Extra-couple HIV transmission in sub-Saharan Africa: a mathematical modelling study of survey data

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Summary

Background **The proportion of heterosexual HIV transmission in sub-Saharan Africa that occurs within cohabiting partnerships, compared with that in single people or extra-couple relationships, is widely debated. We estimated the proportional contribution of different routes of transmission to new HIV infections. As plans to use antiretroviral drugs as a strategy for population-level prevention progress, understanding the importance of different transmission routes is crucial to target intervention efforts.**

Methods **We built a mechanistic model of HIV transmission with data from Demographic and Health Surveys (DHS) for 2003–2011, of 27 201 cohabiting couples (men aged 15–59 years and women aged 15–49 years) from 18 sub-Saharan African countries with information about relationship 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 coverage of antiretroviral therapy (ART). We then estimated the proportion of recorded infections in surveyed cohabiting couples that occurred before couple formation, between couple members, and because of extra-couple intercourse.**

Findings **In surveyed couples, we estimated that extra-couple transmission accounted for 27–61% of all HIV infections in men and 21–51% of all those in women, with ranges showing intercountry variation. We estimated that in 2011, extra-couple transmission accounted for 32–65% of new incident HIV infections in men in cohabiting couples, and 10–47% of new infections in women in such couples. Our findings suggest that transmission within couples occurs largely from men to women; however, the latter sex have a very high-risk period before couple formation.**

Interpretation **Because of the large contribution of extra-couple transmission to new HIV infections, interventions for HIV prevention should target the general sexually active population and not only serodiscordant couples.**

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Introduction

In the past 2 years, major research advances have been made in anti-HIV interventions. 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 led to debate about how best to use ART to further reduce HIV incidence.[5] An approach that combines several biomedical and behavioural interventions will be needed,[6] and policy makers are debating the criteria used to target interventions, including TasP and PrEP.

A serodiscordant couple, defined as an HIV-positive and HIV-negative individual in an ongoing sexual relationship, is a clear example of a susceptible individual being at risk of HIV infection from an infectious individual.[7,8] Targeting of well defined, high-risk groups such as seronegative individuals in serodiscordant partnerships is expected to be resource-efficient. Thus, research of HIV transmission and intervention efficacy has tended to focus on cohorts of serodiscordant couples[7] such that seronegative individuals in these partnerships are often the first group in which a new intervention is shown to work. For example, in response to the proven effectiveness of TasP in prevention of transmission in a cohort of serodiscordant couples,[1] WHO has recommended this strategy to HIV-positive partners in serodiscordant couples, irrespective of immune status.[9] However, not all transmission is within serodiscordant couples; routes also include infection of individuals who are single, and of those in couples by sexual partners outside their relationship (extra-couple relationships). Granich and colleagues[10] propose 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, with immediate and sustained provision of ART to those who test HIV positive. This approach is more expensive and logistically difficult than are targeted approaches, and its value is strongly dependent on the proportion of new transmission events that occur between partners in serodiscordant couples versus those occurring by other routes.

We constructed a mathematical model to estimate rates of HIV transmission before couple formation, rates attributable to extra-couple intercourse, and rates within serodiscordant couples, to assess the proportional contribution of different routes of transmission to new HIV infections. Because the probability that an

individual acquires HIV during any period is a function of the period's duration,[11] we disentangled routes of transmission by relating couple serostatus to information about couple duration, duration of sexual activity before couple formation, the population prevalence of HIV, and age-specific estimates of HIV survival.

Methods

Data sources

See Online for appendix

The appendix provides a complete description and material needed to reproduce our model analyses. We used data from Demographic Health Surveys (DHS) for 2003–2011, from 27 201 cohabiting couples in 18 countries in sub-Saharan Africa. DHS provide data for surveyed men (aged 15–59 years) and women (15–49 years) who self-identified as being in a stable, cohabiting coupled relationship at the time of their DHS interview. Although a small proportion of male partners (<0·1%) and female partners (<2·5%) were younger than 18 years, for convenience, we hereafter refer to them as men and women. We refer to all cohabiting couples as couples (irrespective of marital status), and to intercourse between a couple member and an outside individual as extra-couple intercourse.

