ORIGINAL ARTICLE

# External infections contribute minimally to HIV incidence among HIV sero-discordant couples in sub-Saharan Africa

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## ABSTRACT

**Objective** Recent randomised clinical trials among stable HIV sero-discordant couples (SDCs) in sub-Saharan Africa (SSA) have reported that about 20–30% of new HIV infections are acquired from external sexual partners, rather than transmitted from the infected to the uninfected partner within the couple. The aim of this study is to examine whether, and to what extent, these findings are generalisable to SDCs in the wider population in SSA.

**Methods** A mathematical model was constructed to calculate the fraction of new HIV-1 infections among SDCs that are due to sources external to the couple. The model was parameterised using empirical and population-based data for 20 countries in SSA. Uncertainty and sensitivity analyses were also conducted.

**Results** The contribution of external infections among SDCs was generally modest, but it varied widely across SSA. In low HIV prevalence countries (≤3.0%), it ranged from 0.6–2.9%. In intermediate prevalence countries (3.0–18.0%), it ranged from 4.9–11.7%. In Swaziland and Lesotho, the world's most-intense epidemics, sizable levels of 27.9% and 27.3% were found, respectively.

**Conclusions** In most countries in SSA, nearly all HIV acquisitions by the uninfected partners in SDCs appear to be due to transmissions from the HIV infected partners in the SDCs. The contribution of externally acquired infections varies with HIV population prevalence, but rarely exceeds 10% in the majority of countries. Only in hyperendemic HIV epidemics the contribution of external infections is substantial and may reach the levels reported in recent randomised clinical trials involving SDCs.

## INTRODUCTION

Recent randomised controlled clinical trials (RCTs) among stable HIV sero-discordant couples (SDCs) have reported that about 20–30% of new HIV infections among these SDCs were acquired from external sexual partners, rather than transmitted from the infected to the uninfected partner within the couple.[1 2] In these trials, viral linkages between study-partner pairs were established through phylogenetic analyses and gene sequencing for the C2-V3-C3 regions of the *env* gene[1] or the HIV-1 *pol* gene.[2] The probability of linkage was determined either through measuring the pairwise nucleotide distances between the sequences,[1] or by using Bayes' theorem to compare the genetic similarity of HIV-1 from partner pairs with the genetic similarity of HIV-1 from local control subjects.[2]

The conditions under which these trials were conducted, with sero-status disclosure and counselling, pose a question about the generalisability of the trials' findings to other SDCs within the wider population. This issue has recently received much attention in light of the debate about the contribution of HIV sero-conversions among SDCs to the HIV epidemic in sub-Saharan Africa (SSA).[3–5] Against this background, we constructed a mathematical model parameterised by state of the art empirical data to calculate the population-level fraction of new HIV-1 infections among SDCs that are due to sources external to the couple in 20 countries in SSA.

## METHODS

### Model structure

The annual risk of HIV transmission from the infected to the uninfected partner within an SDC ($\phi$) is determined by HIV transmission probability per coital act (p), the number of coital acts per year (n), the fraction of coital acts protected by condom use ($f_{condom}$), the efficacy of condom use in preventing HIV transmission per sexual act ($E_{condom}$), and whether the susceptible partner in the couple is a circumcised male. In a couple where the male is not circumcised, $\phi$ is given by:

$$\phi = 1-(1-p)^{(1-f_{condom})n}(1-(1-E_{condom})p)^{f_{condom}n}.$$

The average $\phi$ in the population is determined as a weighted average of the annual risk of HIV transmission among SDCs with and without male circumcision (see supplementary online appendix (SOA)).

Let $\lambda$ be the annual risk of the HIV sero-negative individual in an SDC to acquire the infection from a source external to the couple. We assume that the annual risk of any susceptible individual in the population to acquire the infection, that is, the hazard rate of infection or incidence rate, is approximately equal among those individuals in stable couples versus those not in stable couples, and is also approximately equal among those in HIV concordant negative couples versus those in SDCs. Accordingly, $\lambda$ can be approximated by HIV population-level incidence rate. While the strict validity of this assumption is not known, existing empirical data discussed below suggests its plausibility. Moreover, potential violations of this assumption are more likely than not to affirm our

conclusion regarding the contribution of external infections. Further considerations regarding this assumption and its variations are in the Discussion section.

Based on this assumption and using competing hazards, that is, comparing the likelihood of acquiring the HIV infection from an external source to the likelihood of acquiring the infection from the infected partner in an SDC, the fraction of new HIV-1 infections among SDCs that are due to sources external to the couple ($f_{ext}$) is given by $f_{ext} = \lambda/(\lambda+\phi)$. Further mathematical derivations can be found in SOA.

