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The role of extra-couple HIV transmission in sub-Saharan Africa

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Summary

Background—The proportion of heterosexual HIV transmission in Sub-Saharan Africa that occurs within cohabiting partnerships, as opposed to among single people, or in extra-couple relationships, is a subject of active debate. This question is of immediate importance. As plans to use antiretroviral drugs as a strategy for population-level prevention progress, understanding the importance of different transmission routes is critical to targeting intervention efforts.

Methods—We built a mechanistic HIV transmission model using data from Demographic and Health Surveys covering 27,201 cohabiting couples from 18 sub-Saharan African countries with information on couple duration, age at sexual debut, and HIV serostatus. We combined this model with estimates of HIV survival times and country-specific estimates of HIV prevalence and ART coverage. We then estimated the proportion of observed infections in surveyed cohabiting couples that occurred prior to couple formation, between couple members, and through extra-couple intercourse.

Findings—We estimate that extra-couple transmission accounts for between 27-61% and 21-51% of all infected males and females, respectively, in surveyed couples, with the ranges given reflecting inter-country variation. We project that over the next year extra-couple transmission will account for 30-65% and 10-47% of new incident HIV infections in males and females, respectively, in cohabiting couples. Our results also suggest that the directionality of transmission within couples is largely from males to females; however, females experience a very high-risk period prior to couple formation.

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Author Contributions

SEB, KJF, BGW and JD developed the study concept. SEB, WMG, and JD developed the model framework. SEB, KJF and JD acquired and cleaned the data. SEB, KJF, and DYM reviewed the literature. SEB performed the model analyses and wrote the initial draft. All authors participated in the interpretation of results and the preparation and approval of the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Interpretation—Due to the large contribution of extra-couple transmission, HIV prevention interventions should target the general sexually active population, and not just serodiscordant couples.

Keywords

Demographic and Health Surveys; HIV sero-discordant couple; heterosexual transmission; Markov Chain Monte Carlo; marriage; extramarital transmission; HIV/AIDS; mathematical modeling; cohabiting partnership

Introduction

The last two years have seen major research advances relating to anti-HIV interventions. Studies have shown that antiretroviral drugs can help prevent HIV transmission either by reducing infectiousness when given as antiretroviral therapy (ART) to HIV-positive individuals (treatment as prevention—TasP)^{1, 2} or by reducing the susceptibility of HIV-negative individuals when given as oral or topical pre-exposure prophylaxis (PrEP).^{3, 4} These advances have ignited debate about how best to use ART in efforts to further reduce HIV incidence.⁵ An approach combining multiple biomedical and behavioral interventions will be required,⁶ and policy makers are currently debating the criteria used to target interventions, including TasP and PrEP.

Many proposed strategies revolve around serodiscordant couples, defined as an HIV-positive and HIV-negative individual engaged in an ongoing sexual relationship. Such couples represent a clear instance of a susceptible individual being at risk of HIV infection from an infectious individual.^{7, 8} Aiming interventions at well-defined, high-risk groups such as seronegative individuals in serodiscordant partnerships is expected to be resource-efficient. Thus, research on HIV transmission and intervention efficacy has often focused on cohorts of serodiscordant couples,⁷ so that seronegative individuals in such couples are also often the first group in which a new intervention has been demonstrated to work. For example, in response to the demonstrated effectiveness of TasP in preventing transmission within a cohort of serodiscordant couples,¹ the World Health Organization (WHO) has recommended offering TasP to HIV positive partners in serodiscordant couples, regardless of immune status.⁹

Not all transmission happens within serodiscordant couples: transmission routes also include infection of single (uncoupled) individuals, and of coupled individuals by sexual partners outside their relationship. Granich and colleagues¹⁰ propose a much more aggressive use of TasP in a ‘test and treat’ policy that would target all heterosexual routes of transmission. This approach consists of annual voluntary testing of the entire sexually active population along with immediate and sustained provision of ART to anyone testing HIV-positive. This approach is more expensive and logistically difficult than targeted approaches, and its value depends strongly on the proportion of new transmission events that occur between partners in serodiscordant couples versus otherwise. This study seeks to inform this debate by assessing the proportional contribution of different routes of transmission to new HIV infections.

We use Demographic and Health Surveys (DHS) to investigate the proportion of heterosexual HIV transmission that occurs within marriages or other cohabiting partnerships. DHS provide rich data sets on the proportion of couples in each of the four possible couple serostatus groups (concordant positive, male positive discordant, female positive discordant, and concordant negative). We refer to all cohabiting couples as “couples” (regardless of marital status) and refer to intercourse between a couple member

and an outside individual during the duration of the partnership as “extra-couple” intercourse.

