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Rethinking the Heterosexual Infectivity of HIV-1: A Systematic Review and Meta-analysis

Kimberly A. Powers, MSPH, **Charles Poole, ScD**, **Audrey E. Pettifor, PhD**, and **Myron S. Cohen, MD**
Departments of Epidemiology (Powers, Poole, Pettifor, Cohen), Medicine (Cohen), and Microbiology & Immunology (Cohen), The University of North Carolina, Chapel Hill, North Carolina, USA

Abstract

Background—Studies of cumulative HIV incidence suggest that co-factors such as genital ulcer disease (GUD), HIV disease stage, and circumcision influence HIV transmission; however, the heterosexual infectivity of HIV-1 is commonly cited as a fixed value (~0·001, or 1 transmission per thousand contacts). We sought to estimate transmission co-factor effects on the heterosexual infectivity of HIV-1 and to quantify the extent to which study methods have affected infectivity estimates.

Methods—We conducted a systematic search (through April 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 by co-factors and study methods.

Findings—Infectivity estimates were extremely heterogeneous, ranging from zero transmissions after more than 100 penile-vaginal contacts in some sero-discordant couples to one transmission for every 3·1 episodes of heterosexual anal intercourse. Estimates were only weakly associated with study methods. Infectivity differences (95% confidence intervals), expressed as number of transmissions per 1000 contacts, were 8 (0-16) comparing uncircumcised to circumcised male susceptibles, 6 (3-9) comparing susceptible individuals with and without GUD, 2 (1-3) comparing late-stage to mid-stage index cases, and 3 (0-5) comparing early-stage to mid-stage index cases.

Interpretation—A single value for the heterosexual infectivity of HIV-1 fails to reflect the variation associated with important co-factors. The commonly cited value of ~0·001 was estimated among stable couples with low prevalences of high-risk co-factors, and represents a lower bound. Co-factor effects are important to include in epidemic models, policy considerations, and prevention messages.

Corresponding author: Kimberly A. Powers, CB# 7435, McGavran-Greenberg Hall, UNC-CH, Chapel Hill NC 27599-7435, Email: powersk@email.unc.edu, Phone: +1 919-843-4703; Fax: +1 919-966-4914.

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Introduction

Over 33 million people are HIV-infected 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 ~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 extremely 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 may be influenced by multiple factors, such as direction of transmission (male-to-female vs. 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 (STI) (21-23). The effects of these transmission co-factors on *cumulative* HIV incidence have been characterized; 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 co-factor 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) summarize existing infectivity estimates, 2) relate these estimates to methodological features of the studies producing them, 3) quantify co-factor effects on infectivity, and 4) identify gaps in understanding.

Methods

Study Selection

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). 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 generally to heterosexual transmission in the title (if the abstract was unavailable). Third, we conducted 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, we 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 co-factor category. The co-factors of interest were genital ulcer disease (GUD), any (non-specific) STI, male circumcision, female bacterial vaginosis (BV), age, HIV-1 subtype, disease stage, viral load, antiretroviral (ARV) 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-nonspecific 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 (Appendix 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 Appendix 2. We applied a half-integer continuity correction when 0 transmission events were reported.

Multiple articles could share (partially 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 co-factor 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 conducted 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 conducted 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 conducted 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 co-factors. For each co-factor, we performed 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 co-factor, we created one multiple meta-regression model for each combination of co-factors with at least one infectivity estimate available for each stratum. Due to the limited number of stratified estimates, we did not perform influence analyses around transmission co-factor results.

We used Stata software (StataCorp., College Station, Texas), version 9·2, to conduct 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" (ID) associated with study methods or transmission co-factors. In the analysis of study methods, the ID is the absolute difference in (weighted) average infectivity contrasting studies using one type of method (e.g., longitudinal measurements) with studies at a "reference" level (e.g., cross-sectional measurement). In the co-factor analysis, the ID compares infectivity for populations at one co-factor level (e.g., 100% GUD) with infectivity for populations at a "reference" level (e.g., 0% GUD). For example, a weighted average infectivity of 15 transmission events per thousand contacts among those with a co-factor, compared with a value of 10 transmission events per thousand contacts among those without the co-factor, corresponds to an infectivity difference of 5 (=15-10) transmission events per thousand contacts. In other words, an average of 5 more transmission events per thousand contacts occurred in the group with the co-factor than in the group without the co-factor.

Role of the funding sources

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Literature Search

The literature 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 behaviors, 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 (25) provided only graphical representations of continuous infectivity functions produced with data used in other (included) articles to generate point estimates, and one (26) produced only upper and lower infectivity limits from data used in other (included) articles to generate point estimates, so our final set contained 27 articles (18,27-52). The 27 articles reported on a total of 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 (highlighted in gray in Table 1) 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 (e.g., studies in which the susceptible individuals were commercial 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.

