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

Steve E Bellan, Kathryn J Fiorella, Dessalegn Y Melesse, Wayne M Getz, Brian G Williams, Jonathan Dushoff

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.**

Funding **US National Institutes of Health, US National Science Foundation, and J S McDonnell Foundation.**

Published **Online**
February 5, 2013
http://dx.doi.org/10.1016/S0140-6736(12)61960-6

See **Online/Comment**
http://dx.doi.org/10.1016/S0140-6736(13)60147-6

Department of Environmental Science, Policy and Management, University of California, Berkeley, CA, USA (S E Bellan PhD, K J Fiorella AB, Prof W M Getz DSc)**; The Centre for Global Public Health, Department of Community Health Sciences, University of Manitoba, Winnipeg, MB, Canada** (D Y Melesse MSc)**; School of Mathematical Sciences, University of KwaZulu-Natal, Durban, South Africa** (W M Getz)**; South African Center for Epidemiological Modeling and Analysis, Stellenbosch, South Africa** (B G Williams PhD)**; and Department of Biology, McMaster University, Hamilton, ON, Canada** (Prof J Dushoff PhD)

Correspondence to:
Dr Steve E Bellan, Center for Computational Biology and Bioinformatics, University of Texas, Austin, TX 78712, USA
steve.bellan@gmail.com

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.

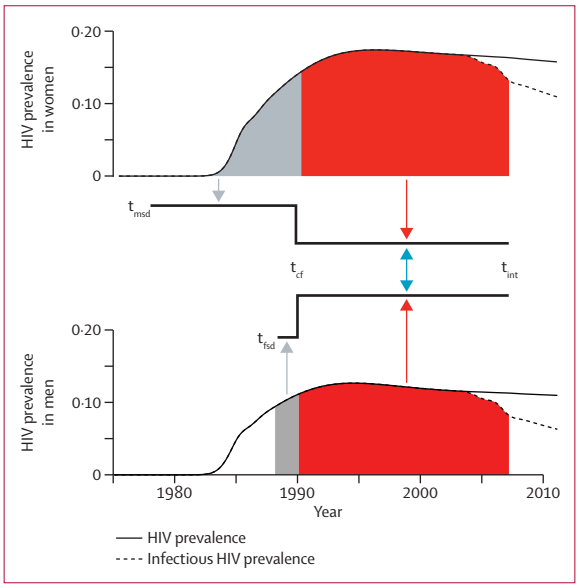

Figure 1: **Schematic diagram of the couple transmission model**
The diagram shows how the model relates the infection process to a couple's relationship and sexual histories for an example Zambian couple. Each partner (thick black lines) can be infected before couple formation (grey arrows) beginning 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**

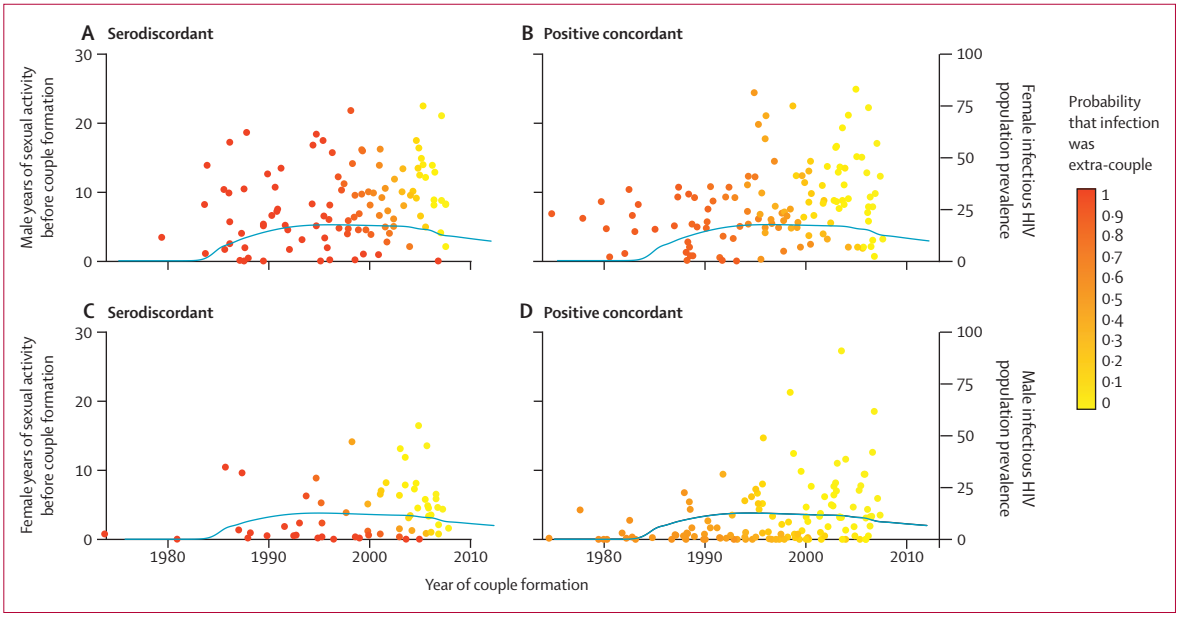

Figure 2: **Model fit to Zambian couples' Demographic Health Surveys data**
Each point represents a couple. Couples are divided between panels on the basis of their serostatus: male positive discordant (A), female positive discordant (C), and concordant positive (B, D). Points are plotted as a function 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).

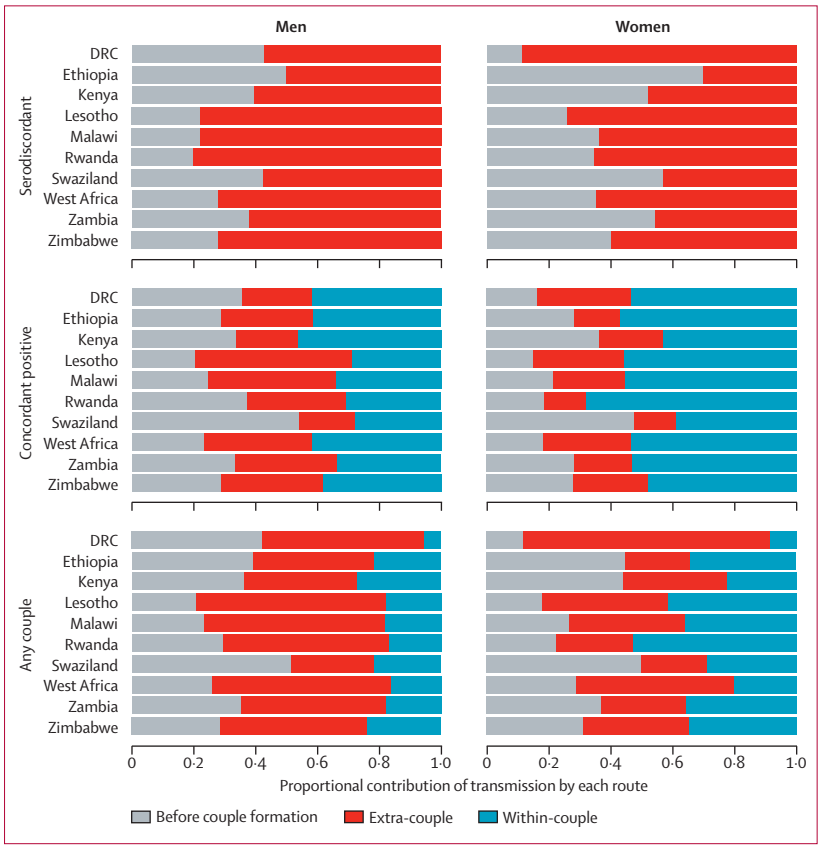

Figure 3: **Estimated proportion of transmission from each route of transmission by sex, country, and couple serostatus**

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.

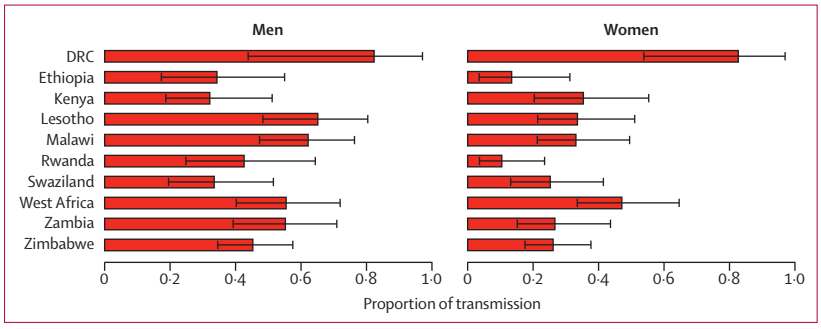

Figure 4: **Estimated proportion of transmission in 2011 in cohabiting couples that was caused by extra-couple intercourse, by country**

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.

Acknowledgments

The 2011 Clinic on the Meaningful Modeling of Epidemiological Data, where this work was started, was funded by the National Institutes of Health Framework Programs for Global Health Innovations (grant R24TW008822 to Lee Riley), the Henry Wheeler Center for Emerging and Neglected Diseases, the NSF-NIH Ecology of Infectious Diseases program (NSF award 1134964 to Juliet R C Pulliam), the African Institute for Mathematical Sciences, and the South African Centre for Excellence in Epidemiological Modelling and Analysis. This work was partly supported by a Chang-Lin Tien Environmental Fellowship, Andrew and Mary Thompson Rocca Fellowships, University of California, Berkeley Environmental Science, Policy and Management and Entomology Society Travel Grants to SEB; the National Science Foundation Graduate Research Fellowship Program, UC Global Health Institute One Health Summer Research Program, Sigma Xi Grants-in-Aid of Research, Andrew and Mary Thompson Rocca Pre-Dissertation Research Award in African Studies, and Sara's Wish Foundation to KJF; the Centre for Global Public Health, University of Manitoba, Canada support to DYM; National Institutes of Health Ecology of Infectious Disease grant (GM83863) to WMG; and a J S McDonnell Foundation grant to JD. We thank Juliet R C Pulliam, James C Scott, Travis C Porco, John W Hargrove, Alex Welte, and Wim Delva for their help in organising the Meaningful Modeling of Epidemiological Data workshop where this work was started; Damian Kajunguri, Mateusz Plucinski, and Zindoga Mukandavire for their comments on early versions of this work, and Savannah Nuwagaba for work on early formulations of this project; Juliet R C Pulliam, Paul Cross, Ben Bolker, Andy Lyons, and Karen Weinbaum for their feedback.

References

1 Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* 2011; **365:** 493–505.

2 Donnell D, Baeten JM, Kiarie J, et al. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. *Lancet* 2010; **375:** 2092–98.

3 Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med* 2012; **367:** 399–410.

4 Abdool Karim Q, Abdool Karim SS, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science* 2010; **329:** 1168–74.

5 Zachariah R, Harries AD, Philips M, et al. Antiretroviral therapy for HIV prevention: many concerns and challenges, but are there ways forward in sub-Saharan Africa? *Trans R Soc Trop Med Hyg* 2010; **104:** 387–91.

6 Padian NS, Isbell MT, Russell ES, Essex M. The future of HIV prevention. *J Acquir Immune Defic Syndr* 2012; **60** (suppl 2)**:** S22–26.

7 Guthrie BL, de Bruyn G, Farquhar C. HIV-1-discordant couples in sub-Saharan Africa: explanations and implications for high rates of discordancy. *Curr HIV Res* 2007; **5:** 416–29.

8 Curran K, Baeten JM, Coates TJ, Kurth A, Mugo NR, Celum C. HIV-1 prevention for HIV-1 serodiscordant couples. *Curr HIV/AIDS Rep* 2012; **9:** 160–70.

9 WHO. Guidance on couples HIV testing and counselling including antiretroviral therapy for treatment and prevention in serodiscordant couples: recommendations for a public health approach. Geneva: World Health Organization, 2012.

10 Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *Lancet* 2009; **373:** 48–57.

11 Bongaarts J. Late marriage and the HIV epidemic in sub-Saharan Africa. *Popul Stud-J Demogr* 2007; **61:** 73–83.

12 Collaborative Group on AIDS Incubation and HIV Survival, including the CASCADE EU Concerted Action. Time from HIV-1 seroconversion to AIDS and death before widespread use of highly-active antiretroviral therapy: a collaborative re-analysis. *Lancet* 2000; **355:** 1131–37.

13 UNAIDS. Global report: UNAIDS report on the global AIDS epidemic 2010. Geneva: UNAIDS, 2010.

14 Busch MP, Satten GA. Time course of viremia and antibody seroconversion following human immunodeficiency virus exposure. *Am J Med* 1997; **102:** 117–24.

15 Gilks WR, Richardson S, Spiegelhalter DJ. Markov chain Monte Carlo in practice. New York: Chapman and Hall, 1995.

16 Boily MC, Baggaley RF, Wang L, et al. Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies. *Lancet Infect Dis* 2009; **9:** 118–29.

17 Eyawo O, de Walque D, Ford N, Gakii G, Lester RT, Mills EJ. HIV status in discordant couples in sub-Saharan Africa: a systematic review and meta-analysis. *Lancet Infect Dis* 2010; **10:** 770–77.

18 Shelton JD, Stanton DL. Source of new infections in generalised HIV epidemics. *Lancet* 2008; **372:** 1299.

19 Dunkle KL, Stephenson R, Karita E, et al. New heterosexually transmitted HIV infections in married or cohabiting couples in urban Zambia and Rwanda: an analysis of survey and clinical data. *Lancet* 2008; **371:** 2183–91.

20 De Walque D. Sero-discordant couples in five African countries: implications for prevention strategies. *Popul Dev Rev* 2007; **33:** 501–23.

21 Lurie MN, Williams BG, Zuma K, et al. Who infects whom? HIV-1 concordance and discordance among migrant and non-migrant couples in South Africa. *AIDS* 2003; **17:** 2245–52.

22 Glynn JR, Caraël M, Buve A, et al; Study Group on the Heterogeneity of HIVEiAC. HIV risk in relation to marriage in areas with high prevalence of HIV infection. *J Acquir Immune Defic Syndr* 2003; **33:** 526–35.

23 Chemaitelly H, Abu-Raddad LJ. External infections contribute minimally to HIV incidence among HIV sero-discordant couples in sub-Saharan Africa. *Sex Transm Infect* 2012; published online Aug 28. DOI:10.1136/sextrans-2012-050651.

24 Eyawo O, de Walque D, Ford N, Gakii G, Lester RT, Mills EJ. HIV status in discordant couples in sub-Saharan Africa: a systematic review and meta-analysis. *Lancet Infect Dis* 2010; **10:** 770–77.

25 Celum C, Wald A, Lingappa JR, et al. Acyclovir and transmission of HIV-1 from persons infected with HIV-1 and HSV-2. *N Engl J Med* 2010; **362:** 427–39.

26 Trask SA, Derdeyn CA, Fideli U, et al. Molecular epidemiology of human immunodeficiency virus type 1 transmission in a heterosexual cohort of discordant couples in Zambia. *J Virol* 2002; **76:** 397–405.

27 Ndase P, Celum C, Thomas K, et al. Outside sexual partnerships and risk of HIV acquisition for HIV uninfected partners in african HIV serodiscordant partnerships. *J Acquir Immune Defic Syndr* 2012; **59:** 65–71.

28 Chemaitelly H, Cremin I, Shelton J, Hallett TB, Abu-Raddad LJ. Distinct HIV discordancy patterns by epidemic size in stable sexual partnerships in sub-Saharan Africa. *Sex Transm Infect* 2012; **88:** 51–57.

29 Allen S, Meinzen-Derr L, Kautzman M, et al. Sexual behavior of HIV discordant couples after HIV counseling and testing. *AIDS* 2003; **17:** 733–40.