Previous studies employing DHS and similar cross-sectional couple data have arrived at diverse conclusions.¹¹⁻¹⁷ Analyses of DHS couples data have noted that the proportion of serodiscordant couples with seropositive females, versus males, was slightly less than half;^{11, 14} others used mathematical models to estimate the proportion of transmission that occurred from outside serodiscordant partnerships versus between partners.^{15, 16} These studies all conclude that the high prevalence of both female and male positive serodiscordant partnerships suggests that, contrary to mainstream beliefs,¹⁴ females as well as males often have risky extra-couple intercourse, with the modeling studies estimating that a large proportion of transmission to both genders occurs from ‘outside’ rather than within the couple.

These studies have largely overlooked the fact that routes of infection cannot be directly inferred from cross-sectional data such as DHS. Estimating transmission from ‘outside’ a couple conflates infections occurring from extra-couple intercourse with those acquired prior to that couple’s formation, while the individual was either single or in another couple. Thus, the existence of serodiscordant couples does not necessarily indicate extra-couple transmission, and estimates of the proportion of transmission from ‘outside’ existing partnerships do not measure extra-couple transmission.

A second important factor largely overlooked in analyses of cross-sectional couples data is survival bias: only couples where both partners survive to be sampled are observed. Median survival time after seroconversion is approximately 6-13 years, depending on the age at seroconversion.¹⁸ Many couples in which one or both partners became infected have thus been removed from the population before the sample was taken. This effect will be different for serodiscordant and seroconcordant couples. Studies analyzing cross-sectional couple data while ignoring mortality^{11, 14-16, 19} may therefore yield biased conclusions regarding the proportional contribution of extra-couple intercourse to incidence.

The aforementioned studies^{11, 14-16} used cross-sectional data to infer the proportion of observed infections occurring via different transmission routes. In contrast, two other modeling studies^{13, 17} used similar data to project forward in time. Using seronegative individuals’ self-reported rates of intercourse with cohabiting and non-cohabiting partners in DHS data and a wide range of estimates of transmission rates, Dunkle and colleagues¹³ concluded that 55-92% of *all* ongoing HIV transmission (including single and coupled individuals) in urban populations in Zambia and Rwanda was due to transmission between serodiscordant partners. However, self-reported rates of intercourse with non-cohabiting partners are frequently biased downwards due to cultural norms,²⁰ and could lead to substantial underestimation of the contribution of extra-couple intercourse. In a similar analysis, focused only on serodiscordant couples, Chemaitelly and colleagues¹⁷ concluded that extramarital transmission contributes “minimally” to infections of the seronegative partner in most countries, but do not attempt to extrapolate to concordant negative couples. Neither of these studies assessed whether their transmission models could adequately explain observed levels of serodiscordance.¹²

Analyses that account for the limitations of existing studies are necessary to clarify the relative contribution of extra-couple and within-couple intercourse to heterosexual transmission and inform the development of TasP and PrEP policies. To address this issue, we constructed a mathematical model to estimate rates of HIV transmission prior to couple formation, due to extra-couple intercourse, and within serodiscordant couples. Since the probability that an individual acquires HIV during any period is a function of the period’s

duration,²¹ we disentangle routes of transmission by relating couple serostatus to information on couple duration, duration of sexual activity before couple formation, the population prevalence of HIV, and age-specific estimates of HIV survival.

Methods

We describe the data and model analyses here briefly and provide a complete description as well all material necessary to reproduce these analyses in the online web appendix.

Data Sources

Couple-level variables taken from DHS data included each partner's serostatus, current age, age at sexual debut, and partnership duration. In earlier surveys, information on couple duration is not directly available, but was ascertainable if at least one partner was in their first partnership; couples were otherwise excluded from analysis. Other exclusion criteria included: missing HIV serostatus, polygamy, if male and female accounts of the couple duration differed by greater than 25% of their average, if sexual debut was given as greater than one year after couple formation or if age at couple formation was less than eight years of age. Our analysis also relies on age-at-seroconversion-specific estimates of HIV survival times¹⁸ and the prevalence of infectious HIV-positive individuals by gender in all countries analyzed over the duration of the HIV epidemic. We assume that individuals on ART are not infectious. We thus calculated infectious prevalence as the estimated prevalence multiplied by the proportion of the infected individuals not on ART, using UNAIDS estimates of ART coverage.²² We assumed no effect of ART coverage on within-couple transmission, because infected individuals would have exposed their partners to infection for a long time before receiving ART, typically at a CD4 cell $<200/\mu\text{L}$. West African countries were pooled for analysis due to small numbers of infected individuals.