Thirteen of the 15 overall estimates were generated by one of four basic study designs (Figure 1). Four (39,40,46,50) were generated by "discordant couples studies," that is, longitudinal studies of susceptible individuals who were partners of a known HIV-positive index case. Three (45,47,52) were produced by longitudinal studies of susceptible and presumptively HIV-exposed individuals (e.g. sex workers or their clients) recruited without specific index cases. In each of the longitudinal study types, susceptible individuals were HIV-seronegative at enrollment, and exposures and transmission events were measured prospectively. Five (30, 32,36,38) estimates (including two from different study populations in (32)) were from cross-sectional studies of susceptible individuals who were partners of a known HIV-positive index case. One (33) estimate was produced by a cross-sectional study of susceptible and presumptively HIV-exposed individuals recruited without specific index cases. 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 (18) measured HIV outcomes longitudinally among seronegative individuals reporting (retrospectively) a single sex worker contact just prior to enrollment. The other (27) 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.

Of the six studies that calculated the start of infectious contacts as the index case's infection date, two (30,32) (including the estimate using O'Brien data in (32)) were able to determine the index infection date as the date of blood transfusion. The remaining four (27,32,36,38) (including the estimate using California Partner Study data in (32)) used roughly estimated index infection dates based on epidemic curves or incubation periods from previous studies. In longitudinal analyses, the length of the interval between HIV tests ranged from 2 weeks to 10 months. Nine (18,27,30,32,36,40,46,50) 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 (32)), but only eight (30,32,39,40,46,47,52) (including two from different populations in (32)) accounted for condom-protected acts or noted that condom use was rare, and only three overall estimates were adjusted for self-report error (36,39,50). Seven (18,38-40,46,50,52) of the estimates were calculated as the number of transmission events divided by the total number of exposures, five (30,33,36,45,47) were calculated with a Bernoulli model (Appendix 1), and three (27,32) (including two in (32)) were calculated as failure probabilities (Appendix 1).

Transmission co-factors—We included six estimates stratified by type of act, nine by susceptibles' GUD 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 (27,30,32,36,38,40,46) overall estimates (including two in (32)) were obtained in the US or Europe, six (18,39,45,47,50,52) in Africa, and one (33) in Asia. Estimates stratified simultaneously by more than one co-factor ranged from approximately 0 among susceptible males without GUD, 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 females (approximately half of whom had an STI). (37)

Information was available in fewer than two study populations for susceptible BV and for index STI, GUD, BV, viral load, ARV use, and viral subtype. We were unable to include these co-factors 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 illustrated in Figure 1, the overall infectivity estimates were extremely heterogeneous ($p<0{\cdot}0001$ on homogeneity test).

Study design 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 (ID) was larger than one transmission event per thousand contacts: among longitudinal studies, infectivity was inversely associated with the HIV testing interval. Influence analyses did not reveal any undue influence of any single study on the meta-regression results.

Transmission co-factors—Numerous transmission co-factors were associated with increased infectivity (Table 3, Figure 2). In meta-regression analysis, the co-factors most strongly associated with infectivity were GUD in susceptible individuals (ID vs. no GUD: 6·0, 95% CI:3·3-8·8), lack of circumcision in susceptible males (ID vs. circumcised males: 8.1, 95% CI: 0.4-15.8), early-stage infection in index cases (ID vs. mid-stage: 2.5, 95% CI: 0.2-4.9), and late-stage infection in index cases (ID vs. mid-stage: 1.9, 95% CI: 0.9-2.8). Infectivity was only weakly associated with geographic region (Africa vs. US/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 susceptibles with (vs. without) STI, and for older (vs. younger) index cases; however, there were insufficient data to conduct meta-regression analyses on these co-factors. The single estimate produced in an Asian setting was considerably higher than estimates produced in the US or Europe.

We were able to fit only four multiple meta-regression models, due to missing co-factor information, the limited number of studies, and collinearities 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 co-factors. Perhaps more importantly, the particular value of ~0·001 (i.e., 1 infection per 1,000 contacts between infected and uninfected individuals) that is commonly used appears to represent a lower bound. As such, it dramatically underestimates the infectivity of HIV-1 in many heterosexual contexts. Of the 11 overall estimates near or below 0·001 identified in this study, 9 were produced in analyses of stable couples with low prevalences of high-risk co-factors. 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- or late-stage infection – heterosexual infectivity can exceed 0·1 (1 transmission per 10 contacts) for penile-vaginal contact or even 0·3 (1 transmission per 3 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 extremely difficult to transmit heterosexually are dangerous in any context where the possibility of HIV exposure exists.