30 Hargrove JW, Humphrey JH, Mahomva A, et al. Declining HIV prevalence and incidence in perinatal women in Harare, Zimbabwe. *Epidemics* 2011; **3:** 88–94.

31 Caldwell JC, Caldwell P, Quiggin P. The social context of AIDS in sub-Saharan Africa. *Popul Dev Rev* 1989; **15:** 185–234.

32 Coates TJ, Richter L, Caceres C. Behavioural strategies to reduce HIV transmission: how to make them work better. *Lancet* 2008; **372:** 669–84.

33 Dunkle KL, Jewkes RK, Brown HC, Gray GE, McIntryre JA, Harlow SD. Transactional sex among women in Soweto, South Africa: prevalence, risk factors and association with HIV infection. *Soc Sci Med* 2004; **59:** 1581–92.

Serodiscordancy and HIV prevention in sub-Saharan Africa

Published Online
February 5, 2013
http://dx.doi.org/10.1016/S0140-6736(13)60147-6

See Online/Articles
http://dx.doi.org/10.1016/S0140-6736(12)61960-6

Breakthroughs in HIV prevention—including antiretroviral therapy (ART) to reduce the infectiousness of HIV-infected individuals[1] and antiretroviral pre-exposure prophylaxis (PrEP) to reduce the susceptibility of uninfected people[2]—have prompted optimistic discussion about reversal of the global HIV epidemic, particularly in Africa, which has a disproportionate burden. To achieve the potential benefits of these promising strategies, delivery of interventions should be prioritised to those at highest risk, with high uptake through linkages with HIV testing, and in combination with other key prevention interventions, including voluntary medical male circumcision, provision of condoms, and behaviour change.

Defining priority populations specific to each setting for targeted HIV prevention has been hotly debated. For sub-Saharan Africa, one possible priority population is stable, heterosexual partnerships in which one partner is HIV infected (ie, an HIV serodiscordant couple). Investigators undertaking mathematical modelling studies, which are generally based on cross-sectional data from Demographic and Health Surveys (DHS), have reported wide-ranging proportions of population-level HIV transmissions that take place within HIV serodiscordant couples: 55–92% in one study from urban Rwanda and Zambia,[3] but 10–52% for another study with data from 20 African countries.[4]

In *The Lancet*, Steve Bellan and colleagues[5] report results of their mathematical modelling study attempting to disentangle routes of HIV transmission risk for 27 201 cohabiting couples in 18 countries in sub-Saharan Africa. The investigators used data for serostatus, relationship history, and age at sexual debut from DHS, and national HIV prevalence estimates from UNAIDS, to estimate the contribution of infections in cohabiting couples that happened before couple formation, within couples, and from outside partnerships (so-called extra-couple transmission). Results estimate that for all cohabiting couples, extra-couple transmissions accounted for 32–65% of new HIV infections in men and 10–47% of those in women in 2011. Bellan and colleagues tried to improve on past models by accounting for survival bias with temporal changes in HIV prevalence and ART coverage, age mixing, and exclusion of couples with missing or inconsistent data. These new data emphasise that substantial HIV risk in coupled relationships occurs before relationship establishment and from sexual encounters outside an established partnership. Most important is the conclusion that HIV risk within established partnerships and from outside partners should be addressed with prevention strategies.

By definition, all HIV transmissions were from an infected to an uninfected partner. Debate about the precise proportion of transmissions occurring within cohabiting HIV serodiscordant partnerships compared with those from extra-couple transmissions indicate the difficult decisions to be made about resource allocation for known HIV serodiscordant couples versus the larger population of sexually active people without a known HIV-infected partner. However, the debate should not be an either-or argument or detract from the key messages of these models. First, transmissions within HIV serodiscordant couples account for an important fraction of infections (18–53% in the present model). Couples jointly aware of their status are likely to partake in use of interventions for HIV prevention,[1,2,6,7] with secondary benefits including reduced morbidity, and prevention of mother-to-child transmission. Second, many transmissions in coupled relationships are from outside partnerships; indeed, viral sequencing studies

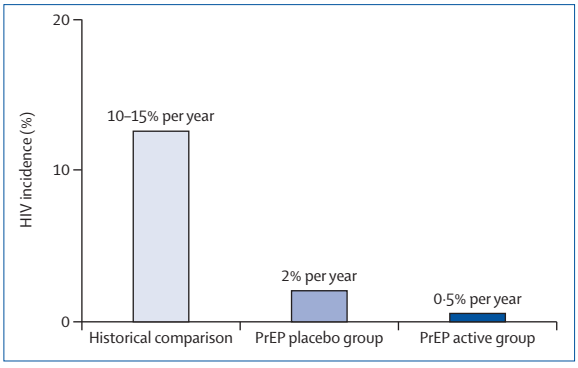

Figure: **An example of combination HIV prevention in HIV serodiscordant couples from sub-Saharan Africa**
Data from the Partners PrEP Study,[2] a randomised, double-blind, placebo-controlled clinical trial of antiretroviral PrEP for HIV prevention in 4747 HIV serodiscordant couples from Kenya and Uganda. Couples received a standard, combination package of HIV-prevention services: couples' HIV testing with facilitated serostatus disclosure, ongoing HIV testing with pre-test and post-test counselling, risk-reduction counselling for individual and couples, screening and treatment for sexually transmitted infections, condoms, and referral for male circumcision and start of ART according to national policies. In patients randomised to placebo, HIV incidence was substantially lower than in historical cohorts of HIV serodiscordant couples outside clinical trials (10–15% per year),[11] which shows the effect of the standard prevention package. PrEP further decreased HIV incidence to 0·5% per year. PrEP=pre-exposure prophylaxis.

have shown that even in mutually disclosed HIV serodiscordant couples, 25–30% of transmissions are from an outside partner.[8,9] Relationships are not static—ie, partnerships dissolve, some temporarily, and new, sometimes concurrent, partnerships are established, often with partners of unknown HIV serostatus with whom condoms are rarely used and HIV risk can be substantial.[10] These observations underscore the need for ongoing HIV prevention, potentially including PrEP, for HIV-susceptible men and women who have partners of positive or unknown serostatus. Third, in view of the high proportion of people in DHS who regard themselves to be in partnered relationships, making HIV prevention a couple-focused activity—with HIV testing and prevention counselling as a couple—should be a priority. At the same time, strategies to reduce extra-couple transmissions are needed, including continued ART rollout, male circumcision, and counselling interventions targeting extra-couple risk for people in coupled relationships. For women, substantial HIV risk is present before partnership formation, emphasising the ongoing need for prevention strategies for young women, who in some settings face a staggeringly high risk of HIV infection. One important challenge arising from Bellan and colleagues' model is that a major proportion of new infections in couples occur within previously HIV-concordant seronegative relationships. This group is a large one to target for HIV prevention, with probably only a small, but potentially difficult to identify, subset at greatest HIV risk.

Serodiscordant couples could be an identifiable, targetable, vanguard population for implementation of evidence-based, combination HIV prevention. A package of prevention strategies provided to couples can substantially reduce HIV incidence (figure). WHO recommends that ART be offered to all HIV-infected partners in serodiscordant couples, irrespective of CD4 count, and that demonstration studies be done of PrEP in couples, as a first step towards increased implementation of ART and PrEP for HIV prevention.[12,13] Lessons learned from initial implementation of combination HIV prevention directed at HIV serodiscordant couples will inform implementation for broader populations, in the recognition that HIV prevention for only HIV serodiscordant couples will not be enough to reverse the HIV epidemic completely. HIV prevention is at a crucial stage: strategies to deliver evidence-based combination prevention efficiently and effectively, targeted at high-risk populations and with high coverage for those at risk, will maximise this incredible opportunity in the history of the HIV epidemic.

Connie Celum, Jared M Baeten
Departments of Global Health, Medicine, and Epidemiology, University of Washington, Seattle, WA 98104, USA
ccelum@uw.edu

We declare that we have no conflicts of interest.

1 Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* 2011; **365:** 493–505.
2 Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med* 2012; **367:** 399–410.
3 Dunkle KL, Stephenson R, Karita E, et al. New heterosexually transmitted HIV infections in married or cohabiting couples in urban Zambia and Rwanda: an analysis of survey and clinical data. *Lancet* 2008; **371:** 2183–91.
4 Chemaitelly H, Shelton JD, Hallett TB, Abu-Raddad LJ. Only a fraction of new HIV infections occur within identifiable stable discordant couples in sub-Saharan Africa. *AIDS* 2013; **27:** 251–60.
5 Bellan SE, Fiorella KJ, Melesse DY, Getz WM, Williams BG, Dushoff J. Extra-couple HIV transmission in sub-Saharan Africa: a mathematical modelling study of survey data. *Lancet* 2013; published online Feb 5. http://dx.doi.org/10.1016/S0140-6736(12)61960-6.
6 Ware N, Wyatt M, Haberer J, et al. What's love got to do with it? A theory of adherence to once-daily oral pre-exposure prophylaxis (PrEP) for HIV prevention derived from qualitative data among HIV serodiscordant couples. *J Acquir Immune Defic Syndr* 2012; **59:** 463–68.
7 Curran K, Baeten JM, Coates TJ, Kurth A, Mugo NR, Celum C. HIV-1 prevention for HIV-1 serodiscordant couples. *Curr HIV/AIDS Rep* 2012; **9:** 160–70.
8 Campbell MS, Mullins JI, Hughes JP, et al. Viral linkage in HIV-1 seroconverters and their partners in an HIV-1 prevention clinical trial. *PLoS One* 2011; **6:** e16986.
9 Eshleman SH, Hudelson SE, Redd AD, et al. Analysis of genetic linkage of HIV from couples enrolled in the HIV Prevention Trials Network 052 trial. *J Infect Dis* 2011; **204:** 1918–26.
10 Ndase P, Celum C, Thomas K, et al. Outside sexual partnerships and risk of HIV acquisition for HIV uninfected partners in African HIV serodiscordant partnerships. *J Acquir Immune Defic Syndr* 2012; **59:** 65–71.
11 Quinn TC, Wawer MJ, Sewankambo N, et al, for the Rakai Project Study Group. Viral load and heterosexual transmission of human immunodeficiency virus type 1. *N Engl J Med* 2000; **342:** 921–29.
12 WHO. Guidance on couples HIV testing and counselling including antiretroviral therapy for treatment and prevention in serodiscordant couples: recommendations for a public health approach. April, 2012. http://apps.who.int/iris/bitstream/10665/44646/1/9789241501972_eng.pdf (accessed Jan 29, 2013).
13 WHO. Guidance on pre-exposure oral prophylaxis (PrEP) for serodiscordant couples, men and transgender women who have sex with men at high risk of HIV: recommendations for use in the context of demonstration projects. July, 2012. http://apps.who.int/iris/bitstream/10665/75188/1/9789241503884_eng.pdf (accessed Jan 29, 2013).

THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Bellan SE, Fiorella KJ, Melesse DY, Getz WM, Williams BG, Dushoff J. Extra-couple HIV transmission in sub-Saharan Africa: a mathematical modelling study of survey data. *Lancet* 2013; published online Feb 5. http://dx.doi.org/10.1016/S0140-6736(12)61960-6.

Online Web Appendix

Table of Contents

1. Introduction

We built a model to interpret cross-sectional data collected by the Demographic & Health Survey (DHS) on human immunodeficiency virus (HIV) serostatus and other variables in stable, cohabiting couples. We use information on couple serostatus, partnership duration, and age at first intercourse to infer the probability that an HIV positive individual was infected prior to couple formation, during the duration of their partnership from their partner, or during their partnership from extra-couple intercourse. For brevity in the rest of this appendix, we collectively refer to couples married or living as married (i.e. stable, cohabiting couples) as a "couple". This appendix serves two distinct purposes: (1) to include supplementary results and sensitivity analyses we were unable to fit in the main text, and (2) to provide a thorough technical description for the interested reader. Readers that are uninterested in the technical detail are advised to skip Sections 3, 5, and 6 and the mathematical parts of Section 4.

Please note that in addition to the data and code being provided as supplementary material, we have made the Amazon Machine Image (AMI) we used to perform this analysis publically available (AMI ID: ami-8174ffe8).

2. Data sets

2a. Demographic and Health Surveys

All available DHS data sets in sub-Saharan Africa that tested stable, cohabiting couples for HIV were downloaded and cleaned. The following list describes the inclusion criteria for our analysis as well as data imputation methods we used when data were slightly inconsistent:

- We excluded couples for which HIV serostatus was not available for one or both partners.
- Our model relies heavily on knowledge of a couple's relationship duration. DHS surveys, up to DHS phase V (i.e., all surveys before 2009), however, do not ask couples how long they have been together. Interviewers do ask if interviewees are in their first couple, and when they entered their first couple. Thus, for these earlier surveys we restrict our analysis to couples in which at least one individual is in the first stable, cohabiting couple of their lifetime because we can infer relationship duration from the latter question.
- We removed all polygamous couples from the analysis because such couples require consideration of more complex within-partnership transmission dynamics.
- When the male and female's listed date of couple formation differed we used the mean. We excluded couples from the analysis if this discrepancy was greater than 25% of the mean or if either partner reported a date of couple formation that occurred before they were 8 years old.
- We excluded couples that included individuals giving an age of sexual debut (i.e. age at first intercourse) as more than a year after the date of couple formation.
- For individuals who listed the age at sexual debut as within 1 year after the date of couple formation, we assumed that they began having intercourse when they formed the stable, cohabiting couple.
- Couples with individuals stating that their sexual debut occurred at less than 5 years old were also excluded from the analysis.

We did not include data on condom usage or other behavioral risk factors reported in the DHS because all questions only asked about behavior within the last 12 months. We believe that such data are inappropriate to use as indices of

risk for relationship histories that are several years or decades long. We assessed the sensitivity of our results to the exclusion of couples due to missing HIV serostatus as outlined in our model section below.

2b. UNAIDS Data

For each country analyzed, we obtained from the UNAIDS Global Report 2010 (1) yearly model-fitted estimates of prevalence of HIV in adults between 15-49 years of age by sex and (2) yearly model-fitted estimates of the prevalence of adults on antiretroviral therapy (ART).[1] Because HIV positive individuals on ART are much less infectious than those who are not,[2] we calculated infectious prevalence by assuming ART usage was proportional to the HIV prevalence in each sex and multiplying the prevalence of HIV times the proportion of individuals not on ARV. We then made monthly estimates of infectious prevalence by fitting a cubic smoothing spline to the UNAIDS annual model using a logistic link function, and setting prevalence to be 10^{-6} in 1980 for all countries (Figure S1-2).

2c. HIV Survival Time Data

Interpretation of cross-sectional survey data for a fatal disease such as AIDS must take into account survival bias—many individuals will have died before sampling and this can bias the results. In particular, ignoring AIDS deaths will lead to underestimates of infection hazard, since infected individuals are less likely to survive to be surveyed. Differential effects of survival on the rates at which concordant positive and serodiscordant couples are removed from the population (via the death of one or more partners) may further lead to biases in estimates of the proportion of infection contributed by each route of transmission.[3] We account for survival directly by estimating the conditional probability that a couple exhibits the observed serostatus given both individuals were alive at the time of the DHS sampling (see model section below). To do this, we modeled cumulative survival after HIV seroconversion following estimates in the CASCADE collaboratory review of HIV survival times and accounting for increased mortality rates with increasing age v at seroconvsersion.[4-6] For T months beyond seroconversion, we obtained the following one-parameter (v) class of Weibull distributions $S(T, v)$ to qualitatively match the CASCADE data displayed in Figure 1 of the cited study:

$$S(T, v) = e^{-\left(\frac{T}{\Lambda}\right)^k}, \text{ with } \Lambda = \frac{2000}{k\left(\frac{v}{12}\right)^{0.53}}., \text{ and } k = 2{\cdot}3,$$

Cumulative survival curves are plotted in Figure S3.

