A double-edged sword: does highly active antiretroviral therapy contribute to syphilis incidence by impairing immunity to Treponema pallidum?
Supporting Information

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1 Model

1.1 Model structure

We developed a susceptible-infective-treated coinfection model with heterogeneous mixing. Model consists of 9 states which are classified by syphilis and HIV infection status: SS_i, IS_i, TS_i, SI_i, II_i, TI_i, ST_i, IT_i, and TT_i. Given a state XY_i, X represents the HIV infection status; Y represents the syphilis infection status; and i represents the risk group. For simplicity, we do not consider progression through different stages of the disease, and assume that there are only two risk groups: $i = 1, 2$.

We assume that all individuals leave at-risk population at a rate μ, and individuals enter at-risk population as SS (susceptible to both diseas) at a constant rate that is proportional to the proportion of each risk group at a disease-free equilibrium: μN_0. Individuals infected syphilis receive treatment (acquiring partial immunity) at a rate γ and lose immunity (becoming susceptible) at a rate δ. Individuals infected with HIV receive ARV treatment at a rate τ. They can also leave ARV treament or treatment may fail (entering infective compartment) at a rate σ. Individuals infected with HIV die at a rate α but if they're receiving ARV treatment, they die at a slower rate of $\epsilon_\alpha \alpha$, where $\epsilon_\alpha < 1$. Individuals infected with syphilis and HIV can infect a susceptible partner at a probability of β_{syph} and β_{HIV} per partnership, respectively. ARV treatment reduces HIV transmission rate by the factor of ϵ_β, and syphilis infection increases acuiqition and transmission rate of HIV by the factor of ν_r and ν_t, respectively (Deschamps et al., 1996; Røttingen et al., 2001). For simplicity, we do not consider explicit partnership dynamics but we assume assortative mixing.

1.2 Assortativity

Assortative mixing is modeled based on the work of Grassly et al. (2005). Proportion ρ of an individual's mixing is reserved for their own risk group, and the rest is used randomly in the whole population. Force of infection, λ_i, that susceptible individuals in a risk group, i, experience from a particular disease is given by the following equation:

$$\lambda_i = \rho\beta_i \frac{Y_i}{N_i} + (1-\rho)\beta_i \frac{\sum_i c_i Y_i}{\sum_i c_i N_i}, \tag{1}$$

where i is the mixing group, c_i is the partnership rate, N_i is total number of people in the mixing group, and $\beta_i = \beta * c_i$ (β is the transmission probability per partnership of the disease).

1.3 Transmission

In the equations introduced above, Y_i is the number of individuals in a risk group i that are infected with a particular disease. However, in order to account for varying transmissibility depending on the infection status, We define $J_i^{HIV} = IS_i + \nu_t II_i + IT_i + \epsilon_\beta(TS_i + \nu_t TI_i + TT_i)$ and $J_i^{syph} = SI_i + II_i + TI_i$, which are used to calculate force of infection of two diseases:

$$\begin{aligned}
\lambda_i^{HIV} &= \rho\beta_i^{HIV} \frac{J_i^{HIV}}{N_i} + (1-\rho)\beta_i^{HIV} \frac{\sum_i c_i J_i^{HIV}}{\sum_i c_i N_i}, \\
\lambda_i^{syph} &= \rho\beta_i^{syph} \frac{J_i^{syph}}{N_i} + (1-\rho)\beta_i^{syph} \frac{\sum_i c_i J_i^{syph}}{\sum_i c_i N_i}.
\end{aligned} \tag{2}$$

Increased susceptibility to HIV due to syphilis is modeled by multiplying the term ν_r to the infection term going from SI_i to II_i: $SI_i' = -\nu_r \lambda_i^{HIV} SI_i$ and $II_i' = -\nu_r \lambda_i^{HIV} SI_i$.

1.4 Mathematical model

$$\begin{aligned}
SS_i' &= \mu N(0)_i - (\lambda_i^{HIV} + \lambda_i^{syph})SS_i + \delta ST_i - \mu SS_i \\
IS_i' &= -\lambda_i^{syph} IS_i + \lambda_i^{HIV} SS_i - \tau IS_i + \sigma TS_i + \delta IT_i - \alpha IS_i - \mu IS_i \\
TS_i' &= -\lambda_i^{syph} TS_i + \tau IS_i - \sigma TS_i + \delta TT_i - \epsilon_\alpha \alpha TS_i - \mu TS_i \\
SI_i' &= -\nu_r \lambda_i^{HIV} SI_i + \lambda_i^{syph} SS_i - \gamma SI_i - \mu SI_i \\
II_i' &= \nu_r \lambda_i^{HIV} SI_i + \lambda_i^{syph} IS_i - \tau II_i + \sigma TI_i - \gamma II_i - \alpha II_i - \mu II_i \\
TI_i' &= \lambda_i^{syph} TS_i + \tau II_i - \sigma_i TI_i - \gamma TI_i - \epsilon_\alpha \alpha TI_i - \mu TI_i \\
ST_i' &= -\lambda_i^{HIV} ST_i + \gamma SI_i - \delta ST_i - \mu ST_i \\
IT_i' &= \lambda_i^{HIV} ST_i - \tau IT_i + \sigma TT_i + \gamma II_i - \delta IT_i - \alpha IT_i - \mu IT_i \\
TT_i' &= \tau IT_i - \sigma TT_i + \gamma TI_i - \delta TT_i - \epsilon_\alpha \alpha TT_i - \mu TT_i
\end{aligned} \tag{3}$$