Modelling analysis

For each gender, we allowed for three routes of transmission—infection before couple formation, infection from an infected partner, or extra-couple infection during the partnership—yielding six different hazard rates (Figure 1). Each hazard rate is the product of a gender-route-specific transmission coefficient and the probability a sexual partner is seropositive. This probability changes over time and is based on partner serostatus for within-couple transmission, and estimated as the opposite gender's current population infectious HIV prevalence for before-partnership or extra-couple transmission. The transmission coefficients can thus be defined as prevalence-standardized hazard rates and considered as the product of behavioral factors (e.g., rate of intercourse, number and relative riskiness of partners) and the per coital act probability of transmission.

We assume that both partners were seronegative before they became sexually active. Starting when the first partner became sexually active, we iteratively calculate the probability of each partner's serostatus for each month of sexual activity before and during the partnership (Figure 1B). We assumed that individuals infected < 1 month before sampling would test seronegative.²³ For each country analysis, we estimate the conditional probability of each couple having its observed serostatus given their survival to DHS sampling, and then use Bayesian Markov Chain Monte Carlo²⁴ to estimate parameter values. All estimates shown are medians of posterior distributions with 95% credible intervals (the Bayesian analogue to confidence intervals). All transmission coefficients were given uninformative priors except for the ratio of female-to-male and male-to-female transmission within couples for which, based on available literature,²⁵ we set an informative lognormal prior centered at one with a standard deviation of 0.5.

From model fits we estimate the proportion of observed infections (i.e., infected individuals in couples sampled by the DHS) arising from each transmission route. We also account for survival bias to estimate the per-route contribution to transmission for total infections, including couples that did not survive to be sampled. We estimate total infections arising from each route by calculating the probabilities of each transmission route for each couple, and inflating them using the inverse estimated probability that a couple will survive to be observed by DHS and counted in a given calculation. To estimate ongoing transmission, we use fitted transmission coefficients to project HIV incidence over the next year in individuals testing seronegative at DHS sampling, tracking proportional contributions of transmission from seropositive partners or extra-couple intercourse (using 2011 estimates of HIV prevalence and ART coverage²²).

We validated the model fitting procedure by fitting simulated data from an independently coded event-driven simulation of couple transmission events and comparing fitted estimates of all quantities of interest to their simulated values. We also assessed the robustness of our results by performing several sensitivity analyses. First, we assessed the assumption that individuals are homogenous with respect to their transmission coefficients by simulating transmission with a population where each individual's pre- and extra-couple transmission coefficients varied together. The log of the risk multiplier was a standard normal deviate: this yields forces of infection differing by a factor of 50 between individuals at the 2.5% and 97.5% riskiness quantiles). We then fitted the resulting heterogeneous data with a homogenous model and assessed all estimates for bias. Second, we recalculated transmission-route contributions in our fitted model while including demographic information from couples that lacked HIV serostatus data. Third, we relaxed the assumption that individuals on ART are absolutely non-infectious. Fourth, we relaxed our assumption that ART did not affect within-couple transmission. Finally, we assessed sensitivity to reporting bias by assuming that 30% of females who stated that their sexual debut occurred with their current partner actually became sexually active a year earlier. A list of model assumptions, justifications, and implications is provided in Table S2.

Role of the funding source

Study sponsors had no role in the process of research, data analysis, or decision to publish. The authors had access to all data, and had final responsibility for the decision to submit for publication.

Results

After applying our exclusion criteria, between 41% and 80% of couples in each country remained available for analysis (Table 1). Of couples analyzed, 52-93% consisted of couples in which both partners were in their first stable cohabiting relationship.

Transmission coefficient estimates are summarized in Table 2. Results demonstrated that (1) male and female extra-couple transmission coefficients were similar, (2) females experienced a relatively high risk per unit time of transmission before couple formation, and (3) partners of both sexes had larger pre-couple than extra-couple transmission coefficients. Goodness of fit tests and simulation analyses did not indicate any problems with the model fits (Figure S4, Table S4). Our results were robust to the assumption of homogeneity (Table S5), the exclusion of couples missing HIV serostatus data (Table S6), the proportion of individuals on ART assumed to be non-infectious, whether ART reduced within-couple transmission, and reporting bias of females' sexual debuts (Tables S11-12).

