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Could Condoms Stop the AIDS Epidemic?

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Although therapeutic treatment strategies appear promising for retarding the progression of HIV-related diseases, prevention remains the most effective strategy against the HIV/AIDS epidemic. This paper focuses on the effect of condom use as a single-strategy approach in HIV prevention in the absence of any treatment. There are two primary factors in the use of condoms to halt the HIV/AIDS epidemic: condom efficacy and compliance. Our study is focused on the effect of these factors in stopping the epidemic by constructing a new deterministic mathematical model. The current estimate of condom effectiveness against HIV transmission, based on the latest meta-analysis, is 60–96%, with a mean of 87%. Since the parameter estimates are subject to different kinds of uncertainty, to achieve adequate quality assurance in predictions, uncertainty and sensitivity analyses are carried out using latin hypercube sampling (LHS) and partial rank correlation coefficients (PRCCs). Using stability and sensitivity analyses, based on a plausible range of parameter values, key parameters that govern the persistence or eradication of HIV are identified. This analysis shows that the product of efficacy and compliance, which we call 'preventability' (p), has a negative effect on the epidemic; as increasing p decreases the level of epidemicity. It is also shown that the threshold preventability (p_c) increases with increasing average number of HIV-infected partners of susceptible individuals, especially those in the AIDS stage. For populations where the average number of HIV-infected partners is large, the associated preventability threshold is high and perhaps unattainable, suggesting that for such a population, HIV may not be controlled using condoms alone. On the other hand, for a population where the average number of HIV-infected partners is low (within a reasonable range), it is shown that p_c is about 75%, suggesting that the epidemic could be stopped using condoms. Thus, for such a population, public health measures that can bring preventability above the threshold and continuous quantitative monitoring to make sure it stays there, are what would be necessary. In other words, for populations with reasonable average numbers of HIV-infected partners, given the will and effort, it is within our means to halt this epidemic using condoms.

Keywords: Basic reproductive number; Condom; Compliance; Epidemic model; Equilibrium; Stability; Sensitivity analysis; Latin hypercube sampling; Partial rank correlation; HIV/AIDS

INTRODUCTION

Ever since the recognition of condoms as tools for controlling the spread of human immunodeficiency virus (HIV), numerous experimental and clinical studies have been conducted to ascertain their effectiveness. The clinical studies have been critically evaluated in a recent NIH report (Adam *et al.*, 2001) which relies upon the meta-analysis of Davis and Weller (1999). The overall consensus is an estimated condom effectiveness of 60–96%, with a mean of 87%. We would like to test, via mathematical modelling, whether these effective figures are sufficient to stop the AIDS epidemic in a community.

In mathematical biology, the basic reproductive number of infection ($\mathcal{R}_0$) is known to be the critical threshold that determines the dynamics (persistence or lack thereof) of an epidemic (Anderson and May, 1991). This threshold is essentially the number of new people infected by an infected person during the course of infection. More rigorously, in our context, it is the number of secondary infectious cases generated by each HIV-infected person over the course of the disease. Consequently, it is of great public health interest, in the event of an epidemic, to design control strategies that can make $\mathcal{R}_0 < 1$ (leading, in general, to disease eradication) (see, Gordon, 1989; Anderson and May, 1991; Moghadas and Gumel, 2002).

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Attempts have been made to estimate $\mathcal{R}_0$ for models that incorporate condom use. For instance, Gordon (1989) estimated $\mathcal{R}_0$ based on data for condom efficacy to avoid pregnancy. Greenhalgh *et al.* (2001) analyzed the dynamics of a two-group deterministic model for assessing the impact of condom use on the sexual transmission of HIV and AIDS within a homo-sexual population. Their study, which assumes that condoms are 100% effective, shows that although reducing $\mathcal{R}_0$ to values less than unity does not guarantee eradication of the disease, controlling the initial sizes of the susceptible and infected populations (when $\mathcal{R}_0 < 1$) can lead to eradication of the disease (instead of disease persistence). This (bistability) phenomenon, where a stable disease-free equilibrium and a stable endemic equilibrium co-exist when $\mathcal{R}_0 < 1$, has been observed in a number of epidemiological studies (see Kribs-Zaleta, 2002 for a general reference).

In line with the empirical data endorsed by the NIH report (Adam *et al.*, 2001), there is a clear need to examine the role of condom use, with (realistic) efficacy less than 100%, on HIV transmission dynamics. Another critical factor in preventing HIV transmission is compliance in condom use. This factor is defined as the proportion of the sexually-active population that uses condoms consistently and correctly. Consistent use is defined as using a condom for all acts of penetrative vaginal intercourse or anal sex.

The aim of our study is to construct and analyse a deterministic mathematical model for assessing the effect of condom use (based on efficacy and compliance) in controlling (or, if possible, eradicating) HIV within a given community. In other words, this new model shall allow us to extract quantitative public health goals for community and worldwide control of HIV/AIDS using condoms. An additional advantage of this modelling approach is that it suggests directions for future research. It may, for instance, permit us to give up strategies that could not lead towards stopping this epidemic.

Our model monitors the temporal dynamics of the susceptible population (S), the HIV-infected individuals (I) and infected individuals with AIDS (A). The model incorporates the following two key HIV control parameters.

Efficacy of Condoms (ϵ)

It is important to distinguish between efficacy of condoms and condom effectiveness. Efficacy of condoms is the protection that the user would receive when the condoms are used correctly and consistently. This protection depends on a number of factors including the physical properties of the condom such as breakage, slippage and leak rates (Gordon, 1989; Frezieres *et al.*, 1998; 1999; Macaluso *et al.*, 1999). On the other hand, condom effectiveness is the proportionate reduction in disease transmission due to the use of condoms. It is the protection that condoms provide under actual conditions of use which depends on the characteristics

of the condoms and the users. The recent NIH report on the effectiveness of condoms in preventing HIV transmission (Adam *et al.*, 2001) identifies the work of Davis and Weller (1999) as the latest meta-analysis of condom effectiveness.

Condom Compliance (α)

Condoms do not offer 100% protection and a high level of individual compliance (the frequency of condom use) is required for condoms to be effective in use. The protection also depends on whether the condom is used consistently and correctly. Thus, this parameter models the proportion of the sexually-active population (including HIV-infected individuals or their susceptible partners) that uses condoms consistently and correctly (100% compliant). A re-examination of HIV seroconversion studies suggests that condoms are 90–95% effective when used consistently. That is, consistent condom users are 10–20 times less likely to become infected when exposed to the virus than are inconsistent or non-users (see Pinkerton and Abramson, 1997).

Since efficacy and compliance will be seen to feature in our model as a product $\epsilon\alpha$, we define this product as the condom-induced preventability ($p = \epsilon\alpha$) of HIV transmission per year. This parameter represents the level of protection against HIV transmission using condoms.

The other parameters of the model are as follows.

