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Discussion and revision of the mathematical modeling tool described in the previously published article "Modeling HIV Transmission risk among Mozambicans prior to their initiating highly active antiretroviral therapy"

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Discussion and revision of the mathematical modeling tool described in the previously published article "Modeling HIV Transmission risk among Mozambicans prior to their initiating highly active antiretroviral therapy"

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Mathematical models are increasingly used in social and behavioral studies of HIV transmission; however, model structures must be chosen carefully to best answer the question at hand and conclusions must be interpreted cautiously. In Pearson et al. (2007), we presented a simple analytically tractable deterministic model to estimate the number of secondary HIV infections stemming from a population of HIV-positive Mozambicans and to evaluate how the estimate would change under different treatment and behavioral scenarios. In a subsequent application of the model with a different data set, we observed that the model produced an unduly conservative estimate of the number of new HIV-1 infections. In this brief report, our first aim is to describe a revision of the model to correct for this underestimation. Specifically, we recommend adjusting the population-level sexually transmitted infection (STI) parameters to be applicable to the individual-level model specification by accounting for the proportion of individuals uninfected with an STI. In applying the revised model to the original data, we noted an estimated 40 infections/1000 HIV-positive persons per year (versus the original 23 infections/1000 HIV-positive persons per year). In addition, the revised model estimated that highly active antiretroviral therapy (HAART) along with syphilis and herpes simplex virus type 2 (HSV-2) treatments combined could reduce HIV-1 transmission by 72% (versus 86% according to the original model). The second aim of this report is to discuss the advantages and disadvantages of mathematical models in the field and the implications of model interpretation. We caution that simple models should be used for heuristic purposes only. Since these models do not account for heterogeneity in the population and significantly simplify HIV transmission dynamics, they should be used to describe general characteristics of the epidemic and demonstrate the importance or sensitivity of parameters in the model.

Keywords: mathematical modeling; HIV; prevention

Mathematical models are useful tools for examining the potential effects of the proximate biological and behavioral determinants of human immunodeficiency virus (HIV) transmission dynamics, such as condom use, circumcision, and antiretroviral treatment (Baggaley, Ferguson, & Garnett, 2005; Cassels, Clark, & Morris, 2008; Law, Prestage, Grulich, Van de Ven, & Kippax, 2001; Salomon & Hogan, 2008; Tuckwell, Shipmana, & Perelson, 2008). However, mathematical models vary considerably, defined by the way the model elements (e.g., people) are organized into states (e.g., susceptible, infected, or recovered) and how the model characterizes the movement of those elements between states. The type of model selected in research and the way it is interpreted should depend on the specific topic at hand.

The Bernoulli-based model we presented in Pearson et al. (2007) was an analytically tractable deterministic model, meaning the model could be represented in a closed form with the outcome on the left-hand side of equation (Pinkerton & Abramson, 1998; Pinkerton, Abramson, Kalichman, Catz, & Johnson-Masotti, 2000; Weinhardt et al., 2004). The goal of the model was to estimate the number of sexual partners who would acquire HIV-1 as a consequence of sexual contact with study participants

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within the three months prior to highly active antiretroviral therapy (HAART) initiation and to evaluate how sensitive the estimate was to possible treatment and behavioral interventions. The data used in this model were from 350 HIV-positive men and women ($\geq$18 years) initiating HAART between October, 2004 and April, 2005 at the HIV care clinic in Beira Mozambique. Most (75%) knew their HIV serostatus for less than one year, 53.7% were female, and 97% were on one fixed-dose combination pill twice-a-day regimen.

The model was specified as follows:

$$P_{ij} = (1 - \lambda_j)\left[1 - \left(1 - \left(\prod_{t=1}^{5} RR_t\right)\beta_{si}\right)^{a_{ij}}\right],$$