3. Model Structure

3a. Transmission routes and the hazard of infection

For each partner in a couple, we assume there are three possible sources of infection (Figure 1):

1. they were infected prior to formation of the current partnership (pre-couple transmission),
2. they were infected during their partnership from extra-couple intercourse (extra-couple transmission),
3. they were infected during the partnership by their partner (within-couple transmission).

Each couple is only observed once in a cross-sectional survey. Thus, the serostatus of a couple can either be $\{M^-, F^-\}, \{M^+, F^-\}, \{M^-, F^+\}, \{M^+, F^+\}$. The probability that an infection occurs via any of the three routes of transmission is a function of the hazard of infection through that route, λ, defined to be the rate of new infections per susceptible individual per month. Susceptible individuals are infected when they have intercourse with another individual, that individual is infectious, and during intercourse HIV is successfully transmitted to them. The hazard can thus be broken down into $\lambda = caP$, where c a behavioral factor relating to rate and riskiness of intercourse, P is the probability that given coital act is infectious, and a is the per coital act probability of transmission. We make the simplifying assumption that males and females mix homogenously which allows us to interpret P as the population prevalence in the opposite gender. We do, however, allow the product of the parameters $\beta = ca$ to depend on both the type of relationship and be gender specific and note that only β itself rather than the two parameters c and a themselves are identifiable when fitting the hazard of infection function $\lambda = \beta P$ to DHS data. Note that β is equivalent to the transmissibility coefficient used in classical SIR (susceptible, infected, recovered) models and their variations.[7] The six transmission coefficients are therefore before (b) couple formation ($\beta_{\mathrm{M,b}}$ and $\beta_{\mathrm{F,b}}$), during the

partnership (p) by a positive partner ($\beta_{\mathrm{M,p}}$ and $\beta_{\mathrm{F,p}}$), or during the partnership by engaging in extra-couple (e) intercourse ($\beta_{\mathrm{M,e}}$ and $\beta_{\mathrm{F,e}}$). Note that all subscripted gender indices always refer to the partner who is at risk of transmission so that $\beta_{\mathrm{M,p}}$ is the transmission coefficient for transmission to a male from his female partner. For within-couple transmission prevalence is always either 0 or 1, depending on the infection status of the partner. For before-couple or extra-couple transmission the prevalence $P(t)$ experienced by each sex is the estimated national-level prevalence from UNAIDS.

3b. Iterating serostatus state variables through time

We calculate the probability that individuals are infected through various routes of transmission using the rate to probability transformation $p = 1 - \exp(-\lambda \Delta t)$ where Δt is one month. Our general approach is to iterate the probability that a couple is in any given couple serostatus through time (month by month) while keeping track of the joint probability both individuals survive to DHS sampling. We also keep track of the cumulative probability for each route of transmission. For the i-th of K couples we define $t_{\mathrm{msd},i}$, $t_{\mathrm{fsd},i}$, $t_{\mathrm{cf},i}$, and $t_{\mathrm{int},i}$, i=1,…,K, to respectively be the points in time (months) of the male (msd) and female (fsd) partners' sexual debuts, the month they formed a couple (cf), and the month during which they were sampled/interviews (int) by the DHS survey. We define $t_{\mathrm{sd},i} = \min(t_{\mathrm{msd},i}, t_{\mathrm{fsd},i})$ to be the time of the first sexual debut amongst partners in the i-th couple. Then we can iteratively calculate the probability that the i-th couple is in either of the four states $\{s_i, m_i, f_i, h_i\}$, corresponding to concordant HIV negative, serodiscordant male-HIV-positive, serodiscordant female-HIV-positive, and concordant HIV positive states.

We, however, keep track of routes of infection and so divide the latter three state variables into more specific states. We use a subscripting convention similar to the transmission coefficients above but give the route of infection for both males (first subscript) and females (second subscript), and use "-" when an individual is negative. As examples, $m_{\mathrm{b}-,i}$ denotes a male-positive serodiscordant couple where the male was infected before partnership formation, $f_{-\mathrm{e},i}$ is a female-positive serodiscordant couple where the female was infected extra-couply, and $h_{\mathrm{pe},i}$ denotes a concordant positive couple where the female was infected extra-couply and then infected her male partner. We also keep track of the order of infection when both genders are infected—i.e. before couple formation always occurs earliest and from-partner transmission latest. When both partners are infected pre-couply or extracouply we track who was infected first using, for example, $h_{\mathrm{e_2e_1},i}$ to represent a couple in which both partners were infected before couple formation but the female was infected first. This yields 15 serostatuses:

$$\{s_{--,i}, m_{\mathrm{b}-,i}, m_{\mathrm{e}-,i}, f_{-\mathrm{b},i}, f_{-\mathrm{e},i}, h_{\mathrm{b_1b_2},i}, h_{\mathrm{b_2b_1},i}, h_{\mathrm{be},i}, h_{\mathrm{eb},i}, h_{\mathrm{bp},i}, h_{\mathrm{pb},i}, h_{\mathrm{ep},i}, h_{\mathrm{pe},i}, h_{\mathrm{e_1e_2},i}, h_{\mathrm{e_2e_1},i}\},$$

All individuals are assumed to be HIV negative before they become sexually active (i.e., when $T < t_{\mathrm{sd},i}$), and all serostatus states involving transmission during the couple formation have zero probabilities before the couple formation (i.e., when $T < t_{\mathrm{cf},i}$):

$s_{--,i}(T < t_{\mathrm{sd},i}) = 1$
$m_{\mathrm{b}-,i}(T < t_{\mathrm{sd},i}) = 0$
$m_{\mathrm{e}-,i}(T < t_{\mathrm{cf},i}) = 0$
$f_{-\mathrm{b},i}(T < t_{\mathrm{sd},i}) = 0$
$f_{-\mathrm{e},i}(T < t_{\mathrm{cf},i}) = 0$
$h_{\mathrm{b_1b_2},i}(T < t_{\mathrm{sd},i}) = 0$
$h_{\mathrm{b_2b_1},i}(T < t_{\mathrm{sd},i}) = 0$
$h_{\mathrm{be},i}(T < t_{\mathrm{cf},i}) = 0$
$h_{\mathrm{eb},i}(T < t_{\mathrm{cf},i}) = 0$
$h_{\mathrm{bp},i}(T < t_{\mathrm{cf},i}) = 0$
$h_{\mathrm{pb},i}(T < t_{\mathrm{cf},i}) = 0$
$h_{\mathrm{ep},i}(T < t_{\mathrm{cf},i}) = 0$
$h_{\mathrm{pe},i}(T < t_{\mathrm{cf},i}) = 0$
$h_{\mathrm{e_1e_2},i}(T < t_{\mathrm{cf},i}) = 0$
$h_{\mathrm{e_2e_1},i}(T < t_{\mathrm{cf},i}) = 0$

When ignoring the routes of transmission and only focusing on serostatuses we use the following notation,

Negative seroconcordant couples: $s_i = s_{--,i}$
Male positive serodiscordant couples: $m_i = m_{\mathrm{b}-,i} + m_{\mathrm{e}-,i}$
Female positive serodiscordant couples: $f_i = f_{-\mathrm{b},i} + f_{-\mathrm{e},i}$
Positive seroconcordant couples: $h_i = h_{\mathrm{b_1b_2},i} + h_{\mathrm{b_2b_1},i} + h_{\mathrm{be},i} + h_{\mathrm{eb},i} + h_{\mathrm{bp},i} + h_{\mathrm{pb},i} + h_{\mathrm{ep},i} + h_{\mathrm{pe},i} + h_{\mathrm{e_1e_2},i} + h_{\mathrm{e_2e_1},i}$

In calculating these iterative state probabilities, we also keep track of the probability that an infected couple in each of the latter three categories will be alive at the time of the DHS survey. We use a primed notation to distinguish between the probabilities that would arise if mortality were not taken into account and the probabilities that arise once the effects of these differential mortalities have been incorporated. These serostatus states, viz.

$\{s_{--,i}, m'_{\mathrm{b}-,i}, m'_{\mathrm{e}-,i}, f'_{-\mathrm{b},i}, f'_{-\mathrm{e},i}, h'_{\mathrm{b_1b_2},i}, h'_{\mathrm{b_2b_1},i}, h'_{\mathrm{be},i}, h'_{\mathrm{eb},i}, h'_{\mathrm{bp},i}, h'_{\mathrm{pb},i}, h'_{\mathrm{ep},i}, h'_{\mathrm{pe},i}, h'_{\mathrm{e_1e_2},i}, h'_{\mathrm{e_2e_1},i}\}$ are thus the probabilities of the denoted serostatus and route of transmission given both partners have survived to the time of the DHS sampling event. These states have the same initial conditions as their corresponding marginal serostatus states above. Similarly, when ignoring transmission routes, we use $\{s_i, m'_i, f'_i, h'_i\}$ to denote the probability of couple serostatus and given survival to DHS sampling.

In formulating our equations, we make the assumption that the effect of non-AIDS deaths can be neglected within these AIDS classes because, unlike with AIDS deaths, we expect non-AIDS causes of death to cause couples of each serostatus to drop from the DHS sample population base at the same rate. We iterate couples through the period $[t_{\mathrm{sd},i}, t_{\mathrm{cf},i})$ to determine the male and female probabilities, $p_{\mathrm{M,b}}(T)$ and $p_{\mathrm{F,b}}(T)$, respectively that each partner is infected by the beginning of their partnership. We do this for each month $T = t_{\mathrm{sd},i}, \ldots, t_{\mathrm{cf},i}$. The model is iterated monthly so that monthly time steps are $\Delta t = 1$ month. These probabilities are functions of the infectious HIV population prevalences $P_{\mathrm{M}}(T)$ and $P_{\mathrm{F}}(T)$ in males and females, respectively, in the country of the i-th couple's residence at time T (as taken from the UNAIDS models described above). Using the indicator function $I(t_1, t_2) = 1$ if $t_{\mathrm{msd},i} \leq T < t_{\mathrm{cf},i}$ and $I(t_1, t_2) = 0$ otherwise, we obtain:

$$p_{\mathrm{M,b}}(T) = (1 - \exp(-\beta_{\mathrm{M,b}} \times P_{\mathrm{F}}(T)\Delta t)\, I(t_{\mathrm{msd},i}, t_{\mathrm{cf},i}), \quad \text{and}$$
$$p_{\mathrm{F,b}}(T) = (1 - \exp(-\beta_{\mathrm{F,b}} \times P_{\mathrm{M}}(T)\Delta t)\, I(t_{\mathrm{fsd},i}, t_{\mathrm{cf},i}).$$

These transition probabilities give the following Markov Chain for $T = t_{\mathrm{sd},i}, \ldots, t_{\mathrm{cf},i} - \Delta t$,

$$s_{--,i}(T) = s_{--,i}(T - \Delta t)(1 - p_{\mathrm{M,b}}(T))(1 - p_{\mathrm{F,b}}(T))$$
$$m_{\mathrm{b}-,i}(T) = m_{\mathrm{b}-,i}(T - \Delta t)\left(1 - p_{\mathrm{F,b}}(T)\right) + s_{--,i}(T - \Delta t)p_{\mathrm{M,b}}(T)\left(1 - p_{\mathrm{F,b}}(T)\right)$$
$$f_{-\mathrm{b},i}(T) = f_{-\mathrm{b},i}(T - \Delta t)\left(1 - p_{\mathrm{M,b}}(T)\right) + s_{--,i}(T - \Delta t)p_{\mathrm{F,b}}(T)\left(1 - p_{\mathrm{M,b}}(T)\right)$$
$$h_{\mathrm{b_1b_2},i}(T) = h_{\mathrm{b_1b_2},i}(T - \Delta t) + \left(\frac{p_{\mathrm{M,b}}(T)}{p_{\mathrm{M,b}}(T) + p_{\mathrm{F,b}}(T)}\right)\left(s_{--,i}(T - \Delta t)p_{\mathrm{M,b}}(T)p_{\mathrm{F,b}}(T)\right) + m_{\mathrm{b}-,i}(T - \Delta t)p_{\mathrm{F,b}}(T)$$
$$h_{\mathrm{b_2b_1},i}(T) = h_{\mathrm{b_2b_1},i}(T - \Delta t) + \left(\frac{p_{\mathrm{F,b}}(T)}{p_{\mathrm{M,b}}(T) + p_{\mathrm{F,b}}(T)}\right)\left(s_{--,i}(T - \Delta t)p_{\mathrm{M,b}}(T)p_{\mathrm{F,b}}(T)\right) + f_{-\mathrm{b},i}(T - \Delta t)p_{\mathrm{M,b}}(T)$$

where the fraction is used to split up couples in which both partners were infected in the same month into the two different infection order states based on the competing risks of occurrence. The probabilities of being infected and surviving are simply the above infection probabilities multiplied by the probability of surviving the $t_{\mathrm{int},i} - T$ months until the DHS sampling for an individual aged $v_{\mathrm{M},i}(T)$ (where $v_{\mathrm{M},i}(T)$ is a function of T because individuals' ages are a function of time) the time of seroconversion which we estimate as described above and denote by $S(t_{\mathrm{int},i} - T, v_{\mathrm{M},i}(T))$,

$$p'_{\mathrm{M,b}}(T)=p_{\mathrm{M,b}}(T)S\left(t_{\mathrm{int},i}-T,v_{\mathrm{M},i}(T)\right),\ \text{and}$$
$$p'_{\mathrm{F,b}}(T)=p_{\mathrm{F,b}}(T)S\left(t_{\mathrm{int},i}-T,v_{\mathrm{F},i}(T)\right),$$

where yielding the following iterative transition equations for the probabilities of being infected and also surviving until DHS sampling,

$$m'_{\mathrm{b-},i}(T)=m'_{\mathrm{b-},i}(T-\Delta t)\left(1-p_{\mathrm{F,b}}(T)\right)+s_{--,i}(T-\Delta t)p'_{\mathrm{M,b}}(T)\left(1-p_{\mathrm{F,b}}(T)\right)$$
$$f'_{\mathrm{-b},i}(T)=f'_{\mathrm{-b},i}(T-\Delta t)\left(1-p_{\mathrm{M,b}}(T)\right)+s_{--,i}(T-\Delta t)p'_{\mathrm{F,b}}(T)\left(1-p_{\mathrm{M,b}}(T)\right)$$
$$h'_{\mathrm{b_1b_2},i}(T)=h'_{\mathrm{b_1b_2},i}(T-\Delta t)+\left(\frac{p'_{\mathrm{M,b}}(T)}{p'_{\mathrm{M,b}}(T)+p'_{\mathrm{F,b}}(T)}\right)\left(s_{--,i}(T-\Delta t)p'_{\mathrm{M,b}}(T)p'_{\mathrm{F,b}}(T)\right)$$
$$+m'_{\mathrm{b-},i}(T-\Delta t)p'_{\mathrm{F,b}}(T)$$
$$h'_{\mathrm{b_2b_1},i}(T)=h'_{\mathrm{b_2b_1},i}(T-\Delta t)+\left(\frac{p'_{\mathrm{F,b}}(T)}{p'_{\mathrm{M,b}}(T)+p'_{\mathrm{F,b}}(T)}\right)\left(s_{--,i}(T-\Delta t)p'_{\mathrm{M,b}}(T)p'_{\mathrm{F,b}}(T)\right)+f'_{\mathrm{-b},i}(T$$
$$-\Delta t)p'_{\mathrm{M,b}}(T)$$