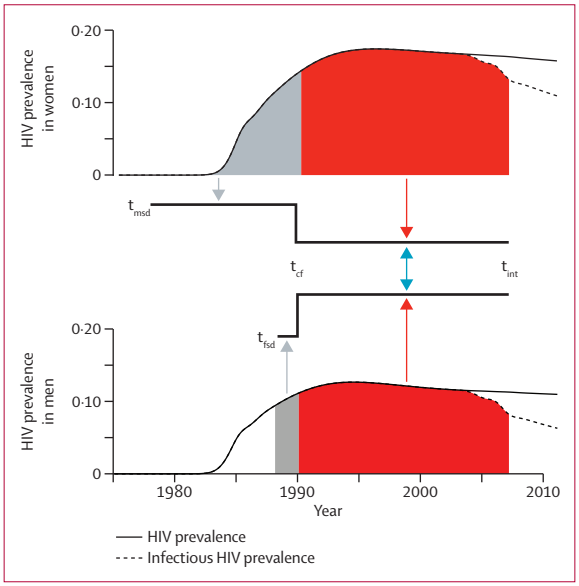

Figure 1: **Schematic diagram of the couple transmission model**
The diagram shows how the model relates the infection process to a couple's relationship and sexual histories for an example Zambian couple. Each partner (thick black lines) can be infected before couple formation (grey arrows) beginning from the month of their sexual debut (t_{msd} for men and t_{fsd} for women) until the month the couple is formed (t_{cf}). From couple formation until the month before their Demographic Health Surveys 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 (ie, one parameter for each arrow) and the probability that intercourse is with an infectious individual. The probability that intercourse is with an infectious individual is established by the probability that the partner is HIV positive for within-couple transmission, and is estimated as the population infectious HIV prevalence of the opposite sex for before-partnership or extra-couple transmission. We assume that individuals on antiretroviral therapy (ART) are not infectious and calculate infectious HIV prevalence as (HIV prevalence)×(1–ART coverage). Thus, the difference between the solid and dashed lines is ART coverage. For this example couple, the areas under the prevalence curves represent the infectious HIV prevalence in the opposite sex that the partners would associate with during before-couple (grey areas) or extra-couple (red areas) intercourse.

Couple-level variables from DHS data included each partner's serostatus, current age, age at sexual debut, and partnership duration. In surveys done before 2008, information about relationship duration was 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 were 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 1 year after couple formation, or if either sex was aged younger than 8 years at couple formation.

Our analysis relies on age-at-seroconversion-specific estimates of HIV survival times[12] and the prevalence of infectious HIV-positive individuals by sex in all countries analysed during the HIV epidemic. We assumed that individuals receiving ART were not infectious. We thus calculated prevalence of infectious individuals as the estimated prevalence of infection multiplied by the proportion of infected individuals not receiving ART, with UNAIDS estimates of HIV prevalence and ART coverage.[13] 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 therapy, typically at a CD4 cell count of less than 200 cells per μL. We pooled data from west African countries for analysis.

Modelling analysis

For each sex, we considered 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 that a sexual partner is seropositive. This probability changes over time, is based on partner serostatus for within-couple transmission, and is estimated as the current infectious HIV prevalence in the opposite sex's population for before-partnership or extra-couple transmission. We therefore defined the transmission coefficients as prevalence-standardised hazard rates and regarded them as the product of behavioural factors—eg, rate of intercourse, number and relative riskiness of partners—and the probability of transmission per coital act.

We assumed that both partners were seronegative before they became sexually active. Starting from when the first partner became sexually active, we iteratively calculated the probability of each partner's serostatus for

each month of sexual activity before and during the partnership (figure 1). We assumed that individuals infected for less than 1 month before sampling would test seronegative.[14] For each country analysis, we estimated the probability of each couple having its recorded serostatus conditional on their survival to DHS sampling, and then used Bayesian Markov chain Monte Carlo[15] 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 assigned uninformative prior distributions, except for the ratio of female-to-male and male-to-female transmission within couples for which, on the basis of available published work,[16] we set an informative log-normal prior centred at 1 with a standard deviation of 0·5.

From model fits we estimated the proportion of recorded infections (ie, infected individuals in couples sampled by the DHS) arising from each transmission route. We accounted for survival bias to estimate the per-route contribution to transmission for total infections, including couples who did not survive to be sampled. We estimated total infections arising from each transmission route by calculating the probabilities of each route for every couple, and inflating the probabilities with the inverse estimated probability that a couple would survive to be sampled by DHS and counted in a given calculation. To estimate the contribution of each route to ongoing transmission, we used fitted transmission coefficients and the most recent (ie, 2011) estimates[13] of HIV prevalence and ART coverage to predict HIV incidence in individuals who tested seronegative at DHS sampling, while monitoring of the proportional contributions of transmission from seropositive partners or extra-couple intercourse.