Figure 2 shows how our model disentangled the proportional contribution of each route of transmission. Seropositive partners were more likely to have been infected after couple

formation if (1) they had a shorter duration of sexual activity prior to couple formation, (2) couple formation occurred earlier on in the HIV epidemic (when population prevalence was low), or (3) couple duration was longer (because otherwise they would probably have died before sampling). Seropositive individuals likely to have been infected after couple formation in serodiscordant couples were therefore likely to have been infected by extra-couple transmission. In concordant positive couples, infections likely to have occurred after couple formation could have also been caused by within-couple transmission.

All ranges given below reflect inter-country variation (see online web appendix for country-specific estimates and credible intervals) excluding results from the Democratic Republic of Congo, for which there were too few seropositive individuals to yield precise estimates. Model fits indicated that extra-couple transmission was responsible for a large proportion of observed infections in serodiscordant couples, with estimates ranging from 58-80% and 43-74% of infected males and females, respectively, infected through extra-couple intercourse, with the remainder of infections occurring prior to couple formation. In concordant positive couples, we estimated the per-route contribution to infection for males and females, respectively, to be 17-54% and 15-48% from before partnership formation, 18-51% and 13-29% from extra-couple intercourse, and 28-46% and 39-68% from an infected partner (Figure 3C-D, Table S7). Individuals who were alive at the survey, however, were likely to be infected relatively recently and these estimates therefore underrepresent infections occurring before couple formation. Even when accounting for survival bias, however, we estimate that over the course of the epidemic (amongst couples that did and did not survive to be surveyed) that 31-77% of index infections within couples (i.e., the first infection in a given couple) were due to extra-couple transmission rather than transmission occurring before couple formation (Figure 3, Table S8), with the majority of the former being extra-couple infections of males.

Based on 2011 HIV prevalence and ART coverage estimates, we projected estimates of extra-couple transmission within serodiscordant couples, and within all cohabiting couples. Within serodiscordant couples, we projected 0.18-13% and 0.071-6.2% of new infections of seronegative male and female individuals within serodiscordant couples over the next year will result from extra-couple transmission, with the remainder due to within-couple transmission (Table S9). However, amongst all cohabiting couples we projected that extra-couple transmission will be responsible for respectively 30-65% and 10-47% of HIV incidence in males and females (Figure 4, Table S10).

Discussion

Our results yielded three major conclusions. First, extra-couple transmission has played and continues to play a major role in driving HIV incidence for both genders, but particularly for males. Second, within couples, HIV appears to be propagated more from males to females than vice versa. Third, females go through a period of high infection risk before entering a cohabiting partnership.

We emphasize that the fitted transmission coefficients aggregate multiple behavioral and physiological processes and thus must be interpreted cautiously. Because the hazard of infection is the product of transmission coefficients and prevalence in the opposite gender, comparisons between male and female transmission coefficients must be made in light of the differing HIV prevalences for each gender. For instance, even though we estimate that more males than females are infected through extra-couple transmission, the estimated extra-couple transmission *coefficients* are roughly similar. This is because female infectious HIV prevalence is greater than that of males. The transmission coefficients will also partially absorb un-modeled mixing patterns. For example, young females tend to mix with older men

who have a greater probability of being seropositive. This effect would tend to increase female incidence before partnership formation, requiring greater fitted female before-partnership transmission *coefficients* to fit the observed data, but not necessarily biasing the estimate of *incidence* through this route.

Extra-couple transmission

We find that extra-couple and within-couple transmission are both important, and each will continue to account for a large proportion of observed infections in both males and females, though results vary considerably by country. We obtained this result despite finding fitted extra-couple transmission coefficients to be by far the smallest amongst the three routes of infection. This is consistent with Chemaitelly and colleagues¹⁹ finding that most infections *inside* serodiscordant couples are due to within-couple transmission. The large contribution of extra-couple transmission at the population level is because the majority of cohabiting couples are concordant negative and, on average, the surveyed individuals spent most of their time since their sexual debut in a couple. Thus, the large amount of population-level time spent at risk from extra-couple transmission more than compensates for its smaller transmission coefficients. Our results, which only analyzed couples, are in stark contrast to those of Dunkle and colleagues¹³ findings that within-couple transmission accounts for the majority of all HIV incidence, including that in single individuals. This disagreement is likely due to their reliance on downwards-biased self-reported rates of intercourse with non-cohabiting partners.²⁰