Recruitment (Π)

Recruitment is the inflow of people (either by birth or immigration) into a community. Since this study considers only sexual mode of HIV transmission (i.e. we do not take into account other methods of HIV transmission such as mother-to-child, needle sharing, blood transfusion etc), we define recruitment in terms of the number of sexually-active individuals admitted into the community per unit time. We assume that this rate of recruitment also covers children who become adults (as sexually-active individuals). Furthermore, our model categorizes all individuals recruited into the community as susceptible (we ignore the small proportion of HIV-resistant individuals; see Fowke *et al.*, 1996).

Death Rates (μ, γ)

We will assume, to a first approximation, that the death rate μ of infected individuals due to other causes is independent of the state of the disease. Therefore, we assume that the natural death rate for all individuals is the same and constant. But death rate γ due to AIDS may vary depending on which other diseases an individual has at the same time (Petruckevitch *et al.*, 1998). However, the model assumes that γ is constant (see also Porco and Blower, 1998; Greenhalgh *et al.*, 2001).

Rate of Progression to AIDS (σ)

Although the rate of progression from HIV infection to AIDS appears to be higher for homosexual men than heterosexual (Wannamethee *et al.*, 1998), the model assumes the same rate of progression to AIDS for all HIV-infected individuals in the population (Porco and Blower, 1998; Greenhalgh *et al.*, 2001).

Average Number of Sexual Partners (c_1, c_2)

These parameters model the average number of sexual partners for a typical susceptible individual per unit time. It is assumed that the average number of sexual partners for a susceptible individual with HIV-infected individuals (c_1) and persons with AIDS (c_2) (per unit time) are constants (see Anderson and May, 1991; Hadeler and Castillo-Chavez, 1994; Hethcote, 2000; Hsieh and Sheu, 2001; Moghadas, 2002; Moghadas and Gumel, 2002).

Probability of Infection (β_1, β_2)

Contact between a susceptible and an HIV-infected individual (either in asymptomatic or AIDS stage) is associated with a risk (probability) of infection. We assume that the probability of infection with a person with AIDS (β_2) is greater than that with an HIV-infected individual in the asymptomatic stage (β_1) (see Anderson and May, 1991). May and Anderson (1987) estimate that the probability of HIV infection may vary from 0.05 to 0.5 per partnership. Hyman *et al.* (1999) take the probability of infection in the range (0.001–0.3) (see also Porco and Blower, 1998; Greenhalgh *et al.*, 2001 and the references therein). Gray *et al.* (2001) estimated that probability of HIV-1 transmission per act in monogamous heterosexual, HIV-1-discordant couples in Rakai (Uganda) varies between 0.0011 and 0.0041 (with respect to viral loads). The probability of HIV transmission per partnership (β) is given by:

$$\beta = 1 - (1 - \delta)^n,$$

where n is the total number of sexual acts per year and δ is the probability of transmission per act. The total number of sexual contacts with HIV-infected individuals (n) corresponds to a maximum number of sexual partners per year. This means that the number of contacts per partners can be high when the person has a few partners. On the other hand, the number of contacts drops rapidly for people who have more partners. For example, the number of contacts for a susceptible individual who has the maximum number of partners is one per partner. With the mean of $n = 107$ estimated in Gray *et al.* (2001) and $\delta \in (0.0011, 0.0041)$, the probability of HIV infection per partnership varies between 0.11 and 0.36, which is consistent with the ranges estimated by May and Anderson (1987); Hyman *et al.* (1999).

The focus of this study is to determine the minimum condom efficacy and compliance rates needed for community-wide eradication of HIV. The model is formulated in "The Mathematical Model" section and analyzed qualitatively in the "Stability Analysis" section. The model will be analyzed for its uncertainty and sensitivity to variations in the parameter values in the "Sensitivity Analysis" section. Conclusions from the model are given in the "Conclusion" section, and placed in the context of public health strategy in the "Discussions" section.

THE MATHEMATICAL MODEL

The model monitors the rate of change of the populations of susceptible individuals (S), HIV-infected individuals in asymptomatic stage (I), and persons with AIDS (A) as follows.

Susceptible Individuals (S)

All sexually-active individuals recruited into the population, at a rate Π per unit time, are assumed to be susceptible. The susceptible population is diminished by natural death (at a rate μ) and by infection following contact with an infected individual (with probability β_1) or with an individual who has AIDS (with probability β_2). This leads to the non-linear differential equation:

$$\frac{\mathrm{d}S}{\mathrm{d}t} = \Pi - \frac{(1 - \epsilon\alpha)(c_1\beta_1 I + c_2\beta_2 A)S}{N} - \mu S,$$

where ϵ is the efficacy of condoms against HIV infection, α is the compliance rate in condom use, c_1 and c_2 are the average numbers of sexual partners for a susceptible with HIV-infected individuals and AIDS patients per unit time, respectively. Note that $N \equiv N(t) = S(t) + I(t) + A(t)$ is the total population size of sexually-active individuals within the community. The force of infection $c_1\beta_1 I/N$ is the rate of infection for a susceptible individual with HIV-infected individuals per unit time. Similarly, $c_2\beta_2 A/N$ is the rate of infection for a susceptible individual with persons with AIDS per unit time. Thus, the incidence of infection (the number of new infected cases of susceptibles per unit time when condoms are used) is $(1 - \epsilon\alpha)(c_1\beta_1 I + c_2\beta_2 A)S/N$.

HIV-Infective Individuals (I)

This population, assumed to be in asymptomatic stage, increases through the infection of susceptibles, and diminishes by natural death (at a rate μ), and by development of AIDS (at a rate σ). This gives:

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \frac{(1 - \epsilon\alpha)(c_1\beta_1 I + c_2\beta_2 A)S}{N} - (\mu + \sigma)I.$$

TABLE I   Description and estimation of the model parameters

Parameters	Estimated values
Π: recruitment rate of sexually-active individuals	$1000 \leq \Pi$ people $(\text{year})^{-1}$
c_1: average number of sexual partners for a susceptible individual with HIV-infected individuals per unit time	$1 \leq c_1 \leq 100$ people $(\text{year})^{-1}$
c_2: average number of sexual partners for a susceptible individual with AIDS patients per unit time	$1 \leq c_2 \leq 100$ people $(\text{year})^{-1}$
μ: natural death rate	$0.015 \leq \mu \leq 0.025$ $(\text{year})^{-1}$
σ: rate of progression to AIDS of HIV-infected individuals	$0.067 \leq \sigma \leq 0.2$ $(\text{year})^{-1}$
γ: death rate due to AIDS	$0.4 \leq \gamma \leq 0.5$ $(\text{year})^{-1}$
β_1: probability of infection per contact with an HIV-infected individual	$0.003 \leq \beta_1 \leq 0.05$ $(\text{people})^{-1}$
β_2: probability of infection per contact with an AIDS patient	$0.05 \leq \beta_2 \leq 0.5$ $(\text{people})^{-1}$
ϵ: efficacy of condom	$0 \leq \epsilon \leq 1$
α: compliance rate of condom use	$0 \leq \alpha \leq 1$
p: condom-induced preventability	$0 \leq p \leq 1$

Source of estimates: Gray *et al.*, 2001; Greenhalgh *et al.*, 2001; Maticka-Tyndale, 1997; Porco and Blower, 1998.

