Behaviour change in generalised HIV epidemics: The impact of reducing cross-generational sex and delaying age of sexual debut

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SUPPLEMENTARY MATERIAL

Full Description of the Mathematical Model

The model is defined by a set of partial differential equations with respect to time and age that are solved numerically with a four-stage Runge-Kutta algorithm (time-step = 0.02 years). The population is stratified by gender (k=1 for males, k=2 for females) and sexual activity (m=0 (lowest) to 4 (highest)). The model treats HIV infection status as either HIV negative (X), HIV acute infection (Y^1), latent infection (Y^2), pre-AIDS (Y^3) or full blown AIDS (Z). The model is run for 100 years to establish a stable population structure before the introduction of infection with 0.01% of males aged 25-29 years in the highest sexual activity group moving from X to Y^1.

The partial differential equations are:

$$\frac{\partial X_{k,m}}{\partial t}+\frac{\partial X_{k,m}}{\partial a}=-X_{k,m}\left(\mu_k(a).+\lambda_{k,m}(a,t)\right)$$

$$\frac{\partial Y^1_{k,m}}{\partial t}+\frac{\partial Y^1_{k,m}}{\partial a}=\lambda_{k,m}(a,t).X_{k,m}-Y^1_{k,m}\left(\mu_k(a)+\upsilon_1\right)$$

$$\frac{\partial Y^2_{k,m}}{\partial t}+\frac{\partial Y^2_{k,m}}{\partial a}=\upsilon_1(a).Y^1_{k,m}-Y^2_{k,m}\left(\mu_k(a)+\upsilon_2(a)\right)$$

$$\frac{\partial Y^3_{k,m}}{\partial t}+\frac{\partial Y^3_{k,m}}{\partial a}=\upsilon_2(a).Y^2_{k,m}-Y^3_{k,m}\left(\mu_k(a)+\upsilon_3\right)$$

$$\frac{\partial Z_{k,m}}{\partial t}+\frac{\partial Z_{k,m}}{\partial a}=\upsilon_3 Y^3_{k,m}-Z_{k,m}(\mu_k(a)+\alpha)$$

$\mu_k(a)$ is the gender and age-specific per-capita death rate; $\lambda_{k,m}(a,t)$ is the force of infection to individuals of that gender, age and activity-group at time t; $\frac{1}{\upsilon_1},\frac{1}{\upsilon_2(a)}$ and $\frac{1}{\upsilon_3}$ are the mean number of years spent with acute infection, latent infection and pre-AIDS, respectively; $\alpha(a)$ is the AIDS-associated mortality rate.

At each moment, the number of new-borns introduced into each gender and sexual activity-group in the population is:

$$X_{k,m}(0,t) = \varpi_k \gamma_m \int \varphi(a) \sum_m X_{2,m}(a,t)da + (1-\sigma)\int \varphi(a) \sum_m \left[Y^1_{2,m}(a,t) + Y^2_{2,m}(a,t) + Y^3_{2,m}(a,t)\right]da$$

$$Y^1{}_{k,m}(0,t) = \varpi_k \gamma_m \sigma \int \varphi(a) \sum_m \left[Y^1_{2,m}(a,t) + Y^2_{2,m}(a,t) + Y^3_{2,m}(a,t)\right]da$$

where $\varphi(a)$ is the age-specific fertility (assumed to be the same for uninfected and infected females), σ is the probability of mother to child transmission, ϖ_k is the fraction of babies born that gender and γ_m is the fraction of babies born into that sexual activity-group.

The risk of a susceptible individual becoming infected is a function of the yearly age-group rather than a continuous function of age such that: $\lambda_{k,m}(i-0.5 \le i < i+0.5, t) = F_{k,i,m}(t)$. We define the pattern of contact within the population through a matrix determining the age and activity group-specific rates of partnership formation with the age and activity groups of the opposite gender. Here one's own age and activity category is denoted *i* and *m*, respectively, and those of members of the opposite gender are distinguished with a prime (*i'* and *m'*).

$$F_{k,i,m}(t) = \sum_{m'} \sum_{i'} \left(c_{k,i,m,i',m'}(t).P_{k',i',m'}(t).\left(1-\psi_{i,i',m,m'}\right)\right)$$

where $c_{k,i,m,i',m'}$ is the number of partnerships formed with individuals of the opposite gender by age and activity group, $P_{k',i',m'}$ is the risk of acquiring infection when forming partnerships with individuals of the opposite gender by age and sexual activity, and $\psi_{i,m,i',m'}$ is the chance that condoms are used consistently in partnerships formed between such individuals. The definition of each of these terms follows.

