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A population model applied to HIV transmission considering protection and treatment

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An epidemiological population model is proposed to assess the impact of protection and/or treatment strategies applied to HIV infection. Sex-education campaigns are the available protection strategy, and drug (or association of drugs) administration is the treatment strategy considered. In this model we assumed recruitment and differential mortality rates for the homosexual population. In addition to the classical threshold contact rate related to the establishment of the disease, we obtained a threshold input rate.

Keywords: protection; treatment; steady state; sensitivity; HIV/AIDS.

1. Introduction

In addition to the biological aspects, to control an epidemic epidemiologists must take into account social factors that can influence the transmission mechanisms of the disease. Protection of the population through preventive education (and/or vaccination, if available) and treatment of infected individuals who are transmitting the disease are important. Estimation of the influence exerted by those factors in the overall transmission of the disease could help in designing intervention to control an epidemic.

There are many papers describing mathematical models dealing with vaccination as a control strategy for directly transmitted diseases (Anderson & May, 1991; Azevedo *et al.*, 1994; Dietz, 1975; Greenhalgh, 1990; Hethcote, 1988; Massad *et al.*, 1995; Yang, 1998). However, there is still no such protection for HIV/AIDS, a disease with a variety of social components. Looking into HIV sexual route transmission (Anderson & May, 1991; Yang *et al.*, 1999), preventive education and treatment are available as controlling strategies.

Greenhalgh (1992a) considered a population model for directly transmitted diseases with a density dependent death rate and, he proposed (1992b) a vaccination strategy and analysed its effects. Pugliese (1990) applied population models to describe directly sexually transmitted diseases, taking into account the probability of infection dependent on the density of susceptible individuals. Both authors considered a constant input rate but treatment strategies are absent from their models. Mena-Lorca & Hethcote (1992) analysed a population model with constant mortality and input rates, and Gao & Hethcote (1992) used logistic functions for both rates. In this paper we propose and analyse a population model with protection and/or treatment considering a logistic function as an input rate and constant natural and disease-induced (differential) mortality rates.

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Our model is applied to the acquired immune deficiency syndrome (AIDS) disease induced by the human immunodeficiency virus (HIV) to assess the impact of protection and treatment strategies in a homosexual population. Without an effective vaccine, the protection of the population can only be achieved by (Strang & Stimson, 1990) sex-education campaigns (Anderson *et al.*, 1989; Morton, 1992) aiming to induce a behavioural change. On the other hand, a therapy for HIV-infected and individuals with AIDS is available (Longini *et al.*, 1992), although it only prolongs the infectious period without preventing progression to the AIDS disease. However, in order to receive treatment, HIV infectious individuals must be reached, and their acquiescence to participate in the therapy programme obtained.

Two threshold values related to the epidemics are obtained. The first is the threshold contact rate concerning establishment of the disease to an endemic level. The other is the threshold input rate which relates the population survival to the additional mortality induced by the disease. Both threshold values, which are dependent on the protection and treatment strategies and also on the differential mortality rate, influence the three equilibrium states: population extinction, disease-free community, and the endemic situation.

The influences of protection and/or treatment strategies are assessed for desirable effects on the endemic level with respect to external efforts. The stability and the sensitivity of equilibrium points are analysed by considering variations in the model parameters, and dynamical approaches to the equilibrium points are also shown. The analysis of the effort–benefit relation of intervention is left to a further paper.

2. The model

Our model deals with HIV transmission among homosexual individuals within a population. The model takes into account—in addition to the classically considered susceptible, latent, infectious, and diseased individuals—a new group of protected individuals. Also, infectious individuals are subdivided into classes of participating and nonparticipating individuals among the available treatments.

Protected individuals (Hyman & Stanley, 1988) are those reached by a sex-education campaign resulting in the use of condoms, the identification and full knowledge of cofactors, and a decrease in the number of partners, among others factors. However, this is not a lifelong protection, because the consciousness of HIV transmission can be lost with the abandonment of protection practices (Power, 1990).

The treatment assumption, of course, is a drastic simplification of the real situation, where HIV infectious individuals are found by vigilant HIV testing and case tracing, and then treated. This procedure delays the manifestation of the AIDS disease. In our approach, the proportion of treated individuals in the whole infectious group might be taken as the effectiveness of HIV vigilance.