### Model parameterisation

We used the most recent Demographic and Health Survey (DHS) databases for 20 countries in SSA[6] to calculate the country-specific: HIV prevalence (P), fraction of HIV-infected females among the SDCs ($f_{index}$), fraction of circumcised males in SDCs with HIV-infected females ($f_{mc}$), and condom use at last sexual act among stable couples ($f_{condom}$) (see table S1 in SOA). HIV population-level incidence rate was obtained from the Joint United Nations Programme on HIV/AIDS SPECTRUM model predictions for each country for the specific year of the DHS survey (Gouws E, Joint United Nations Programme on HIV/AIDS (UNAIDS). Personal Communication. 2011).[7] For countries where SPECTRUM model predictions are not available, or where the bounds of the 95% CI are not precisely specified, estimates for HIV incidence rate were derived using the DHS country-specific HIV-1 prevalence (SOA). We calculated p as the average from the Rakai Study[8] and the Partners in Prevention Study (Hughes JP. Personal communication. 2010),[1 9] and derived n from the Rakai Study[8] as data on frequency of coital acts were not available in the DHS databases from which we derived these measures. We opted to use n in the Rakai Study because this choice implies values for $\phi$ that are consistent with the existing empirical measures, and in fact are at the mid-range of these estimates.[8–10] Further discussion of the model parameters can be found in SOA.

### Uncertainty and sensitivity analyses

An uncertainty analysis was conducted to generate country-specific likelihood distributions for $f_{ext}$ using Monte Carlo sampling from the uncertainty ranges of p, n, country-specific $\lambda$, country-specific $f_{index}$, country-specific $f_{mc}$, country-specific $f_{condom}$, $E_{condom}$, and the efficacy of male circumcision in preventing HIV acquisition among susceptible males ($E_{mc}$). The distributions were used to calculate the country-specific means and 95% CIs of $f_{ext}$ across SSA. Further description of the uncertainty analysis can be found in SOA.

To explore the impact of alternative assumptions to our model assumptions, we conducted a sensitivity analysis for $f_{ext}$ by varying $\phi$ and $\lambda$ over a range starting from half to twice the values for these measures (figure 1B). We also conducted an additional sensitivity analysis where we examined the variation of $f_{ext}$ across a spectrum of values for $\lambda$ and $\phi$ (section IV and figure S1 of SOA).

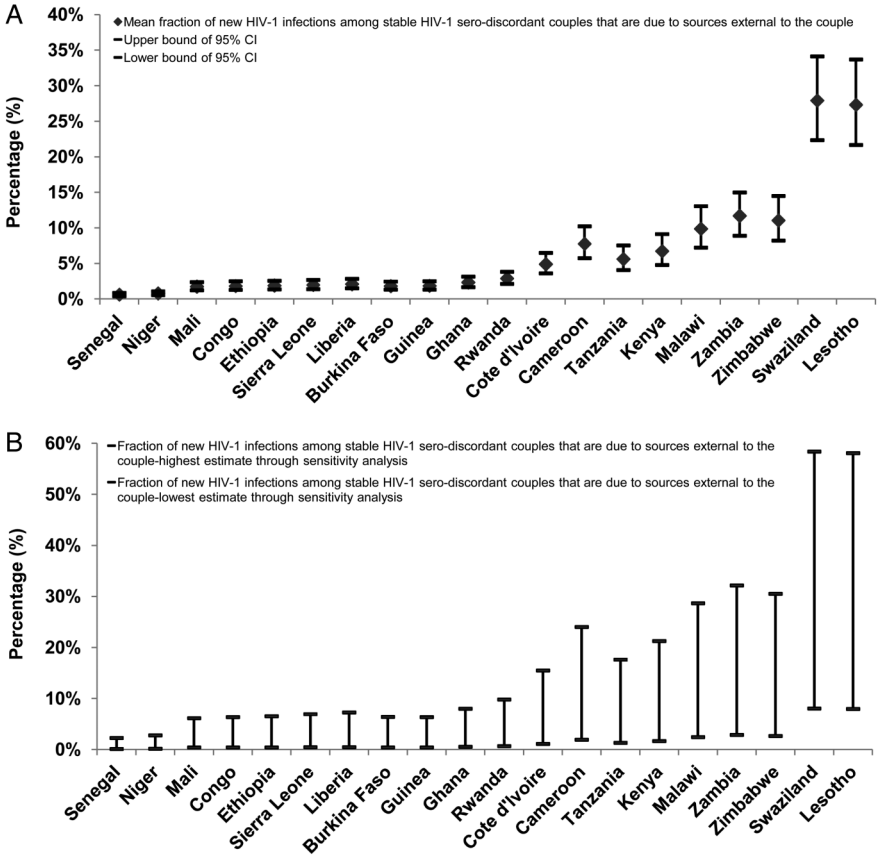


**Figure 1** Fraction of new HIV-1 infections among stable HIV-1 sero-discordant couples that are due to sources external to the couple ($f_{ext}$) across sub-Saharan Africa (SSA). (A) Country-specific means and 95% CIs for $f_{ext}$ across 20 countries in SSA. (B) Country-specific ranges for $f_{ext}$ using a sensitivity analysis on our model assumptions. Countries are shown in order of increasing HIV-1 prevalence. This figure is only reproduced in colour in the online version.