Observation of co-factor effects at the level of *cumulative* incidence has been critical to the development of interventions designed to reduce HIV incidence. Understanding co-factor

effects at the *per-contact* level is also important, as 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 numerous studies of cumulative HIV incidence showing that STIs, decreased age, and lack of circumcision increase susceptibility; that increased age and both early- 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 is consistent with infectivity studies conducted 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 may reflect differences by disease stage, as the infectivity study (33) conducted in Asia took place at the start of the epidemic when a large proportion of index cases were in early stages of infection (33,34). The elevated infectivity in the Asian study also may reflect unmeasured STI co-factor effects, as 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 conducted among commercial sex workers' clients (rather than specifically identifiable index cases), HIV prevalence estimates among the commercial sex worker population were required to estimate the probability of HIV exposure in infectivity calculations. If prevalence were underestimated in these calculations, the infectivity would have been biased upward. The higher infectivity in this setting may also reflect differences by subtype or unmeasured or poorly measured co-factors.

The reduced infectivity observed among circumcised male susceptibles is consistent with results of randomized trials of circumcision for HIV prevention (16,68,69). The observed increases in infectivity associated with STI and GUD are less readily compared to randomized trials of bacterial STI treatment (60,70-72) and HSV-2 suppression (73,74). While 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 HSV-2 in both intervention and control communities (60,71). Similarly, recent trials of acyclovir among HSV-2 seropositive individuals did not find an effect of HSV-2 suppression on HIV acquisition (73, 74), possibly due to high proportions of GUD unrelated to HSV-2 (75), inadequate ulcer suppression (73,74), or insufficient compliance with the acyclovir regimen (74). Because the “STI” and “GUD” 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 HSV-2 treatment trials are not directly comparable to the ”STI” and “GUD” 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 1 transmission per 1000 acts. The probability of transmission is likely much higher outside of this period, especially during acute (pre-seroconversion) HIV, when viral loads are sharply elevated, 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” infectivity estimate of Leynaert et al (37) was based on a retrospective exposure period with crudely estimated

dates of index infection, and the estimate of Wawer et al (50) corresponded to the period up through 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 prior to the true index infection date. Inclusion of these non-exposures in infectivity calculations will have resulted in deflated estimates.

A number of 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 study (50) assumed (without molecular analysis) that transmission events occurred via exposure to index partners, but molecular analysis in other studies has revealed 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. Because transmission via oral-genital contact is believed to be extremely inefficient (78), though, 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 have 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 conduct even univariable stratified and meta-regression analyses of several co-factors, such as viral load, viral subtype, and ARV use; however, we have some information for assessing these variables. In the single population for which viral load was analyzed (48), infectivity increased from 0.1 transmission per thousand acts to 2·3 transmissions per thousand acts as blood viral load increased from <1700 copies/ml to >38500 copies/ml. In this same population, infectivity was similar across the subtypes (A, D, and V3) analyzed. The increased infectivity values associated with early- and late-stage infection and with the Thai population at the beginning of the epidemic indirectly suggest amplifying effects of high viral load. All studies were conducted prior to the advent or widespread use of ARV, so the estimates reported here correspond to infectivity in the absence of therapy.

In some co-factor 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 modeling 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 extremely difficult to conduct 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 co-factors, the impossibility of adequately controlling for confounding with multivariable analyses, and the methodological issues of existing studies, the true independent effects of co-factors and study features may differ substantially from the estimates that we obtained. Given these limitations of the existing data, we caution against interpreting any quantitative value reported here as “the” infectivity for a particular study design or co-factor 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 co-factor strata (e.g., estimates stratified by STI status), as well as pooled estimates within strata where heterogeneity exists. While many of the summary *infectivity* estimates that we report are subject to considerable uncertainty due to 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 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 or late infection – the heterosexual infectivity of HIV-1 may 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 co-factors, which create a more favorable 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 co-factor 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 co-factors – will help us to grasp the magnitude of the HIV epidemic, accurately communicate the level of risk involved in heterosexual sex, and identify the optimal intervention strategies for slowing the epidemic's spread.