The population model for HIV transmission based on protection and/or treatment strategies is described by compartmentalization of individuals and by parameters relating their flow between compartments.

The population is, then, subdivided into six compartments x_1, x_2, x_3, x_4, x_5, and x_6, representing, respectively, the number of susceptible, latent, infectious not-treated, infectious

treated, diseased, and protected individuals. The variable x_7, given by

$$x_7 = \sum_{i=1}^{6} x_i, \tag{1}$$

is the total population size.

The parameters to be used in the model are defined as follows.

(a) The sex-education campaigns for safe sex (blood-derived HIV infection is not considered) are represented by the protection rate ν which influences distinctive effects on the different classes.

(b) There is a loss of protection described by

$$\zeta(\nu) = \zeta_0 e^{-\zeta_1 \nu}, \tag{2}$$

where ζ_0 is the maximum protection loss rate, ζ_1 (dimension of *time*) is such that the exponential decay indicates an increasing average period of permanence in the protected group as a result of an education campaign.

(c) Effective HIV vigilance detects a proportion p of infectious individuals. The average period of AIDS disease manifestation can be set as

$$\gamma^{-1}(p) = \begin{cases} \gamma_0^{-1} & \text{if } p = 0, \\ \gamma^{*-1} & \text{if } p > 0, \end{cases} \tag{3}$$

where γ_0^{-1} is the natural infectious period and γ^{*-1} is the delayed infectious period. This infectious period is followed by a period of HIV incubation σ^{-1}.

(d) The force of infection λ (Anderson & May, 1991) takes the form

$$\lambda = \beta \frac{\varepsilon_1(\nu)x_3 + \varepsilon_2(\nu)x_4 + \varepsilon_3(\nu)x_5}{x_7}, \tag{4}$$

where β is the contact rate and the $\varepsilon_i(\nu)$ $(i = 1, 2, 3)$ are the effectiveness of contacts of susceptible individuals with infectious not-treated, infectious treated, and diseased individuals, respectively. The dynamics of sexually transmitted diseases are strongly affected by education campaigns, because of changes in partnership relations (social and behavioural (Morton, 1992)) resulting from acquired protective habits. Therefore, the effectiveness of contact could be described as a function of the protection rate given by

$$\varepsilon_i(\nu) = \left(\varepsilon_i - \varepsilon_i^0\right) e^{-\varepsilon_i^* \nu} + \varepsilon_i^0, \tag{5}$$

decreasing from ε_i to ε_i^0, where ε_i^* is the *reluctant* factor (dimension of $time$). Anderson *et al.* (1988) gave a different interpretation to the parameters β and ε, calling them, respectively, the probability of acquiring infection from any one infected partner and the average rate of acquiring partners.

(e) The recruitment rate ϕ of susceptible individuals will be taken as

$$\phi = \phi_0 x_7 \left(1 - \frac{x_7}{n}\right), \tag{6}$$

where ϕ_0 is the intrinsic input rate and n is the saturation level of the homosexual population.

(f) Finally, μ and α are the natural and differential mortality rates.

The dynamics of HIV infection based on the above descriptions can be represented by a system of differential equations

$$\dot{\mathbf{x}} = \mathbf{F}[\mathbf{x}, \theta], \tag{7}$$

where the dynamic variable space is

$$\mathbf{x} = [x_1, x_2, x_3, x_4, x_5, x_6]^{\mathsf{T}}, \tag{8}$$

and the parameter space is

$$\theta = \left[\nu, \zeta_0, \zeta_1, \gamma_0, \gamma^*, p, \sigma, \beta, \varepsilon_i, \varepsilon_i^*, \varepsilon_i^0, \phi_0, n, \mu, \alpha\right]^{\mathsf{T}}. \tag{9}$$

The components of $\mathbf{F}[\mathbf{x}, \theta]$ are given by

$$\left.\begin{aligned}
F_1 &= \phi_0 x_7 \left(1 - \frac{x_7}{n}\right) - (\mu + \nu + \lambda)\, x_1 + \zeta(\nu) x_6, \\
F_2 &= \lambda x_1 - (\mu + \sigma)\, x_2, \\
F_3 &= \sigma\,(1 - p)\, x_2 - (\mu + \gamma_0)\, x_3, \\
F_4 &= \sigma p x_2 - (\mu + \gamma^*)\, x_4, \\
F_5 &= \gamma_0 x_3 + \gamma^* x_4 - (\mu + \alpha)\, x_5, \\
F_6 &= \nu x_1 - [\mu + \zeta(\nu)]\, x_6,
\end{aligned}\right\} \tag{10}$$

with the total population following

$$\dot{x}_7 = \phi_0 x_7 \left(1 - \frac{x_7}{n}\right) - \mu x_7 - \alpha x_5, \tag{11}$$

from relation (1).