## RESULTS

Figure 1A and online supplementary table S1 show the estimates for the country-specific $f_{ext}$. In low HIV prevalence countries (≤3.0%), $f_{ext}$ had a range of 0.6–2.9%. In intermediate prevalence countries (3.0–18.0%), the range was 4.9–11.7%. In Swaziland and Lesotho, the world's most-intense epidemics, high levels of 27.9% and 27.3% were found, respectively. The uncertainty analysis showed narrow CIs particularly in low to intermediate HIV prevalence countries (figure 1A). The sensitivity analyses showed that overall $f_{ext}$ is unlikely to exceed 30% even with extreme variations in our model assumptions, and that for most countries $f_{ext}$ is no more than just few percentage points (figure 1B and figure S1 of SOA).

## DISCUSSION

In most countries in SSA, nearly all new HIV acquisitions by the uninfected partners in SDCs appear to be due to transmissions from the HIV infected partners in the SDCs. The contribution of external infections to SDCs is minimal and substantially lower than what has been observed recently in RCTs involving SDCs.[1 2]

However, the risk of HIV acquisition from external partners varies across SSA, and depends strongly on HIV prevalence in the population (figure 1). While less than 3% of HIV infections are from external partners in low prevalence countries, as much as 12% of infections are externally acquired in intermediate prevalence countries. Moreover, in the high-prevalence countries of Swaziland and Lesotho, the contribution of external partnerships reaches sizable levels, comparable to those measured in the RCTs.[1 2] These findings were found robust to the limitations in our knowledge of some of the model parameters as the uncertainty analysis in figure 1A demonstrates.

We have tested our model by applying it to a specific site with robust empirical data: Rakai, Uganda. Our estimate for $f_{ext}$ in Rakai agreed nicely with the data from the Rakai Study. In this setting, HIV population-level incidence rate ($\lambda$) was reported to be 1.5 per 100 person-years,[11] and the annual risk of HIV transmission within an SDC ($\phi$) to be 9.2 per 100 person-years.[12] Accordingly using our model, the contribution of external infections to HIV incidence among SDCs is estimated at 14%. Phylogenetic analysis was performed in the Rakai Study, by sequencing the gag (p24) and gp41 regions, to establish the level of HIV viral linkage within the couples, and accordingly estimate $f_{ext}$.[13] It was found that 86% of HIV transmissions were strongly or moderately linked.[13] This suggests that $f_{ext}$ is of the order of 15%, a value that is, in close agreement with our estimate.

The strong dependence of $f_{ext}$ on HIV prevalence is easily understood considering that $\lambda$ depends on the likelihood of forming a partnership with an HIV infected individual, and that the probability of selecting at random an HIV infected individual in a given population, that is, HIV population prevalence, varies widely across SSA. Indeed, it is 50 times higher in Lesotho, with an HIV prevalence of 23.0%, compared to Senegal, with an HIV prevalence of only 0.5%.

Although $\phi$ and $\lambda$ vary across the countries, these variations had minimal impact on our conclusion that $f_{ext}$ is overall small except in countries at high HIV prevalence (see eg, online supplementary figure S1). It bears notice that our country-specific estimates for $\phi$ are consistent with available empirical measures and are at the mid-range of the reported values.[8–10]

Our findings suggest that the values found recently in RCTs[1 2] are not representative of the population-based $f_{ext}$ in the majority of countries. Sero-status disclosure, intensive counselling, and access to prevention methods may explain the larger $f_{ext}$ in RCTs. For instance, sero-disclosure in the Partners in Prevention RCT resulted in a reduction in sexual activity within the SDC and an increased engagement of the uninfected partners in external partnerships.[14] This is affirmed by the low HIV incidence rate among SDCs that has been reported in these RCTs (~2 per 100 person-years),[1 2] which is much smaller than that observed in observational studies (~10 per 100 person-years).[8 10] These considerations indicate that the large values of $f_{ext}$ reported in these RCTs are on the extreme end of the actual values for $f_{ext}$ in the wider population across SSA.

The essential assumption in our methodology is that the risk of infection from external sources does not vary substantially based on the individual's marital status, or engagement in a concordant negative couple versus an SDC. The validity of this assumption is not known, but empirical data from the Rakai Study suggests its plausibility. In Rakai, the risk of HIV acquisition per person was 0.5% (95% CI 0.3% to 0.8%) in round I prior to antiretroviral therapy availability among persons in concordant negative couples, versus 0.7% (95% CI 0.4% to 1.0%) among unmarried persons (over about 14 months of follow-up). These estimates were calculated from the data in Gray *et al*.[5] In round II post antiretroviral therapy availability, it was 0.7% (95% CI 0.5% to 0.9%) versus 1.1% (95% CI 0.8% to 1.4%) (over about 18 months of follow-up). These values suggest that the risk of external infection among persons in stable couples is comparable, though possibly somewhat lower, than those among unmarried persons. If married persons engage in less extra-marital sex than unmarried persons, this would further lower our $f_{ext}$ estimates.

On the other hand, it is reasonable to assume that HIV sero-status disclosure can increase the risk of external infection among SDCs in comparison to concordant negative stable couples.[14] However, the low levels of condom use at last sex reported by the couples in the DHS databases (table S1 of SOA) suggest that sero-disclosure is rather limited in the wider population in SSA. Hence, the actual current levels of sero-disclosure in SSA are not likely to affect our conclusion.