Infection during the partnership follows a similar iterative algorithm, though the forms of transmission are now from an HIV positive partner or from extra-couple intercourse with an individual of the opposite sex in the population at large. Because individuals infected in the last month prior to DHS sampling are unlikely to have yet seroconverted when sampled, we only iterate infections in couples up to the month prior to the interview, $T=t_{\mathrm{cf},i},\ldots,t_{\mathrm{fin},i}$, where $t_{\mathrm{fin},i}=t_{\mathrm{int},i}-\Delta t$. The respective probabilities of a male being infected by his female partner given she is HIV positive and vice versa are

$$p_{\mathrm{M,p}}=1-\exp\left(-\beta_{\mathrm{M,p}}\Delta t\right),\ \text{and}$$
$$p_{\mathrm{F,p}}=1-\exp\left(-\beta_{\mathrm{F,p}}\Delta t\right),$$

and do not change over the couple duration. The corresponding joint probabilities of infection and survival to DHS sampling are, in contrast, dependent on timing and are respectively given by

$$p'_{\mathrm{M,p}}(T)=p_{\mathrm{M,p}}S\left(t_{\mathrm{int},i}-T,v_{\mathrm{M},i}(T)\right),\ \text{and}$$
$$p'_{\mathrm{F,p}}(T)=p_{\mathrm{F,p}}S\left(t_{\mathrm{int},i}-T,v_{\mathrm{F},i}(T)\right).$$

The respective probabilities of the male and female partner being infected during extra-couple intercourse in month $T=t_{\mathrm{cf},i},\ldots,t_{\mathrm{fin},i}$ vary with population prevalence in the opposite sex (as for transmission before couple formation above),

$$p_{\mathrm{M,e}}(T)=1-\exp\left(-\beta_{\mathrm{M,e}}\times P_{\mathrm{F}}(T)\Delta t\right),\text{and}$$
$$p_{\mathrm{F,e}}(T)=1-\exp\left(-\beta_{\mathrm{F,e}}\times P_{\mathrm{M}}(T)\Delta t\right).$$

The corresponding joint probabilities of extra-couple infection in month T with survival up until $t_{\mathrm{int},i}$ are then

$$p'_{\mathrm{M,e}}(T)=p_{\mathrm{M,e}}(T)S\left(t_{\mathrm{int},i}-T,v_{\mathrm{M},i}(T)\right),\text{and}$$
$$p'_{\mathrm{F,e}}(T)=p_{\mathrm{F,e}}(T)S(t_{\mathrm{int},i}-T,v_{\mathrm{F},i}(T)).$$

We then can iterate couple serostatus probabilities with the following transition equations for $T=t_{\mathrm{cf},i},\ldots,t_{\mathrm{fin},i}$,

$$s_{--,i}(T)=s_{--,i}(T-\Delta t)(1-p_{\mathrm{M,e}}(T))(1-p_{\mathrm{F,e}}(T))$$
$$m_{\mathrm{b-},i}(T)=m_{\mathrm{b-},i}(T-\Delta t)(1-p_{\mathrm{F,p}})(1-p_{\mathrm{F,e}}(T))$$
$$m_{\mathrm{e-},i}(T)=m_{\mathrm{e-},i}(T-\Delta t)(1-p_{\mathrm{F,p}})\left(1-p_{\mathrm{F,e}}(T)\right)+s_{--,i}(T-\Delta t)p_{\mathrm{M,e}}(T)(1-p_{\mathrm{F,e}}(T))$$

$$
\begin{aligned}
f_{-\mathrm{b},i}(T) &= f_{-\mathrm{b},i}(T-\Delta t)(1-p_{\mathrm{M,p}})(1-p_{\mathrm{M,e}}(T))\\
f_{-\mathrm{e},i}(T) &= f_{-\mathrm{e},i}(T-\Delta t)(1-p_{\mathrm{M,p}})\left(1-p_{\mathrm{M,e}}(T)\right)+s_{--,i}(T-\Delta t)p_{\mathrm{F,e}}(T)(1-p_{\mathrm{M,e}}(T))\\
h_{\mathrm{b_1b_2},i}(T) &= h_{\mathrm{b_1b_2},i}(T-\Delta t)\\
h_{\mathrm{b_2b_1},i}(T) &= h_{\mathrm{b_2b_1},i}(T-\Delta t)\\
h_{\mathrm{be},i}(T) &= h_{\mathrm{be},i}(T-\Delta t)+m_{\mathrm{b-},i}(T-\Delta t)(1-p_{\mathrm{F,p}})p_{\mathrm{F,e}}(T)\\
h_{\mathrm{eb},i}(T) &= h_{\mathrm{eb},i}(T-\Delta t)+f_{-\mathrm{b},i}(T-\Delta t)(1-p_{\mathrm{M,p}})p_{\mathrm{M,e}}(T)\\
h_{\mathrm{bp},i}(T) &= h_{\mathrm{bp},i}(T-\Delta t)+m_{\mathrm{b-},i}(T-\Delta t)p_{\mathrm{F,p}}\\
h_{\mathrm{pb},i}(T) &= h_{\mathrm{pb},i}(T-\Delta t)+f_{-\mathrm{b},i}(T-\Delta t)p_{\mathrm{M,p}}\\
h_{\mathrm{ep},i}(T) &= h_{\mathrm{ep},i}(T-\Delta t)+m_{\mathrm{e-},i}(T-\Delta t)p_{\mathrm{F,p}}\\
h_{\mathrm{pe},i}(T) &= h_{\mathrm{pe},i}(T-\Delta t)+f_{-\mathrm{e},i}(T-\Delta t)p_{\mathrm{M,p}}\\
h_{\mathrm{e_1e_2},i}(T) &= h_{\mathrm{e_1e_2},i}(T-\Delta t)+\left(\frac{p_{\mathrm{M,e}}(T)}{p_{\mathrm{M,e}}(T)+p_{\mathrm{F,e}}(T)}\right)\left(s_{--,i}(T-\Delta t)p_{\mathrm{M,e}}(T)p_{\mathrm{F,e}}(T)\right)+m_{\mathrm{e-},i}(T-\Delta t)(1\\
&\quad -p_{\mathrm{F,p}})p_{\mathrm{F,e}}(T)\\
h_{\mathrm{e_2e_1},i}(T) &= h_{\mathrm{e_1e_2},i}(T-\Delta t)+\left(\frac{p_{\mathrm{F,e}}(T)}{p_{\mathrm{M,e}}(T)+p_{\mathrm{F,e}}(T)}\right)\left(s_{--,i}(T-\Delta t)p_{\mathrm{M,e}}(T)p_{\mathrm{F,e}}(T)\right)+f_{-\mathrm{e},i}(T-\Delta t)(1\\
&\quad -p_{\mathrm{M,p}})p_{\mathrm{M,e}}(T)
\end{aligned}
$$

making the assumption that with each month, within-partnership transmission occurs before individuals have the opportunity for extra-couple transmission. The corresponding joint probabilities of a couple being in a serostatus group at month T as well as being alive at the time of DHS sampling are given by

$$
\begin{aligned}
m'_{\mathrm{b-},i}(T) &= m'_{\mathrm{b-},i}(T-\Delta t)(1-p_{\mathrm{F,p}})(1-p_{\mathrm{F,e}}(T))\\
m_{\mathrm{e-},i}(T) &= m'_{\mathrm{e-},i}(T-\Delta t)(1-p_{\mathrm{F,p}})\left(1-p_{\mathrm{F,e}}(T)\right)+s_{--,i}(T-\Delta t)p'_{\mathrm{M,e}}(T)(1-p_{\mathrm{F,e}}(T))\\
f'_{-\mathrm{b},i}(T) &= f'_{-\mathrm{b},i}(T-\Delta t)(1-p_{\mathrm{M,p}})(1-p_{\mathrm{M,e}}(T))\\
f'_{-\mathrm{e},i}(T) &= f'_{-\mathrm{e},i}(T-\Delta t)(1-p_{\mathrm{M,p}})\left(1-p_{\mathrm{M,e}}(T)\right)+s_{--,i}(T-\Delta t)p'_{\mathrm{F,e}}(T)(1-p_{\mathrm{M,e}}(T))\\
h'_{\mathrm{b_1b_2},i}(T) &= h'_{\mathrm{b_1b_2},i}(T-\Delta t)\\
h'_{\mathrm{b_2b_1},i}(T) &= h'_{\mathrm{b_2b_1},i}(T-\Delta t)\\
h'_{\mathrm{be},i}(T) &= h'_{\mathrm{be},i}(T-\Delta t)+m'_{\mathrm{b-},i}(T-\Delta t)(1-p_{\mathrm{F,p}})p'_{\mathrm{F,e}}(T)\\
h'_{\mathrm{eb},i}(T) &= h'_{\mathrm{eb},i}(T-\Delta t)+f'_{-\mathrm{b},i}(T-\Delta t)(1-p_{\mathrm{M,p}})p'_{\mathrm{M,e}}(T)\\
h'_{\mathrm{bp},i}(T) &= h'_{\mathrm{bp},i}(T-\Delta t)+m'_{\mathrm{b-},i}(T-\Delta t)p'_{\mathrm{F,p}}\\
h'_{\mathrm{pb},i}(T) &= h'_{\mathrm{pb},i}(T-\Delta t)+f'_{-\mathrm{b},i}(T-\Delta t)p'_{\mathrm{M,p}}\\
h'_{\mathrm{ep},i}(T) &= h'_{\mathrm{ep},i}(T-\Delta t)+m'_{\mathrm{e-},i}(T-\Delta t)p'_{\mathrm{F,p}}\\
h'_{\mathrm{pe},i}(T) &= h'_{\mathrm{pe},i}(T-\Delta t)+f'_{-\mathrm{e},i}(T-\Delta t)p'_{\mathrm{M,p}}\\
h'_{\mathrm{e_1e_2},i}(T) &= h'_{\mathrm{e_1e_2},i}(T-\Delta t)+\left(\frac{p'_{\mathrm{M,e}}(T)}{p'_{\mathrm{M,e}}(T)+p'_{\mathrm{F,e}}(T)}\right)\left(s_{--,i}(T-\Delta t)p'_{\mathrm{M,e}}(T)p'_{\mathrm{F,e}}(T)\right)\\
&\quad +m'_{\mathrm{e-},i}(T-\Delta t)(1-p_{\mathrm{F,p}})p'_{\mathrm{F,e}}(T)\\
h'_{\mathrm{e_2e_1},i}(T) &= h'_{\mathrm{e_1e_2},i}(T-\Delta t)+\left(\frac{p'_{\mathrm{F,e}}(T)}{p'_{\mathrm{M,e}}(T)+p'_{\mathrm{F,e}}(T)}\right)\left(s_{--,i}(T-\Delta t)p'_{\mathrm{M,e}}(T)p'_{\mathrm{F,e}}(T)\right)\\
&\quad +f'_{-\mathrm{e},i}(T-\Delta t)(1-p_{\mathrm{M,p}})p'_{\mathrm{M,e}}(T)
\end{aligned}
$$

The probability that a couple is then observed at month $t_{\mathrm{int},i}$ with any of the four serostatuses is then given by

$$
y_i \sim \mathrm{Multinomial}\left(\frac{s_i(t_{\mathrm{fin},i})}{n'_i(t_{\mathrm{fin},i})},\frac{m'_i(t_{\mathrm{fin},i})}{n'_i(t_{\mathrm{fin},i})},\frac{f'_i(t_{\mathrm{fin},i})}{n'_i(t_{\mathrm{fin},i})},\frac{h'_i(t_{\mathrm{fin},i})}{n'_i(t_{\mathrm{fin},i})}\right),
$$

where y_i is the observed serostatus for the i-th couple and

$$n_i'(t_{\text{fin},i}) = s_i(t_{\text{fin},i}) + m_i'(t_{\text{fin},i}) + f_i'(t_{\text{fin},i}) + h_i'(t_{\text{fin},i}).$$

We use infection status at time $t_{\text{int},i} - \Delta t$ to indicate an approximately one month lag between infection and seroconversion (i.e., individuals infected less than a month before being tested are unlikely to test positive). We can explore how ignoring AIDS deaths biases the analysis by using the marginal serostatus probabilities,

$$y_i \sim \text{Multinomial}\left(s_i(t_{\text{fin},i}), m_i(t_{\text{fin},i}), f_i(t_{\text{fin},i}), h_i(t_{\text{fin},i})\right),$$

and comparing the results. These probability distributions account only for sampling stochasticity: that is, we ignore demographic stochasticity, an assumption that holds well for large population sizes.

3c. Proportion of observed infections from each transmission route

Aside from estimating the six transmission coefficients $\{\beta_{\text{M,b}}, \beta_{\text{M,p}}, \beta_{\text{M,e}}, \beta_{\text{F,b}}, \beta_{\text{F,p}}, \beta_{\text{F,e}}\}$, we would also like to know the probability that a given observed infection occurred through each of the three possible routes (before partnership, from partner during partnership, extra-couply during partnership). When we do this, we can condition on survival and serostatus. For instance, the probability a male-positive serodiscordant couple sampled by DHS was infected by extra-couple transmission is

$$\pi'_{\text{e-},i} = \frac{m'_{\text{e-},i}(t_{\text{fin},i})}{m'_i(t_{\text{fin},i})},$$

where π' are used more generally to give the probability of the specified route of transmission (e-) and survival given the serostatus group (+-) and survival. Thus, the probability a male in a concordant positive couple sampled by DHS was infected extra-couply is

$$\pi'_{\text{e+},i} = \frac{h'_{\text{eb},i}(t_{\text{fin},i}) + h'_{\text{ep},i}(t_{\text{fin},i}) + h'_{\text{ee},i}(t_{\text{fin},i})}{h'_i(t_{\text{fin},i})}.$$

Finally, as a last example, the probability a female in a concordant positive couple sampled by DHS was infected by her male partner is

$$\pi'_{\text{+p},i} = \frac{h'_{\text{bp},i}(t_{\text{fin},i}) + h'_{\text{ep},i}(t_{\text{fin},i})}{h'_i(t_{\text{fin},i})}.$$

We can estimate the proportion of all observed concordant positive couples in which the female was infected by her partner by simply averaging this quantity across couples,

$$\pi'_{\text{+p}} = \frac{\sum \pi'_{\text{+p},i}}{K_h} \text{ for each } i\text{th couple that is concordant positive}$$

where K_h is the number of such couples in the data set.

3d. Proportion of infections from each transmission route inferred to the greater population

While the above π''s give us the probability of specified transmission routes for observed couples, they do not account for survival bias (i.e., the couples that are unobserved due to death which are systematically different from live couples). We take an inclusion probability approach to extrapolate to unobserved couples. This approach is best illustrated with an example followed by a more general, rigorous mathematical description.

As an example, imagine observe one HIV positive man in a random sample. Imagine we also know that (based on his date of infection and studies of HIV survival times) he had only had a 50% chance of having survived up to the

date we saw him. Then we can state that though we only found one infected man in this study, we know that other infected men may have died. We thus extrapolate to a population not biased by AIDS mortality and estimate that this one infected man represents 1/0·5 = 2 infected men in such a population. Now, imagine we also know that the probabilities his infection occurred pre-couply, extra-couply, or within-couple are 60%, 30%, and 10%, respectively, and given each of those transmission routes the probability he survived was 0·2, 0·4, and 0·3, respectively (survival probabilities differ because the timing of seroconversion depends on the route). Then we can similarly extrapolate to a population not biased by AIDS survival: we estimate the total number of pre-couple infections this man represents as 0.6/0.2 = 3.