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Appendix

Appendix 1

Studies estimated the infectivity (β) in one of four general ways: by dividing the total number of susceptibles who became infected by the total number of unprotected sex acts occurring in the study population during the risk period (Eq. 1); by estimating the transmission rate per unit time during the risk period and then converting the rate into a failure probability (Eq. 2); by fitting the "Bernoulli model" (Eq. 3a) to individual-level sexual contact data with maximum-likelihood methods to estimate β; or by substituting population-average sexual contact data into the Bernoulli model (Eq. 3b) and solving for β.

$$\widehat{\beta}=\frac{\sum_{i=1}^{n} x_i}{\phi \sum_{i=1}^{n} s_i} \qquad \text{(Equation 1)}$$

$$\widehat{\beta}=1-e^{-\lambda(t)/\overline{s}(t)} \qquad \text{(Equation 2)}$$

$$\frac{\sum_{i=1}^{n} x_i}{N}=1-(1-\phi\beta)^{s_i} \qquad \text{(Equation 3a)}$$

$$\frac{\sum_{i=1}^{n} x_i}{N}=1-(1-\phi\beta)^{\overline{s}} \qquad \text{(Equation 3b)}$$

In these equations, the variable *x* represents susceptible individuals and the variable *s* represents unprotected sex acts. If susceptible individual *i* becomes HIV-infected during the risk period, then x_i=1, and if susceptible individual *i* remains uninfected during the risk period, then x_i=0; therefore, $\sum_{i=1}^{n} x_i$ represents the total number of transmission events observed among the *N* susceptible individuals in a population. The parameter s_I is the number of unprotected sex acts

for a given susceptible individual during the risk period, λ(t) is the transmission rate per unit time, $\bar{s}(t)$ is the average number of sex acts per unit time during the risk period, $\bar{s}$ is the average number of sex acts occurring during the entire risk period, and φ is the probability that a susceptible individual's partner is HIV-infected. When a susceptible individual is the partner of someone known to be HIV-positive, φ=1; when the index case is not specifically identifiable, φ is estimated as the population prevalence of HIV-1.

Appendix 2

When 95% confidence limits were reported for an infectivity estimate, we calculated the corresponding standard error as (upper confidence limit - lower confidence limit) / 3.92. When 95% confidence limits were not reported for an infectivity estimate, we calculated an approximate standard error as follows:

1. If the Eq. 1 (Appendix 1) denominator $\phi\sum_{i=1}^{n} s_i$ (the total number of unprotected exposures) and numerator $\sum_{i=1}^{n} x_i$ (the total number of transmission events) were provided, or if the numerator was provided and the denominator could be calculated as $\phi\sum_{i=1}^{n} s_i = \frac{\sum_{i=1}^{n} x_i}{\widehat{\beta}}$, we used $\sum_{i=1}^{n} x_i$ and $\phi\sum_{i=1}^{n} s_i$ with Stata's cii command, which calculates Wald confidence intervals and corresponding standard errors.

2. If values $\sum_{i=1}^{n} s_{i,j=1}$, $\sum_{i=1}^{n} s_{i,j=2}$, $\sum_{i=1}^{n} x_{i,j=1}$, and $\sum_{i=1}^{n} x_{i,j=2}$ were unavailable for stratified estimates with two categories (j=1, j=2) , we first obtained the unstratified values $\sum_{i=1}^{n} s_i$ and $\sum_{i=1}^{n} x_i$. If $\sum_{i=1}^{n} s_i$ was not reported, we either used method 1 to calculate $\sum_{i=1}^{n} s_i$, or we estimated $\sum_{i=1}^{n} s_i$ as $N\bar{s}$, where N = the number of susceptibles at risk and $\bar{s}$ = the average number of unprotected sexual HIV exposures occurring during the risk period. If $\sum_{i=1}^{n} x_i$ was not reported, we used Eq. 1 to estimate $\sum_{i=1}^{n} x_i = \widehat{\beta}\sum_{i=1}^{n} s_i$. After obtaining $\sum_{i=1}^{n} s_i$ and $\sum_{i=1}^{n} x_i$, we solved the following system of equations for $\sum_{i=1}^{n} s_{i,j=1}$, $\sum_{i=1}^{n} s_{i,j=2}$, $\sum_{i=1}^{n} x_{i,j=1}$, and $\sum_{i=1}^{n} x_{i,j=2}$:

$$\sum_{i=1}^{n} s_i = \sum_{i=1}^{n} s_{i,j=1} + \sum_{i=1}^{n} s_{i,j=2} \qquad \sum_{i=1}^{n} x_i = \sum_{i=1}^{n} x_{i,j=1} + \sum_{i=1}^{n} x_{i,j=2}$$

$$\widehat{\beta}_{j=1} = \frac{\sum_{i=1}^{n} x_{i,j=1}}{\sum_{i=1}^{n} s_{i,j=1}} \qquad \widehat{\beta}_{j=2} = \frac{\sum_{i=1}^{n} x_{i,j=2}}{\sum_{i=1}^{n} s_{i,j=2}}$$

After solving the system of equations, we used the cii command in Stata with the stratum-specific numerators and denominators to estimate the stratum-specific standard error.

