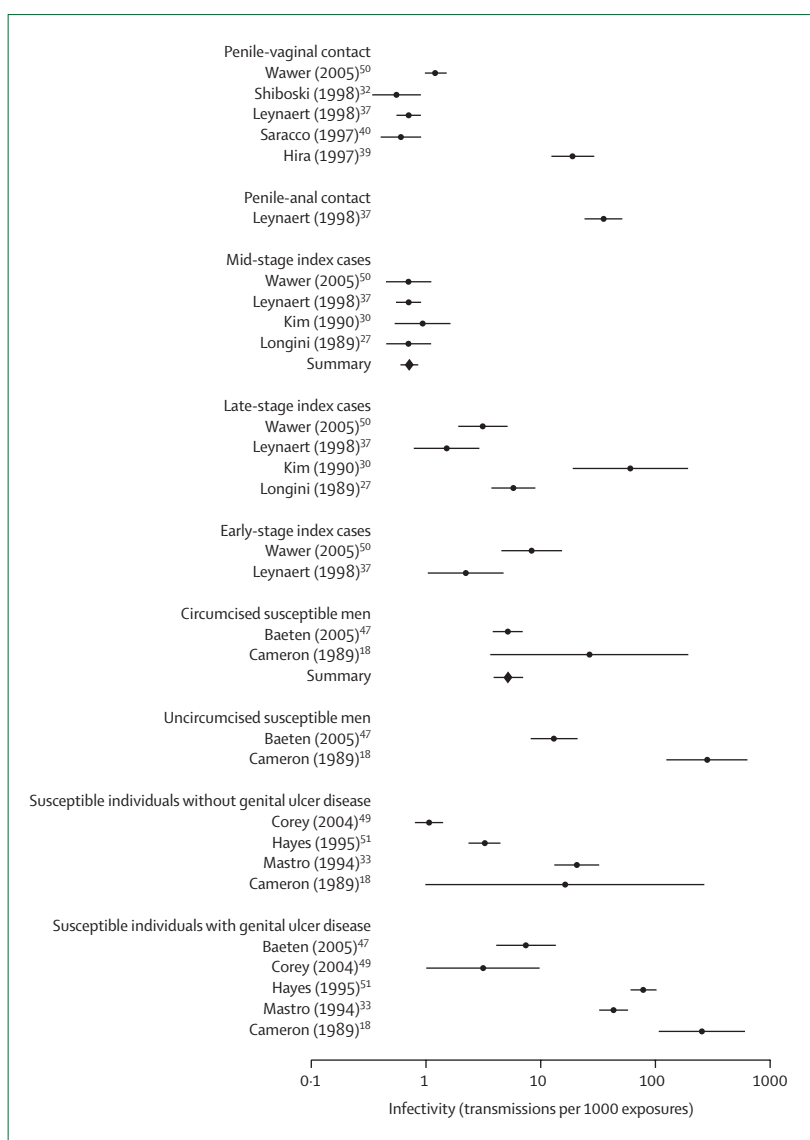


Figure 3: Forest plot of estimates stratified by selected transmission cofactors

Study-specific and pooled infectivity estimates and 95% CIs stratified by sexual contact type, index infection stage, male susceptibles' circumcision status, and susceptible individuals' genital ulcer disease status. Pooled (summary) estimates are shown only for strata with homogeneity $p > 0.2$. For symmetry of CIs on the log axis, the plotted values were calculated from logit-transformed transmission probabilities and their corresponding CIs.

Untransformed values were used in all meta-analyses.

contacts) for penile-anal contact.^{18,30,33,37,47} Claims in both the popular media^{62,63} and the peer-reviewed literature^{5,6} that HIV is very difficult to transmit heterosexually are dangerous in any context where the possibility of HIV exposure exists.

Observation of cofactor effects at the level of cumulative incidence has been crucial to the development of interventions designed to reduce HIV incidence. Understanding cofactor effects at the per-contact level is also important, since HIV exposure and transmission occur during discrete contacts between infected and uninfected individuals, and many epidemic models rely

on parameter inputs at the per-contact level. Our results, which relate to transmission at the per-contact level, are consistent with many studies of cumulative HIV incidence showing that STIs, decreased age, and lack of circumcision increase susceptibility; that increased age and both early-stage and late-stage index infection amplify transmissibility;^{13–18,21–23} and that heterosexual transmission is more efficient through penile-anal contact than through penile-vaginal contact.^{11,12} Additionally, our finding that penile-anal transmission is more efficient than penile-vaginal transmission is consistent with infectivity studies undertaken among men who have sex with men.^{64,65} Studies of cumulative HIV incidence have provided mixed evidence in support of differences between male-to-female and female-to-male transmission;⁶⁶ our results suggest that there is no meaningful difference by direction of transmission at the per-contact level.