When available, molecular evidence also indicates the importance of extra-couple transmission. In several serodiscordant couple cohort studies,^{1, 2, 26-28} 13-32% of incident infections were found to be from virus not linked to the virus isolated from the seroconverter's partner and were presumably due to extra-couple intercourse. Our attribution of a smaller proportion of transmission within serodiscordant couples to extra-couple intercourse may arise because individuals enrolled in cohort studies differ systematically from the general population, which is more representatively sampled by DHS. Further, seronegative individuals enrolled in cohort studies may engage in more extra-couple and less within-couple intercourse upon finding that their partner is seropositive.²⁸ This behavioral effect may also explain why our estimated rates of within-couple transmission (6.3-27 per 100 person-years) are generally greater than those from cohort studies.^{1, 2, 26}

Gender differences in transmission

Our analysis also suggests that, within couples, HIV propagates from males to females more than vice versa. This directionality is both due to males' greater average duration of sexual activity prior to couple formation and their greater hazard rate for extra-couple infection. While females' average duration of sexual activity before partnership formation is much shorter than that of males, we found that, as reported elsewhere,²¹ this is partially compensated by their greater risk of infection per unit time before partnership formation.

Model assumptions and limitations

By using relationship and serostatus data to explicitly tease apart pre-couple, within-couple, and extra-couple transmission in the context of a changing prevalence background and AIDS mortality, our model addresses several limitations of previous studies, and represents an advance in estimation of transmission breakdown by behavioral routes from cross-sectional data. Despite this added realism, our model retains certain assumptions, discussed here.

We assumed homogenous mixing between age groups for sexual partners chosen before couple formation or during extra-couple intercourse. Although this assumption may bias our

results, to the extent that age-mixing patterns cause a *consistent* bias towards over or under estimates in the estimated prevalence that individuals are exposed to, this bias will be counteracted by under or over estimates in transmission coefficients, not affecting estimates of total hazard and per-route contributions to transmission.

We also assumed that the probability of infection via a particular transmission route depends only on the duration an individual is at risk by that route, the time-varying HIV prevalence in the population of the opposite gender (or partner seropositivity for within-partner transmission), and a single transmission coefficient for each gender-route combination. In reality, the frequency of intercourse and the number and riskiness of partners also affect transmission. Other causes of heterogeneity not considered here include genetic and immunological factors, the type of sexual exposure, STIs, viral loads, viral characteristics, tendency to seek care, male circumcision, and protected sex; many of these vary both between individuals, and through time within individuals.^{7, 25} While we assumed individuals were homogeneous in our model, our results were robust to this assumption. Our sensitivity analysis shows that even with a large individual-level heterogeneity in hazard rates the relationship between relationship histories and serostatuses was strong enough for the model to accurately infer the proportional breakdown of infections by transmission routes.

Hazards may also vary over time for reasons other than changing prevalence. Declines in HIV prevalence in several countries have been attributed to behavioral changes in response to interventions or overall HIV awareness.²⁹ Such changes would lead to decreasing transmission coefficients over the course of the epidemic, but it is not clear how this decrease might be partitioned among the routes of transmission we considered, so we were unable to include it.

We did not include effects of ART on HIV survival times or within-couple transmission in our main analysis. This is both because individuals' drug status is not available from DHS surveys, and because we believe that the within-couple effects of ART are minimal. Given policy up until WHO's new 2012 TasP recommendations, most treated individuals will have already exposed their partners to infection for a long time by the time they become sick, get tested, have CD4 counts drop below 200/ μ l, and initiate ART. Further, ART coverage in the countries analyzed was negligible for most of the period covered by the couples in our survey.²² Indeed, this explains why our results were found to be robust in sensitivity analyses allowing for ART to affect within-couple transmission or relaxing the assumption that all individuals on ART are non-infectious.

Finally, given the breadth of the DHS and the relatively narrow scope of our study, we necessarily excluded a large proportion of couples due to missing or inconsistent data. However, we believe that these exclusions are unlikely to cause major selection bias and that our results are roughly generalizable to the couples in the population as sampled by DHS. In particular, our results are likely to be more representative of the general population than virological linkage cohort studies, which have both more specific selection criteria and alter the behavior of participants.²⁸

Policy implications and conclusion

We have shown that substantial HIV transmission occurs through all transmission routes—within serodiscordant couples, as well as prior to couple formation and from extra-couple intercourse. This implies that attempts to reduce HIV incidence should address all of these routes. We emphasize that we make no assumptions about the morality³⁰ or potential for mitigation³¹ of extra-couple sex. Extra-couple sex does not necessarily constitute a choice and may be motivated by basic needs or reflect larger social support structures.³² However,

policy choices should be made in light of our finding that extra-couple transmission by both genders continues to play a major role in the HIV epidemic in sub-Saharan Africa.