In the next section the analysis of the stability of the equilibrium values is performed.

3. Steady-state analysis

We first present the three equilibrium values of system (10), and the stability analysis will be given later on.

(1) The population is made extinct by the disease; i.e.,

$$\mathbf{x}^1 = \{x_i = 0 : \text{ for } i = 1, 2, \ldots, 7\}. \tag{12}$$

We observe that this is always possible.

(2) The population is disease free; i.e.,

$$\mathbf{x}^2 = \begin{cases} x_1 = \left(1 - \dfrac{\mu}{\phi_0}\right) \dfrac{\mu + \zeta(\nu)}{\mu + \nu + \zeta(\nu)} n, \\ x_i = 0 \quad \text{for } i = 2, 3, 4, 5, \\ x_6 = \left(1 - \dfrac{\mu}{\phi_0}\right) \dfrac{\nu}{\mu + \nu + \zeta(\nu)} n, \\ x_7 = \left(1 - \dfrac{\mu}{\phi_0}\right) n. \end{cases} \tag{13}$$

We observe that this is meaningful if and only if $\phi_0 > \mu$.

(3) The disease is at an endemic level in the population; i.e.,

$$\mathbf{x}^3 = \begin{cases} x_1 = \dfrac{\mu + \zeta(\nu)}{\mu + \nu + \zeta(\nu)} g(\nu, p) \left[\phi_0 - \phi_0^{th}(\nu, p)\right] \dfrac{n}{\phi_0}, \\ x_2 = \dfrac{\mu}{\mu + \sigma} \dfrac{1 - g(\nu, p)}{1 - f(p)} \left[\phi_0 - \phi_0^{th}(\nu, p)\right] \dfrac{n}{\phi_0}, \\ x_3 = \dfrac{\mu\sigma(1 - p)}{(\mu + \sigma)(\mu + \gamma_0)} \dfrac{1 - g(\nu, p)}{1 - f(p)} \left[\phi_0 - \phi_0^{th}(\nu, p)\right] \dfrac{n}{\phi_0}, \\ x_4 = \dfrac{\mu\sigma p}{(\mu + \sigma)(\mu + \gamma^*)} \dfrac{1 - g(\nu, p)}{1 - f(p)} \left[\phi_0 - \phi_0^{th}(\nu, p)\right] \dfrac{n}{\phi_0}, \\ x_5 = \mu \dfrac{f(p)}{\alpha} \dfrac{1 - g(\nu, p)}{1 - f(p)} \left[\phi_0 - \phi_0^{th}(\nu, p)\right] \dfrac{n}{\phi_0}, \\ x_6 = \dfrac{\nu}{\mu + \nu + \zeta(\nu)} g(\nu, p) \left[\phi_0 - \phi_0^{th}(\nu, p)\right] \dfrac{n}{\phi_0}, \\ x_7 = \left[\phi_0 - \phi_0^{th}(\nu, p)\right] \dfrac{n}{\phi_0}, \end{cases} \tag{14}$$

where the auxiliary functions $f(p)$ and $g(\nu, p)$ are

$$f(p) = \frac{\alpha\sigma}{(\mu + \sigma)(\mu + \alpha)} \left[\frac{\gamma_0(1 - p)}{\mu + \gamma_0} + \frac{\gamma^* p}{\mu + \gamma^*}\right], \tag{15}$$

$$g(\nu, p) = \frac{\beta^{th}(\nu, p)}{\beta},$$

with the threshold contact rate $\beta^{th}(\nu, p)$ given by

$$\beta^{th}(\nu, p) = \frac{(\mu+\gamma_0)(\mu+\sigma)(\mu+\alpha)\dfrac{\mu+\nu+\zeta(\nu)}{\mu+\zeta(\nu)}}{\sigma\left\{[(\mu+\alpha)\,\varepsilon_1(\nu)+\gamma_0\varepsilon_3(\nu)](1-p)+\dfrac{\mu+\gamma_0}{\mu+\gamma^*}\left[(\mu+\alpha)\,\varepsilon_2(\nu)+\gamma^*\varepsilon_3(\nu)\right]p\right\}}, \tag{16}$$