The distribution of partnerships $c_{k,i,m,i',m'}$ is calculated by sharing the total number of partnerships that are allocated to individuals in each gender, age and activity group, $C_{k,i,m}$,amongst the age and activity groups of the opposite gender.

$$c_{k,i,m,i',m'} = C_{k,i,m}\left[(1-\varepsilon)\delta_{m,m'} + \varepsilon\left\{\frac{N_{k',i',m'}C_{k',i',m'}}{\sum_{m'} N_{k',i',m'}C_{k',i',m'}}\right\}\right]\Delta_{k,i,i'}$$

$$N_{k,i,m} = \int_{i-0.5}^{i+0.5} X_{k,m}(a,t) + Y^1_{k,m}(a,t) + Y^2_{k,m}(a,t) + Y^3_{k,m}(a,t)da$$

where and $\delta_{m,m'}$ is the identity matrix. Thus the pattern of mixing with respect to activity ranges from assortative (like-with-like, ε=0) to random (ε=1) and the pattern of mixing with respect to age is determined by the distribution $\Delta_{k,i,i'}$ - the fraction of an *i*-aged individual's partnerships that are formed with individuals of age *i*'. Data from rural Zimbabwe (1) indicates the distribution of age-difference between partners does not depend on the age of female (Figure S1). Here we assume that $\Delta_{k,i,i'}$ depends only on the age difference between partners: which for females is:

$$\Delta_{2,i,i'} = \frac{\kappa\rho^{\kappa}(i'-i+r)^{\kappa-1}}{1+((i'-i+r)^{\kappa})^{2}} \quad \text{if } i' > \text{i}$$

$$\Delta_{2,i,i'} = 0 \qquad \text{otherwise}$$

And for males is:

$$\Delta_{1,i,i'} = \sum_{i'} \Delta_{2,i',i}$$

$\Delta_{k,i,i'}$ is scaled so that $\sum_{A_2'}^{B_2'} \Delta_{k,i,i'} = 1$ where A_k and B_k are the ages at which sexual activity begins and ends for that gender, respectively. Here κ, ρ and r are the shape parameters for the log-logistic distribution. This distribution allows most partnerships to be formed between women and men a few years older but a few partnerships to involve women and men many more years their senior. The distribution was parameterised by fitting to cross-sectional survey data collected in rural Zimbabwe (Figure S2).

The rate of partnership formation in the sexual activity groups is defined as:

$$C_{k,i,m} = \frac{M_{k,i}}{\tau^{\sum m\gamma_m}} \tau^{m}$$

Here $M_{k,i}$ is the gender- and age-specific geometric mean of partnership formation rate and τ independently determines the common ratio of partner change rate between the sexual-activity categories.

At each moment, the pattern of partnership formation ($c_{i,m,i',m'}$) is constrained such that the total number of sexual partnerships formed by males of type *i,m* with females type *i',m'* must equal the total number of partnerships formed by females of type *i',m'* with males of type *i,m*. That is,:

$$N_{1,i,m} c_{1,i,m,i',m'} = N_{2,i',m'} c_{2,i',m',i,m}$$

where $N_{k,i,m}$ is the number of sexually active individuals of that gender, age and activity-group.

If this does not hold $c_{1,i,m,i,m}$ and $c_{2,i,m,i,m}$ are adjusted (denoted with *):

$$D = \frac{N_{1,i,m} c_{1,i,m,i',m'}}{N_{2,i',m'} c_{2,i',m',i,m}}$$

$$c_{1,i,m,i',m'} \rightarrow c_{1,i,m,i',m'} D^{-(1-\theta)}$$

$$c_{2,i',m',i,m} \rightarrow c_{2,i',m',i,m} D^{\theta}$$

In this way θ determines whether the demand for sexual partnerships of males ($0.5 < \theta \leq 1$) or females ($0 \leq \theta < 0.5$) is the strongest determinant of the pattern of partnership formation.

The other two components of $F_{k,i,m}(t)$ are the chance of infection per partnership and the probability that condom are used correctly and consistently throughout those sexual partnerships.