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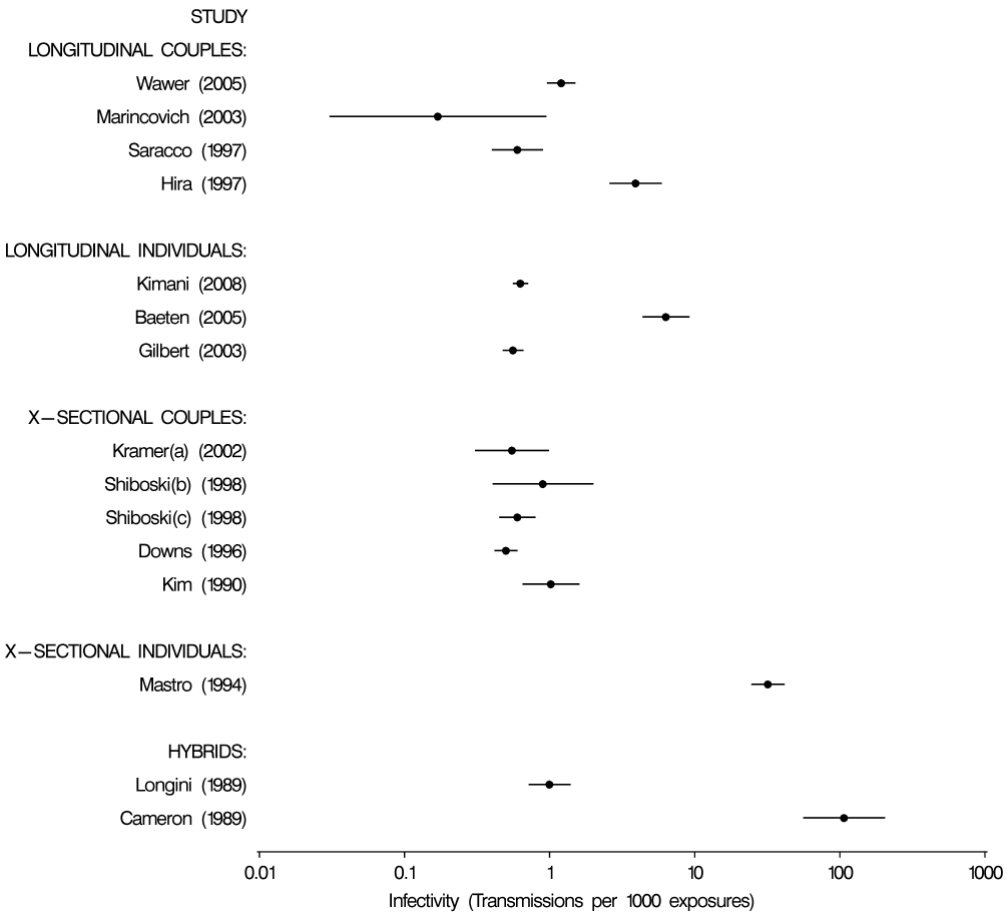

Figure 1. Forest plot of overall (whole-sample) estimates by study design

Study-specific infectivity estimates and 95% confidence intervals. For symmetry of confidence intervals on the log axis, the plotted values were calculated from logit-transformed transmission probabilities and their corresponding confidence limits. Untransformed values were used in all meta-analyses. [a]Ragni data; [b]O'Brien data; [c]California Partners Study data