The risk of acquiring HIV from external sources may vary by age, since HIV incidence rate is strongly dependent on age, and thus may affect our estimates for $f_{ext}$. We examined the age distribution of SDCs across the SSA countries included in our analysis. The mean age of females in SDCs was found overall to be in the range of 25–35 years with an average over countries of 30.5 years. As for males, it was overall in the range of 35–45 years with an average over countries of 38.7 years. These results were invariable regardless of whether the index partner was a female or a male. By comparing these age distributions to empirical measures of HIV incidence-rate age distribution across different settings in SSA,[15 16] we found that HIV incidence rate among these SDCs age groups to be substantially lower than that in the younger age groups and comparable to the overall HIV incidence rate. Indeed, close to half of all HIV infections in SSA are among those younger than 25 years of age, and females acquire HIV at an earlier age group than males.[15–17] These considerations suggest that it is unlikely that the variability in the age distribution of HIV incidence rate will noticeably affect our analysis.

A fraction of HIV population-level incidence rate arises from the incidence of HIV among SDCs. Eliminating this contribution from HIV population incidence rate would further reduce the likelihood of acquiring HIV from external sources among SDCs and hence lower our estimates for $f_{ext}$. This further suggests that our estimates for $f_{ext}$ are more likely to overestimate

rather than underestimate the actual contribution of external infections among SDCs.

On balance, the discussion above suggests the overall validity of our assumptions. Moreover, even considerable deviations to these assumptions are not likely to affect our conclusion of modest role for external infections as shown in the sensitivity analyses (figure 1B and online supplementary figure S1).

To sum up, $f_{ext}$ varies substantially across SSA, but is generally below 10% in most countries. Only in hyperendemic HIV epidemics the contribution of external infections is sizable and may reach up to 30%. The vast majority of HIV acquisitions among SDCs are transmissions from the infected to the susceptible partner. These findings however should not be overinterpreted to believe that HIV incidence within SDCs dominates HIV incidence in the population.

## Key messages

- Nearly all of HIV incidence among stable HIV-1 sero-discordant couples (SDCs) in most countries in sub-Saharan Africa (SSA) appears to be attributed to HIV transmission from the infected to the uninfected partner in the couple.
- The fraction of externally acquired HIV infections among stable HIV-1 SDCs strongly depends on HIV prevalence in the population and varies across SSA.
- Only in hyperendemic HIV epidemics, the contribution of external infections among stable HIV-1 SDCs is sizable and may reach up to 30%.

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**Contributors** HC managed the DHS databases, conducted the bulk of the statistical and mathematical modelling analyses, and wrote the first draft of the paper. LJA conceived and designed the study and led the analyses and drafting of the article.

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# Supplementary Online Appendix

# External infections contribute minimally to HIV incidence among HIV sero-discordant couples in sub-Saharan Africa

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## I. Model structure

We constructed a mathematical model to calculate the fraction of new HIV-1 infections among stable HIV-1 sero-discordant couples (SDCs) that are due to sources external to the couple. This was done by comparing the annual risk of an HIV sero-negative individual in an SDC to acquire the infection from the infected partner in the couple, to that of the annual risk of acquiring it from a source external to the couple.

### A. Acquiring HIV infection from the infected partner in the stable HIV-1 sero-discordant couple

The annual risk of HIV transmission from the infected to the uninfected partner in a stable HIV-1 sero-discordant couple ($\phi$) is determined by HIV transmission probability per coital act ($p$), number of coital acts per year ($n$), fraction of coital acts protected by condom use ($f_{condom}$), efficacy of condoms in preventing HIV transmission per sexual act ($E_{condom}$), fraction of HIV infected females among the SDCs ($f_{index}$), and fraction of males that are circumcised in SDCs with HIV infected females ($f_{mc}$). Consequently, in a partnership between an HIV infected male and a susceptible female, or in a partnership between an HIV infected female and a susceptible uncircumcised male, $\phi$ is given by:

$$\phi_1 = 1-(1-p)^{(1-f_{condom})n}\left(1-(1-E_{condom})\,p\right)^{f_{condom}n}.$$

Meanwhile, in a partnership between an HIV infected female and a susceptible circumcised male, $\phi$ is given by:

$$\phi_2 = 1-\left(1-\left(1-E_{mc}\right)p\right)^{\left(1-f_{condom}\right)n}\left(1-\left(1-E_{condom}\right)\left(1-E_{mc}\right)p\right)^{f_{condom}n}.$$

Here $E_{mc}$ is the efficacy per sexual act of male circumcision in preventing HIV acquisition among susceptible males.