Individuals with AIDS (A)

This population is generated following the progression to AIDS of HIV infected individuals. It decreases by natural death (at a rate μ) and by death due to AIDS (at a rate γ). Thus,

$$\frac{dA}{dt} = \sigma I - (\mu + \gamma)A.$$

In summary, the model is given by the following non-linear system of differential equations:

$$\frac{dS}{dt} = \Pi - \frac{(1 - \epsilon\alpha)(c_1\beta_1 I + c_2\beta_2 A)S}{N} - \mu S,$$

$$\frac{dI}{dt} = \frac{(1 - \epsilon\alpha)(c_1\beta_1 I + c_2\beta_2 A)S}{N} - (\mu + \sigma)I, \quad (1)$$

$$\frac{dA}{dt} = \sigma I - (\mu + \gamma)A.$$

It should be noted that since the model variables are populations, the model imposes a positivity condition (that is, all its dependent variables and parameters are non-negative). The model parameters, together with their realistic estimates, are tabulated in Table I where 'year' is used as the unit of time.

STABILITY ANALYSIS

In this section, rigorous mathematical analysis will be carried out in order to gain deeper insights into the stability (qualitative features) of the model. This analysis

enables us to determine the threshold conditions for stopping the AIDS epidemic using condoms.

Disease-free Equilibrium

In the absence of HIV infection (that is, $I = A = 0$), the model Eq. (1) has a unique disease-free equilibrium (E_0), obtained by setting the derivatives in Eq. (1) to 0, given by $E_0 = (\Pi/\mu, 0, 0)$. Evaluating the Jacobian of Eq. (1) at E_0 gives

$$J_0 = \begin{bmatrix} -\mu & -(1 - \epsilon\alpha)c_1\beta_1 & -(1 - \epsilon\alpha)c_2\beta_2 \\ 0 & (1 - \epsilon\alpha)c_1\beta_1 - (\mu + \sigma) & (1 - \epsilon\alpha)c_2\beta_2 \\ 0 & \sigma & -(\mu + \gamma) \end{bmatrix}.$$

The eigenvalues of J_0 are $\lambda_1 = -\mu$ and the roots of the quadratic $f(\lambda) = \lambda^2 + a\lambda + b$ where

$$a = -[(1 - \epsilon\alpha)c_1\beta_1 - (\mu + \sigma) - (\mu + \gamma)],$$

and

$$b = -(\mu + \gamma)[(1 - \epsilon\alpha)c_1\beta_1 - (\mu + \sigma)]$$

$$- (1 - \epsilon\alpha)c_2\beta_2\sigma.$$

The roots of the quadratic $f(\lambda)$ have negative real parts if $a > 0$ and $b > 0$. Defining

$$\mathcal{R}_0 = \frac{(1 - \epsilon\alpha)[c_1\beta_1(\mu + \gamma) + c_2\beta_2\sigma]}{(\mu + \gamma)(\mu + \sigma)},$$

it follows that $b > 0$ if and only if $\mathcal{R}_0 < 1$. Furthermore, it can be seen that if $\mathcal{R}_0 < 1$, then $(1 - \epsilon\alpha)c_1\beta_1/(\mu + \sigma) < 1$. This implies that $a > 0$. Hence, the local stability of E_0 depends on the threshold $\mathcal{R}_0$. Therefore, we have established the following lemma.

LEMMA 1   The disease-free equilibrium is locally asymptotically stable if $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$.

The threshold quantity $\mathcal{R}_0$ is the *reproduction number*, defined as the number of new infected individuals generated by a single infected individual introduced into a population where condoms are used as control strategy (see Hethcote, 2000). The local stability of the disease-free equilibrium (stated in Lemma 1) shows that every solution of Eq. (1) with an initial condition close to E_0 eventually approaches E_0 (that is initial sizes of the sub-populations are located in the basin of attraction of E_0). In other words, Lemma 1 shows that if the sizes of the sub-populations are close enough to the values of the components of the disease-free equilibrium, then HIV can be eradicated from the population (whenever $\mathcal{R}_0 < 1$).

Non-trivial Equilibrium

The endemic equilibria of the model (if they exist) correspond to the case where HIV persists in the population

$(I \neq 0)$. Although these equilibria cannot be cleanly expressed in closed form, we shall show that if $\mathcal{R}_0 > 1$, then the model has a unique positive endemic equilibrium at $E^* = (S^*, I^*, A^*)$ in which all state variables of the model are nonzero. To do this, we define

$$G(t) = \frac{(1 - \epsilon\alpha)c_1\beta_1 I(t)}{N(t)} \quad \text{and}$$

$$H(t) = \frac{(1 - \epsilon\alpha)c_2\beta_2 A(t)}{N(t)}, \quad (2)$$

to be the forces of infection (the rate of acquisition of new infected individuals per unit time) from infected and AIDS individuals, respectively (see Velasco-Hernandez, 1994). It follows from Eq. (1) that the associated expressions for the population densities at equilibrium are:

$$S^* = \frac{\Pi}{\mu + G^* + H^*}, \quad I^* = \frac{(G^* + H^*)\Pi}{(\mu + \sigma)(\mu + G^* + H^*)},$$

and

$$A^* = \frac{\sigma(G^* + H^*)\Pi}{(\mu + \gamma)(\mu + \sigma)(\mu + G^* + H^*)}.$$

Substituting the above into the expressions for G and H in Eq. (2) gives

$$G^* = \frac{(1 - \epsilon\alpha)c_1\beta_1(G^* + H^*)\Pi}{(\mu + \sigma)(\mu + G^* + H^*)N^*}, \quad (3)$$

and

$$H^* = \frac{(1 - \epsilon\alpha)c_2\beta_2\sigma(G^* + H^*)\Pi}{(\mu + \gamma)(\mu + \sigma)(\mu + G^* + H^*)N^*}, \quad (4)$$

where $N^* = S^* + I^* + A^*$.

Let $\phi_1(G, H)$ and $\phi_2(G, H)$ be the right hand sides of Eqs. (3) and (4), respectively. Thus, the equilibria of Eq. (1) correspond to the fixed points of the following equation:

$$\begin{pmatrix} G \\ H \end{pmatrix} = \Phi(G, H) = \begin{pmatrix} \phi_1(G, H) \\ \phi_2(G, H) \end{pmatrix}.$$

Clearly, $(0,0)$ is a fixed point of Φ which corresponds to the disease-free equilibrium (E_0) of Eq. (1). The task ahead is to show that Φ has a unique nonzero fixed point corresponding to the positive endemic equilibrium of Eq. (1). For fixed $H > 0$, we consider the real-valued function $\phi_1^H(G) = \phi_1(G, H)$. It can be seen that $\phi_1^H(0) \geq 0$ and $\lim_{G \to \infty} \phi_1^H(G) < \infty$. Thus, $\phi_1^H(G)$ is a bounded function for every fixed $H > 0$. Since, in this case, $\mathcal{R}_0 > 1$ (needed for E_0 to be unstable), it can be shown (after some tedious manipulations) that $\partial\phi_1^H(G)/\partial G > 0$ and $\partial^2\phi_1^H(G)/\partial G^2 < 0$. This implies that $\phi_1^H(G)$ is an increasing concave down function which has no change in convexity. Consequently, there is a unique G^* such that $\phi_1^H(G^*) = G^*$.