Generally speaking, if we estimate that an event X occurred with probability p_X and we had probability d_X of detecting it, we estimate there were $n_X = p_X/d_X$ such events X in total. If we estimate that event X occurred with probability p_X but it could have occurred in one of two ways, X_1 or X_2, each with a distinct probability of having happened, p_{X_1} and p_{X_2} such that $p_X = p_{X_1} + p_{X_2}$, and a distinct probability of detection, d_{X_1} and d_{X_2}, then we estimate the total number of events X_1 and X_2 represented by the observed event X as

$$n_{X_1} = \frac{p_{X_1}}{p_{X_1}+p_{X_2}} \times \left(\frac{p_{X_1}d_{X_1}+p_{X_2}d_{X_2}}{p_{X_1}+p_{X_2}}\right)^{-1},$$
$$n_{X_2} = \frac{p_{X_2}}{p_{X_1}+p_{X_2}} \times \left(\frac{p_{X_1}d_{X_1}+p_{X_2}d_{X_2}}{p_{X_1}+p_{X_2}}\right)^{-1},$$

where the first term in each equation is the probability X_1 or X_2, respectively, occurred given X occurred, and the second term is the probability of detecting any event of type X given that it occurred and its inverse can be considered an inflation factor that extrapoloates to the total number of such events that we think occurred for every event X observed. Scaling up to multiple events occurs similarly. If we observed ten such events X, each with probability $p_{X_i} = p_{X_{1,i}} + p_{X_{2,i}}$ of occurring for $i = 1, \ldots, 10$, and probabilities $d_{X_{1,i}}$ and $d_{X_{2,i}}$ of being detected given that X occurred as X_1 or X_2, respectively, then the total number of events X_1 and X_2, that we think are represented by our observations are

$$N_{X_1} = \sum_{i=1}^{10} \frac{p_{X_{1,i}}}{p_{X_{1,i}} + p_{X_{2,i}}} \times \left(\frac{p_{X_{1,i}}d_{X_{1,i}} + p_{X_{2,i}}d_{X_{2,i}}}{p_{X_{1,i}} + p_{X_{2,i}}}\right)^{-1}, \text{and}$$
$$N_{X_2} = \sum_{i=1}^{10} \frac{p_{X_{2,i}}}{p_{X_{1,i}} + p_{X_{2,i}}} \times \left(\frac{p_{X_{1,i}}d_{X_{1,i}} + p_{X_{2,i}}d_{X_{2,i}}}{p_{X_{1,i}} + p_{X_{2,i}}}\right)^{-1}.$$

These can be simplified to

$$N_{X_1} = \sum_{i=1}^{10} \frac{p_{X_{1,i}}}{p_{X_{1,i}}d_{X_{1,i}} + p_{X_{2,i}}d_{X_{2,i}}},$$

which is also equivalent to

$$N_{X_1} = \sum_{i=1}^{10} \frac{p_{X_{1,i}}d_{X_{1,i}}}{p_{X_{1,i}}d_{X_{1,i}} + p_{X_{2,i}}d_{X_{2,i}}} \times \left(d_{X_{1,i}}\right)^{-1},$$

where the latter form can be seen as the conditional probability of X_1 having occurred and being detected given X occurred and was detected inflated by the detection probability of event X_1 given it occurred. We hereafter use the shortest version, though all are equivalent.

The proportion of times that event X occurred as X_1 or X_2, respectively, in the total (observed & unobserved) population is then estimated as

$$\pi_{X_1} = \frac{N_{X_1}}{N_{X_1} + N_{X_2}}, \text{and}$$
$$\pi_{X_2} = \frac{N_{X_2}}{N_{X_1} + N_{X_2}}.$$

We now apply these principles to our model where the probability of detection is equivalent to the probability of survival-to-sampling in this framework. First we define the sets $S, M, F,$ and H to include all values of i for which the i-th couple is concordant negative, male-positive serodiscordant, female-positive serodiscordant, and positive concordant, respectively. If we want to estimate the proportion of all seropositive males in serodiscordant couples that were infected via extra-couple transmission unconditional on both partners' survival to sampling, we have

$$\pi_{\mathrm{e}-} = \frac{\sum_{i\in M} \frac{m_{\mathrm{e}-,i}(t_{\mathrm{fin},i})}{m'_{\mathrm{b}-,i}(t_{\mathrm{fin},i}) + m'_{\mathrm{e}-,i}(t_{\mathrm{fin},i})}}{\sum_{i\in M} \frac{m_{\mathrm{b}-,i}(t_{\mathrm{fin},i})}{m'_{\mathrm{b}-,i}(t_{\mathrm{fin},i}) + m'_{\mathrm{e}-,i}(t_{\mathrm{fin},i})} + \sum_{i\in M} \frac{m_{\mathrm{e}-,i}(t_{\mathrm{fin},i})}{m'_{\mathrm{b}-,i}(t_{\mathrm{fin},i}) + m'_{\mathrm{e}-,i}(t_{\mathrm{fin},i})}},$$

where summations occur over all couples i that are male-positive serodiscordant. This simplifies to

$$\pi_{\mathrm{e}-} = \frac{\sum_{i\in M} \frac{m_{\mathrm{e}-,i}(t_{\mathrm{fin},i})}{m'_i(t_{\mathrm{fin},i})}}{\sum_{i\in M} \frac{m_{\mathrm{b}-,i}(t_{\mathrm{fin},i})}{m'_i(t_{\mathrm{fin},i})} + \sum_{i\in M} \frac{m_{\mathrm{e}-,i}(t_{\mathrm{fin},i})}{m'_i(t_{\mathrm{fin},i})}},$$

and finally to

$$\pi_{\mathrm{e}-} = \frac{\sum_{i\in M} \frac{m_{\mathrm{e}-,i}(t_{\mathrm{fin},i})}{m'_i(t_{\mathrm{fin},i})}}{\sum_{i\in M} \frac{m_i(t_{\mathrm{fin},i})}{m'_i(t_{\mathrm{fin},i})}}.$$

At this point, however, we remark that while we do account for AIDS deaths, our model implicitly has seropositive individuals infecting their partners after they die. Modelling death times accurately in this Markovian framework is not possible because we would have to track both individuals' time since infection for each potential month they get infected in, increasing the number of state variables to unreasonable numbers. Even with this problem, however, our model state probabilities for couples being in each of the live states are still correct and, thus, this does not impact or bias our ability to fit data on live couples ($s'_i(t_{\mathrm{fin},i}), h'_i(t_{\mathrm{fin},i}), m'_i(t_{\mathrm{fin},i})$ or $f'_i(t_{\mathrm{fin},i})$). However, this limits our ability to infer transmission routes for unobserved couples because some of the probability that is in $h_i(t_{\mathrm{fin},i})$ should actually be in $m_i(t_{\mathrm{fin},i})$ or $f_i(t_{\mathrm{fin},i})$. Thus, the above expression for $\pi_{\mathrm{e}-}$ is not accurate. This is only a problem for the second infection in a couple, however, because the first infection can never have occurred after an AIDS death of a partner. Thus, we restrict our estimates of the proportion of transmission by route only to index infections within couples. In other words, we ask what transmission routes are responsible for first introducing HIV into a previously concordant negative couple. For instance, the proportion of all index infections that were extra-couple infections of males can be estimated by either

$$\pi^G{}_{\mathrm{e}_1\cdot} = \frac{\sum_{i\in M,F,H} \frac{m_{\mathrm{e}-,i}(t_{\mathrm{fin},i}) + h_{\mathrm{e}_1\mathrm{e}_2,i}(t_{\mathrm{fin},i}) + h_{\mathrm{ep},i}(t_{\mathrm{fin},i})}{m'_i(t_{\mathrm{fin},i}) + f'_i(t_{\mathrm{fin},i}) + h'_i(t_{\mathrm{fin},i})}}{\sum_{i\in M,F,H} \frac{m_i(t_{\mathrm{fin},i}) + f_i(t_{\mathrm{fin},i}) + h_i(t_{\mathrm{fin},i})}{m'_i(t_{\mathrm{fin},i}) + f'_i(t_{\mathrm{fin},i}) + h'_i(t_{\mathrm{fin},i})}}$$

or

$$\pi^{G}{}_{e_1\cdot} = \frac{\sum_{\forall i} \frac{m_{e-,i}(t_{\text{fin},i}) + h_{e_1e_2,i}(t_{\text{fin},i}) + h_{ep,i}(t_{\text{fin},i})}{s_i(t_{\text{fin},i}) + m'_i(t_{\text{fin},i}) + f'_i(t_{\text{fin},i}) + h'_i(t_{\text{fin},i})}}{\sum_{\forall i} \frac{m_i(t_{\text{fin},i}) + f_i(t_{\text{fin},i}) + h_i(t_{\text{fin},i})}{s_i(t_{\text{fin},i}) + m'_i(t_{\text{fin},i}) + f'_i(t_{\text{fin},i}) + h'_i(t_{\text{fin},i})}},$$

where the numerator is the number of inflated male-index infections and the denominator is the total number of inflated index infections. In the former case, only infected couples are used in the estimator, while the latter uses all couples. Given the complexity of these estimators, we use a simulation approach in which the proportion of transmission occurring from each route is known even amongst couples in which one or more partner dies prior to DHS sampling. We compared the above estimators (which only use data from couples where both partners live to DHS sampling) of their respective true values for 100 simulations. We chose the second estimator due to its lower bias and variance (Table S3).

In summary, we track the following proportions (unconditional on survival) the proportion of all index infections in couples that were male or female infections before couple formation ($\pi^{G}{}_{b_1\cdot}, \pi^{G}{}_{\cdot b_1}$) and via extra-couple transmission ($\pi^{G}{}_{e_1\cdot}, \pi^{G}{}_{\cdot e_1}$).

3e. Projecting future incidence over the next year

To calculate the probability that a new infection in the next 12 months is from any specified route of transmission, we use the fitted β parameters and the modeled ART-subtracted HIV prevalence for males and females in January 2011 from the UNAIDS model to project forward the probability of a couple with susceptible individuals (i.e., all couples except concordant positive) transitioning to the other states. The same transition equations as used above to fit the model (i.e., for transmission during the partnership duration) were used here to project transmission forward as well as to track the probability a new infection was due to within-couple or extra-couple transmission. These quantities were monitored during the fitting Markov Chain Monte Carlo algorithm outlined below. Projected incidence by country is given in Table S3 and the proportion thereof that is due to extra-couple transmission is given in Table S4 (this is the table equivalent of Figure 3C-D in the main text).

3f. Model Fitting

All β transmission coefficients were given uniform priors (over positive real numbers) except for $\beta_{F,p}$ which was set by using a log-normally distributed prior on the ratio between male to female and female to male transmission within couples $\rho = \frac{\beta_{F,p}}{\beta_{M,p}}$. A recent meta-analysis estimated the ratio of male-to-female to female-to-male transmission in low-income countries to be 1·02 (95% CI: 0·53-2·00), though in developed countries it may be closer to two[8]. We chose our prior as the lognormal distribution $\log(\rho) \sim N(0, 0{\cdot}5)$ to yield a slightly less informative distribution: the 95% region of this distribution is (0.37-2.67).

The above model was fitted to 11 individual countries' data sets and nine West African DHS data sets pooled together due to universally low prevalence amongst couples in this region of Africa. The model was fit using Markov Chain Monte Carlo (MCMC) sampling of the posterior distribution of all six parameters $\{\beta_{M,b}, \beta_{F,b}, \beta_{M,e}, \beta_{F,e}\beta_{M,p}, \rho\}$ which we collectively denote as θ. The posterior probability can be written as:

$$P(\theta|\text{data}) = \frac{P(\text{data}|\theta)P(\theta)}{P(\text{data})}$$

where the data contain all variables in the model other than θ (i.e., couple serostatus and relationship history, country-specific infectious HIV prevalence trends, age-dependent HIV survival times). We use MCMC to sample $P(\text{data}|\theta)P(\theta)$ and approximate $P(\theta|\text{data})$. $P(\theta)$ is the prior distribution of all parameters. Since we use flat uniform priors on all parameters except for all parameters except for ρ, $P(\theta) = P(\rho)$ which is the log-normal distribution specified above. $P(\text{data}|\theta)$ is the likelihood and can be calculated by noting that we have specified a multinomial model for couple serostatus:

$$P(\text{data}|\theta) = \prod_{i \in S} \frac{s_i(t_{\text{fin},i})}{n_i(t_{\text{fin},i})} \prod_{i \in M} \frac{m_i(t_{\text{fin},i})}{n_i(t_{\text{fin},i})} \prod_{i \in F} \frac{f_i(t_{\text{fin},i})}{n_i(t_{\text{fin},i})} \prod_{i \in H} \frac{h_i(t_{\text{fin},i})}{n_i(t_{\text{fin},i})}$$

MCMC sampling of the posterior was performed in R using parallel processing with library 'multicore' on Amazon Cloud Computing High CPU Extra-Large instances. All scripts and data necessary to reproduce our analyses are provided in Files S1-6. Each fit was done with eight 5000 iteration chains with a burn-in of 500 with block sampling of. The covariance-variance of the posterior distributions from these six parameters from an initial adaptive phase was used as the covariance-variance for a multivariate normal proposal distribution during a sampling phase to facilitate efficient block sampling of all six parameters. This improved the acceptance rate from 3-10% to close to 21-28% which is in the range of the optimal rate of 23%. Model fitting took between 7 hours (Swaziland 2006-2007; 431 couples) and 76 hours (9 West African counties pooled; 7,902 couples). Chains of the above length converged as checked by visually examining trace plots and requiring that Gelman-Rubin statistics were < 1·05.

We assessed our MCMC algorithm fitting's performance through simulation. Simulation was performed by using a DHS data set (except serostatus data) and simulation transmission coefficients (chosen to reflect the values fitted from the real data sets) to simulate the probability that a couple was in any of the four possible serostatus states as well as the probability that both partners were alive at the time of the DHS sampling. Each couple's serostatus was chosen randomly from a multinomial probability distribution with these probabilities. Couples for which one or more members were dead before sampling were removed from the data set. These data were then analyzed as above to assess whether our model fitting algorithm could accurately estimate the original transmission coefficients used to generate the data. Estimates were accurate as shown in Figure S4. In all fits to data we noted collinearity between ρ, $\beta_{\text{M,p}}$, $\beta_{\text{M,e}}$, and $\beta_{\text{F,e}}$. The epidemiological explanation is that for increasing values of ρ an approximately equally good fit can be obtained by choosing a $\beta_{\text{M,p}}$ that is very small, a large $\beta_{\text{M,e}}$ and a small $\beta_{\text{F,e}}$, such that the within-couple and extra-couple transmission rates to males are small and large, respectively, and vice versa for females). The impact of this non-identifiability problem was limited by our choice of an informative prior for ρ based on the available literature. There were no identifiability issues concerning the transmission coefficients for infections arising prior to couple formation because these could be easily teased apart based on the relationship history (i.e., duration of sexual activity prior to couple formation, and couple duration).

We diagnosed model fit performance using a calibrated Bayesian goodness-of-fit test where our discrepancy measure was the likelihood and we chose a sampled posterior p-value approach.[9] In brief, after fitting models to real data, we assessed goodness of fit by the following approach:

- Fit the model to a data set as described above
- Take 1000 random samples from the posterior distribution of fitted parameters.
- Calculate the multinomial distribution for each couple's serostatus given they survived for each sampled parameter set.
- Simulate couple serostatus from above multinomial distributions.
- Calculate the probability of observing these simulated serostatuses given the chosen posterior sample (i.e., calculate the likelihood).
- Calculate the probability of observing the serostatuses in the real data given the chosen posterior sample (i.e., the likelihood).
- Average the likelihoods from the previous step to calculate a likelihood that integrates over the posterior.
- Use the 1000 likelihoods from the simulated data as a null distribution with which to compare the averaged likelihood for the real data and use the quantile as a P-value.

For poor model fits we would expect the probability of observed serostatuses would be in the far lower tail of the null distribution, indicating that the data used to explain couple serostatus in our model and multinomial sampling variation were insufficient to explain patterns in observed couple serostatus. This test is conservative because simulated likelihoods are calculated using the parameters that actually generated the simulated data, while for the real data the parameters are one set drawn from the posterior. We show these P-values (i.e., the probability of seeing such a poor fit by sampling variation alone) in Table S4.