where P_{ij} is the probability that participant i would transmit HIV-1 to sex partner j, given behaviors and characteristics reported for the three months prior to HAART initiation. The right-hand side of the equation can be considered in two parts. λ_j is the probability that the partner has already been infected with HIV; thus $(1-\lambda_j) = 0$ if the partner is HIV-positive and therefore the probability of HIV transmission is also equal to zero. The second part of the equation is the probability of HIV transmission given behaviors and biological characteristics of the individuals, the stage of HIV infection (Chakraborty et al., 2001; Gray et al., 2001; Gray et al., 2004; Wawer et al., 2005), and the number of sex acts. We considered individual and partnership behaviors and biological characteristics that have been consistently reported as influencing HIV transmission or acquisition (Auvert et al., 2001; Grosskurth, Gray, Hayes, Mabey, & Wawer, 2000; Reynolds & Quinn, 2005): circumcision (Auvert et al., 2005; Bailey et al., 2007; Gray et al., 2007), condom use (Hearst & Hulley, 1988), HAART (Perelson et al., 1997; Porco et al., 2004), syphilis (Korenromp et al., 2005), and HSV-2 (Celum, Robinson, & Cohen, 2005; Freeman et al., 2006). The probability of HIV transmission is multiplied by the risk ratios (RR) associated with these cofactors. Thus the model is based on published estimates of RR; however, better parameters for the model are per-exposure cofactors because we are modeling the risk of HIV per sex act. Often, per exposure cofactors can be derived from RR if the number of exposures (i.e., unprotected sexual acts in our case) during the exposure period are reported. If the number of exposures are not reported, one can assume that the RR approximates the per exposure cofactor if the probability of transmission is sufficiently small (as is the case with HIV) and the duration of exposure in which the RR was derived is short (Korenromp, De Vlas, Nagelkerke, & Habbema, 2001). Table 1 summarizes the RRs used in the model. For a complete description of the model, see the original report (Pearson et al., 2007).

The Pearson et al. (2007) model mostly used individual-level data from a survey conducted by several of the authors in Beira, Mozambique. Since we lacked individual-level data on sexually transmitted infection (STI) status for the respondent or partner, we used population-level data to act as a proxy. Local syphilis prevalence (denoted S) near the study site was 17%, and herpes simplex virus type-2 (HSV-2) prevalence (H) was 90%. We used published estimates of the relative risk of HIV acquisition due to co-infection with STI, which were 7.5 for syphilis (R_S) and 2.7 for HSV-2 (R_H) (Celum et al., 2005; Corey, Wald, Celum, & Quinn, 2004; Fleming & Wasserheit, 1999; Freeman et al., 2006; Korenromp et al., 2005; Wald & Link, 2002). We did not include the potential effect of increased risk of HIV transmission given positive STI status of the respondent; this effect is much harder to discern (Corey et al., 2004). Since the original model was published, two acyclovir trials failed to show that treating HSV-2 infection was effective in reducing risk of HIV acquisition (Celum et al., 2008; Watson-Jones et al., 2008). In the sensitivity analysis, we explored how the number of secondary HIV transmissions would change if STI treatment completely eliminated the increased risk of HIV acquisition (i.e., reduced the RR to one). Clearly given the recent acyclovir trials, treatment regimens are not likely to be effective in eliminating the enhanced risk of HIV *acquisition*; trial data are still forthcoming on whether HSV-2 treatment reduces the risk of HIV-1 *transmission* among those who are HIV-1 and HSV-2 co-infected. Therefore, the results of the sensitivity analysis presented here are to suggest the magnitude of secondary HIV transmission events due to STIs (Abu-Raddad et al., 2008).

In the original report, we estimated the RR for HIV transmission to be S^*R_S, or the prevalence of STI in the population multiplied by the relative risk of increased HIV acquisition by an STI-seropositive partner. This parameterization did not account for the proportion of individuals uninfected with an STI, and resulted in an underestimation of the impact of STI co-infection on HIV transmission risk. When using population-level data, the model should be adjusted to account for both infected and uninfected individuals. The proportion of individuals not infected with an STI contributes a RR of one, and those that are infected contribute a RR of x, which represents the increased risk of HIV acquisition for an individual with the STI. Therefore, the original model underestimated the STI co-factor because it essentially assumed that those not infected with an

Table 1. Description of values and assumptions for the risk ratios included in the model.