Substituting G^* into the expression for $\phi_2(G, H)$ gives the real valued function $\phi_2^{G^*}(H) = \phi_2(G^*, H)$. Since, from Eqs. (3) and (4), $\phi_2(G^*, H) = (\sigma c_2\beta_2/(\mu + \gamma)c_1\beta_1)\phi_1(G^*, H)$, it follows that there is a unique H^* such that $\phi_2(G^*, H^*) = H^*$ (using a similar argument for $\phi_1(G, H)$). Therefore, a unique nonzero fixed point of the bounded function Φ is $(G^*, \sigma c_2\beta_2 G^*/(\mu + \gamma)c_1\beta_1)$. By evaluating the spectral radius ρ^* of the Jacobian of Φ at $(G^*, \sigma c_2\beta_2 G^*/(\mu + \gamma)c_1\beta_1)$, we can determine the threshold condition for the local stability of E^* (see Velasco-Hernandez, 1994). Therefore, we have established the following lemma.

LEMMA 2 If $\mathcal{R}_0 > 1$, then the model has a unique positive endemic equilibrium E^*. This equilibrium is locally asymptotically stable if $\rho^* < 1$ and unstable if $\rho^* > 1$. Moreover, if $\mathcal{R}_0 < 1$, the model has no endemic equilibrium.

Adapting the technique used by Moghadas and Gumel (2002) (involving the normalization of the model and using Lemma 3.1 of Busenberg and Van den Driessche, (1990)), the following theoretical result can be proven.

THEOREM 3 If $\mathcal{R}_0 < 1$, then E_0 is globally asymptotically stable. If $\mathcal{R}_0 > 1$, then E_0 is unstable and E^* is globally asymptotically stable.

This theorem states that all solution trajectories will be attracted to E_0 (irrespective of the initial sizes of the subpopulations) whenever $\mathcal{R}_0 < 1$. The epidemiological implication of this theorem is that the HIV disease can be eradicated if the threshold parameter $\mathcal{R}_0$ is less than unity. Furthermore, based on the definition of condom-induced preventability, we claim the following result.

THEOREM 4 HIV can be eradicated from the community if the preventability $p = \alpha\epsilon$ exceeds the threshold value p_c.

Proof Using the expression for $\mathcal{R}_0$, it is easy to see that if

$$\alpha_c = \frac{1}{\epsilon}\left[1 - \frac{(\mu + \gamma)(\mu + \sigma)}{[c_1\beta_1(\mu + \gamma) + c_2\beta_2\sigma]}\right], \quad (5)$$

then $\mathcal{R}_0(\alpha_c) = 1$ (assuming $\epsilon > 0$). Further, if

$$\epsilon_c = \frac{1}{\alpha}\left[1 - \frac{(\mu + \gamma)(\mu + \sigma)}{[c_1\beta_1(\mu + \gamma) + c_2\beta_2\sigma]}\right], \quad (6)$$

then $\mathcal{R}_0(\epsilon_c) = 1$ (assuming $\alpha > 0$). Since $\mathcal{R}_0$ is a decreasing function of both α and ϵ, it follows that $\mathcal{R}_0 < 1$ whenever $\alpha > \alpha_c$ or $\epsilon > \epsilon_c$. It should be noted that since $p = \alpha\epsilon$, $\mathcal{R}_0$ is also a decreasing function of p. This implies that, using Theorem 3, HIV can be eradicated from the community if $p > p_c = \alpha_c\epsilon_c$.

SENSITIVITY ANALYSIS

Mathematical models often include parameters, estimated from experiments, for which their actual values are not

known precisely. Hence, the effects of parameter uncertainties on the model predictions should be addressed. This can be accomplished by sensitivity and uncertainty analysis using the proposed ranges of the model parameters. Such analysis can be used for various purposes, such as ranking the parameters in order of their relative importance to the results and for assessing changes in the results due to variability in the parameter ranges. This is particularly important in studying complex models whose behaviour may only be understood by numerical analysis (Blower and Dowlatabadi, 1994).

In this section, we consider a sampling approach that allows for the simultaneous variation of all eight parameters associated with $\mathcal{R}_0$. Upon construction of such a sample, we describe and perform a sensitivity analysis of the model. The objective of this analysis is to properly identify those parameters that have the most effect in changing $\mathcal{R}_0$.

Latin Hypercube Sampling

To ensure full coverage of the parameter space when constructing a random sample, McKay *et al.* (1979) introduced the notion of latin hypercube sampling (LHS). In LHS the range of each variable is divided into n intervals of equal probability and one value is then selected at random from each interval. Thus, there are n observations on each of the k parameters. Consider the selection of one sample point. An observation on x_1 is randomly selected and then paired with a randomly selected observation on x_2. This pair is then randomly paired with an observation on x_3. The process continues in a similar fashion through x_k. This sample point selection process is repeated n times to form the sample. Note that, under LHS, each of the n intervals for a given parameter may be sampled only once. This implies that within the sample, each parameter value is unique.

In LHS, parameters are treated as random variables. Thus, probability functions must be defined for each parameter prior to the selection of the parameter values. Our analysis assumes that the parameters associated with $\mathcal{R}_0$ (namely, c_1, c_2, μ, σ, γ, β_1, β_2 ϵ and α) are independent and uniformly distributed with ranges given in Table I. Under these assumptions, we obtain a sample of size $n = 100$ using the methodology of the preceding paragraph. The uniform distribution was chosen over the Gaussian (normal) because we have no evidence that the ends of the ranges are any less probable than the values in the middle.

Partial Rank Correlation Coefficients

A common measure of sensitivity is the Pearson product moment correlation coefficient, which provides a one number summary as to the linear relationship between an x_i and a response. However, such correlation analyses often perform poorly when the relationship between the parameters and response variables is nonlinear

(Saltelli *et al.*, 2000). In such a scenario, problems may be mitigated by use of a rank transformation on the data. Specifically, the use of partial rank correlation coefficients (PRCCs) allows one to quantify the strength of the relationship between each parameter and each response while keeping all of the other parameters constant (Conover, 1980; Blower and Dowlatabadi, 1994). Note that a PRCC measures the degree of monotonicity between a parameter and a response. Thus, the PRCC approach assumes a monotonic relationship between the response variables and the model parameters. We may ascertain the relative importance of the model parameters by comparing the values of the PRCCs. A PRCC must be between -1 and $+1$ with values approaching either bound indicating a larger role for the parameter in predicting the response.