and the threshold value for the intrinsic input rate $\phi_0^{th}(\nu, p)$ is given by

$$\phi_0^{th}(\nu, p) = \mu\frac{1-f(p)g(\nu, p)}{1-f(p)}. \tag{17}$$

Since $f(p) < 1$ is always true, $\mathbf{x}^3$ is meaningful if and only if $\phi_0 > \phi_0^{th}(\nu, p)$ and $R > 1$ (from the $1 - g(\nu, p)$ factor), where the *reproduction ratio* R is defined as

$$R = \frac{1}{g(\nu, p)}. \tag{18}$$

Note also that $\phi_0^{th}(\nu, p) \geqslant \mu$, with equality holding if $\alpha = 0$. The *basic reproduction ratio* is $R_0 = 1/g(0, 0)$ (Anderson & May, 1991).

The stability of the equilibrium points (12), (13), and (14) is analysed in Appendix A. In the next section we present some simulations which will further illustrate these results.

4. Numerical simulations

In this section we take values for the model parameters considering a moderately at-risk homosexual population. The disease-related parameters are $\alpha = 0.7$ years^{-1}, $\sigma = 2.0$ years^{-1}, $\gamma_0 = 0.102$ years^{-1} (Hessol *et al.*, 1990; Longini *et al.*, 1989), and $\gamma^* = 0.079$ years^{-1} (according to Longini *et al.* (1992) treatment increases the delayed infectious period by about 30%). The behavioural parameters are $\beta = 20.0$ years^{-1}, $\varepsilon_1 = 0.05$ (Anderson *et al.* (1988) used $\beta\varepsilon = 0.5$ years^{-1}), considering arbitrary values $\varepsilon_1^0 = 0.0001$ and $\varepsilon_1^* = 4.0$ years (50% reduction over a one-year time interval (Anderson *et al.*, 1989); i.e., $\nu\varepsilon_1^* \simeq 0.7$). Assuming that the infectious individuals in treatment and diseased individuals are positively affected by the protection strategy, we consider $\varepsilon_2 = 0.005$, $\varepsilon_2^0 = 0.0001$, $\varepsilon_2^* = 10.0$ years, $\varepsilon_3 = 0.001$, $\varepsilon_3^0 = 0.0001$, and $\varepsilon_3^* = 20.0$ years. The parameters for the induced protection are $\zeta_0 = 0.5$ and $\zeta_1 = 5.0$ years (supposing that when $\nu = 1.0$ years^{-1} the protection loss is near zero) and the populational parameters are $\mu = 0.015$ years^{-1}, $\phi_0 = 0.12$ years^{-1}, and $n = 10\,000$. All these values are assumed to be fixed, unless otherwise specified. The protection rate ν and the proportion p of treated infectious individuals are the parameters being investigated.

The effects of the protection strategy on the protection loss rate $\zeta(\nu)$ and the effectiveness of contact of susceptible individuals with infectious but not-treated individuals $\varepsilon_1(\nu)$ are shown in Fig. 1. The exponential decay mimics a kind of Weber–Fechner law (Stevens, 1970) which states that a psychological effect is proportional to the *relative* increase of the stimulus.

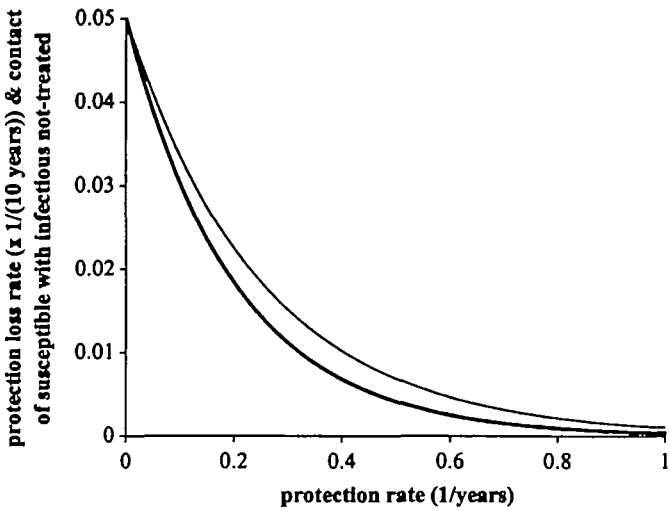


FIG. 1. (—) The protection loss rate ($\zeta(\nu) \times (10 \text{ years})^{-1}$) and (—) the effectiveness of contact ($\varepsilon_1(\nu)$) of susceptible individuals with infectious but not-treated individuals as a function of the protection rate ν.