4. Sensitivity analyses

Table S2 describes our model assumptions, their justifications, and their implications in tabular form. We conducted sensitivity analyses to several of these assumptions as outlined below.

4a. Heterogeneity

For computational simplicity in model fitting, we assumed no individual heterogeneity in our model. However, we explored the robustness of our results to this assumption using a simulation approach. We simulated data under behavioral heterogeneity by allowing the hazard term $\lambda = \beta P$ to vary individually for transmission occurring prior to couple formation and extra-couply. For example, in the homogenous model

$$p_{\mathrm{M,e}}(T) = 1 - \exp\left(-\beta_{\mathrm{M,e}} \times P_{\mathrm{F}}(T)\Delta t\right),$$
$$p_{\mathrm{F,e}}(T) = 1 - \exp\left(-\beta_{\mathrm{F,e}} \times P_{\mathrm{M}}(T)\Delta t\right),$$

while in the heterogenous model

$$p_{\mathrm{M,e},i}(T) = 1 - \exp\left(-z_{\mathrm{M},i} \times \beta_{\mathrm{M,e}} \times P_{\mathrm{F}}(T)\Delta t\right),$$
$$p_{\mathrm{F,e},i}(T) = 1 - \exp\left(-z_{\mathrm{F},i} \times \beta_{\mathrm{F,e}} \times P_{\mathrm{M}}(T)\Delta t\right),$$

where $z_{\mathrm{M},i}$ and $z_{\mathrm{F},i}$ are random risk factors for the male and female partners, respectively, of the *i*-th couple. We take these risk factors to be log-normally distributed around 0 with standard deviation 1,

$$\log\left(z_{\mathrm{M},i}\right) \sim \mathrm{Normal}(0,1),$$
$$\log\left(z_{\mathrm{F},i}\right) \sim \mathrm{Normal}(0,1).$$

This yields a 55-fold different in risk between the lower 2·5% and 97·5% percentiles of the population. Taking the true relationship histories from Zambia (dates of sexual debut, couple formation, and interview) and parameters similar to those fitted in the homogenous model, we simulated data under this high level of heterogeneity. We then fit the homogenous model to these data and compared estimates of the proportion of transmission from each route to their true values (known under simulation). Bias and coverage of the median fitted values and their 95% credible intervals, respectively, did not substantially changed when data was simulated with individual heterogeneity versus homogeneity (Table S5). Therefore, while the assumption of homogeneity is a strong one, our results are robust to this assumption.

4b. Excluded couples

Systematic differences between couples excluded and included in our analyses could bias our results. We make no attempt to draw inferences regarding polygamous couples and therefore are not concerned with their exclusion from the analysis. We believe that couples excluded due to inconsistent data or data errors are unlikely to be systematically different from other couples in a significant way pertaining to their relationship history or HIV data. Rather, these are probably random errors that are unlikely to have a significant impact on results. In any case, without knowing their relationship history data (i.e., the reason they were excluded) it is not possible to perform sensitivity analyses to their exclusion. Couples excluded because neither partners were in their first relationship (and thus relationship duration was unavailable) are systematically different from couples analyzed. This is a limitation of DHS surveys[11] and difficult to correct for. However, only 1·7-15·6% of couples were excluded because both individuals were in their second or later partnership. Thus, even if there are systematic differences in behavior between first and subsequent partnerships, our analyses still reflect data from the vast majority of couples (because most individuals at any given time are in their first partnership) and are thus highly relevant to shaping HIV policy.

Couples excluded because HIV serostatus was unavailable may also be systematically different from those who were not because the refusal to test may be associated with certain population groups. Because relationship history is available for such couples, we conducted a sensitivity analysis of our results to their exclusion. Using the

posterior median parameters in each model analyses, we calculated the predicted proportion of transmission by each behavioral route for the analyzed data sets and an augmented data set that also included couples that were excluded only because they were missing serostatus data. Our results were robust to the exclusion of these couples (Table S6). This test addresses the possibility that there are demographic factors correlated with the decision to accept a DHS HIV test, but does not address possible bias that could arise if the decision is additionally correlated with serostatus. This could happen, for example, if individuals who have had HIV for longer are more (or less) likely to accept the test than those who have had it for a shorter period. However, it is impossible to ascertain whether this is the case for the very reason that we do not know these couples' serostatuses.

4c. ART coverage

In the above model we assumed that the infectious HIV prevalence was equal to the population HIV prevalence multiplied by the proportion of infected individuals not on ART (1 - ART coverage). However, actual reductions in infectiousness may be lower in the population due to adherence or the fact that individuals on ART may be less sexually active. Thus, we also ran the analysis assuming that infectious prevalence equals (prevalence)×(1 – 0.5×ART coverage). Our results were conservative to this assumption with less coverage being correlated to greater estimates of extramarital transmission (Tables S11-12).

4d. ART and within-couple transmission

We assume that ART did not reduce within-couple transmission for the couples analyzed in the DHS data sets analyzed because, given contemporary guidelines, infected individuals within couples only would have begun ART once they were tested and once their CD4 cell count dropped below 200/μl, by which time they would already have exposed their partner for many years. Thus, ART is unlikely to have affected within-couple transmission substantially. We assessed the sensitivity of our results to this assumption by allowing ART to reduce within-couple transmission homogenously (since there is no information in the DHS on who is on ART) yielding

$$p_{\mathrm{M,p},i}(T) = 1 - \exp\left(-\beta_{\mathrm{M,p}} \times \left(1 - (\text{ART coverage}(T)\right)\Delta t\right),$$
$$p_{F,\mathrm{p},i}(T) = 1 - \exp\left(-\beta_{\mathrm{F,p}} \times \left(1 - (\text{ART coverage}(T)\right)\Delta t\right).$$

We also combined this with the above sensitivity analysis so that

$$p_{\mathrm{M,p},i}(T) = 1 - \exp\left(-\beta_{\mathrm{M,p}} \times \left(1 - 0.5 \times (\text{ART coverage}(T)\right)\Delta t\right),$$
$$p_{F,\mathrm{p},i}(T) = 1 - \exp\left(-\beta_{\mathrm{F,p}} \times \left(1 - 0.5 \times (\text{ART coverage}(T)\right)\Delta t\right).$$

Our results were conservative to this assumption with less coverage being correlated to greater estimates of exta-couple transmission (Tables S11-12).

4e. Reporting bias

The only sensitive variable relied on by our analysis is age at sexual debut. Females in particular may feel pressured to report having had a sexual debut at marriage even when they became sexually active earlier. To assess the sensitivity of our results to this potential bias, we assumed that 30% of females who reported having had their sexual debut at relationship onset actually became sexually active a year earlier. Under this result estimates of extra-couple transmission are slightly smaller, though bias due to this effect is much smaller than the 95% credible intervals (Tables S11-12).

5. Reproduction of results and extension to the model

To increase the transparency of our methods and encourage the use of our modeling paradigm to understand cross-sectional survey data, we have provided the cleaned data sets necessary to replicate this work in an online supporting information file along with the R scripts needed to do fit the model. Any publications relying on the DHS data provided here (or on the DHS website) must be first registered on the DHS website, send DHS copies of the publication, and properly credit DHS (http://www.measuredhs.com/).

6. List of online supplementary files

All scripts and data sets necessary to reproduce our results are provided in the files listed below.

File S1 - areldisc.R: R script to run a country analysis (requires the below files),

File S2 – pcalc.R: R script for the above model, MCMC samplers, and plotting functions,

File S3 – finalcountryresults.R: R script to combine multiple country analyses into summary figures and tables.

File S4 – sim dhs dat.R: R script to simulate serostatus data from DHS couples.

File S5 – Bellan R data files.zip: ZIP archive containing the following *.Rdata files for use by the above scripts:

> **csurv.Rdata:** R data file with cumulative survival distributions used for age-at-seroconversion dependent survival times.
>
> **allepicm.Rdata:** R data file with fitted infectious HIV prevalence in males from UNAIDS estimates.
>
> **allepicf.Rdata:** R data file with fitted infectious HIV prevalence in females from UNAIDS estimates.
>
> **allepicm.5.Rdata:** R data file with fitted infectious HIV prevalence in males from UNAIDS estimates under the assumption that ART is only 50% effective.
>
> **allepicf.5.Rdata:** R data file with fitted infectious HIV prevalence in females from UNAIDS estimates under the assumption that ART is only 50% effective.
>
> **alldhs.Rdata:** R data file with cleaned DHS data. **PLEASE NOTE: any further work using this data must first seek DHS approval and acknowledge the DHS as indicated on their website.** (http://www.measuredhs.com/),

Cited References

1 UNAIDS. Global report: UNAIDS report on the global AIDS epidemic 2010. Geneva, Switzerland: UNAIDS; 2010.

2 Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. 2011; **365**(6): 493-505.

3 Glynn JR, Carael M, Buve A, Musonda RM, Kahindo M, Study Group on the Heterogeneity of HIVEiAC. HIV risk in relation to marriage in areas with high prevalence of HIV infection. *J Acquir Immune Defic Syndr*. 2003; **33**(4): 526-35.

4 Time from HIV-1 seroconversion to AIDS and death before widespread use of highly-active antiretroviral therapy: a collaborative re-analysis. *The Lancet*. 2000; **355**(9210): 1131-7.

5 Todd J, Glynn JR, Marston M, Lutalo T, Biraro S, Mwita W, et al. Time from HIV seroconversion to death: a collaborative analysis of eight studies in six low and middle-income countries before highly active antiretroviral therapy. *Aids*. 2007; **21**.

6 Glynn JR, Sonnenberg P, Nelson G, Bester A, Shearer S, Murray J. Survival from HIV-1 seroconversion in Southern Africa: a retrospective cohort study in nearly 2000 gold-miners over 10 years of follow-up. *Aids*. 2007; **21**(5): 625-32.
7 Hethcote HW. The mathematics of infectious diseases. *Siam Review*. 2000; **42**(4): 599-653.
8 Boily MC, Baggaley RF, Wang L, Masse B, White RG, Hayes RJ, et al. Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies. *Lancet Infect Dis*. 2009; **9**(2): 118-29.
9 Gosselin F. A new calibrated bayesian internal goodness-of-fit method: sampled posterior p-values as simple and general p-values that allow double use of the data. *PLoS ONE*. 2011; **6**(3): e14770.
10 Sidak Z. Rectangular Confidence Regions for the Means of Multivariate Normal Distributions. *Journal of the American Statistical Association*. 1967; **62**(318): 626-33.
11 Epstein H, Morris M. Concurrent partnerships and HIV: an inconvenient truth. *J Int AIDS Soc*. 2011; **14**: 13.
12 Cohen MS, Dye C, Fraser C, Miller WC, Powers KA, Williams BG. HIV Treatment as Prevention: Debate and Commentary-Will Early Infection Compromise Treatment-as-Prevention Strategies? *PLoS Med*. 2012; **9**(7): e1001232.

Table S1. Summary of Demographic & Health Surveys data sets and grouping for analysis.

group	data set(s)
DRC	Demographic Republic of Congo 2007
Ethiopia	Ethiopia 2005; Ethiopia 2011
Kenya	Kenya 2003; Kenya 2008-9
Lesotho	Lesotho 2004; Lesotho 2009
Malawi	Malawi 2004; Malawi 2010
Rwanda	Rwanda 2005
Swaziland	Swaziland 2006-7
West Africa	Burkina Faso 2003; Cameroon 2004; Ghana 2003; Guinea 2005; Liberia 2007; Mali 2006; Niger 2006; Senegal 2005; Sierra Leone 2008
Zambia	Zambia 2007
Zimbabwe	Zimbabwe 2005-6; Zimbabwe 2010-1

Table S2 Description of model assumptions.

Assumption	Justification	Implications
Only couples in which at least one member was in their first stable relationship were analyzed, and these couples are an approximately representative sample.	We can only infer a couple's relationship duration from DHS questionnaires for couples in which at least one individual is in their first relationship.	Only 1·7-15·6% of couples were excluded because both individuals were in their 2nd or later partnership (Table 1). Thus, even if there are systematic differences in behavior between first and subsequent partnerships, our analyses still reflect data from the vast majority of couples (because most individuals at any given time are in their first partnership) and are thus highly relevant to shaping HIV policy.
The ratio of male-to-female transmission and female-to-male transmission rates within serodiscordant couples is 1 with some degree of uncertainty.	Boily and colleagues' meta-analysis yielded an estimate of 1·02 (95% CI: 0·53-2·00) for this ratio in developing countries.[8] We chose a prior distribution with slightly more variance with a 95% CI of (0·37-2·67).	We accurately reflect the uncertainty of this parameter in the model. Larger values (or priors with greater means) would result in more females being infected within-couple versus extra-couply, and vice versa for males.
Random age mixing for unidentified partners (i.e., during transmission prior to couple formation or extra-couply)	While we know the ages of both members of surveyed couples, we do not know the ages of all their sexual partners over their lifetime.	Males are generally older than their female sexual partners. Females are exposed to a higher prevalence population than the age-pooled infectious prevalence used in our model, and vice versa for males. This behavioral difference will be absorbed in the transmission coefficients. Thus, fitted females' transmission coefficients will be slightly greater to account for our model's underestimate of the HIV prevalence amongst males they are mixing with to fit hazards (which are the product of transmission coefficients an infectious HIV prevalence) able to explain their observed serostatuses. Whether the fitted hazards are achieved by greater transmission coefficients and smaller prevalences or vice versa will not affect the estimated proportion of transmission from each, however.
Random mixing by risk class	We do not have enough information to determine a risk index for each individual over their entire sexual history (most risk variables in DHS only pertain to the last 12 months).	This is a conservative assumption. If individuals associate based on risk or HIV status, then more of the concordant positive couples will be due to non-random mixing than within-partner transmission, biasing our within-partner transmission estimates high.
Infectiousness of HIV positive partners assumed to be constant throughout disease progression.	A recent review of the acute stage indicates that much weaker evidence for the acute stage's importance in transmission than commonly believed.[12]	If the acute stage was important, this assumption could affect how the model fits concordant positive couples, in which the secondarily infected partner would miss the acute stage or experience it, respectively, if the index partner was infected prior to or after partner formation. In the former case our model would overestimate the probability an infection is extra-couple versus within-partner while in the latter case it would underestimate it. These would partly cancel each other out and we would not expect qualitative changes in our results.
Homogenous transmission	Fitting this model with individual heterogeneity is extremely computationally	A sensitivity analysis based on analyzing simulated heterogeneous data with a homogenous model indicates our results are robust to this

coefficients between individuals	challenging.	assumption.
Homogenous transmission coefficients over time	While risky sexual behavioral may have decreased over the course of the epidemic in response to increased awareness and behavioral interventions, it is unclear how they partition across behavioral routes.	The direction and strength of bias resulting from this assumption would depend on how sexual behavioral has changed over the course of the epidemic. It is unlikely to have a major effect on the results because the model can still disentangle whether infections occurred before or after couple formation based on relationship histories.
Ignored effect of ART on within-couple transmission	DHS does not identify which individuals are on ART (let alone ask them their HIV status).	A sensitivity analysis indicated our results were robust to this assumption because ART coverage ramped up beginning 2005 and coverage was negligible until a few years later (Figures S1-2) while DHS data sets analyzed were only collected around 2005 or shortly thereafter (Table S1). Further, this assumption is realistic because (1) Most couples would have been together for many years pre-ART and thus ART would be unlikely to have affected their serostatus (2) Given policy up until WHO's new 2012 TasP recommendations, many individuals will have already infected their partner by the time they become sick, get tested, and go on ART (indeed the problem with current policy is that ART is not being give early enough to prevent infections). (3) The extent to which ART did prevent transmission within observe serodiscordant couples will be reflected in our results in terms of lower within-couple transmission coefficients and thus still give a realistic breakdown of current transmission patterns.
No effect of ART on mortality	DHS does not identify which individuals are on ART (let alone ask them their HIV status).	This is unlikely to affect results for the same reason as the previous assumption. There has been too little time since ART has been ramped up for a significant effect on life expectancy to affect our model.