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 assessed the robustness of our results by undertaking several sensitivity analyses. First, we assessed the assumption that individuals were homogeneous in terms of their transmission coefficients by simulating transmission with a population in which each individual's pre-couple and extra-couple transmission coefficients varied together. The log of the risk multiplier was a standard normal deviate, which yields hazards 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 homogeneous model and assessed all estimates for bias. Second, we recalculated the contributions of transmission routes in our fitted model with inclusion of demographic information from couples with no data for HIV serostatus. Third, we relaxed the assumption that individuals receiving ART were absolutely not infectious. Fourth, we relaxed the assumption that ART did not affect within-couple transmission. Finally, we assessed sensitivity to reporting bias by assuming that 30% of women who stated that their sexual debut occurred with their present partner actually became sexually active 1 year earlier. Appendix pp 17–18 list model assumptions, justifications, and implications.

Role of the funding source

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

Results

All ranges given below indicate intercountry variation (see appendix for country-specific estimates and credible intervals) with exclusion of results from the

	Couples (n)	Exclusion criteria				Couples analysed					
		No serostatus	Polygamous	Data missing	Data inconsistent	Total	First partnership	Both seronegative	M seropositive, F seronegative	M seronegative, F seropositive	Both seropositive
DRC	2373	228 (10%)	648 (27%)	287 (12%)	343 (15%)	1197 (50%)	859 (72%)	1172 (98%)	13 (1%)	10 (<1%)	2 (<1%)
Ethiopia	9713	1050 (11%)	732 (8%)	1518 (16%)	1565 (16%)	5671 (58%)	2972 (52%)	5572 (98%)	35 (<1%)	25 (<1%)	39 (<1%)
Kenya	2861	550 (19%)	308 (11%)	101 (4%)	515 (18%)	1618 (57%)	1266 (78%)	1481 (92%)	37 (2%)	48 (3%)	52 (3%)
Lesotho	1640	265 (16%)	55 (3%)	28 (2%)	262 (16%)	1099 (67%)	1017 (93%)	738 (67%)	113 (10%)	64 (6%)	184 (17%)
Malawi	5614	977 (17%)	582 (10%)	864 (15%)	801 (14%)	3043 (54%)	2166 (71%)	2675 (88%)	134 (4%)	81 (3%)	153 (5%)
Rwanda	2189	49 (2%)	124 (6%)	177 (8%)	156 (7%)	1749 (80%)	1396 (80%)	1676 (96%)	28 (2%)	10 (<1%)	35 (2%)
Swaziland	802	143 (18%)	56 (7%)	41 (5%)	198 (25%)	431 (54%)	262 (61%)	247 (57%)	33 (8%)	38 (9%)	113 (26%)
West Africa	19 349	1987 (10%)	6336 (33%)	2778 (14%)	3610 (19%)	7902 (41%)	4676 (59%)	7671 (97%)	86 (1%)	90 (1%)	55 (<1%)
Zambia	3129	829 (27%)	293 (9%)	401 (13%)	365 (12%)	1599 (51%)	1161 (73%)	1310 (82%)	107 (7%)	60 (4%)	122 (7%)
Zimbabwe	5567	1352 (24%)	504 (9%)	439 (8%)	1038 (19%)	2892 (52%)	2138 (74%)	2268 (78%)	189 (7%)	121 (4%)	314 (11%)

Data are n (%), unless otherwise indicated. Exclusion criteria were at least one partner missing HIV serostatus, polygamy, insufficient data to identify partnership duration, inconsistencies in partnership duration, age at sexual debut occurring 1 or more years after partnership formation, or partnership formation occurring earlier than 8 years old. M=male. F=female. DRC=Democratic Republic of Congo.