In the next subsections, the steady-state analysis provides us with threshold conditions to assess different controlling strategies, this is followed by a dynamics analysis of state variables, and finally, a sensitivity analysis of the parameters is performed.

4.1 *Steady-state analysis*

We obtained three equilibrium values (12), (13), and (14) dependent on the *reproduction ratio* (18) and on the threshold value for the intrinsic input rate (17), in order to evaluate the effectiveness of the intervention.

In Fig. 2 the relationship between the threshold contact rate (16) and the treatment parameter p (with $\nu = 0$) and between ν (with $p = 0$) is shown.

The range of the threshold values are: $2.35 \text{ years}^{-1} \leqslant \beta^{th}(0, p) \leqslant 18.53 \text{ years}^{-1}$ for pure treatment, and $2.35 \text{ years}^{-1} \leqslant \beta^{th}(\nu, 0) < 6355.75 \text{ years}^{-1}$ for pure protection. Figure 2 shows that the pure-treatment strategy is not sufficient to eradicate the disease if the estimated contact rate β is higher than 18.53 years^{-1}. This can be seen more easily in Fig. 3.

In Fig. 3 the relationship between the *reproduction ratio* (18) and the treatment parameter p (with $\nu = 0$) and between ν (with $p = 0$) is shown. We use $\beta = 20.0 \text{ years}^{-1}$. The range of variation of these values are: $8.51 \geqslant R(0, p) \geqslant 1.08$ and $8.51 \geqslant R(\nu, 0) > 0.0031$. The eradication of the disease can be achieved by a pure-protection strategy whenever ν is higher than $\nu^* = 0.271 \text{ years}^{-1}$, while a pure-treatment strategy can never eradicate the disease.

This value of the critical protection rate can be evaluated from the transcendental equation

$$R(\nu^*, p) = 1 \tag{19}$$

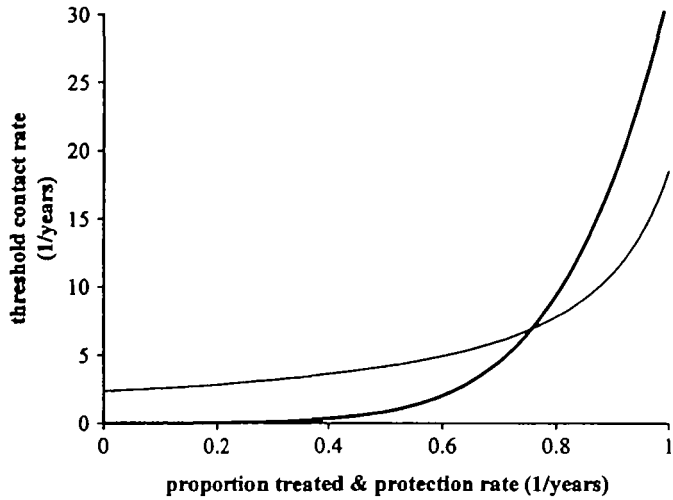


FIG. 2. The threshold contact rate β^{th} as a function of: (—) p ($\nu = 0$), and (—) ν ($\times 0.005$, $p = 0$).

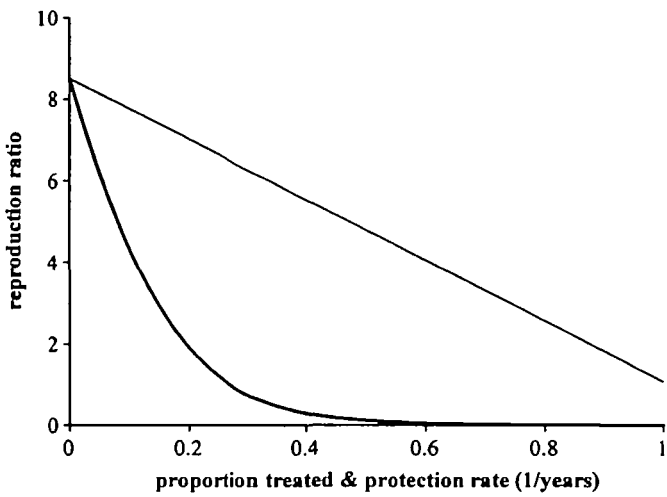


FIG. 3. The *reproduction ratio* R, setting $\beta = 20.0$ years^{-1}, as a function of: (—) p ($\nu = 0$), and (—) ν ($p = 0$).