The probability of getting infected through sexual partnerships with individuals of the opposite gender aged *i* and in sexual activity group *m*, is $P_{k,i',m'}(t)$:

$$P_{k,i,m}(t) = \frac{\int_{i-0.5}^{i+0.5} \beta^1 Y_{k,i}^1(a,t) + \beta^2 Y_{k,m}^2(a,t) + \beta^3 Y_{k,m}^3(a,t) + \beta^4 Z_{k,m}(a,t)da}{\int_{i-0.5}^{i+0.5} X_{k,m}(a,t) + Y_{k,m}(a,t) + Y_{k,m}^2(a,t) + Y_{k,m}^3(a,t) + Z_{k,m}(a,t)da}$$

where β^1, β^2, β^3 and β^4 are the probabilities per partnership of transmission of HIV during acute infection, latent infection, pre-AIDS and AIDS respectively.

We assume that condom use is protective of infection if they are used consistently with the partnership. For simplicity we assume that the fraction of partnerships in which condoms used consistently $(\psi_{i,i',m,m'})$ depends on the age of both sexual partner and the sexual activity group of the individual in the highest (most active) sexual activity group. These values are shown in the main paper (Figure 3(a)).

Calculating Lifetime Risk

The lifetime risk of infection with HIV *R* is the expected probability at birth that an individual will have been infected with HIV by their 55th birthday. The measure is taken 10 years after the intervention is implemented (at time T).

$$R_k = 1 - \prod_{i=0}^{i=55} \left(1 - \Gamma_{k,i}(T+10)\right)$$

$$\Gamma_{k,i}(t) = \sum_m \left(\frac{N_{k,i,m}(t)}{\sum_m N_{k,i,m}(t)} \lambda_{k,i,m}(t) \right)$$

Interventions are evaluated by the relative lifetime risk of infection with an intervention ($R_{intervention}$) relative to the case when there is no intervention ($R_{baseline}$), which we call *RR*.

$$RR = \frac{R_{\text{intervention}}}{R_{baseline}}$$

Intervention Scenarios

- Changes in cross-generational mixing

  The parameterisation of the pattern of partnership formation with respect to age ($\Delta_{k,i,i'}$) is varied to create a range of scenarios of cross-generational mixing (Figure S3). To simulate 'peer-to-peer mixing', individuals enter the population in yearly cohorts and form partnerships exclusively within their own cohort. The intervention which reduces the proportion of partnerships that are cross-generational from 25% to 5% is simulated (i) by changing the parameterisation of the mixing distribution $\Delta_{k,i,i'}$ and (ii) by blocking transmission of HIV in all but 5% of cross-generational partnerships.

- Changes in age at first sex

  The parameter A_k specifies the age at which individuals of that gender begin sexual activity. When age at first sex is delay by J_k years the distribution of sexual partnership becomes:

  $$c_{1,[A_1,A_1+J_1],m,i',m'} = 0$$
  $$c_{2,[A_2,A_2+J_2],m,i',m'} = 0$$

  If males seek to maintain their current number of sexual partnerships formed per year then the following change is also made:

  $$c_{1,i,m,[A_2,A_2+H],m'} \to c_{1,i,m,[A_2,A_2+H],m'} + \frac{\sum_{i'=A_2}^{A_2+J_2} c_{1,i,m,i',m'}}{H}$$

  This allows males to seek to recoup the sexual partnerships they lost when their young would-be partners became abstinent from the sexual partnerships offered by young women in the first *H* years of sexually activity.

  Where we assume that the biological susceptibility of women decreases with older age, we multiply the probability of transmission to women in those partnerships by some factor, ω2(a) which depends on female age, a.

$\omega_2(a) = 1.5$	$a \leq 14$
$\omega_2(a) = (1.5 - (a-14)*0.0625)$	$15 \leq a \leq 22$

$\omega_2(a) = 1.0$ $\qquad\qquad$ $a > 22$

The importance of timing of marriage is addressed with an alternative model which simply calculates risk of infection as:

Risk of infection = 1- [(1-risk infection per year when single)$^{\text{years before marriage}}$.(1-risk infection per year when married)$^{\text{years after marriage}}$]

where: Years after marriage = Years sexually active – Years before marriage

The ‘Years sexually active’ is set at 55 and data from Zimbabwe (2) suggest that the risk of infection for sexually active unmarried women and sexually active married women are approximately 0.02 and 0.01 per person-years at risk, respectively.