Table 1: **Summary of data analysed from the Demographic and Health Surveys**

Democratic Republic of Congo, for which too few individuals were seropositive to yield precise estimates. After application of exclusion criteria, between 41% and 80% of couples in each country remained available for analysis (table 1). In 52–93% of analysed couples both partners were in their first stable cohabiting relationship (table 1). Table 2 summarises estimated transmission coefficients. Our results show that male and female extra-couple transmission coefficients were similar; compared with men, women had a high risk per unit time of transmission before couple formation; and partners of both sexes generally had larger pre-couple than extra-couple transmission coefficients (table 2). Goodness-of-fit tests and simulation analyses did not indicate any issues with the model fits (appendix pp 19 and 27). Our results were robust to the assumption of homogeneous hazards (appendix p 19); the exclusion of couples with missing data for HIV serostatus (appendix p 19); the proportion of individuals given ART who we assumed to be non-infectious; whether ART reduced within-couple transmission; and reporting bias in the sexual debuts of women (appendix pp 23–24).

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

	Transmission before 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	0·25 (0·15–0·38)	0·83 (0·50–1·20)	0·043 (0·022–0·068)	0·028 (0·0075–0·061)	0·082 (0·044–0·13)	0·079 (0·046–0·12)
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)

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

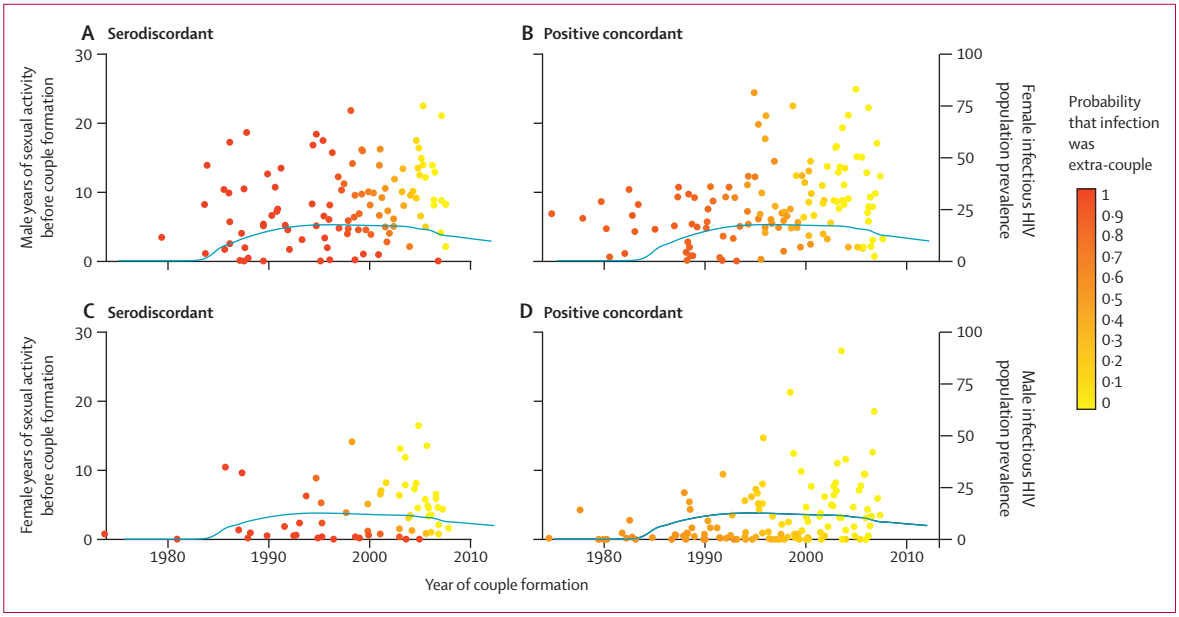

Figure 2: **Model fit to Zambian couples' Demographic Health Surveys data**
Each point represents a couple. Couples are divided between panels on the basis of their serostatus: male positive discordant (A), female positive discordant (C), and concordant positive (B, D). Points are plotted as a function of the date of couple formation and the number of years that the man (A, B) or woman (C, D) was sexually active before the couple formed. Blue lines show the population prevalence of HIV, excluding the proportion of individuals receiving antiretroviral treatment (and thus not infectious), in the opposite sex—ie, from whom before-partnership or extra-couple transmission occurs. The colour of each point represents the median fitted posterior probability that a seropositive man (A, B) or woman (C, D) was infected from extra-couple transmission rather than before couple formation for serodiscordant couples or from positive partner for concordant positive couples.

infected after couple formation if they had a shorter duration of sexual activity before couple formation, if couple formation occurred early on in the HIV epidemic when population prevalence was low, or the relationship duration was long (not only because longer durations accrue greater risk, but also because otherwise the positive partner would probably have died before the couple was sampled). Seropositive individuals who were likely to have been infected after couple formation in serodiscordant couples were therefore likely to have been infected by extra-couple transmission. We noted the same patterns in concordant-positive couples (figure 2); however, the probability of extra-couple transmission was reduced because within-partner transmission was possible.