1.5 Delayed introduction of ARV

Instead of using the model as it is above, we introduce ARV treatment 20 years after the beginning of the simulation. It is simply done by multiplying T_{start} to τ ($\tau_{adj} = T_{start}\tau$) and setting $T_{start} = 0$ when $t < 20$ and 1 otherwise. With the introduction of ARV, we introduce two more variables to the model: ν_{IS}

and c_{inc}. ν_{IS} is the ratio of increased susceptibility to syphilis due to ARV immunosuppression effect and c_{inc} is the effect of ARV on behaviour (also given as a ratio). ν_{IS} is simply multiplied to syphilis infection term going from TS_i to TI_i. $TS_i' = -\nu_{IS}\lambda_i^{syph}TS_i$ and $TI_i' = \nu_{IS}\lambda_i^{syph}TS_i$.

With the introdction of ARV, behaviour change is introduced to people who are receiving ARV. The behaviour change is modeled by multiplying c_{inc} to the partnership change rate of those who are receiving ARV. It is done by modifying J, N, as well as the infection term going from TS_i to TI_i:

$$\begin{aligned}
J_i^{HIV} &= IS_i + \nu_t II_i + IT_i + c_{inc}\epsilon_\beta(TS_i + \nu_t TI_i + TT_i),\\
J_i^{syph} &= SI_i + II_i + c_{inc}TI_i,\\
N_i &= SS_i + IS_i + SI_i + II_i + ST_i + TT_i + c_{inc}(TS_i + TI_i + TT_i)\\
TS_i' &= -c_{inc}\nu_{IS}\lambda_i^{syph}TS_i\\
TI_i' &= c_{inc}\nu_{IS}\lambda_i^{syph}TS_i.
\end{aligned} \tag{4}$$

Increase in behaviour change is modeled by using the exponential function: $c_{inc} = c_f + (c_0 - c_f)exp((T_{start} - t)/T_c)$. These equations replace the equations in the above model.

References

Champredon, D., S. Bellan, and J. Dushoff (2013). HIV sexual transmission is predominantly driven by single individuals rather than discordant couples: a model-based approach. *PloS one 8*(12), e82906.

Cohen, M. S., Y. Q. Chen, M. McCauley, T. Gamble, M. C. Hosseinipour, N. Kumarasamy, J. G. Hakim, J. Kumwenda, B. Grinsztejn, J. H. Pilotto, et al. (2011). Prevention of HIV-1 infection with early antiretroviral therapy. *New England journal of medicine 365*(6), 493–505.

Deschamps, M.-M., J. W. Pape, A. Hafner, and W. D. Johnson (1996). Heterosexual transmission of HIV in haiti. *Annals of internal medicine 125*(4), 324–330.

Garnett, G. P., S. O. Aral, D. V. Hoyle, W. Cates Jr, and R. M. Anderson (1997). The natural history of syphilis: implications for the transmission dynamics and control of infection. *Sexually transmitted diseases 24*(4), 185–200.

Granich, R. M., C. F. Gilks, C. Dye, K. M. De Cock, and B. G. Williams (2009). Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *The Lancet 373*(9657), 48–57.

Grant, R. M., J. A. Wiley, and W. Winkelstein (1987). Infectivity of the human immunodeficiency virus: estimates from a prospective study of homosexual men. *The Journal of infectious diseases 156*(1), 189–193.

Grassly, N. C., C. Fraser, and G. P. Garnett (2005). Host immunity and synchronized epidemics of syphilis across the united states. *Nature 433*(7024), 417–421.

Ray, M., R. Logan, J. Sterne, S. Hernandez-Diaz, J. Robins, C. Sabin, L. Bansi, A. van Sighem, F. de Wolf, D. Costagliola, et al. (2010). The effect of combined antiretroviral therapy on the overall mortality of HIV-infected individuals. *AIDS 24*(1), 123–137.

Røttingen, J.-A., D. W. Cameron, and G. P. Garnett (2001). A systematic review of the epidemiologic interactions between classic sexually transmitted diseases and HIV: how much really is known? *Sexually transmitted diseases 28*(10), 579–597.

Table 1: Parameter values

Notation	Description	Value(s)	Source
c	Partnership change rate	40 and 5	Garnett et al. (1997)
N_0	Proportion of risk group	0.05 and 0.95	Assumption
ρ	Proportion of non-random contact	0.3	Assumption
μ	Rate of entry/exit from at risk population	0.05	Garnett et al. (1997)
β_{HIV}	HIV transmission probability per partnership	0.097	Grant et al. (1987)
ϵ_β	Relative HIV transmission ratio of people on ART	0.04	Cohen et al. (2011)
α	HIV induced mortality	0.125	Champredon et al. (2013)
ϵ_α	Relative mortality ratio of people on ART	0.5	Ray et al. (2010)
τ	ART treatment rate	1	Granich et al. (2009)
σ	ART failure/loss rate	0.015	Granich et al. (2009)
β_{syph}	Syphilis transmission probability per partnership	0.6	Garnett et al. (1997)
γ	Syphilis treatment rate	6	Grassly et al. (2005)
δ	Rate at which syphilis immunity is lost	0.05	Grassly et al. (2005)
ν_t	Relative HIV transmission ratio of people who are infected with syphilis	2	Deschamps et al. (1996)
ν_r	Relative HIV acquisition ratio of people who are infected with syphilis	3	Røttingen et al. (2001)
ν_{is}	Relative syphilis acquiring ratio due to ARV immunosuppression	3	Assumption