- <u>Changes in condom use</u>

The probability that condoms are used consistently in sexual partnerships $\psi_{i,i',\max(m,m')}$ is altered as follows for each of the intervention tried:

(i) ‘Increase condom use overall’ $\quad$ $\psi_{1,i,i',\max(m,m')} \rightarrow 2\psi_{1,i,i',\max(m,m')}$

(ii) ‘Increase condom use among older men’ $\quad$ $\psi_{1,[25,B_1],i',\max(m,m')} \rightarrow \psi_{1,24,i',\max(m,m')}$

$\psi_{2,i,[25,B_1],\max(m,m')} \rightarrow \psi_{2,i,24,\max(m,m')}$

References

1. Gregson S, Nyamukapa CA, Garnett GP, Mason PR, Zhuwau T, Carael M, et al. Sexual mixing patterns and sex-differentials in teenage exposure to HIV infection in rural Zimbabwe. Lancet. 2002 Jun 1;359(9321):1896-903.
2. Gregson S, Garnett GP, Nyamukapa CA, Hallett TB, Lewis JJ, Mason PR, et al. HIV decline associated with behavior change in eastern Zimbabwe. Science. 2006 Feb 3;311(5761):664-6.
3. Anderson RM, May RM, Ng TW, Rowley JT. Age-dependent choice of sexual partners and the transmission dynamics of HIV in Sub-Saharan Africa. Philos Trans R Soc Lond B Biol Sci. 1992 May 29;336(1277):135-55.
4. World Bank. World development report-1991. New York: Oxford University Press; 1991.

Parameter Value	Symbol (or formula)	Value
Mortality rate	$\mu(a)$	Table S2
Fertility rate	$\varphi(a)$	Table S2
Mean time with acute HIV infection	υ_{12}	3 months
Mean time with latent HIV infection	$\upsilon_{23}(a)$	Table S3
Mean time with pre-AIDS	$1/g$	6 months
Mean time in full blown AIDS before dying	$1/\alpha$	6 months
Transmission probability (acute stage, pre-AIDS and full blown AIDS)	$10\,\beta$	0.35
Transmission probability (latent stage)	β	0.035
Probability of mother-to-child transmission	σ	0.35
Fraction of partnerships formed randomly with respect to sexual activity class	ε	0.3
Age-difference between sexual partners (shape parameters for log-logistic distribution)	r κ ρ	0.11 3.04 2.85
Number of partnerships formed per year. Common ratio between sexual activity groups Age and gender-specific geometric mean	τ $M_{k,i}$	4 Table S4
Age at first sex (males and females)	$A^{1}_{1,2}$	16
Age at last sex (males and females)	$A^{2}_{1,2}$	55
Range of ages from which to recoup lost sexual partnerships if opposite gender delays first sex.	H	3

Table S1: Default parameter values

	Deaths per person-year (*$\mu(a)$*)		Births per female person-year (*$\varphi(a)$*)
Age-range	**Male**	**Female**	
<1	0.117	0.100	0
1-4	0.019	0.019	0
5-9	0.007	0.006	0
10-14	0.004	0.004	0
15-19	0.004	0.004	0.175
20-24	0.006	0.005	0.313
25-29	0.007	0.006	0.324
30-34	0.007	0.006	0.271
35-39	0.008	0.007	0.201
40-44	0.010	0.008	0.125
45-49	0.012	0.009	0.053
50-54	0.016	0.012	0
55-59	0.021	0.016	0
60-64	0.030	0.024	0
65-69	0.044	0.038	0
70-74	0.068	0.060	0
75-79	0.105	0.094	0
80+	0.189	0.174	0

Table S2: Demographic parameter values (baseline values excluding effects of AIDS) (3, 4)

Age-range	Mean years with latent infection Y^2 ($\upsilon_{23}(a)^{-1}$)
0-9	0.75
10-24	6.0
25-29	4.8
30-34	4.0
35-39	3.4
40-44	3.0
45-49	2.7
50-59	2.4
60+	2.2

Table S3: Mean years spent with latent HIV infection

	Mean number of sexual partnerships formed per year ($M_{k,i}$)	
Age-range	**Male**	**Female**
***A*-24**	2.1	1.0
24-34	1.9	1.1
35-44	1.7	0.92
45+	1.6	0.92*

Table S4: Mean partner change rates, by age (based on data from Manicaland, Zimbabwe (1))

** No data available. This value interpolated from younger age-group.*