Figure 3 shows the proportional contribution of different routes of transmission by sex, country, and couple serostatus (the appendix shows country-specific estimates and credible intervals). Model fits showed that many infections in serodiscordant couples were attributable to extra-couple transmission, with estimates in the range 50–80% of men and 31–74% of women infected through extra-couple intercourse, with the remainder of infections occurring before couple formation (figure 3). In concordant-positive couples, we estimated that the per-route contribution to infection was 20–54% for men and 15–48% for women from before couple formation, 18–51% and 13–29%, respectively, from extra-couple intercourse; and 28–46% and 39–68%, respectively, from an infected partner (figure 3, appendix p 20). However, individuals who were alive at the time of survey were likely to have been infected fairly recently. Nevertheless, even when accounting for survival bias, we estimated that during the epidemic (in couples who did and did not survive to be surveyed) 28–77% of index infections within couples (ie, the first infection in a given couple) were attributable to extra-couple transmission rather than transmission occurring before couple formation, with most extra-couple transmissions being extra-couple infections of men (appendix p 22).

On the basis of 2011 estimates of HIV prevalence and ART coverage, we projected that 0·22–13% of new infections of seronegative men, and 0·094–6·2% of new infections of seronegative women within serodiscordant couples over the next year will result from extra-couple transmission, with the remainder attributable to within-couple transmission (appendix p 22). However, for all cohabiting couples we projected that 30–65% of HIV incidence in men and 10–47% of that in women will be attributable to extra-couple transmission (figure 4, appendix p 22).

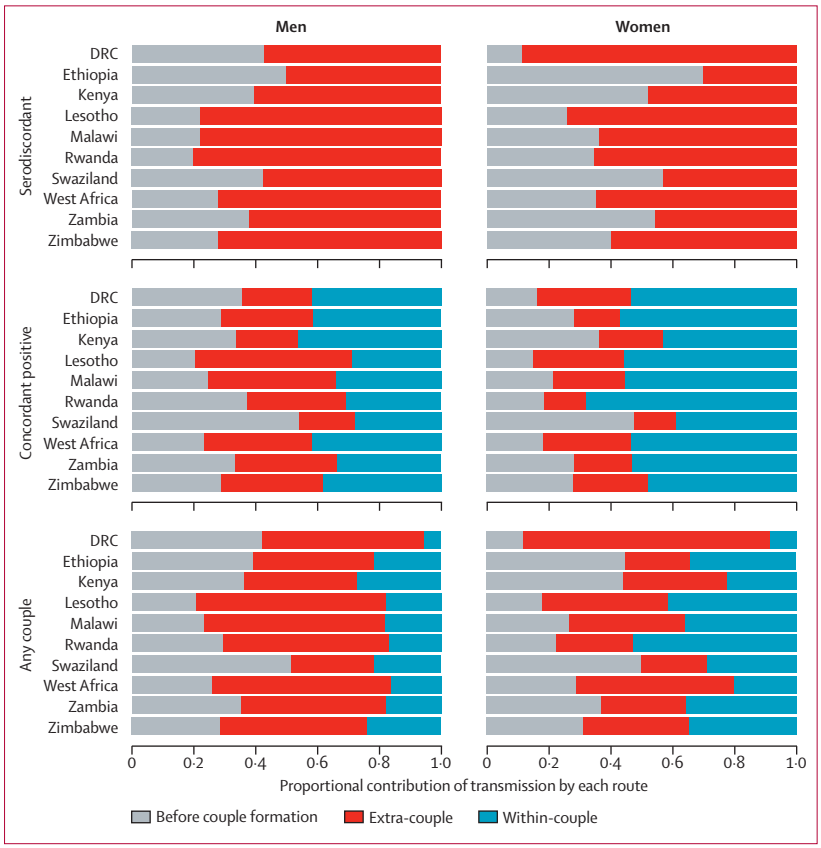

Figure 3: **Estimated proportion of transmission from each route of transmission by sex, country, and couple serostatus**

Bars give posterior median estimates (appendix p 20 shows values and 95% credible intervals) of the contribution of each transmission route to recorded infections in surveyed couples. Appendix p 21 provides estimates of the breakdowns of proportional transmission routes in the total population (ie, including couples in which one or more individuals might have died before Demographic Health Surveys sampling). DRC=Democratic Republic of Congo.