To account for the effect of male circumcision, $\phi$ was determined as a weighted population average of the annual risk of HIV transmission from the infected to the uninfected partner in an SDC with and without male circumcision using the relation:

$$\phi = \left(1-f_{index}\right)\phi_1 + f_{index}\left(1-f_{mc}\right)\phi_1 + f_{index}f_{mc}\phi_2.$$

**B. Acquiring HIV infection from an external source**

We assumed that the annual risk of any susceptible individual in the population to acquire HIV infection ($\lambda$), that is the hazard rate of infection or HIV incidence rate, is approximately equal among an individual in a stable couple versus an individual not in a stable couple. Similarly, we assumed that the annual risk of a susceptible individual in a stable concordant negative couple to acquire HIV infection from an external source to the couple is approximately equal to the annual risk of an HIV sero-negative individual in an SDC to acquire the infection from a source external to the couple. Accordingly, $\lambda$ can be approximated by HIV population-level incidence rate.

**C. Fraction of new HIV-1 infections among stable HIV-1 sero-discordant couples that are due to external sources**

Using competing hazards, the fraction of new HIV-1 infections among SDCs that are due to sources external to the couple ( $f_{ext}$ ) is given by:

$$f_{ext} = \frac{\lambda}{(\lambda + \phi)}.$$

## II. Model parameterization

Our value for the HIV transmission probability per coital act ( $p$ ) is based on the average of the empirical measures for this parameter as available from the Rakai Study [1] and the Partners in Prevention HSV/HIV Transmission Study (Partners in Prevention Study) [2-4] (Table S2). These studies are considered state of the art empirical studies for estimating $p$ and were conducted among SDCs in sub-Saharan Africa.

The country-specific HIV population-level incidence rate, for the specific year in which the Demographic and Health Survey (DHS) was conducted, was obtained from the Joint United Nations Programme on HIV/AIDS (UNAIDS) SPECTRUM model predictions [5, 6]. For countries where estimates from SPECTRUM are not available or where the bounds of the 95% confidence interval are not precisely specified, the HIV population-level incidence rate was derived from the DHS HIV-1 prevalence in the population ( $\mathcal{P}$ ) assuming a stable HIV epidemic and using the relation:

$$\lambda = \frac{\mathcal{P}}{Duration\ of\ \ infection}$$ [7].

This equation can be derived using the simplest possible deterministic model for HIV population-level transmission dynamics at endemic equilibrium (susceptible-infected (SI) model

[8]). The approximation expressed by this equation works best if HIV prevalence is stable or is slowly varying, and is not a good approximation in emerging epidemics where HIV prevalence is growing swiftly, or when HIV prevalence is declining rapidly. The duration of HIV infection in this expression is estimated at 11 years [9]. It bears notice that for the vast majority of countries, including those where SPECTRUM estimates are available, estimates predicted by the SPECTRUM model or derived using the DHS data using this approximation were either similar or within the confidence intervals of each other.

The values of the different model parameters are listed in Tables S1 and S2 below.

**Table S1.** Key epidemiological and demographic measures used for the parameterization of the model, and key model results for 20 countries in sub-Saharan Africa. Countries are shown in order of increasing HIV prevalence.

| Country | Year of the DHS survey | HIV prevalence ($\mathscr{P}$, measured by DHS)[*] | HIV prevalence ($\mathscr{P}$, predicted by SPECTRUM)[‡] | Fraction of HIV infected females in SDCs[§] ($f_{index}$)[*] | Fraction of circumcised males in SDCs[§] with HIV infected females ($f_{mc}$)[*] | Condom use at last sexual act among stable couples ($f_{condom}$)[*] | Annual risk of an HIV sero-negative individual in an SDC[§] to acquire the infection from a source external to the couple (HIV population-level incidence rate per 100 person-years) ($\lambda$) | Annual risk of HIV transmission within an SDC[§] ($\phi$)[@] | Mean fraction of new HIV-1 infections among SDCs[§] that are due to sources external to the couple ($f_{ext}$)[@] |
|---|---|---|---|---|---|---|---|---|---|
| Senegal | 2005 | 0.54% | 0.80% | 38.29% | 100.00% | 1.47% | 0.05[†] | 0.084 | 0.61% |
| Niger | 2006 | 0.68% | 0.90% | 38.94% | 91.14% | 0.19% | 0.06[†] | 0.086 | 0.79% |
| Mali | 2006 | 1.20% | 1.10% | 72.12% | 94.18% | 0.74% | 0.11[†] | 0.066 | 1.74% |
| Congo | 2007 | 1.27% | …[£] | 64.78% | 100.00% | 1.94% | 0.12[†] | 0.068 | 1.82% |
| Ethiopia | 2005 | 1.43% | …[£] | 56.01% | 98.87% | 0.22% | 0.13[†] | 0.074 | 1.89% |
| Sierra Leone | 2008 | 1.47% | 1.60% | 58.75% | 100.00% | 0.99% | 0.13[†] | 0.072 | 1.97% |
| Liberia | 2007 | 1.50% | 1.80% | 61.59% | 100.00% | 2.51% | 0.14[†] | 0.069 | 2.09% |
| Burkina Faso | 2003 | 1.54% | 1.70% | 40.81% | 95.66% | 4.16% | 0.14[†] | 0.082 | 1.82% |
| Guinea | 2005 | 1.57% | 1.50% | 40.97% | 93.55% | 0.83% | 0.14[†] | 0.084 | 1.85% |
| Ghana | 2003 | 2.04% | 2.10% | 45.59% | 100.00% | 3.38% | 0.17[‡] | 0.078 | 2.33% |
| Rwanda | 2005 | 3.00% | 3.10% | 36.50% | 32.51% | 1.00% | 0.27[†] | 0.100 | 2.89% |
| Cote d'Ivoire | 2005 | 4.71% | 4.80% | 62.67% | 30.22% | 4.55% | 0.43[†] | 0.093 | 4.90% |
| Cameroon | 2004 | 5.35% | 5.40% | 52.26% | 100.00% | 4.89% | 0.58[‡] | 0.073 | 7.77% |
| Tanzania | 2007-08 | 5.73% | 5.80% | 45.65% | 53.91% | 4.94% | 0.48[‡] | 0.090 | 5.62% |
| Kenya | 2008-09 | 6.36% | 6.30% | 54.12% | 79.15% | 3.35% | 0.54[‡] | 0.080 | 6.73% |
| Malawi | 2010 | 10.67% | 11.00% | 44.95% | 34.96% | 5.49% | 0.95[‡] | 0.095 | 9.87% |
| Zambia | 2007 | 14.21% | 13.70% | 40.28% | 10.59% | 6.56% | 1.19[‡] | 0.100 | 11.70% |
| Zimbabwe | 2005-06 | 18.14% | 17.20% | 40.01% | 8.63% | 2.99% | 1.14[‡] | 0.104 | 11.05% |
| Swaziland | 2008 | 18.89% | 25.80% | 53.00% | 17.83% | 23.89% | 2.94[‡] | 0.084 | 27.92% |
| Lesotho | 2009 | 22.97% | 23.60% | 44.35% | 62.25% | 24.12% | 2.58[‡] | 0.074 | 27.31% |