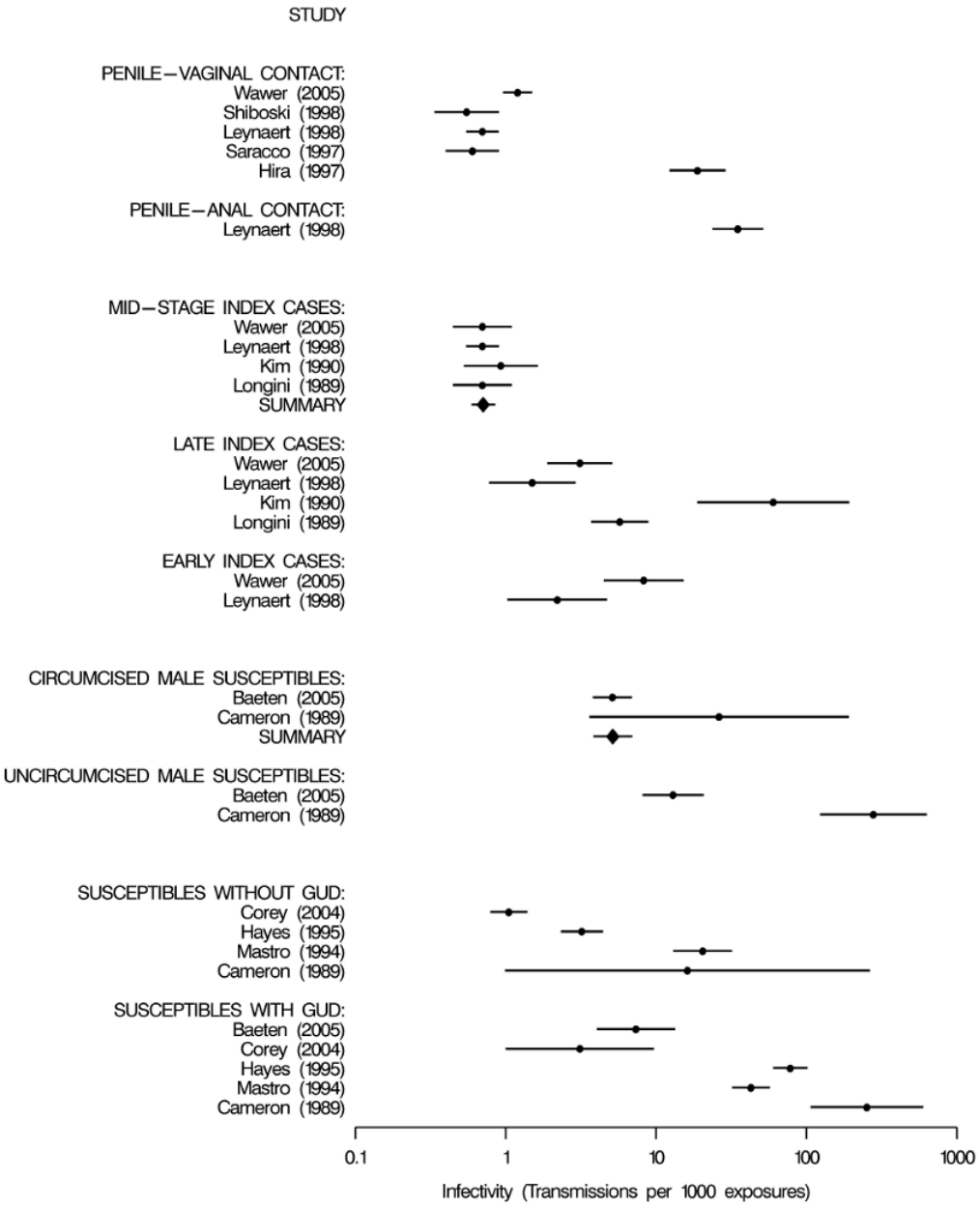

Figure 2. Forest plot of estimates stratified by selected transmission co-factors

Study-specific and pooled infectivity estimates and 95% confidence intervals stratified by sexual contact type, index infection stage, male susceptibles' circumcision status, and susceptible GUD status. Pooled (summary) estimates are shown only for strata with homogeneity p>0.2. For symmetry of confidence intervals on the log axis, the plotted values were calculated from logit-transformed transmission probabilities and their corresponding confidence limits. Untransformed values were used in all meta-analyses.

Table 1

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

Study population	Setting	Susceptible type	1st Author (year published)	Number of susceptibles[a]	Most precise overall infectivity[b] estimate	Standard error[b]
Cameron (18)	Kenya	FSW clients	Cameron (1989) (18)	73	96.7[c]	37.55[d]
Fischl (53)	USA	Partners of HIV+	Longini (1989) (27)	45	1.0	0.2
Peterman (54)	USA	Partners of HIV+	Wiley (1989) (28)	53	1.39	0.44
			Kaplan (1990) (29)	53	1.4	0.41[e]
			Kim (1990) (30)	80	1.02	0.3
			Kramer (1990) (31)	55	1.3	0.41[d]
			Shiboski (1998) (32)	51	0.8	0.41[e]
Thai military conscripts (55)	Thailand	FSW clients	Mastro (1994) (33)	673	31.0	3.8[e]
			Satten (1994) (34)	673	31.0	3.8[e]
European Study Group (56)	Europe	Partners of HIV+	DeVincenzi (1994) (35)	121	1.0	0.31[e]
			Downs (1996) (36)	525	0.5	0.08[e]
			Leynaert (1998) (37)	499	0.9	0.1
			Kramer (2002) (38)	525	0.5[c]	0.08[d]
Hira (39)	Zambia	Partners of HIV+	Hira (1997) (39)	110	3.9[c]	1.0[d]
Saracco (40)	Italy	Partners of HIV+	Saracco (1997) (40)	627	0.6	0.13[e]
California Partners Study (57)	USA	Partners of HIV+	Wiley (1989) (28)	59	0.78	0.25
			Jewell (1990) (41)	159	1.0	0.16[d]
			Jewell (1994) (42)	88	1.29	0.34
			Padian (1997) (43)	360	0.9	0.13[e]
			Shiboski (1998) (32)	302	0.6	0.10[e]