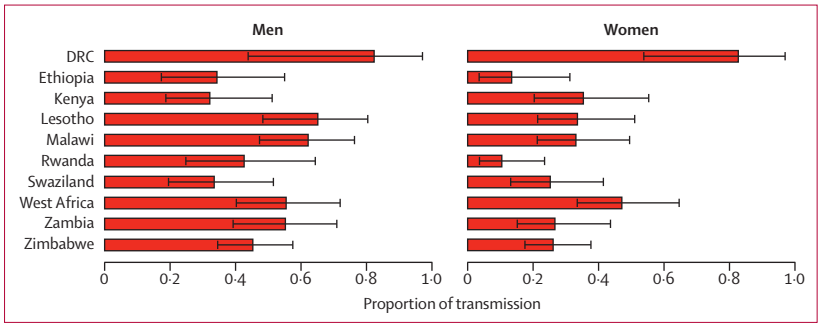

Figure 4: **Estimated proportion of transmission in 2011 in cohabiting couples that was caused by extra-couple intercourse, by country**

Estimates are for all men and women who tested seronegative (ie, either sex in concordant negative couples, men in female-positive serodiscordant couples, and women in male-positive serodiscordant couples) during Demographic Health Surveys sampling. Seronegative individuals in discordant couples can be infected either by extra-couple transmission or by their HIV-positive partner. Seronegative 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. Appendix p 22 shows values and 95% credible intervals. DRC=Democratic Republic of Congo.

Discussion

Our findings show three major conclusions. First, extra-couple transmission has played and still plays a major part in driving HIV incidence for both sexes, but

particularly for men; second, within couples, HIV seems to be propagated more from men to women than vice versa; third, women have a period of high infection risk before entering a cohabiting partnership. We emphasise that the fitted transmission coefficients aggregate several behavioural and physiological processes and thus should be interpreted cautiously. Because the hazard of infection is the product of transmission coefficients and prevalence in the opposite sex, comparisons between male and female transmission coefficients should be made with consideration of the differing HIV prevalences for each sex. For example, although we estimate that more men than women are infected through extra-couple transmission, the estimated transmission coefficients are roughly similar because female infectious HIV prevalence is greater than that of the opposite sex. The transmission coefficients will also partially absorb unmodelled mixing patterns. For example, young women tend to mix with older men, who have a greater probability of being seropositive than do younger men. This effect would tend to increase female incidence before partnership formation, thus needing greater fitted female before-partnership transmission coefficients to fit the recorded data, but not necessarily biasing the estimate of incidence through this route.

Investigators of previous studies[17–23] using DHS and similar cross-sectional couple data have come to diverse conclusions (panel). Analyses of DHS couples data have noted that slightly less than half of serodiscordant couples had seropositive women rather than men;[17,20] others used mathematical models to estimate the proportion of transmission that took place outside serodiscordant partnerships versus between partners.[21,22] These studies all conclude that the high prevalence of female-positive and male-positive serodiscordant partnerships suggests that, contrary to mainstream beliefs,[20] both women and men often have risky extra-couple intercourse, with the modelling studies estimating that much of the transmission to both sexes is from outside rather than within the couple. These studies have largely overlooked that routes of infection cannot be directly inferred from cross-sectional data, such as DHS. Estimations of transmission from outside a couple combine infections occurring from extra-couple intercourse with those acquired before that couple's formation when the individual was either single or in another couple. Thus, the existence of serodiscordant couples does not necessarily suggest 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 couple data is survival bias—ie, only couples in which both partners survive to be sampled are recorded. Median survival time after seroconversion is about 6–13 years, dependent on the age at seroconversion.[12] Many couples in which one or both partners become infected are thus removed from the population before the sample is taken. This effect will be different for serodiscordant and seroconcordant couples. Studies analysing cross-sectional couple data while ignoring mortality[17,20–22,28] could therefore yield biased conclusions for the proportional contribution of extra-couple intercourse to incidence.