[*]Estimates derived using DHS [10]; [‡]Estimates predicted using UNAIDS SPECTRUM model [5, 6]; [£]Data not available; [§]SDC: Stable HIV sero-discordant couple; [†]Derived using HIV prevalence as measured by DHS; [@]Calculated using our model

**Table S2.** Further model assumptions in terms of parameter values.

| Assumptions | Parameter values | Source |
|---|---|---|
| HIV transmission probability per coital act ( $p$ ) | | |
| Average ( $p$ ) using the Rakai Study | 0.0012 | [1] |
| Average ( $p$ ) using the Partners in Prevention Study | 0.0011 | [2-4] |
| Average ( $p$ ) using the Rakai and the Partners in Prevention Studies | 0.00115 | Derived |
| Number of coital acts per year ( $n$ ) | 99.6 acts per year | [1] |
| Efficacy of condoms in preventing HIV transmission per sexual act ( $E_{condom}$ ) | 80% | [4, 11] |
| Efficacy of male circumcision in preventing HIV acquisition per sexual act ( $E_{mc}$ ) | 58% | [12-15] |

## III. Uncertainty analysis

Uncertainty analysis was conducted and country-specific likelihood distributions for $f_{ext}$ were generated using Monte Carlo sampling from uniform distributions for the uncertainty ranges of the epidemiological and demographic parameters of the model (Figure 1B of the main text). For 10,000 runs of the model for each country, random values were selected at each run for the confidence intervals or ranges of plausibility for $p$, $n$, country-specific $\lambda$, country-specific $f_{index}$, country-specific $f_{mc}$, country-specific $f_{condom}$, $E_{condom}$, and $E_{mc}$.

The ranges of uncertainty for $\lambda$ were determined by the lower and upper bounds of the 95% confidence interval around this measure as provided by the SPECTRUM model for each country [5, 6]. In the absence of SPECTRUM estimates or in instances where the bounds of the 95% confidence interval around this measure were not precisely specified, the ranges of uncertainty were derived using the confidence intervals around HIV-1 prevalence measures from the DHS databases [10]. Table S3 shows the ranges of uncertainty of the different model parameters. It is noteworthy that in low HIV prevalence countries small number of SDCs were identified in the DHS sample because of the low HIV prevalence. This resulted in wider confidence intervals for

some of the measures. This is especially true for Senegal where only 12 couples were affected by HIV, out of which 7 were found to be discordant (0.40% out of all couples).

**Table S3.** Model assumptions in terms of the ranges of uncertainty for the model parameters. For parameters describing country-specific values, countries are shown in order of increasing HIV-1 prevalence.