It is tempting to offer TasP only to HIV-positive individuals in stable, sero-discordant couples. The partner is identifiable, and clearly at risk. Our findings show, however, that the aggregate risk to partners not in stable relationships with positive individuals is also high. This does not mean that there is no place for TasP and PrEP programs targeted to serodiscordant couples. These have proven efficacious and represent major advances in HIV prevention strategy. PrEP, in particular, holds the potential to change the gender power dynamics in serodiscordant couples by empowering women to prevent HIV transmission. Given the relatively small proportion of populations in serodiscordant couples these approaches may represent a good starting point for HIV control efforts, especially in the context of current resource limitations.

However, our results do imply that behavioral and biomedical interventions focused on serodiscordant couples will have limited success in reducing HIV incidence. Interventions should be aimed towards all transmission routes to fight the HIV epidemic. Despite its greater expense and logistical demands, the ‘universal test and treat’ strategy offers a unique potential to reduce all forms of heterosexual transmission.

Research in Context Panel

Systematic Review

We searched PubMed on October 21, 2012 with the search terms (HIV) AND (discordant OR serodiscordant) AND (couple) and again with (HIV) AND (virus OR virol*) AND (linked OR linkage). We set no date limits and examined studies resulting from our search, and those cited therein. Studies using cross-sectional analyses and overall levels of serodiscordance consistently found high proportions of transmission occurring from ‘outside’ stable partnerships^{14-16, 33}; but we found no such study that disentangled ‘outside’ transmission into that occurring before partnership formation and from extra-couple transmission. A mathematical modeling study concluded that 55-92% of all HIV incidence in urban Zambia and Rwanda arises from transmission within stable, serodiscordant partnerships.¹³ However, this study relied on self-reported rates of extra-couple intercourse. A similar study¹⁷ assumed making more conservative assumptions regarding extra-couple behavior found that such transmission contributes minimally to incidence in serodiscordant couples, but did not extrapolate to concordant negative couples. Neither of these studies assessed whether their findings were consistent with observed levels of serodiscordancy¹². Cohort studies of serodiscordant couples provide evidence about rates of within-couple and extra-couple (but not pre-couple) transmission. In cohort studies where incident infections are demonstrated to be virologically linked or unlinked to the seroconverter’s partner, 13-32% of infections appear to have occurred from extra-couple transmission^{1, 2, 26-28}. In summary, we found a large variation in current estimates of the proportion of HIV incidence due to various routes depending on assumptions about what constitutes an ‘outside’ infection, whether self-reported risk behavior is a key input, and how the study population was sampled. We did not find any studies that focused on the general population and attempted to disentangle transmission pathways using couples’ relationship histories.

Interpretation

We found that a large proportion of infections in stable, cohabiting couples arises from extra-couple transmission. Our study is the first analysis to interpret couple serostatus data mechanistically, making use of each partner’s duration of sexual activity before couple formation, partnership duration, national HIV prevalence, and age-specific HIV survival times. This approach provides new power to disentangle the pathways through which

individuals became infected. For instance, seropositive individuals in serodiscordant couples whose sexual debuts each occurred with their current partner must have been infected by extra-couple intercourse. Similarly, extra-couple infection likely explains the occurrence of seropositive individuals in serodiscordant couples who coupled with their current partner before the HIV epidemic began. Our findings suggest that pre-couple, extra-couple and within-couple transmission are all common, and that HIV control policies should address all of these routes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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*The Meaningful Modeling of Epidemiological Data (MMED) Organizing Committee includes SEB, BGW, JD, Juliet R.C. Pulliam^{1,2}, James C. Scott³, Travis C. Porco⁴, and John W. Hargrove⁵

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Figure 1. Schematic diagram of the couple transmission model

This diagram illustrates how the model relates the infection process to a couple's relationship and sexual histories for an example Zambian couple. Each partner (represented by the black lines) can be infected prior to couple formation (gray arrows) beginning from the month of their sexual debut (t_{msd} or t_{fsd} for males and females, respectively) until the month the couple is formed (t_{cf}). From couple formation until the month prior to their DHS interview (t_{int}), an individual can be infected by their partner if their partner is positive (blue arrows), or from extra-couple intercourse (red arrows). For each month of an individual's sexual activity, the hazard of infection is the product of a gender-route-specific transmission coefficient (i.e., one parameter for each arrow) and the probability intercourse is with an infectious individual. The probability intercourse is with an infectious individual is determined by the probability the partner is HIV positive for within-couple transmission, and estimated as the opposite gender's population infectious HIV prevalence for before-partnership or extra-couple transmission. We assume individuals on ART are not infectious and calculate infectious HIV prevalence as $(\text{HIV prevalence}) \times (1 - \text{ART coverage})$. Thus, the difference between the solid and dashed lines is ART coverage. For this example couple, the gray (respectively, red) areas under the prevalence curves represent the infectious HIV prevalence in the opposing gender that the partners would be mixing with during before-couple (extra-couple) intercourse.