Study population	Setting	Susceptible type	1st Author (year published)	Number of susceptibles[a]	Most precise overall infectivity[b] estimate	Standard error[b]
O'Brien (58)	USA	Partners of HIV+	Shiboski (1998) (32)	31	0.9	0.41[e]
Ragni (59)	USA	Partners of HIV+	Kramer (2002) (38)	45	0.55[c]	0.23[d]
Senegal cohort (44)	Senegal	FSW	Donnelly (1993) (44)	780	0.27	0.08[d]
			Gilbert (2003) (45)	1948	0.56	0.05[d]
Marincovich (46)	Spain	Partners of HIV+	Marincovich (2003) (46)	74	0.17	0.17[d]
Baeten (47)	Kenya	Male truck drivers	Baeten (2005) (47)	745	6.3	1.43[e]
Rakai study (60)	Uganda	Partners of HIV+	Gray (2001) (48)	174	1.1	0.18[e]
			Corey (2004) (49)	174	1.1	0.18[e]
			Wawer (2005) (50)	235	1.2	0.15[e]
Nairobi cohort (61)	Kenya	FSW	Hayes (1995) (51)	117	2.6[c]	0.30[d]
			Kramer (2002) (38)	232	1.54[c]	0.14[d]
			Kimani (2008) (52)	687	0.63	0.04[d]

FSW = Female sex worker

The most precise estimate and corresponding standard error within each study population are shaded in grey.

[a] Total included in overall infectivity calculation. Stratified analyses were conducted in subsets containing fewer individuals.

[b] Transmission events per 1000 exposures

[c] Calculated from reported data using Eq. 1 (see Appendix 1)

[d] Calculated using method 1 in Appendix 2

[e] Calculated from reported confidence limits (see Appendix 2)

Table 2

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

			Stratified Meta-Analysis Results		Univariable Meta-Regression Results	
Characteristic	**Category**	**# estimates**	**Homogeneity p**	**Infectivity[a,b] (95% CI)**	**Infectivity[a,c] (95% CI)**	**Infectivity[a] difference (95% CI)**
Partnership status	Partner of known HIV+	10	<0.0001	0.73 (0.51-0.96)	0.63 (0.54-0.73)	0.
	Independent individual	5	<0.0001	0.96 (0.42-1.50)	0.61 (0.54-0.68)	-0.02 (-0.14-0.10)
Outcome ascertainment	Any cross-sectional	8	<0.0001	0.88 (0.38-1.38)	0.61 (0.49-0.72)	0.
	All longitudinal	7	<0.0001	0.71 (0.48-0.94)	0.62 (0.56-0.69)	0.01 (-0.11-0.14)
Index infection date[d]	Crude estimate	4	0.1	0.61 (0.44-0.79)	0.59 (0.46-0.71)	0.
	Transfusion date	2	0.8	0.98 (0.50-1.45)	0.98 (0.50-1.46)	0.39 (-0.10-0.89)
External sex exposures[e]	Some exclusions	8	0.0001	0.71 (0.49-0.92)	0.68 (0.52-0.85)	0.
	No exclusions	2	0.002	2.05 (0.00-5.27)	0.78 (0.24-1.31)	0.10 (-0.47-0.65)
Blood exposures	Some exclusions	9	<0.0001	0.71 (0.48-0.95)	0.63 (0.53-0.73)	0.
	No exclusions	6	<0.0001	0.97 (0.52-1.42)	0.61 (0.54-0.68)	-0.02 (-0.14-1.04)
HIV testing interval[f]	> 3 months	6	0.0001	0.67 (0.50-0.84)	0.63 (0.56-0.69)	0.
	≤ 3 months	3	0.02	5.36 (0.84-9.89)	4.73 (3.10-6.37)	4.10 (2.47-5.74)
Condom-protected acts	Some protection	5	<0.0001	1.11 (0.35-1.88)	0.70 (0.57-0.83)	0.
	Protection rare or adjusted for	8	<0.0001	0.70 (0.44-0.97)	0.62 (0.53-0.70)	-0.08 (-0.24-0.08)
Self-report error	Not corrected or mentioned	12	<0.0001	0.71 (0.47-0.95)	0.61 (0.54-0.67)	0.
	Corrected	3	<0.0001	1.19 (0.40-1.97)	0.67 (0.53-0.82)	0.06 (-0.09-0.22)
Analytical model[g]	Bernoulli model	5	<0.0001	1.13 (0.50-1.77)	0.56 (0.48-0.64)	0.
	Transmissions / acts	7	<0.0001	0.71 (0.39-1.03)	0.64 (0.57-0.70)	0.08 (-0.03-0.18)
	Failure probability	3	0.2	0.76 (0.47-1.06)	0.69 (0.52-0.87)	0.13 (-0.06-0.32)