Using the 100 observations from the LHS, PRCCs were calculated between the eight parameters and the response, $\mathcal{R}_0$. Scatterplots were examined to verify the existence of monotonic relationships between the parameters and $\mathcal{R}_0$. The PRCCs are presented in Table II.

Table II identifies c_2, β_2, p, c_1 and β_1 as the parameters most important in predicting the basic reproductive number of infection, $\mathcal{R}_0$. Positive PRCCs for c_2, β_2, c_1 and β_1 imply that as these parameters increase in value so will $\mathcal{R}_0$. Conversely, the negative PRCC for p implies that as condom-induced preventability ("level of protection") increases $\mathcal{R}_0$ will decrease. The PRCCs analysis (Table II) shows that the number of sexual partners in the AIDS class (c_2) is the most important parameter that affects the transmission dynamics of HIV in the population. The third important parameter is the preventability which has a negative effect on the epidemic as increasing p decreases $\mathcal{R}_0$ and, therefore, the level of epidemicity.

Figures 1–3 provide a visual assessment of the effect of p on $\mathcal{R}_0$ for three ranges of c_1 and c_2 as follows:

Figure 1: $1 \leq c_1 \leq 6$, $1 \leq c_2 \leq 3$;

Figure 2: $1 \leq c_1 \leq 30$, $1 \leq c_2 \leq 30$;

Figure 3: $1 \leq c_1 \leq 100$, $1 \leq c_2 \leq 100$.

For each range of c_1 and c_2, we evaluate $\mathcal{R}_0$ at $p = (0.5, 0.6, 0.7, 0.8, 0.9, 0.95, 0.98, 1)$. The five

TABLE II   Partial rank correlation coefficients

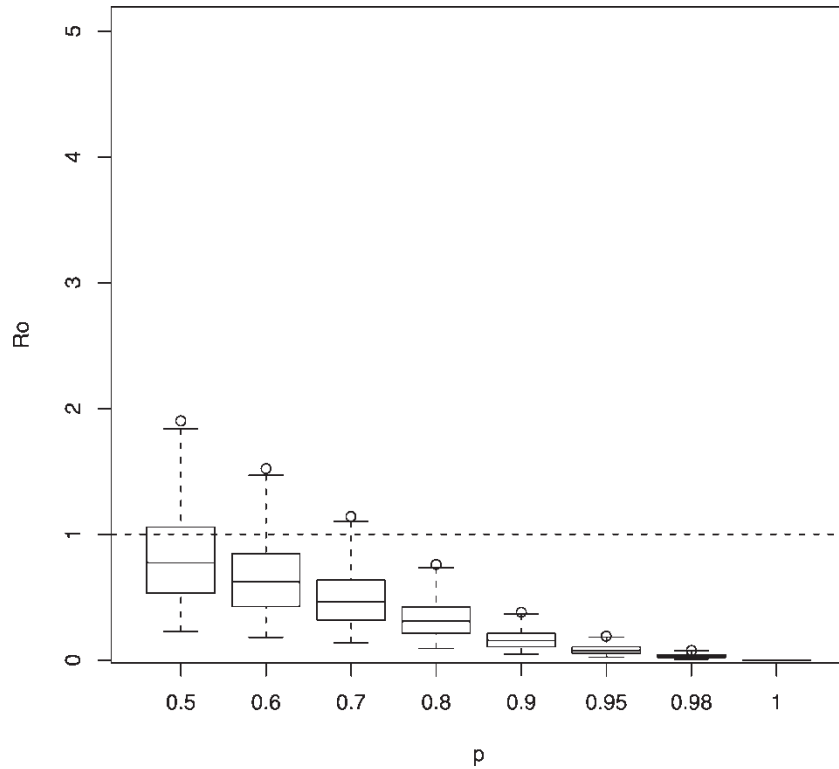| Parameter	PRCCs
c_2	0.86
β_2	0.81
$p = \epsilon\alpha$	-0.74
c_1	0.51
β_1	0.45
σ	-0.26
μ	-0.04
γ	0.03

FIGURE 1   Plot of $\mathcal{R}_0$ vs. preventability (p), when $1 \leq c_1 \leq 6$ and $1 \leq c_2 \leq 3$. The horizontal dashed-line indicates $\mathcal{R}_0 = 1$. The values of $\mathcal{R}_0$ less than one indicate the region in which the epidemic halts. For a given value of p, each boxplot displays the 25th (Q_1) and 75th (Q_3) percentiles of $\mathcal{R}_0$. The 25th percentile is denoted by the lower horizontal line on a box. Note that "whiskers" extend outwards from each box. The whiskers extend to the most extreme value for $\mathcal{R}_0$ which is no more than $1.5(Q_3 - Q_1)$ away from the box. Any value of $\mathcal{R}_0$ plotted beyond the whiskers is considered an outlier.
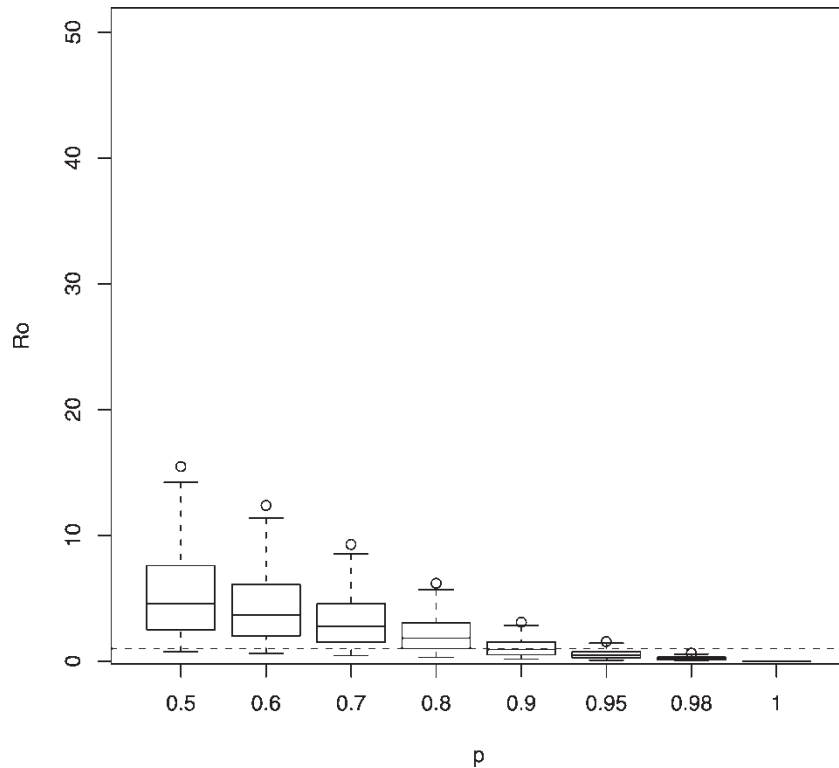

