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 (ϕ) 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, ϕ 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, ϕ 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, ϕ 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 (λ), 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, λ 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) (λ)	Annual risk of HIV transmission within an SDC[§] (ϕ)[@]	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 λ, country-specific f_{index}, country-specific f_{mc}, country-specific f_{condom}, E_{condom}, and E_{mc}.

The ranges of uncertainty for λ 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 (λ)		
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]

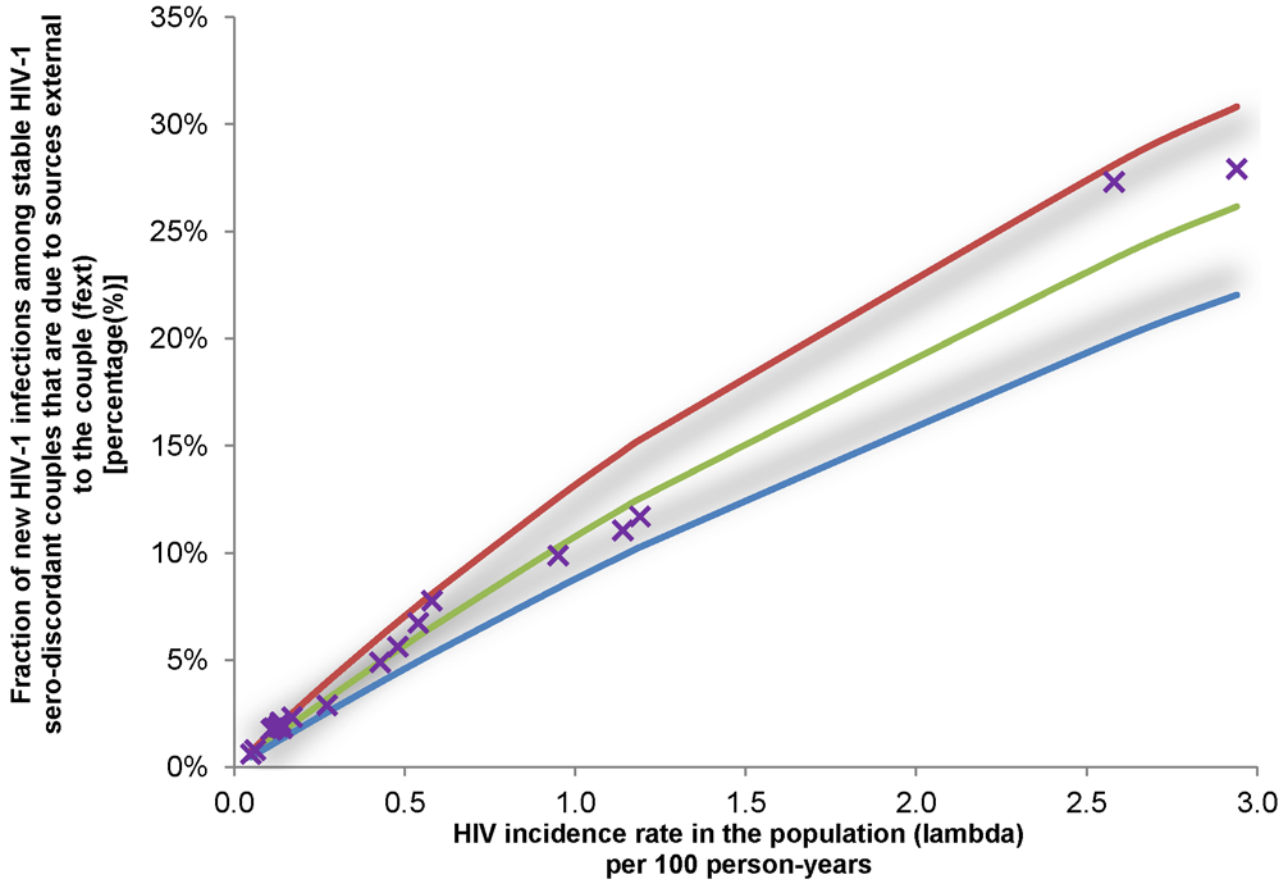
Zimbabwe	33.62-62.32%	[10]
Swaziland	42.99-62.32%	[10]
Lesotho	35.91-52.61%	[10]
Fraction of males that are circumcised in stable HIV-1 sero-discordant couples with HIV infected females (f_{mc})		
Senegal	15.81-100%	[10]
Niger	58.72-99.77%	[10]
Mali	73.97-99.87%	[10]
Congo	84.56-100%	[10]
Ethiopia	81.03-99.91%	[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 λ (that is HIV population-level incidence rate) at variable levels of ϕ. f_{ext} increases monotonically with increasing λ. Furthermore, country-specific variations in ϕ 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 ϕ across all included countries (6.6 to 10.4 per 100 person-years) while the green line marks the median value of ϕ (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 (λ) and the annual risk of HIV transmission from the infected to the uninfected partner within a stable discordant couple (ϕ). The red and the blue lines in the figure mark the extreme low and high values of ϕ 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 ϕ (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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