Our findings show that extra-couple and within-couple transmission are both important routes of HIV infection and both account for many recorded infections in men and women; however, results vary substantially by country. We obtained this result despite finding that fitted extra-couple transmission coefficients were by far the smallest of the three routes of infection. This result is consistent with Chemaitelly and colleagues'[28] finding that most infections in serodiscordant couples are due to within-couple transmission. The large contribution of extra-couple transmission at the population level is because most cohabiting couples are concordant negative and, on average, the surveyed individuals had spent most time in a couple since their sexual debut. Thus, the large amount of person-time spent at risk from extra-couple transmission more than compensates for its small transmission coefficients. Results from our analysis, which was only of couples, greatly contrast those of Dunkle and colleagues,[19] who concluded that within-couple transmission accounts for most of the HIV incidence in sexually active urban populations (ie, in single individuals and those in couples) in Zambia and Rwanda. This contrast is probably because of the reliance of Dunkle and colleagues on downwards-biased self-reported rates of intercourse with non-cohabiting partners, which could lead to substantial underestimation of the contribution of extra-couple intercourse.[29]

When available, molecular evidence shows the importance of extra-couple transmission. In several cohort studies of serodiscordant couples,[1,2,25–27] 13–32% of incident infections were from virus not linked to that isolated from the seroconverter's partner and were presumably due to extra-couple intercourse. Compared with cohort studies, we attributed a smaller proportion of transmission within serodiscordant couples to extra-couple intercourse, which might be because individuals enrolled in cohort studies differ systematically from the general population, which is more representatively sampled by DHS. Furthermore, seronegative individuals in cohort studies might engage in more extra-couple and less within-couple intercourse upon finding that their partner is seropositive.[27] This behavioural effect could explain why our estimated rates of within-couple transmission are generally greater than those from cohort studies (table 2).[1,2,25]

Our finding that, within couples, the directionality of HIV propagation is more from men to women than vice versa is because of the greater average duration of sexual activity in men before couple formation and additionally, for some countries, because of their greater hazard rate for extra-couple infection. Although the

average duration of sexual activity before partnership formation is much shorter for women than for men, we noted that, as reported elsewhere,[11] this difference is partly compensated by the greater risk of infection per unit time in women before partnership formation.

With use of relationship and serostatus data, country-specific trends for the prevalence of HIV, and estimates of HIV survival times to explicitly estimate the probability that infections were because of pre-couple, within-couple, or extra-couple transmission, our model addresses several limitations of previous studies, and advances estimations of transmission breakdown by behavioural routes from cross-sectional data. However, our model retains certain assumptions. We assumed homogeneous mixing between age groups for sexual partners chosen before couple formation or during extra-couple intercourse. Although this assumption might bias our results, to the extent that patterns of age mixing cause a consistent bias for overestimates or under-estimates in the estimated prevalence that individuals are exposed to, this bias will be counteracted by under-estimates or overestimates in transmission coefficients, with no effect on estimates of total hazard and per-route contributions to transmission.

We also assumed that the probability of infection via a particular transmission route is dependent on only the duration an individual is at risk by that route, the time-varying HIV prevalence in the population of the opposite sex (or partner seropositivity for within-partner transmission), and a 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, type of sexual exposure, sexually transmitted infections, viral loads, viral characteristics, tendency to seek care, male circumcision, and protected sex; many of these factors vary both between individuals and through time within individuals.[7,16] Although we assumed that individuals were homogeneous, our results were robust to this assumption. Our sensitivity analysis shows that even with a large individual-level heterogeneity in hazard rates, the association between relationship histories and serostatuses was substantial enough for the model to accurately infer the proportional breakdown of infections by transmission routes.

Hazards can vary over time for reasons other than changing prevalence. Declines in HIV prevalence in several countries have been attributed to behavioural changes in response to interventions or overall HIV awareness.[30] Such changes would lead to decreasing transmission coefficients during the epidemic, but how this decrease might be divided among the routes of transmission we considered is unclear; therefore, we were unable to assess this possibility. We did not include effects of ART on HIV survival times or within-couple transmission in our main analysis because DHS surveys do not provide the drug status of individuals, and because we believe that the within-couple effects of therapy were small. On the basis of policies created before WHO's 2012 TasP recommendations, most treated individuals would have already exposed their partners to infection for a long time before they become ill, get tested, have CD4 counts decrease to less than 200 counts per µL, and start ART. Furthermore, coverage of ART in the countries analysed was negligible for most of the period covered by the couples in our survey.[13] This factor explains why our results were 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, in view of the range of the DHS and the relatively narrow scope of our study, we necessarily excluded many couples because of missing or inconsistent data. However, these exclusions are unlikely to cause major selection bias and our results are roughly generalisable to the couples in the population as sampled by DHS. In particular, our results are likely to be more representative of the general