| **Assumptions** | **Parameter Range** | **Source** |
|---|---|---|
| HIV transmission probability per coital act ( $p$ ) | 0.0009-0.0015 | [1] |
| Number of coital acts per year ( $n$ ) | 48-144 acts per year | [1, 16] |
| HIV population-level incidence rate per 100 person-years ( $\lambda$ ) | | |
| Senegal | 0.03-0.07 | [10] |
| Niger | 0.05-0.08 | [10] |
| Mali | 0.09-0.14 | [10] |
| Congo | 0.09-0.15 | [10] |
| Ethiopia | 0.11-0.16 | [10] |
| Sierra Leone | 0.11-0.17 | [10] |
| Liberia | 0.12-0.16 | [10] |
| Burkina Faso | 0.11-0.17 | [10] |
| Guinea | 0.12-0.18 | [10] |
| Ghana | 0.14-0.21 | [5, 6] |
| Rwanda | 0.24-0.30 | [10] |
| Cote d'Ivoire | 0.37-0.50 | [10] |
| Cameroon | 0.49-0.67 | [5, 6] |
| Tanzania | 0.37-0.60 | [5, 6] |
| Kenya | 0.36-0.71 | [5, 6] |
| Malawi | 0.67-1.23 | [5, 6] |
| Zambia | 1.01-1.40 | [5, 6] |
| Zimbabwe | 0.86-1.48 | [5, 6] |
| Swaziland | 2.56-3.40 | [5, 6] |
| Lesotho | 2.18-3.04 | [5, 6] |
| Fraction of HIV infected females among stable HIV-1 sero-discordant couples ( $f_{index}$ ) | | |
| Senegal | 9.90-81.59% | [10] |
| Niger | 21.10-56.31% | [10] |
| Mali | 49.82-86.25% | [10] |
| Congo | 47.18-78.80% | [10] |
| Ethiopia | 41.33-69.53% | [10] |
| Sierra Leone | 36.35-79.29% | [10] |
| Liberia | 46.38-75.49% | [10] |
| Burkina Faso | 25.63-56.72% | [10] |
| Guinea | 22.66-59.40% | [10] |
| Ghana | 30.17-59.88% | [10] |
| Rwanda | 23.14-50.20% | [10] |
| Cote d'Ivoire | 49.83-73.71% | [10] |
| Cameroon | 42.03-61.57% | [10] |
| Tanzania | 37.32-54.71% | [10] |
| Kenya | 42.83-65.69% | [10] |
| Malawi | 38.84-50.98% | [10] |
| Zambia | 34.42-46.55% | [10] |

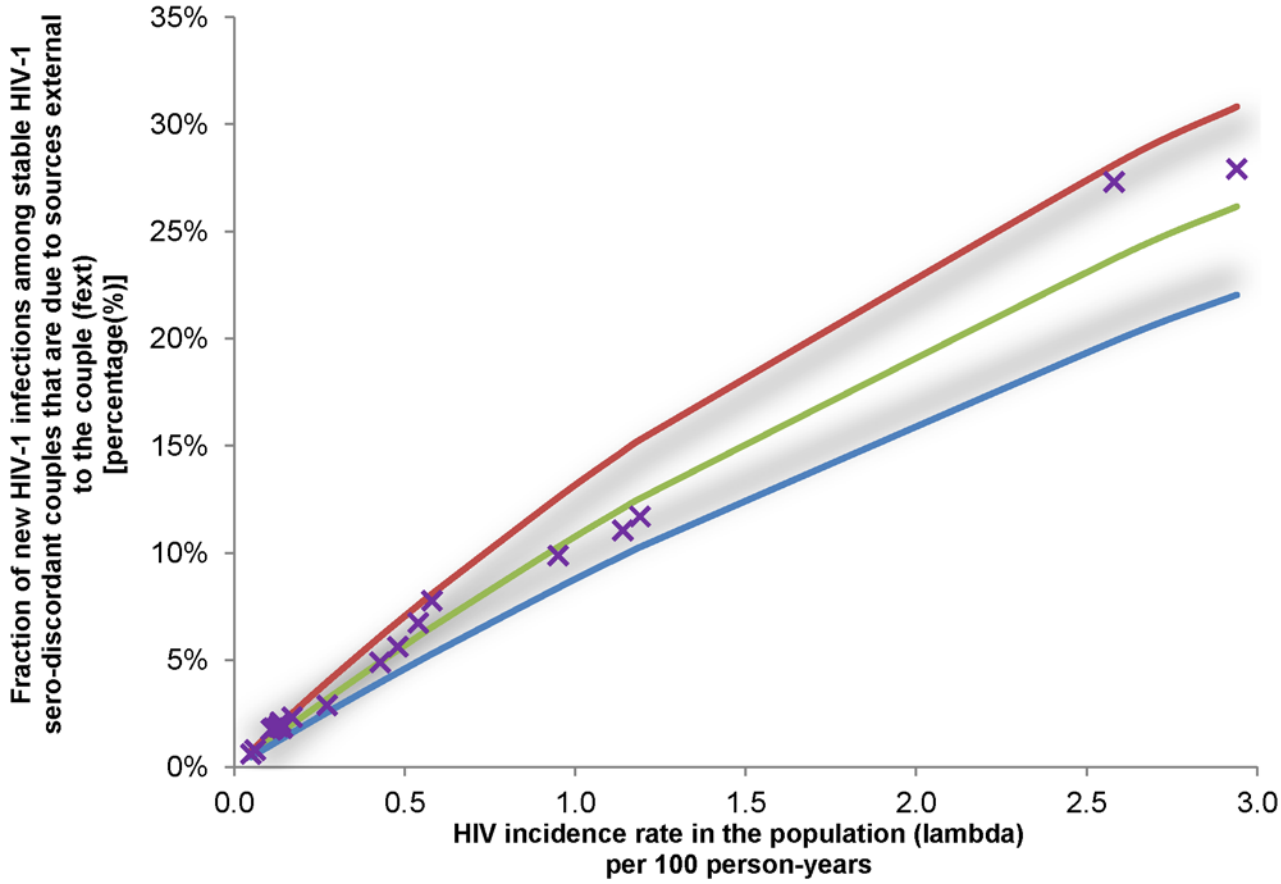
| | | |
|---|---|---|
| Zimbabwe | 33.62-62.32% | [10] |
| Swaziland | 42.99-62.32% | [10] |
| Lesotho | 35.91-52.61% | [10] |
| Fraction of males that are circumcised in stable HIV-1 sero-discordant couples with HIV infected females ( $f_{mc}$ ) | | |
| Senegal | 15.81-100% | [10] |
| Niger | 58.72-99.77% | [10] |
| Mali | 73.97-99.87% | [10] |
| Congo | 84.56-100% | [10] |
| Ethiopia | 81.03-99.91% | [10] |
| Sierra Leone | 76.84-100% | [10] |
| Liberia | 87.66-100% | [10] |
| Burkina Faso | 75.13-99.87% | [10] |
| Guinea | 58.72-99.77% | [10] |
| Ghana | 83.16-100% | [10] |
| Rwanda | 11.89-54.28% | [10] |
| Cote d'Ivoire | 17.18-46.13% | [10] |
| Cameroon | 93.84-100% | [10] |
| Tanzania | 40.12-66.02% | [10] |
| Kenya | 62.39-89.44% | [10] |
| Malawi | 26.07-44.40% | [10] |
| Zambia | 5.82-18.44% | [10] |
| Zimbabwe | 3.79-16.25% | [10] |
| Swaziland | 8.44-28.97% | [10] |
| Lesotho | 49.51-74.30% | [10] |
| Fraction of coital acts protected by condom use ( $f_{condom}$ ) | | |
| Senegal | 0.87-2.36% | [10] |
| Niger | 0.05-0.50% | [10] |
| Mali | 0.44-1.17% | [10] |
| Congo | 1.37-2.62% | [10] |
| Ethiopia | 0.07-0.48% | [10] |
| Sierra Leone | 0.51-1.72% | [10] |
| Liberia | 1.90-3.31% | [10] |
| Burkina Faso | 3.26-5.26% | [10] |
| Guinea | 0.44-1.49% | [10] |
| Ghana | 2.54-4.37% | [10] |
| Rwanda | 0.61-1.51% | [10] |
| Cote d'Ivoire | 3.49-5.92% | [10] |
| Cameroon | 3.96-5.98% | [10] |
| Tanzania | 4.17-5.83% | [10] |
| Kenya | 2.39-4.50% | [10] |
| Malawi | 4.74-6.32% | [10] |
| Zambia | 5.59-7.68% | [10] |
| Zimbabwe | 2.28-3.90% | [10] |
| Swaziland | 20.59-27.27% | [10] |