Risk ratio (RR)	Assumed value	Description
Circumcision	0.4	If the partner is female or an uncircumcised male, the RR = 1. The assumed RR value of 0.4 was derived from an exposure period of around 18 months (Auvert et al., 2005). Since the probability of HIV transmission per sex act is quite small and the mean number of contacts was not large in the study period, the difference between the published RR and the per exposure cofactor is minimal in this case.
Condoms	(1 – Cc*Ce)	Correct and consistent condom use (Cc) was derived from individual level data (Pearson et al., 2007). We assume condom effectiveness (Ce) = 0.95
Syphilis	7.5	We only assume an increased risk of HIV acquisition when the HIV susceptible partner is infected with syphilis. The estimate is based on estimates from the Mwanza, Rakai and Masaka intervention trial that showed the impact of primary syphilis (range: 2.3–8.6) (Korenromp et al., 2005). Additionally, we assume the same risk ratio although the syphilis prevalence reported in the paper is seroprevalence.
HSV-2	2.7	A meta-analysis suggested that HSV-2 infection increased HIV-1 acquisition risk among HIV-1 negative partners with a risk ratio of 2.7 (95% CI = 1.9–3.9) (Freeman et al., 2006).
HAART	0.52	Although the relationship between the probability of HIV transmission per sex act and viral load is non-linear (Garnett & Gazzard, 2008), we make the simplifying assumption that the relative reduction in the probability of HIV transmission is the same regardless of stage of disease or initial viral load. In the model the effectiveness of HAART (0.48) was adjusted by reported adherence as a proportion of dose taken (Baggaley et al., 2005; Gray et al., 2003; Porco et al., 2004).

STI contributed a RR of zero. Both of the STI RR should be increased by the proportion of individuals in the sample uninfected with the relevant STI. The new parameterization is as follows:

$$RR_{syphilis} = (1-S)*1 + (S)(R_s),$$
$$RR_{HSV\text{-}2} = (1-H)*1 + (H)(R_H).$$

This adjustment increases the expected number of HIV transmission events and decreases the estimated magnitude of HIV-1 transmission reduction due to STI treatment. With the adjusted model, the estimate of HIV transmission events increased to 1.57 infections/157 persons per three months (0.99 as a result of sex with men and 0.58 as a result of sex with women) from the originally estimated 0.91 infections/157 persons. This is approximately 40 incident HIV infections per year given 1000 similar HIV-positive individuals, compared to the 23.2 infections/1000 HIV-positive persons per year calculated by the original model. The revised model estimated that HAART combined with syphilis and herpes simplex virus type 2 (HSV-2) treatment could reduce HIV-1 transmission by 72% (as compared to the original 86%). Essentially, the model revision reveals that STIs may be more influential than we had originally reported in increasing HIV risk. At the same time, although treating STIs may still be an important HIV prevention strategy, the reduction in HIV transmission risk from treating STIs may not be as large as originally thought. Note that the general findings of the original report did not change; namely, according to both the original and revised model, the best treatment option is to combine HAART with STI treatment to reduce secondary HIV transmissions. See Table 2 for a comparison of the full results from the original and revised models.

The model presented here can be classified as a "simple" model, but this does not detract from its usefulness. Indeed, it is user friendly, easy to implement, and provides a straightforward way to assess the sensitivity of a parameter in the model. Simple models have limitations as well. The present model only estimates the first generation of transmission from an HIV-infected individual, and does not account for the fact that infected partners can then infect additional individuals, nor can it account for sexual partnership concurrency, which has been hypothesized to enhance epidemic HIV transmission (Morris, Goodreau, & Moody, 2007). In its current form, it disallows individual behavior to change over time. It also significantly simplifies HIV transmission dynamics: the model assumes that co-factors are additive and independent. This is a significant simplifying assumption.

It is necessary for any consumer of models to have basic knowledge of modeling in order to understand the limitations of a model, its structure, and how changes in data inputs can alter the outcome. Model-

Table 2. Estimates of HIV transmission risk resulting from various treatment and prevention modeling assumptions.

	Rate (infections/1000 HIV-positive persons per year)		Reduction in transmission	
Parameters	Original model	Revised model	Original model	Revised model
Base model	23.20	40.00		
Correct and consistent condom use (27% base model prevalence)				
50%	16.60	28.70	0.28	0.28
75%	9.10	15.80	0.61	0.61
Syphilis (16.7% base model prevalence)				
8%	11.70	28.10	0.50	0.30
5%	6.50	22.80	0.72	0.43
HSV-2 (90% base model prevalence)				
45%	11.70	28.10	0.50	0.30
25%	6.50	22.80	0.72	0.43
Male circumcision (31% base model prevalence)				
50%	22.10	37.90	0.05	0.05
75%	20.50	35.20	0.12	0.12
Persons on HAART (base model is 0% adherent)				
95%	12.70	22.00	0.45	0.45
80%	14.40	24.90	0.38	0.38
Treatment only				
Syphilis & HSV2 (50%)	5.90	20.90	0.75	0.48
Syphilis & HSV2 (50%) & HAART (95%)	3.20	11.40	0.86	0.72

ing can help to ground the debate about the trade-offs between treatment and prevention and can provide behavioral scientists with a tool to demonstrate the population impact of a well-designed social or behavioral intervention.

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