The sharply increased infectivity reported among female sex workers' clients in an Asian setting might reflect differences by disease stage, since the infectivity study in Asia³³ took place at the start of the epidemic when a large proportion of index cases were in early stages of infection.^{33,34} The high infectivity in the Asian study might also reflect unmeasured STI cofactor effects, because a large proportion of sex worker index cases were infected with STIs during the study period.⁶⁷ We also note that because the study was done among sex workers' clients (rather than specifically identifiable index cases), HIV prevalence estimates among the sex worker population were required to estimate the probability of HIV exposure in infectivity calculations. If HIV prevalence were underestimated in these calculations, the infectivity would have been biased upward. The higher infectivity in this setting might also reflect differences by HIV subtype, or unmeasured or poorly measured cofactors.

The reduced infectivity seen among circumcised susceptible men is consistent with results of randomised trials of circumcision for HIV prevention.^{16,68,69} The observed increases in infectivity associated with STI and genital ulcer disease are less easy to compare with randomised trials of bacterial STI treatment^{60,70–72} and herpes simplex virus type 2 (HSV2) suppression.^{73,74} Whereas one bacterial STI treatment trial achieved a 40% reduction in HIV incidence through syndromic STI management,⁷⁰ other trials of bacterial STI treatment interventions have failed to show effects on HIV incidence.^{60,71,72} Various explanations have been offered for the lack of bacterial STI treatment effects, including insufficient power,⁷¹ receipt by the control group of ethically mandated STI services,⁶⁰ and high prevalences of HSV2 in both intervention and control communities.^{60,71} Similarly, recent trials of aciclovir among HSV2-seropositive individuals did not find an effect of HSV2 suppression on HIV acquisition,^{73,74} possibly because of high proportions of genital ulcer disease unrelated to HSV2,⁷⁵ inadequate ulcer suppression,^{73,74} or insufficient

compliance with the aciclovir regimen.⁷⁴ Because the STI and genital ulcer disease groups in our analyses were not restricted specifically to those with the same treatable STI targeted in the intervention trials, the results of bacterial STI and HSV2 treatment trials are not directly comparable with the STI and genital ulcer disease results shown here.

The observed differences in infectivity according to index disease stage deserve particular attention. The estimates produced for mid-stage infection were very homogeneous, and the pooled estimate for this stage (0.7 transmissions per 1000 acts) is approximately equal to the commonly cited value of one transmission per 1000 acts. The probability of transmission is likely to be much higher outside of this period, especially during acute (pre-seroconversion) HIV, when viral loads are sharply raised, acquired immunity in acutely infected individuals' partners is absent, and a substantial portion of transmission events occur.⁷⁶ No infectivity study has directly measured transmission during the brief acute phase. The early-stage infectivity estimate of Leynaert and colleagues³⁷ was based on a retrospective exposure period with crudely estimated dates of index infection, and the estimate of Wawer and colleagues⁵⁰ corresponded to the period up to 5 months after seroconversion. As others have noted,^{50,77} couples in whom transmission occurs during the brief acute phase cannot be selected for discordant couples studies, which follow susceptible partners only after the index partner has developed HIV antibodies.

Most infectivity studies have not explicitly accounted for all important cofactors, producing population-average estimates that do not capture variations in infectivity. Additionally, most study designs have been subject to at least one potential bias in determining the number of potentially infectious exposures experienced by susceptible individuals. Estimates from both cross-sectional and longitudinal studies of independent individuals (rather than partners of known HIV-infected index cases) have relied on HIV prevalence estimates to calculate the probability of exposure during a sexual contact. Overestimates of the prevalence will have underestimated infectivity; underestimated prevalence will have had the opposite effect. Cross-sectional analyses have relied on reported sexual contacts that occurred well before the cross-section, and in most of these studies, the start of the exposure period was based on a very crude estimate of the index case's infection date. In several studies, the earliest possible index infection date was used, likely resulting in the inclusion of sex acts that occurred before the true index infection date. Inclusion of these non-exposures in infectivity calculations will have resulted in deflated estimates.

Several biases common to all study designs also could have affected infectivity estimates. First, unadjusted inclusion of condom-protected acts in the count of potentially infectious exposures could bias estimates

downward. Additionally, infectivity estimates could be biased upward if any transmission occurs through “external” (blood or sexual) contacts that are not included in the count of potentially infectious contacts. All but one study⁵⁰ assumed (without molecular analysis) that transmission events occurred via exposure to index partners, but molecular analysis in other studies has shown that 10% or more of apparent transmission events within couples result from exposure to an additional sexual partner. Self-report error in the number of sexual contacts could also bias estimates; this bias could be in either direction. Additionally, no studies included separate counts of oral-genital contacts. However, because transmission via oral-genital contact is believed to be very inefficient,⁷⁸ the failure to account for oral-genital contact in estimating penile-anal and penile-vaginal infectivity is unlikely to have resulted in substantial bias. Finally, because all studies used antibody tests to detect transmission to susceptible individuals, those with acute infections at the time of testing would have been misclassified as uninfected, resulting in underestimated infectivity.