[a] Transmissions per 1000 exposures.

[b] Random-effects estimate pooled within a given stratum of study characteristic.

[c] From random-effects models with overall infectivity as dependent variable and study feature as independent variable.

[d] Applies only to studies basing exposure period start on index infection date.

[e] Applies only to studies of couples.

[f] Applies only to studies with any longitudinal HIV testing to detect incident cases among susceptibles.

[g] See Appendix 1.

Table 3

Results of stratified meta-analysis and meta-regression based on transmission co-factor characteristics

			Stratified Meta-Analysis Results		Univariable Meta-Regression Results	
Characteristic	**Category**	**# estimates**	**Homogeneity p**	**Infectivity[a,b] (95% CI)**	**Infectivity[a,c] (95% CI)**	**Infectivity[a] difference (95% CI)**
Region	USA / Europe	8	0.05	0.59 (0.44-0.75)	0.56 (0.46-0.66)	0.
	Africa	6	<0.0001	0.91 (0.59-1.22)	0.64 (0.57-0.71)	0.08 (-0.04-0.20)
	Asia	1	N/A	31.00 (25.00-40.00)[d]	N/A[e]	N/A[e]
Type of act	Penile-vaginal	5	0.0002	0.84 (0.51-1.17)	N/A[e]	N/A[e]
	Penile-anal	1	N/A	33.80 (18.51-49.09)[d]	N/A[e]	N/A[e]
Transmission direction	Male-to-Female	10	0.001	0.66 (0.54-0.79)	0.64 (0.57-0.72)	0.
	Female-to-Male	6	<0.0001	2.76 (1.19-4.33)	0.64 (0.45-0.84)	-0.002 (-0.21-0.21)
Susceptible GUD status[f]	No GUD	4	<0.0001	3.72 (0.70-6.75)	1.46 (0.94-1.97)	0.
	GUD	5	<0.0001	30.55 (11.27-49.84)	7.46 (4.75-10.17)	6.00 (3.25-8.76)
Susceptible STI status[f]	No STI	1	N/A	12.00 (6.00-25.00)[d]	N/A[e]	N/A[e]
	STI	2	0.1	55.86 (4.43-107.29)	N/A[e]	N/A[e]
Susceptible circum. status	Circumcised	2	0.4	5.13 (3.37-6.89)	5.13 (3.36-6.89)	0.
	Not circumcised	2	0.02	97.33 (0.00-295.16)	13.21 (5.70-20.72)	8.08 (0.37-15.80)
Mean susceptible age	≥ 30 years	6	<0.0001	1.06 (0.56-1.56)	0.94 (0.71-1.16)	0.
	< 30 years	2	<0.0001	15.71 (0.00-45.20)	0.99 (0.58-1.40)	0.05 (-0.41-0.52)
Index disease stage	Mid	4	0.9	0.71 (0.57-0.85)	0.71 (0.57-0.85)	0.
	Early	2	0.05	4.67 (0.00-10.46)	3.25 (0.93-5.56)	2.54 (0.22-4.86)
	Late	4	0.02	3.18 (0.94-5.42)	2.56 (1.58-3.53)	1.85 (0.86-2.83)
Mean index age	< 30 years	1	N/A	0.90 (0.70-1.10)[d]	N/A[e]	N/A[e]
	≥ 30 years	3	0.02	1.31 (0.66-1.96)	N/A[e]	N/A[e]

[a] Transmissions per 1000 exposures

[b] Random-effects estimate pooled within a given stratum of transmission co-factor.

[c] From random-effects models with infectivity as dependent variable and transmission co-factor as independent variable.

[d] Estimate based on single study only.

[e] Meta-regression results computed only when the number of estimates exceeded 1 in the comparison group and in the referent stratum.

[f] Before or during study period