Panel: Research in context

Systematic review

We searched PubMed from Jan 1, 2000, to Oct 21, 2012, with the terms (HIV) AND (discordant OR serodiscordant) AND (couple), and again with (HIV) AND (virus OR virol*) AND (linked OR linkage). We analysed studies identified from our search, and those cited therein. Studies[20–22,24] using cross-sectional analyses and overall levels of serodiscordance consistently noted high proportions of transmission occurring from outside stable partnerships, but no such study separated outside transmission into that occurring before partnership formation and from extra-couple transmission. A mathematical modelling study[19] concluded that 55–92% of all HIV incidence in urban Zambia and Rwanda arises from transmission within stable, serodiscordant partnerships. However, this study relied on self-reported rates of extra-couple intercourse. A similar study[23] making conservative assumptions for extra-couple transmission concluded that such transmission contributes negligibly to incidence in serodiscordant couples, but did not extrapolate to concordant negative couples. Neither study assessed whether their findings were consistent with noted levels of serodiscordancy.[18] Cohort studies[1,2,25–27] of serodiscordant couples provide evidence about rates of within-couple and extra-couple (but not pre-couple) transmission. In cohort studies in which incident infections are virologically linked or unlinked to the seroconverter's partner, 13–32% of infections seem to be attributable to extra-couple transmission.

In summary, we noted a large variation in estimates of the proportion of HIV incidence due to various routes, dependent on assumptions about what constitutes an outside infection, whether self-reported risk behaviour is a key input, and how the study population was sampled. We did not identify any studies that focused on the general population and attempted to identify the behavioural transmission routes responsible for infections with couples' relationship histories.

Interpretation

Many infections in stable, cohabiting couples arise from extra-couple transmission. Our analysis is the first to interpret couple serostatus data mechanistically, with consideration 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 distinguish the pathways through which individuals became infected. Pre-couple, extra-couple, and within-couple transmission are all common, and HIV control policies should address all these routes.

population than are those from virological linkage cohort studies, which have more specific selection criteria and alter the behaviour of participants.[27]

We have shown that substantial HIV transmission occurs through all transmission routes: within serodiscordant couples and before couple formation and from extra-couple intercourse. We make no assumptions about the morality[31] or potential for mitigation[32] of extra-couple sex. Extra-couple sex does not necessarily constitute a choice and could be motivated by basic needs or indicate large social support structures.[33] However, policy choices should be made in view of our finding that extra-couple transmission by both sexes has a major role in the HIV epidemic in sub-Saharan Africa.

Offering of TasP to only HIV-positive individuals in stable, serodiscordant couples is tempting because the partner is identifiable, and clearly at risk. However, the aggregate risk to partners not in stable relationships with positive individuals is also high. This finding does not mean that TasP and PrEP programmes have no place in targeted treatment of serodiscordant couples. These programmes have been effective and represent major advances in HIV prevention strategy. PrEP, in particular, could change the gender power dynamics in serodiscordant couples by empowering women to prevent HIV transmission. In view of this fairly small proportion of populations constituted by serodiscordant couples, these approaches could be a good starting point for HIV control efforts, especially in the context of resource limitations. However, our results do imply that behavioural and biomedical interventions focused on serodiscordant couples will not be sufficient to cause major reductions in HIV incidence at the population level. Interventions should address all transmission routes to fight the HIV epidemic. Despite its expense and logistical demands, the universal test-and-treat strategy could reduce all forms of heterosexual transmission.

Contributors

SEB, KJF, BGW, and JD developed the study idea. SEB, WMG, and JD developed the model framework. SEB, KJF, and JD acquired and cleaned the data. SEB, KJF, and DYM reviewed the scientific literature. SEB did the model analyses and wrote the first draft. All authors interpreted the results and prepared and approved the final manuscript.

Conflicts of interest

We declare that we have no conflicts of interest.

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