We also note that there were insufficient data to undertake even univariable stratified and meta-regression analyses of several cofactors, such as viral load, viral subtype, and antiretroviral use; however, we have some information for assessing these variables. In the single population for which viral load was analysed,⁴⁸ infectivity increased from 0·1 transmission per 1000 acts to 2·3 transmissions per 1000 acts as blood viral load increased from less than 1700 copies per mL to more than 38 500 copies per mL. In this same population, infectivity was similar across the HIV subtypes (A, D, and V3) analysed. The increased infectivity values associated with early-stage and late-stage infection^{27,30,37,50} and with the Thai population at the beginning of the epidemic^{33,34} indirectly suggest amplifying effects of high viral load. All studies were done before the advent or widespread use of antiretroviral drugs, so the estimates reported here correspond to infectivity in the absence of therapy.

In some cofactor and study method strata, the difference between the estimate obtained from stratified meta-analysis and the estimate produced with meta-regression is quite pronounced. Each estimate obtained from stratified meta-analysis made use only of the data in a particular subgroup, whereas each estimate obtained from meta-regression also made use of the data from the other stratum (or strata), and thus involved modelling or smoothing. The stratified estimates are less precise and less model-dependent; the meta-regression estimates are more precise and more model-dependent. The difference between the two methods' estimates tends to be greater when the data are relatively sparse, which can occur from small sample sizes within studies, from small numbers of studies within strata, or both. The potential for differences is accentuated by the use of random-effects meta-

regression, which involves estimation of an among-studies variance. In the meta-regression analyses, this variance is estimated from all studies in either stratum; in the stratified analyses, it is estimated separately within each stratum.

We have focused on one key parameter in HIV transmission dynamics: the conditional probability of HIV transmission given exposure during a single contact. The overall probability of HIV transmission also depends upon the probability of exposure to HIV, which is determined by such factors as HIV prevalence, partner change rate, sexual network position, and contact with partners who are involved in concurrent relationships. These factors, which are outside the scope of this analysis, represent additional, important determinants of HIV transmission.

HIV infectivity studies are very difficult to undertake for both logistical and ethical reasons. As a result, information about infectivity is limited, in terms of both the number of existing estimates and the quality of those estimates. Because of the small number of infectivity studies, the shortage of estimates stratified by cofactors, the impossibility of adequately controlling for confounding with multivariable analyses, and the methodological issues of existing studies, the true independent effects of cofactors and study features could differ substantially from the estimates that we obtained. In view of these limitations of the existing data, we caution against interpreting any quantitative value reported here as “the” infectivity for a particular study design or cofactor stratum, just as we have cautioned against using a value of 0·001 as “the” overall heterosexual infectivity of HIV-1. Caution is especially warranted for estimates associated with particularly sparse cofactor strata (eg, estimates stratified by STI status), as well as pooled estimates within strata where heterogeneity exists. Although many of the summary infectivity estimates that we report are subject to substantial uncertainty because of systematic and random error, we note that the infectivity differences estimated by our meta-regression analyses (which account for across-study variance) represent advances in understanding the variability of HIV infectivity. Further explanations for the heterogeneity of infectivity estimates may yet be discerned.

In addition to study limitations resulting from shortcomings of the literature, it is possible that we inadvertently excluded some existing infectivity estimates or misclassified some variables, despite a thorough literature search and a careful data extraction process. Furthermore, for some infectivity estimates, we were able to obtain only approximate standard errors.

Despite these limitations, our study represents a comprehensive summary and systematic analysis of the current literature on the heterosexual infectivity of HIV-1, a fundamental determinant of the epidemic's spread. Our findings suggest that in many contexts—particularly in the absence of male circumcision or in the presence of STIs, anal sex, or early-stage or late-stage infection—the

Search strategy and selection criteria

These are described in the Methods section.

heterosexual infectivity of HIV-1 might exceed the commonly cited value of 0.001 by more than an order of magnitude. The vast extent of the current epidemic is more easily understood in the context of these biological cofactors, which create a more favourable environment for HIV transmission. In addition to documenting the heterogeneity of infectivity estimates and providing some possible explanations for this heterogeneity, our Review describes the limitations of the existing literature, highlights the need for further infectivity research, and reinforces the importance of including cofactor effects in HIV epidemic models, policy considerations, and prevention messages. Future infectivity studies should carefully count infectious exposures and rigorously account for transmission cofactors. Improved infectivity estimates—especially more detailed estimates that quantify the amplifying effects of biological cofactors—will help us to grasp the magnitude of the HIV epidemic, accurately communicate the level of risk involved in heterosexual sex, and identify the best possible intervention strategies for slowing the epidemic's spread.

Conflicts of interest

We declare that we have no conflicts of interest.

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