Figure 2. Model fit to Zambia couples DHS data

Each point in this figure represents a couple. Couples are divided between panels based on their serostatus: male positive discordant (A), female positive discordant (C), and concordant positive (B, D). Points are plotted as a function of the date of couple formation and the number of years the male (A, B) or female (C, D) was sexual active before the couple formed. Blue lines give the population prevalence of HIV, excluding the proportion on antiretroviral treatment (and thus not infectious), in the opposite gender (i.e., from whom before-partnership or extra-couple transmission occurs). The color of each point represents the median fitted posterior probability that a seropositive male (A, B) or female (C, D) was infected from extra-couple transmission rather than before couple formation for serodiscordant couples and, for concordant positive couples, transmission from a positive partner. For serodiscordant couples (A, C), the probability that transmission occurred extra-couple is greater for seropositive individuals who had shorter durations of sexual activity prior to couple formation, or whose couple formation occurred earlier on in the epidemic or long enough ago such that they would have been unlikely to survive to DHS sampling if infected prior to couple formation. The same patterns hold for concordant positive couples (B, D), though the probability of extra-couple transmission is reduced because within-partner transmission is also possible.

Figure 3. Estimated proportion of transmission from each route of transmission by gender, country, and couple serostatus for couples interviewed in the DHS

This figure shows the estimated proportional contribution of HIV transmission from intercourse before the formation of the current partnership (gray), from extra-couple intercourse during the current partnership (red), and from intercourse with the current partner (blue). Panels show results by couple serostatus and gender. Bars give posterior median estimates (values and 95% credible intervals are given in Table S7). These estimates only reflect the estimated contribution of each transmission route amongst observed couples, and do not account for survival bias due to couples that could not be surveyed because one or more partner died before the DHS sampling (see Table S8).

Figure 4. Projected proportion of incidence over the next year in cohabiting couples that will be due to extra-couple intercourse by country

This figure shows the estimated proportion of projected incidence that will be caused by extra-couple transmission over the next year in all males and females testing seronegative (i.e., either gender in concordant negative couples, males in female-positive serodiscordant couples, and females in male-positive serodiscordant couples) during DHS sampling. Negative individuals in discordant couples can be infected either by extra-couple transmission or by their HIV positive partner. Negative individuals in concordant negative couples can be infected either by extra-couple transmission or by their partner if their partner becomes infected by extra-couple transmission in the next year. Values and 95% credible intervals are reported in Table S10.

Total number of couples analyzed and the number (%) of couples excluded due to 1 partner missing HIV serostatus, polygamy, insufficient data to determine partnership duration, or inconsistencies in partnership duration, age at sexual debut, or age at partnership formation. The portion to the right of the vertical line shows the distribution of serostatuses amongst couples as well as the proportion of analyzed couples in which both individuals were in their first partnership.