FIGURE 2   Plot of $\mathcal{R}_0$ vs. preventability (p), when $1 \leq c_1 \leq 30$ and $1 \leq c_2 \leq 30$.
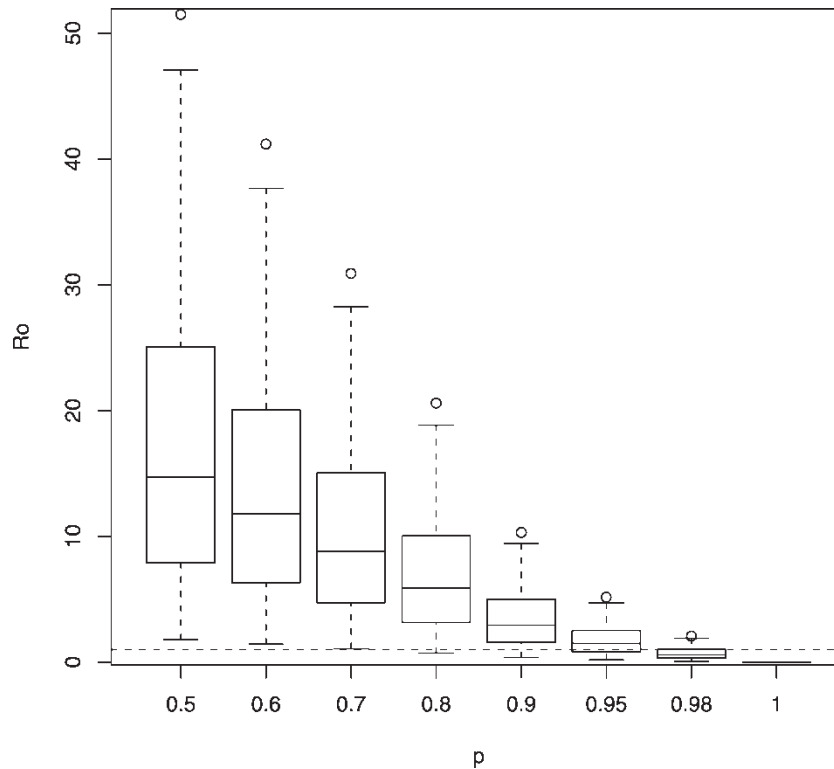
FIGURE 3   Plot of $\mathcal{R}_0$ vs. preventability (p), when $1 \le c_1 \le 100$ and $1 \le c_2 \le 100$.

model parameters $(\beta_1, \beta_2, \sigma, \mu, \gamma)$ take their values at the 100 sample points determined by the LHS. For a given range of c_1 and c_2 we may then form separate boxplots for $\mathcal{R}_0$ evaluated at $p = (0.5, 0.6, 0.7, 0.8, 0.9, 0.95, 0.98, 1)$.

Plotting $\mathcal{R}_0$ vs. p yields an informative graphical summary of the effect of condom-induced preventability on $\mathcal{R}_0$. For $1 \le c_1 \le 6$ and $1 \le c_2 \le 3$, Fig. 1 shows that the threshold preventability, p_c, is approximately 0.75. Note that for larger values of p, the variability of $\mathcal{R}_0$ decreases, as evidenced by the decreasing spread about the median (denoted by the solid-line) in each of the boxplots. In Figure 2, where $1 \le c_1 \le 30$ and $1 \le c_2 \le 30$, we observe that the threshold preventability is at $p_c = 0.97$. When $1 \le c_1 \le 100$ and $1 \le c_2 \le 100$, as in Figure 3, p_c is at about 0.99. These results clearly show an increasing threshold preventability (p_c) with increasing number of sexual partners (c_1 and c_2).

In summary, the results show that the transmission dynamics of the AIDS epidemic is critically dependent on the number of sexual partners and condom-induced preventability (see Table II). Our study confirms that reducing the number of infected sexual-partners (especially those in the AIDS class), and the use of condoms that lead to high preventability level, can force the epidemic to stop. These results are in line with the Reiss and Leik (1989) study, which models the effect of number of sexual partners and condom use in reducing new cases of HIV infection.

CONCLUSIONS

In this paper, we have concentrated on the effect of condom use in HIV prevention in the absence of any treatment. Based on the stability and sensitivity analyses carried out (using realistic parameter estimates), this study suggests that the preventability is a critical quantity that significantly impacts the basic reproductive number of infection ($\mathcal{R}_0$). Using the LHS and PRCC techniques in the uncertainty and sensitivity analysis of the model, it was shown that the number of sexual partners in the AIDS class is the most important parameter that impacts HIV prevalence. Thus, increasing preventability should be an important public health objective. Our study confirms that in order to stop the AIDS epidemic, attention must be focussed on: (i) improving condom efficacy; and (ii) improving compliance in condom use, so that the desired condom-induced preventability level is attained and maintained. These will require development and application of techniques that are effective in setting and monitoring quantitative measures for compliance and efficacy.

DISCUSSION

This paper models the use of condoms as a public health strategy for the control or eradication of HIV infection. The results of this paper permit a more quantitative picture on how to stop the AIDS epidemic than our earlier work

(Gordon, 1989). If the product of the efficacy and compliance for condoms (preventability) exceeds a certain threshold (p_c), then the epidemic will stop. Although for populations where the average number of HIV-infected partners is large, the associated preventability threshold is high and perhaps unattainable (suggesting that for such a population, HIV may not be controlled using condoms alone), our study shows that for populations where the average number of HIV-infected partners is low (within a reasonable range), p_c is about 75%. We think that $p_c = 75\%$ is an attainable goal. Indeed, compliance of 80% has been achieved in Kenya which just crosses $p_c = 75\%$ if condom efficacy is 95% (Plummer, 2003). Thus, repeated statements that only a future HIV vaccine will stop this epidemic (Little *et al.*, 1999; De Cock, 2001) need to be re-examined. Given the will and the effort, it is within our means to halt HIV epidemic in populations with low average number of HIV-infected partners using condoms. For example, the AIDS epidemic in Thailand appears to be declining, and demonstrates what can be achieved with a partially successful '100% Condom Programme' (Hanenberg *et al.*, 1994) and ancillary measures. But it is difficult to maintain a high level of compliance, especially when everyone knows that the epidemic is subsiding:

"… there is no room for complacency. Thailand's HIV/AIDS response (2001) has been a comprehensive multisectoral effort. It has mobilized the various sectors of society at all levels (national, provincial, district, and village) to respond to the epidemic. However, should the sense of urgency be lost and these efforts begin to falter at any level or should men no longer perceive significant risk in visiting sex workers, condom use rates could begin to fall and the epidemic could begin to grow rapidly again." (Thai Working Group on HIV/AIDS, 2001)

Clearly, we need to invest in continuous quantitative monitoring of both efficacy and compliance for condoms, to make sure that the preventability is always above the threshold p_c. The threshold must be reached and held for the epidemic to stop. On the other hand, having a quantitative threshold makes it easier to assess how well we are doing. Expenditures on public advertising and education can be increased or decreased as needed according to how far population behaviour is below or above the preventability threshold. Instructions on proper usage of condoms, and how to be assertive about demanding their use will promote condom compliance, thereby increasing preventability.