| | | |
|---|---|---|
| Lesotho | 21.18-27.34% | [10] |
| Efficacy of condoms in preventing HIV transmission per sexual act ( $E_{condom}$ ) | 70-95% | [11] |
| Efficacy of male circumcision in preventing HIV acquisition per sexual act ( $E_{mc}$ ) | 43-69% | [12] |

## IV. Additional sensitivity analysis

Figure S1 presents the variation of $f_{ext}$ with $\lambda$ (that is HIV population-level incidence rate) at variable levels of $\phi$. $f_{ext}$ increases monotonically with increasing $\lambda$. Furthermore, country-specific variations in $\phi$ appear to have a minimal effect on the scale of $f_{ext}$. The red and the blue lines in Figure S1 mark the extreme low and high values of $\phi$ across all included countries (6.6 to 10.4 per 100 person-years) while the green line marks the median value of $\phi$ (8.3 per 100 person-years). The results of this sensitivity analysis affirm that the values of $f_{ext}$ are likely to be small across sub-Saharan Africa except in areas of high HIV incidence rate.

**Figure S1.** Variation of the fraction of new HIV-1 infections among SDCs that are due to sources external to the couple ( $f_{ext}$ ) with respect to HIV incidence rate in the population ( $\lambda$ ) and the annual risk of HIV transmission from the infected to the uninfected partner within a stable discordant couple ( $\phi$ ). The red and the blue lines in the figure mark the extreme low and high values of $\phi$ across all included countries in this analysis (6.6 to 10.4 per 100 person-years). The green line marks the estimates for $f_{ext}$ at the median value of $\phi$ (8.3 per 100 person-years). The actual predictions for each country are included with the symbol "×".


Fraction of new HIV-1 infections among stable HIV-1 sero-discordant couples that are due to sources external to the couple (fext) [percentage(%)]
35%
30%
25%
20%
15%
10%
5%
0%
0.0
0.5
1.0
1.5
2.0
2.5
3.0
HIV incidence rate in the population (lambda) per 100 person-years

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