Inclusion Criteria							Couples Analyzed				
data set	couples	no serostatus	polygamous	missing data	data inconsistent	couples analyzed	first partnership	M-F-	M+F-	M-F+	M+F+
DRC	2373	228 (9.6%)	648 (27.3%)	287 (12.1%)	343 (14.5%)	1197 (50.4%)	859 (71.8%)	1172 (97.9%)	13 (1.1%)	10 (0.8%)	2 (0.2%)
Ethiopia	9713	1050 (10.8%)	732 (7.5%)	1518 (15.6%)	1565 (16.1%)	5671 (58.4%)	2972 (52.4%)	5572 (98.3%)	35 (0.6%)	25 (0.4%)	39 (0.7%)
Kenya	2861	550 (19.2%)	308 (10.8%)	101 (3.5%)	515 (18%)	1618 (56.6%)	1266 (78.2%)	1481 (91.5%)	37 (2.3%)	48 (3%)	52 (3.2%)
Lesotho	1640	265 (16.2%)	55 (3.4%)	28 (1.7%)	262 (16%)	1099 (67%)	1017 (92.5%)	738 (67.2%)	113 (10.3%)	64 (5.8%)	184 (16.7%)
Malawi	5614	977 (17.4%)	582 (10.4%)	864 (15.4%)	801 (14.3%)	3043 (54.2%)	2166 (71.2%)	2675 (87.9%)	134 (4.4%)	81 (2.7%)	153 (5%)
Rwanda	2189	49 (2.2%)	124 (5.7%)	177 (8.1%)	156 (7.1%)	1749 (79.9%)	1396 (79.8%)	1676 (95.8%)	28 (1.6%)	10 (0.6%)	35 (2%)
Swaziland	802	143 (17.8%)	56 (7%)	41 (5.1%)	198 (24.7%)	431 (53.7%)	262 (60.8%)	247 (57.3%)	33 (7.7%)	38 (8.8%)	113 (26.2%)
WA	19349	1987 (10.3%)	6336 (32.7%)	2778 (14.4%)	3610 (18.7%)	7902 (40.8%)	4676 (59.2%)	7671 (97.1%)	86 (1.1%)	90 (1.1%)	55 (0.7%)
Zambia	3129	829 (26.5%)	293 (9.4%)	401 (12.8%)	365 (11.7%)	1599 (51.1%)	1161 (72.6%)	1310 (81.9%)	107 (6.7%)	60 (3.8%)	122 (7.6%)
Zimbabwe	5567	1352 (24.3%)	504 (9.1%)	439 (7.9%)	1038 (18.6%)	2892 (51.9%)	2138 (73.9%)	2268 (78.4%)	189 (6.5%)	121 (4.2%)	314 (10.9%)

Table 2
Median transmission coefficients (and 95% credible intervals) estimated for each route of infection

Annual hazards of infection (infections per person per year) were obtained by taking the product of the transmission coefficients and the opposite gender's infectious HIV prevalence (where individuals on ART are assumed to be non-infectious). Infectious HIV prevalence varies over the course of the epidemic for the first two routes but, for within-partnership transmission, is given as the probability that the current partner is HIV positive.

	transmission prior to couple formation to		extra-couple transmission to		transmission from a positive partner to	
	male	female	male	female	male	female
DRC	0.15 (0.016, 0.34)	0.12 (0.0065, 0.49)	0.068 (0.017, 0.15)	0.11 (0.049, 0.2)	0.022 (0.0036, 0.085)	0.019 (0.0032, 0.068)
Ethiopia	0.17 (0.073, 0.3)	0.56 (0.26, 0.96)	0.049 (0.031, 0.069)	0.036 (0.017, 0.063)	0.12 (0.06, 0.2)	0.13 (0.074, 0.21)
Kenya	0.082 (0.047, 0.12)	0.36 (0.24, 0.51)	0.035 (0.021, 0.053)	0.049 (0.029, 0.075)	0.1 (0.058, 0.16)	0.11 (0.058, 0.18)
Lesotho	0.12 (0.081, 0.16)	0.32 (0.2, 0.46)	0.12 (0.089, 0.14)	0.091 (0.06, 0.13)	0.15 (0.079, 0.26)	0.17 (0.12, 0.24)
Malawi	0.077 (0.052, 0.11)	0.25 (0.17, 0.34)	0.063 (0.049, 0.077)	0.045 (0.03, 0.066)	0.11 (0.06, 0.17)	0.11 (0.07, 0.14)
Rwanda	0.14 (0.052, 0.25)	0.3 (0.1, 0.61)	0.068 (0.043, 0.1)	0.035 (0.013, 0.074)	0.18 (0.08, 0.37)	0.14 (0.084, 0.22)
Swaziland	0.31 (0.22, 0.41)	0.64 (0.45, 0.85)	0.078 (0.048, 0.12)	0.085 (0.046, 0.14)	0.21 (0.12, 0.34)	0.27 (0.17, 0.43)
West Africa	0.098 (0.059, 0.14)	0.28 (0.18, 0.4)	0.06 (0.044, 0.078)	0.074 (0.054, 0.099)	0.063 (0.034, 0.1)	0.075 (0.042, 0.12)
Zambia	0.12 (0.088, 0.16)	0.32 (0.23, 0.43)	0.068 (0.049, 0.087)	0.043 (0.025, 0.067)	0.13 (0.072, 0.2)	0.11 (0.071, 0.15)
Zimbabwe	0.11 (0.086, 0.14)	0.41 (0.32, 0.5)	0.064 (0.052, 0.078)	0.054 (0.039, 0.072)	0.15 (0.1, 0.21)	0.12 (0.09, 0.16)