Consider an analogy with campaigns to reduce road traffic deaths. There are two major factors here: efficacy of automobiles in permitting people to survive crashes, and compliance with safe driving practice through education, traffic density and weather warnings, and penalties for faulty driving. Efficacy and compliance are the objects of major state and commercial institutions, which cooperate to a significant degree, and provide feedback to one another as to how well they are doing in reducing traffic deaths, via regulation and litigation. We have little or no comparable institutional support or feedback in AIDS prevention. There are no firm incentives to produce

substantially different and safer condoms, perhaps because the condom industry is not held responsible for AIDS prevention the way the automobile industry is held responsible for preventing traffic deaths.

The main causes of condom failure, other than user errors, are slippage and breakage. The NIH Report concludes:

"Only three published articles report results from recent prospective sizeable trials of latex condoms in the U.S. and provide reliable slippage and breakage rates (Frezieres *et al.*, 1998; 1999; Macaluso *et al.*, 1999). Estimates of condom breakage from these studies range from 0.4 to 2.3%. Slippage rates from these three studies ranged from 0.6% to 1.3%." (Adam *et al.*, 2001)

Slippage and breakage may have a common origin in the shear forces applied during condom use. As an example of how condoms might be improved, consider a preliminary study we conducted (Björklund and Gordon, 1990) demonstrating leakage over the rim, and suggesting a modification to prevent it. This study illustrates how research on condom effectiveness can lead to new designs that may prove significantly better. If even a fraction of the effort that is put into crash test dummies for automobiles were applied to condom design, condom effectiveness might indeed increase (see Pinkerton and Abramson, 1995).

Unfortunately, despite the collection of a large qualitative set of data on compliance, no mean or range figures were estimated in (Davis and Weller, 1999). There is a need for collection of compliance data, so that compliance could be monitored quantitatively in a population. Only then could we actually know if the preventability (the product of condom efficacy and compliance) is staying above the threshold p_c for stopping the AIDS epidemic.

It should be mentioned that although the model designed in our study is based on the interactions between susceptibles and infectives, these sub-populations could be further subdivided into subcomponents that incorporate, for instance, the sex and age of the sub-populations (Greenhalgh *et al.*, 2001; Hsieh and Sheu, 2001), or the distinction between condom use with primary and secondary partners (Bracher *et al.*, 2004; Foss *et al.*, 2004). Monitoring of within-group variability would lead to increase in dimensionality of the model and, consequently, would make the model more complicated to analyse mathematically. Our study may also be extended to include the effect of behaviour changes with selective-mixing of susceptible-infective-susceptible (Hyman and Li 1997; 1998). However, the model's ability to predict disease control depends greatly on the assumptions given in the model equations.

Our model, like many other models in the literature, assumes that the influence of all individuals (in the same sub-population) is identical in the spread of the disease. However, there are a few studies on the effect of a core group (the group of individuals who are sexually very active) in the transmission dynamics of STDs. For instance, Moghadas (2002) discussed two group

models for STDs in which the core group is a sub-population of susceptibles or infectives. The results of this study show that the transmission dynamics of epidemic disease is critically dependent on the effect of small sub-populations with varying levels of sexual activity. Therefore, the average number of sexual encounters of the core group can play an important role in the spread of the disease (see Hadeler and Castillo-Chavez, 1994; Moghadas, 2002).

Our study can also be extended to incorporate control strategies such as the use of highly-active anti-retroviral therapy (HAART) and/or anti-HIV preventive vaccines (see Hosseinipour *et al.*, 2002). This may lead to the phenomenon of bistability (as observed in Greenhalgh *et al.*, 2001) where a stable endemic steady-state and the stable disease-free steady-state co-exist. In this case, controlling the initial sizes of the sub-populations can force elimination in place of the persistence of infection. Further details on the phenomenon of bistability in epidemic models can be found in Kribs-Zaleta (2002).

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References

Adam, M.B., Auerbach, J.D., Buehler, J.W., Burk, R., Cohen, P.R., Fitch, J.T., Gerofi, J., Hager, W.D., Hildesheim, A., Hitchcock, P.J., Hook, III, E.W., Kanouse, D.E., Krieger, J.N., Luoto, J., McIlhaney, Jr., J.S., Miller, H., Newcomer, S.F., Orr, D., Pollard, C.M., Ronald, A.R., Santelli, J.S., Schacker, T.W., Schwebke, J.R., Sonenstein, F., Spieler, J., Stanberry, L., Weller, S.C. and Wendel, Jr., G.D. (2001) *Workshop Summary: Scientific Evidence on Condom Effectiveness for Sexually Transmitted Disease (STD) Prevention*, Bethesda: National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services (http://www.niaid.nih.gov/dmid/stds/condomreport.pdf).

Anderson, R.M. and May, R.M. (1991) *Infectious Diseases of Humans* (Oxford University Press, London/New York).

Björklund, N.K. and Gordon, R. (1990) "If semen were red: the spread of red dye from the tips of condoms during intercourse and its consequences for the AIDS epidemic", *International Conference, Assessing AIDS Prevention*, (Montreux, Switzerland), (http://www.umanitoba.ca/faculties/ medicine/radiology/stafflist/rgordon.html).

Blower, S.M. and Dowlatabadi, H. (1994) "Sensitivity and uncertainty analysis of complex models of disease transmission: an HIV model, as an example", *Int. Stat. Rev.* **62**, 229–243.

Bracher, M., Santow, G. and Watkins, S.C. (2004) "Assessing the potential of condom use to prevent the spread of HIV: a microsimulation study", *Stud. Fam. Plann.* **35**(1), 48–64.

Busenberg, S. and Van den Driessche, P. (1990) "Analysis of a disease transmission model in a population with varying size", *J. Math. Biol.* **28**, 257–270.

Conover, W.J. (1980) *Practical Nonparametric Statistics*, 2nd Ed. (John Wiley and Sons Inc., New York, NY).

Davis, K.R. and Weller, S.C. (1999) "The effectiveness of condoms in reducing heterosexual transmission of HIV", *Fam. Plann. Perspect.* **31**(6), 272–279.

De Cock, K.M. (2001) "Epidemiology and the emergence of human immunodeficiency virus and acquired immune deficiency syndrome", *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **356**(1410), 795–798.

Foss, A.M., Watts, C.H., Vickerman, P. and Heise, L. (2004) "Condoms and prevention of HIV", *BMJ* **329**, 185–186.

Fowke, K.R., Nagelkerke, N.J., Kimani, J., Simonsen, J.N., Anzala, A.O., Bwayo, J.J., MacDonald, K.S., Ngugi, E.N. and Plummer, F.A. (1996) "Resistance to HIV-1 infection among persistently sero-negative prostitutes in Nairobi", *Kenya. Lancet* **348**(9038), 1347–1351.