Table S3. Simulation assessment of inflation estimators. We used simulated data to assess the bias and precision of two inclusion-probability-type inflation estimators of the proportion of index infections from each of the four possible was an infection could first enter a couple (the index infection could have been male or female could have first been infected before couple formation or extra-couply). Estimator 1 only relies on couples with at least one infected partner in estimates, while Estimator 2 uses all couples probability of having an index case from each route of transmission regardless of the couple serostatus.

bias (standard deviation)	Male before	Male extra-couple	Female before	Female extra-couple
Estimator 1	0·0023 (0·0355)	0·000499 (0·0265)	-0·00313 (0·02)	0·000329 (0·0225)
Estimator 2	0·00055 (0·00977)	0·000728 (0·00778)	-0·00187 (0·0101)	0·000592 (0·00639)

Table S4. Goodness of model fits. Probability of obtaining model fits as least as poor as observed with the real data due to multinomial sampling variability alone.

	p value
DRC	0·695
Ethiopia	0·53
Kenya	0·411
Lesotho	0·35
Malawi	0·514
Rwanda	0·524
Swaziland	0·153
West Africa	0·516
Zambia	0·363
Zimbabwe	0·424

Table S5. Bias and 95% credible interval coverage (in parentheses) for model estimates of the proportion of transmission from each route (by gender) for data simulated with and without individual heterogeneity. Bias for estimates of the proportion of transmission from a behavioral route was calculated as (fitted proportion – true proportion) / (true proportion). Coverage specifies the percentage of 95% credible intervals that contained the true value. Bias and coverage are reported for 100 simulated data sets each for homogenous (i.e., those found in main model analysis) and heterogeneous transmission.

	male			**female**		
	before	extra-couple	from partner	before	extra-couple	from partner
Homogenous	-0·03 (92%)	-0·043 (96%)	0·045 (98%)	-0·0082 (89%)	0·032 (98%)	-0·071 (99%)
Heterogeneous	0·03 (85%)	-0·074 (91%)	0·049 (100%)	0·0029 (80%)	0·02 (96%)	-0·062 (99%)

Table S6. **Sensitivity of model results to the exclusion of couples for which HIV serostatus was unavailable for one or both partners.** Values reported are the proportional change in the estimated proportion of transmission from the each transmission route when couples with missing serostatus were included vs. excluded in the estimation.

	male			**female**		
	before	extra-couple	from partner	before	extra-couple	from partner
DRC	0·0214	0·0247	-0·0108	-0·00555	-0·0122	0·000686
Ethiopia	0·00723	-0·000774	-0·00699	-0·00469	0·00216	0·00192
Kenya	-0·0261	-0·0298	0·0183	0·0189	-0·000893	0·00266
Lesotho	-0·0414	-0·021	0·0125	0·0121	0·00841	-0·00334
Malawi	0·0152	0·0194	-0·00661	-0·00507	0·00203	-0·00616
Rwanda	0·00106	-0·00394	-0·00031	0·000137	-0·000438	0·00129
Swaziland	-0·00378	-0·0236	0·00421	0·00531	$7{\cdot}47\times10^{-5}$	0·0203
West Africa	0·00077	0·00253	-0·000926	-0·00127	0·00225	0·00113
Zambia	-0·0193	-0·0215	0·0104	0·0108	0·00405	0·00557
Zimbabwe	0·0202	0·0303	-0·0114	-0·0112	0·000998	-0·00912

Table S7. Proportional contribution of transmission routes to observed infections. This table gives the posterior median and 95% credible intervals for the proportional contribution of each transmission route (before couple formation; extra-couple transmission during the couple duration; transmission within the couple) as shown in Figure 3 of the main text. Proportional contributions are given by gender and by couple serostatus (i.e., serodiscordant if his/her partner is seronegative; concordant if he/she is seropositive) or aggregated (i.e., any couple serostatus).

		Male			Female		
		Before-couple	Extra-couple	Within-couple	Before-couple	Extra-couple	Within-couple
Serodiscordant Couples	**DRC**	0·43 (0·058, 0·75)	0·57 (0·25, 0·94)	-	0·11 (0·0066, 0·32)	0·89 (0·68, 0·99)	-
	Ethiopia	0·5 (0·38, 0·61)	0·5 (0·39, 0·62)	-	0·69 (0·55, 0·85)	0·31 (0·15, 0·45)	-
	Kenya	0·4 (0·31, 0·48)	0·6 (0·52, 0·69)	-	0·52 (0·44, 0·59)	0·48 (0·41, 0·56)	-
	Lesotho	0·22 (0·19, 0·26)	0·78 (0·74, 0·81)	-	0·26 (0·21, 0·31)	0·74 (0·69, 0·79)	-
	Malawi	0·22 (0·18, 0·27)	0·78 (0·73, 0·82)	-	0·36 (0·29, 0·44)	0·64 (0·56, 0·71)	-
	Rwanda	0·2 (0·11, 0·29)	0·8 (0·71, 0·89)	-	0·35 (0·2, 0·49)	0·65 (0·51, 0·8)	-
	Swaziland	0·42 (0·36, 0·48)	0·58 (0·52, 0·64)	-	0·57 (0·5, 0·64)	0·43 (0·36, 0·5)	-
	West Africa	0·28 (0·22, 0·33)	0·72 (0·67, 0·78)	-	0·35 (0·3, 0·4)	0·65 (0·6, 0·7)	-
	Zambia	0·38 (0·32, 0·44)	0·62 (0·56, 0·68)	-	0·54 (0·47, 0·61)	0·46 (0·39, 0·53)	-
	Zimbabwe	0·28 (0·24, 0·32)	0·72 (0·68, 0·76)	-	0·4 (0·35, 0·45)	0·6 (0·55, 0·65)	-
Concordant Positive Couples	**DRC**	0·36 (0·043, 0·66)	0·23 (0·047, 0·56)	0·42 (0·16, 0·71)	0·16 (0·0091, 0·5)	0·3 (0·12, 0·57)	0·53 (0·22, 0·78)
	Ethiopia	0·29 (0·21, 0·38)	0·3 (0·13, 0·44)	0·41 (0·24, 0·62)	0·28 (0·19, 0·37)	0·15 (0·034, 0·33)	0·57 (0·36, 0·74)
	Kenya	0·34 (0·21, 0·46)	0·2 (0·1, 0·31)	0·46 (0·28, 0·65)	0·37 (0·25, 0·47)	0·2 (0·11, 0·31)	0·43 (0·25, 0·61)
	Lesotho	0·2 (0·15, 0·24)	0·51 (0·35, 0·64)	0·29 (0·15, 0·47)	0·15 (0·11, 0·19)	0·29 (0·17, 0·47)	0·56 (0·36, 0·71)
	Malawi	0·25 (0·18, 0·31)	0·41 (0·28, 0·53)	0·34 (0·2, 0·52)	0·22 (0·16, 0·26)	0·23 (0·12, 0·38)	0·55 (0·38, 0·69)
	Rwanda	0·37 (0·18, 0·53)	0·32 (0·19, 0·47)	0·31 (0·14, 0·53)	0·19 (0·08, 0·3)	0·13 (0·04, 0·31)	0·68 (0·45, 0·84)
	Swaziland	0·54 (0·44, 0·62)	0·18 (0·11, 0·25)	0·28 (0·16, 0·41)	0·48 (0·39, 0·55)	0·14 (0·07, 0·21)	0·39 (0·27, 0·51)
	West Africa	0·23 (0·15, 0·31)	0·35 (0·21, 0·48)	0·42 (0·24, 0·62)	0·18 (0·11, 0·26)	0·28 (0·16, 0·44)	0·53 (0·33, 0·71)
	Zambia	0·33 (0·25, 0·41)	0·33 (0·22, 0·43)	0·34 (0·2, 0·5)	0·28 (0·22, 0·34)	0·19 (0·094, 0·31)	0·53 (0·37, 0·66)
	Zimbabwe	0·29 (0·24, 0·34)	0·33 (0·24, 0·41)	0·38 (0·27, 0·5)	0·28 (0·23, 0·32)	0·24 (0·16, 0·34)	0·48 (0·36, 0·59)
Any Couple Serostatus	**DRC**	0·42 (0·056, 0·73)	0·53 (0·22, 0·88)	0·054 (0·022, 0·094)	0·12 (0·0077, 0·34)	0·79 (0·59, 0·91)	0·086 (0·037, 0·13)
	Ethiopia	0·39 (0·3, 0·47)	0·39 (0·26, 0·52)	0·22 (0·13, 0·33)	0·44 (0·35, 0·53)	0·21 (0·082, 0·37)	0·35 (0·22, 0·45)
	Kenya	0·36 (0·27, 0·45)	0·37 (0·28, 0·46)	0·27 (0·16, 0·38)	0·44 (0·37, 0·51)	0·34 (0·26, 0·42)	0·22 (0·13, 0·32)
	Lesotho	0·21 (0·17, 0·24)	0·61 (0·5, 0·7)	0·18 (0·091, 0·29)	0·18 (0·14, 0·21)	0·41 (0·3, 0·55)	0·41 (0·27, 0·52)
	Malawi	0·23 (0·19, 0·28)	0·58 (0·5, 0·66)	0·18 (0·1, 0·28)	0·27 (0·22, 0·31)	0·37 (0·28, 0·49)	0·36 (0·25, 0·45)
	Rwanda	0·3 (0·15, 0·41)	0·54 (0·43, 0·65)	0·17 (0·077, 0·29)	0·22 (0·12, 0·32)	0·25 (0·15, 0·41)	0·53 (0·35, 0·65)
	Swaziland	0·51 (0·43, 0·58)	0·27 (0·2, 0·34)	0·22 (0·13, 0·32)	0·5 (0·43, 0·56)	0·21 (0·15, 0·28)	0·29 (0·2, 0·38)
	West Africa	0·26 (0·2, 0·31)	0·58 (0·5, 0·65)	0·16 (0·093, 0·24)	0·29 (0·24, 0·33)	0·51 (0·44, 0·59)	0·2 (0·12, 0·27)
	Zambia	0·35 (0·29, 0·41)	0·47 (0·38, 0·54)	0·18 (0·11, 0·26)	0·37 (0·32, 0·41)	0·27 (0·19, 0·38)	0·36 (0·25, 0·44)
	Zimbabwe	0·29 (0·25, 0·32)	0·48 (0·41, 0·54)	0·24 (0·17, 0·31)	0·31 (0·28, 0·35)	0·34 (0·27, 0·42)	0·35 (0·26, 0·43)

Table S8. Proportional contribution of transmission routes to index infections. This table gives posterior medians (95% credible intervals). Estimates in this figure account for survival bias and thus reflect the proportional contribution of routes of infection unconditional on whether a couple survived to be sampled by the DHS.

	Male		Female	
	Before-couple	Extra-couple	Before-couple	Extra-couple
DRC	0·35 (0·049, 0·59)	0·26 (0·064, 0·55)	0·09 (0·0051, 0·29)	0·29 (0·14, 0·47)
Ethiopia	0·37 (0·26, 0·46)	0·24 (0·13, 0·34)	0·29 (0·2, 0·37)	0·11 (0·03, 0·21)
Kenya	0·28 (0·18, 0·36)	0·21 (0·13, 0·3)	0·31 (0·23, 0·38)	0·21 (0·13, 0·29)
Lesotho	0·16 (0·12, 0·2)	0·48 (0·37, 0·57)	0·11 (0·078, 0·14)	0·25 (0·17, 0·36)
Malawi	0·21 (0·15, 0·26)	0·4 (0·32, 0·47)	0·19 (0·14, 0·24)	0·2 (0·13, 0·28)
Rwanda	0·36 (0·18, 0·49)	0·39 (0·26, 0·53)	0·12 (0·05, 0·2)	0·13 (0·049, 0·27)
Swaziland	0·37 (0·3, 0·45)	0·17 (0·11, 0·24)	0·32 (0·25, 0·39)	0·14 (0·078, 0·2)
West Africa	0·2 (0·14, 0·26)	0·34 (0·26, 0·41)	0·17 (0·13, 0·21)	0·29 (0·22, 0·37)
Zambia	0·32 (0·25, 0·39)	0·31 (0·24, 0·39)	0·22 (0·17, 0·28)	0·14 (0·085, 0·22)
Zimbabwe	0·26 (0·22, 0·31)	0·33 (0·27, 0·39)	0·21 (0·17, 0·24)	0·2 (0·15, 0·26)

Table S9. **Estimated proportion of infections of seronegative partners in serodiscordant couples in 2011 that is due to extra-couple intercourse by gender.** Estimates are posterior medians (95% credible intervals) acquired by using fitted transmission coefficients.

	Males	Females
DRC	0·04 (0·0066, 0·23)	0·052 (0·013, 0·27)
Ethiopia	0·0022 (0·00088, 0·0053)	0·00094 (0·00021, 0·0028)
Kenya	0·014 (0·0069, 0·031)	0·013 (0·0059, 0·029)
Lesotho	0·13 (0·067, 0·25)	0·062 (0·034, 0·12)
Malawi	0·045 (0·025, 0·087)	0·023 (0·012, 0·045)
Rwanda	0·0041 (0·0017, 0·01)	0·0018 (0·00057, 0·0049)
Swaziland	0·06 (0·029, 0·12)	0·036 (0·016, 0·074)
West Africa	0·024 (0·013, 0·049)	0·015 (0·0083, 0·03)
Zambia	0·05 (0·026, 0·095)	0·026 (0·013, 0·055)
Zimbabwe	0·039 (0·025, 0·063)	0·026 (0·016, 0·044)

Table S10. **Estimated proportion of incidence in all cohabiting couples in 2011 that is due to extra-couple intercourse by gender.** Estimates are posterior medians (95% credible intervals) acquired by using fitted transmission coefficients.

	Males	Females
DRC	0·83 (0·44, 0·97)	0·83 (0·54, 0·97)
Ethiopia	0·34 (0·17, 0·55)	0·13 (0·034, 0·31)
Kenya	0·32 (0·19, 0·51)	0·35 (0·2, 0·55)
Lesotho	0·65 (0·48, 0·8)	0·34 (0·21, 0·51)
Malawi	0·62 (0·47, 0·76)	0·33 (0·21, 0·5)
Rwanda	0·43 (0·25, 0·64)	0·1 (0·036, 0·24)
Swaziland	0·34 (0·2, 0·52)	0·25 (0·13, 0·41)
West Africa	0·56 (0·4, 0·72)	0·47 (0·33, 0·65)
Zambia	0·55 (0·39, 0·71)	0·27 (0·15, 0·44)
Zimbabwe	0·45 (0·35, 0·58)	0·26 (0·18, 0·38)

Table S11. **Sensitivity analysis of the proportional contribution of extra-couple transmission to observed infections.** We conducted sensitivity analyses of the results presented in the main text (Main) to (1) allowing ART coverage to reduce within-couple ART (wcART), (2) assuming that only 50% of individuals on ART were non-infectious (ART 50%), (3) the previous two combined (wcART & ART 50%), and (4) assuming that 30% of females who stated that their sexual debut occurred at relationship onset actually became sexually active a year earlier (aFSD). Values presented give estimated proportion of transmission in observed couples that occurred from extra-couple transmission. Data sets that were obtained just as ART coverage began to ramp up (i.e. Swaziland 2006-2007) are almost entirely unaffected by ART assumptions.