Frezieres, R.G., Walsh, T.L., Nelson, A.L., Clark, V.A. and Coulson, A.H. (1998) "Breakage and acceptability of a polyurethane condom: a randomized, controlled study", *Fam. Plann. Perspect.* **30**(2), 73–78.

Frezieres, R.G., Walsh, T.L., Nelson, A.L., Clark, V.A. and Coulson, A.H. (1999) "Evaluation of the efficacy of a polyurethane condom: results from a randomized, controlled clinical trial", *Fam. Plann. Perspect.* **31**(2), 81–87.

Gordon, R. (1989) "A critical review of the physics and statistics of condoms and their role in individual versus societal survival of the AIDS epidemic", *J. Sex Marital Ther.* **15**(1), 5–30.

Gray, R.H., Wawer, M.J., Brookmeyer, R., Sewankambo, N.K., Serwadda, D., Wabwire-Mangen, F., Lutalo, T., Li, X., vanCott, T. and Quinn, T.C. (2001) "Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda", *Lancet* **357**, 1149–1153.

Greenhalgh, D., Doyle, M. and Lewis, F. (2001) "A mathematical treatment of AIDS and condom use", *IMA J. Math. Appl. Med. Biol.* **18**(3), 225–262.

Hadeler, K.P. and Castillo-Chavez, C. (1994) "A core group model for disease transmission", *Math. Biosci.* **128**, 41–55.

Hanenberg, R.S., Rojanapithayakorn, W., Kunasol, P. and Sokal, D.C. (1994) "Impact of Thailand's HIV-control programme as indicated by the decline of sexually transmitted diseases", *Lancet* **344**(8917), 243–245.

Hethcote, H.W. (2000) "The mathematics of infectious diseases", *SIAM Review* **42**(4), 599–653.

Hosseinipour, M., Cohen, M.S., Varnazza, P.L. and Kashuba, A.D.M. (2002) "Can antiretroviral therapy be used to prevent sexual transmission of human immunodeficiency virus type 1?", *Clinical infectious Diseases* **34**, 1391–1395.

Hsieh, Y.H. and Sheu, S.P. (2001) "The effect of density dependent treatment and behavior change on the dynamics of HIV transmission", *J. Math. Biol.* **43**, 69–80.

Hyman, J.M. and Li, J. (1997) "Behavior changes in SIS STD models with selective mixing", *SIAM J. Appl. Math.* **57**(4), 1082–1094.

Hyman, J.M. and Li, J. (1998) "Modeling the effectiveness of isolation strategies in preventing STD epidemics", *SIAM J. Appl. Math.* **58**(3), 912–925.

Hyman, J.M., Li, J. and Stanley, E.A. (1999) "The differential infectivity and staged progression models for the transmission of HIV", *Math. Biosci.* **155**, 77–109.

Kribs-Zaleta, C.M. (2002) "Center manifold and normal forms in epidemic models", *The IMA volumes in mathematics and its applications* **125**, 269–286.

Little, S.J., McLean, A.R., Spina, C.A., Richman, D.D. and Havlir, D.V. (1999) "Viral dynamics of acute HIV-1 infection", *J. Exp. Med.* **190**(6), 841–850.

Macaluso, M., Kelaghan, J., Artz, L., Austin, H., Fleenor, M., Hook, 3rd, E.W. and Valappil, T. (1999) "Mechanical failure of the latex condom in a cohort of women at high STD risk", *Sex. Transm. Dis.* **26**(8), 450–458.

Maticka-Tyndale, E. (1997) "Reducing the incidence of sexually transmitted disease through behavioural and social change", *Can. J. Hum. Sex.* **6**(2), 1–25.

May, R.M. and Anderson, R.M. (1987) "Transmission dynamics of HIV infection", *Nature* **326**, 137–142.

McKay, M.D., Conover, W.J. and Beckman, R.J. (1979) "A comparison of three methods for selecting values of input variables in the analysis of output from a computer code", *Technometrics* **21**, 239–245.

Moghadas, S.M. (2002) "Two core group models for sexual transmission of disease", *Ecol. Model.* **148**, 15–26.

Moghadas, S.M. and Gumel, A.B. (2002) "Global stability of a two-stage epidemic model with generalized non-linear incidence", *Math. Comput. Simulation* **60**, 107–118.

Petruckevitch, A., Del Amo, J., Phillips, A.N., Johnson, A.M., Stephenson, J., Desmond, N., Hanscheid, T., Low, N., Newell, A., Obasi, A., Paine, K., Pym, A., Theodore, C. and De Cock, K.M. (1998) "Disease progression and survival following specific AIDS-defining conditions: a retrospective cohort study of 2048 HIV-infected persons in London", *AIDS* **12**(9), 1007–1013.

Pinkerton, S.D. and Abramson, P.R. (1995) "The joys of diversification: vaccines, condoms, and AIDS prevention", *AIDS and Public Policy J.* **10**(3), 148–156.

Pinkerton, S.D. and Abramson, P.R. (1997) "Effectiveness of condoms in preventing HIV transmission", *Soc. Sci. Med.* **44**, 1303–1312.

Plummer, F.A. (2003) Report. University of Manitoba Bulletin, Vol. 6, 36 (20), pp.11.

Porco, T.C. and Blower, S.M. (1998) "Designing HIV vaccination policies: subtypes and cross-immunity", *Interfaces* **28**, 167–190.

Reiss, I. and Leik, R. (1989) "Evaluating strategies to avoid AIDS: number of partners vs. use of condoms", *J. Sex Res.* **26**, 411–433.

Royce, R.A., Sena, A., Cates, W. and Cohen, M.S. (1997) "Sexual transmission of HIV", *N. Engl. J. Med.* **336**, 851–854.

Saltelli, A., Chan, K. and Scott, E.M. (2000) *Sensitivity Analysis* (John Wiley and Sons Ltd., West Sussex, England).

Thai Working Group on HIV/AIDS (2001) HIV/AIDS Projections for Thailand: 2000–2020. Executive summary. Thai Working Group on HIV/AIDS Projection, Feb 10, 2001.

Thailand Ministry of Public Health (2001) The Success of the 100% Condom Programme in Thailand: Policy Implications and Recommendations, Thailand Ministry of Public Health [http://www.cdcnet. moph.go.th/cdcdept/Aids/aids-en.htm].

Velasco-Hernandez, J.X. (1994) "A model for chagas disease involving transmission by vector and blood transfusion", *Theor. Popul. Biol.* **46**(1), 1–31.

Wannamethee, S.G., Sirivichayakul, S., Phillips, A.N., Ubolyam, S., Ruxrungtham, K., Hanvanich, M. and Phanuphak, P. (1998) "Clinical and immunological features of human immunodeficiency virus infection in patients from Bangkok", *Thai. Int. J. Epidemiol.* **27**(2), 289–295.