	Male					Female				
	Main	wcART	ART 50%	wcART & ART 50%	afSD	Main	wcART	ART 50%	wcART & ART 50%	afSD
DRC	0·53 (0·22, 0·88)	0·52 (0·21, 0·88)	0·53 (0·22, 0·88)	0·52 (0·23, 0·87)	0·52 (0·22, 0·88)	0·79 (0·59, 0·91)	0·79 (0·58, 0·91)	0·79 (0·59, 0·91)	0·79 (0·59, 0·91)	0·8 (0·6, 0·91)
Ethiopia	0·39 (0·26, 0·52)	0·4 (0·26, 0·52)	0·4 (0·26, 0·52)	0·4 (0·27, 0·53)	0·39 (0·26, 0·51)	0·21 (0·082, 0·37)	0·22 (0·085, 0·37)	0·21 (0·083, 0·37)	0·22 (0·087, 0·38)	0·22 (0·092, 0·38)
Kenya	0·37 (0·28, 0·46)	0·37 (0·28, 0·46)	0·37 (0·29, 0·46)	0·37 (0·29, 0·46)	0·37 (0·29, 0·46)	0·34 (0·26, 0·42)	0·34 (0·26, 0·42)	0·34 (0·26, 0·42)	0·34 (0·26, 0·42)	0·32 (0·23, 0·4)
Lesotho	0·61 (0·5, 0·7)	0·61 (0·5, 0·69)	0·61 (0·5, 0·7)	0·61 (0·5, 0·7)	0·61 (0·5, 0·69)	0·41 (0·3, 0·55)	0·42 (0·31, 0·55)	0·42 (0·31, 0·56)	0·42 (0·31, 0·56)	0·41 (0·31, 0·56)
Malawi	0·58 (0·5, 0·66)	0·59 (0·5, 0·66)	0·59 (0·5, 0·66)	0·59 (0·5, 0·66)	0·58 (0·49, 0·66)	0·37 (0·28, 0·49)	0·37 (0·28, 0·49)	0·37 (0·28, 0·49)	0·37 (0·28, 0·49)	0·38 (0·28, 0·5)
Rwanda	0·54 (0·43, 0·65)	0·53 (0·43, 0·65)	0·53 (0·43, 0·65)	0·54 (0·43, 0·65)	0·53 (0·43, 0·65)	0·25 (0·15, 0·41)	0·25 (0·15, 0·41)	0·25 (0·15, 0·41)	0·25 (0·15, 0·41)	0·26 (0·15, 0·42)
Swaziland	0·27 (0·2, 0·34)	0·27 (0·2, 0·34)	0·27 (0·2, 0·34)	0·27 (0·2, 0·34)	0·27 (0·21, 0·34)	0·21 (0·15, 0·28)	0·21 (0·15, 0·28)	0·21 (0·15, 0·28)	0·21 (0·15, 0·28)	0·19 (0·12, 0·27)
West Africa	0·58 (0·5, 0·65)	0·58 (0·5, 0·65)	0·57 (0·5, 0·65)	0·57 (0·5, 0·65)	0·58 (0·5, 0·65)	0·51 (0·44, 0·59)	0·51 (0·44, 0·59)	0·51 (0·44, 0·59)	0·51 (0·44, 0·59)	0·51 (0·44, 0·59)
Zambia	0·47 (0·38, 0·54)	0·47 (0·39, 0·54)	0·47 (0·39, 0·55)	0·47 (0·38, 0·55)	0·47 (0·38, 0·54)	0·27 (0·19, 0·38)	0·28 (0·2, 0·38)	0·28 (0·19, 0·38)	0·28 (0·2, 0·39)	0·27 (0·19, 0·38)
Zimbabwe	0·48 (0·41, 0·54)	0·48 (0·41, 0·54)	0·48 (0·41, 0·54)	0·48 (0·42, 0·54)	0·48 (0·41, 0·54)	0·34 (0·27, 0·42)	0·34 (0·27, 0·42)	0·34 (0·27, 0·43)	0·34 (0·27, 0·42)	0·33 (0·26, 0·42)

Table S12. **Sensitivity analysis of the proportion of projected incidence over the next year that is due to extra-couple intercourse by gender.** We conducted four sensitivity analyses as outlined in the caption of Table 10. For future projections results are based on ART coverage and prevalence in 2011.

	Male					Female				
	Main	wcART	ART 50%	wcART & ART 50%	afSD	Main	wcART	ART 50%	wcART & ART 50%	afSD
DRC	0·83 (0·44, 0·97)	0·83 (0·44, 0·97)	0·83 (0·44, 0·97)	0·84 (0·48, 0·97)	0·83 (0·46, 0·97)	0·83 (0·54, 0·97)	0·84 (0·56, 0·97)	0·83 (0·55, 0·97)	0·84 (0·57, 0·97)	0·83 (0·54, 0·97)
Ethiopia	0·34 (0·17, 0·55)	0·48 (0·27, 0·69)	0·46 (0·25, 0·67)	0·51 (0·3, 0·72)	0·34 (0·17, 0·55)	0·13 (0·034, 0·31)	0·21 (0·059, 0·45)	0·19 (0·053, 0·42)	0·23 (0·068, 0·48)	0·14 (0·038, 0·32)
Kenya	0·32 (0·19, 0·51)	0·41 (0·25, 0·59)	0·38 (0·23, 0·57)	0·42 (0·26, 0·61)	0·33 (0·2, 0·52)	0·35 (0·2, 0·55)	0·44 (0·26, 0·64)	0·42 (0·25, 0·61)	0·45 (0·28, 0·65)	0·34 (0·19, 0·53)
Lesotho	0·65 (0·48, 0·8)	0·7 (0·54, 0·83)	0·68 (0·52, 0·82)	0·7 (0·54, 0·83)	0·65 (0·47, 0·8)	0·34 (0·21, 0·51)	0·4 (0·26, 0·58)	0·37 (0·24, 0·55)	0·4 (0·26, 0·58)	0·34 (0·22, 0·52)
Malawi	0·62 (0·47, 0·76)	0·69 (0·55, 0·81)	0·66 (0·52, 0·8)	0·69 (0·55, 0·81)	0·62 (0·47, 0·76)	0·33 (0·21, 0·5)	0·39 (0·26, 0·55)	0·37 (0·24, 0·54)	0·39 (0·26, 0·56)	0·34 (0·21, 0·51)
Rwanda	0·43 (0·25, 0·64)	0·71 (0·51, 0·86)	0·59 (0·39, 0·78)	0·69 (0·49, 0·85)	0·42 (0·24, 0·64)	0·1 (0·036, 0·24)	0·27 (0·11, 0·51)	0·19 (0·07, 0·38)	0·26 (0·1, 0·48)	0·11 (0·037, 0·24)
Swaziland	0·34 (0·2, 0·52)	0·42 (0·26, 0·61)	0·4 (0·24, 0·6)	0·44 (0·27, 0·64)	0·35 (0·2, 0·54)	0·25 (0·13, 0·41)	0·33 (0·18, 0·51)	0·31 (0·17, 0·49)	0·35 (0·2, 0·54)	0·24 (0·12, 0·42)
West Africa	0·56 (0·4, 0·72)	0·61 (0·46, 0·76)	0·59 (0·44, 0·75)	0·61 (0·46, 0·77)	0·56 (0·4, 0·72)	0·47 (0·33, 0·65)	0·54 (0·39, 0·7)	0·51 (0·37, 0·68)	0·54 (0·4, 0·71)	0·47 (0·33, 0·65)
Zambia	0·55 (0·39, 0·71)	0·65 (0·49, 0·79)	0·61 (0·45, 0·75)	0·64 (0·49, 0·78)	0·55 (0·4, 0·7)	0·27 (0·15, 0·44)	0·36 (0·21, 0·54)	0·31 (0·18, 0·48)	0·35 (0·21, 0·54)	0·27 (0·15, 0·44)
Zimbabwe	0·45 (0·35, 0·58)	0·51 (0·4, 0·63)	0·51 (0·4, 0·63)	0·54 (0·42, 0·65)	0·45 (0·35, 0·58)	0·26 (0·18, 0·38)	0·31 (0·21, 0·44)	0·3 (0·2, 0·43)	0·32 (0·22, 0·45)	0·26 (0·17, 0·38)

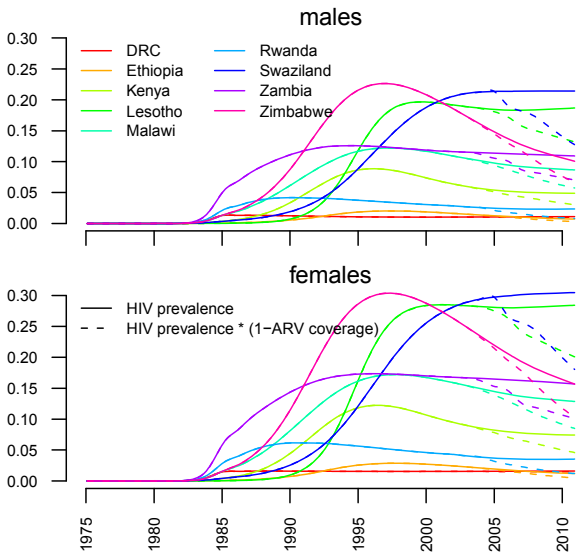

Figure S1. UNAIDS estimates of population HIV prevalence and infectious population HIV prevalence (i.e. prevalence of HIV infected individuals who are not on antiretroviral therapy) in non-West-African countries (see Figure S2).

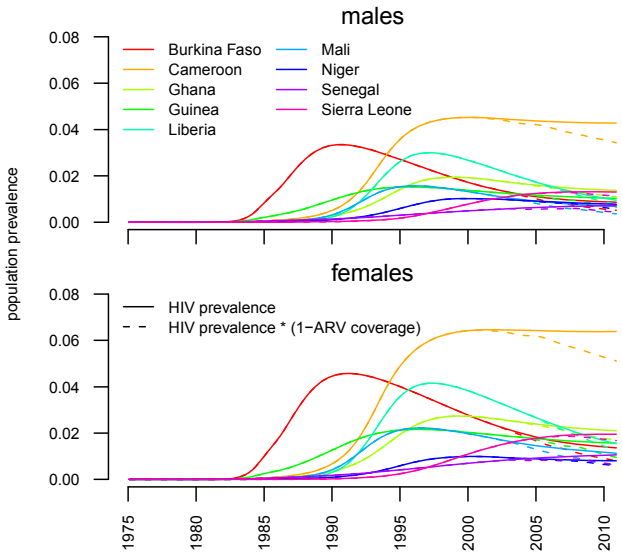

Figure S2. UNAIDS estimates of population HIV prevalence and infectious population HIV prevalence (i.e. prevalence of HIV infected individuals who are not on antiretroviral therapy) in West-African countries (note difference in y-axis limits between Figures S1-2).

Figure S3. Cumulative probability of survival up to a specified number of years past seroconversion by age at seroconversion. Weibull hazards of death were fitted to data in Figure 1 of the CASCADE study[4].

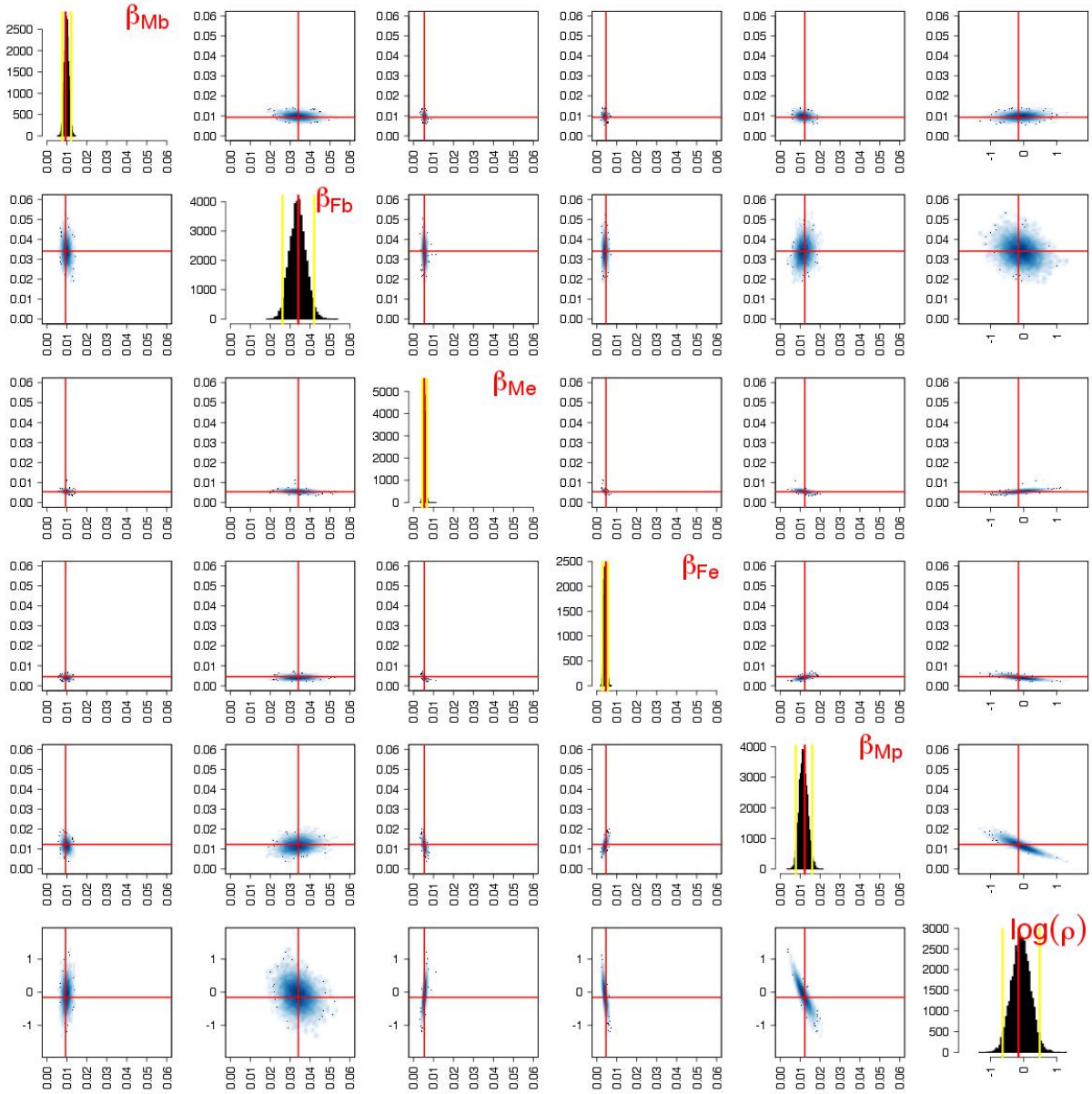

Figure S4. Model fits to simulated data with known parameters ($\beta_{\mathrm{M,b}} = 0 \cdot 0093$, $\beta_{\mathrm{F,b}} = \cdot 034$, $\beta_{\mathrm{M,e}} = \cdot 0054$, $\beta_{\mathrm{F,e}} = 0 \cdot 0045$, $\beta_{\mathrm{M,p}} = 0 \cdot 012$, $\log(\rho) = -0 \cdot 16$) . Histograms down the diagonal show posterior distributions of each fitted parameter where red lines indicate the true parameter value and yellow lines indicate 95% credible intervals. Blue cloud plots off the diagonal show posterior densities for all pairwise combinations of parameters as well as the true parameter values (red lines). These plots demonstrate the existence of collinearity between the latter four parameters. For greater values of ρ (i.e., more efficient witin-couple transmission from males to females than vice versa), the data can still be fit approximately well for smaller values of $\beta_{\mathrm{M,p}}$ and $\beta_{\mathrm{F,e}}$ and greater values of $\beta_{\mathrm{M,e}}$ (i.e., females are infected more from within-couple transmission and males are infected more from extra-couple transmission). Our informative prior on ρ limits the impact of this collinearity on our model results, but the extent to which collinearity still occurs is reflected in all credible intervals.