setting $p = 0$. The range of the critical value with both strategies is 0.271 years$^{-1} \geqslant \nu^* \geqslant$ 0.0064 years^{-1}, as shown in Fig. 4. The joint strategy shows a decreasing critical value as the proportion of infectious individuals increases.

In Fig. 5 the relationship between the threshold intrinsic input rate given by (17), and the treatment parameter p (with $\nu = 0$) and between ν (with $p = 0$) is shown. The range of variations are: 0.088 years$^{-1} \geqslant \phi_0^{th}(0, p) \geqslant 0.020$ years^{-1}, and 0.088 years$^{-1} \geqslant$

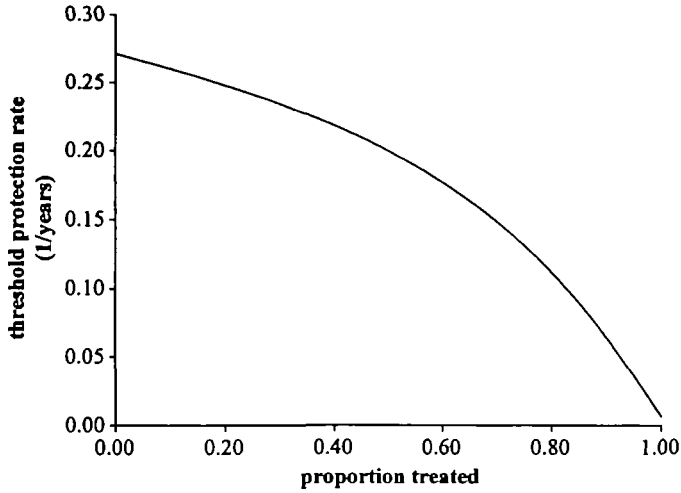


FIG. 4. The critical protection rate ν^* as a function of the proportion of infectious individuals in treatment, p

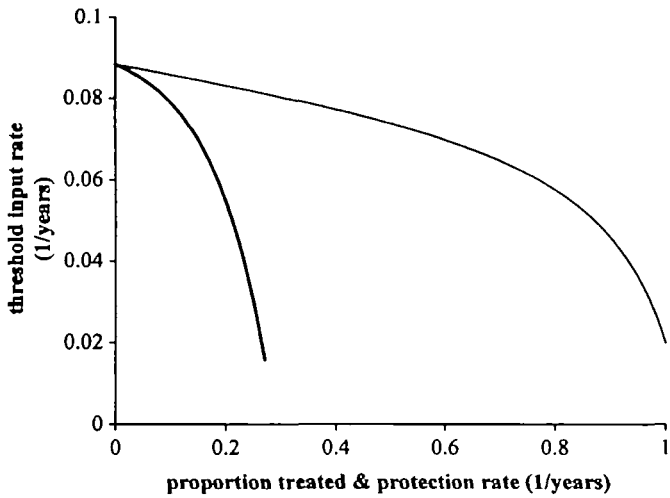


FIG. 5. The threshold intrinsic input rate ϕ_0^{th}, setting $\beta = 20.0$ years^{-1}, as a function of: p (—) ($\nu = 0$), and (—) ν ($p = 0$).

$\phi_0^{th}(\nu, 0) \geqslant \mu = 0.015$ years^{-1}. When $\nu > \nu^*$ (and $p = 0$), then $R < 1$ so $g(\nu, p) > 1$ and $\phi_0^{th}(\nu, 0) < \mu$. Therefore, in this situation we expect the population to die out if $\phi_0 < \mu$ and for it to tend to the disease-free equilibrium if $\phi_0 > \mu$.

The relationship between the equilibrium values (given by their fractions X_i) as a function of the treatment parameter p ($\nu = 0$) and between ν (with $p = 0$) is shown in Fig. 6(a) and (b), respectively.

We used equilibrium fractions $X_1 = 0.118$, $X_2 = 0.042$, $X_3 = 0.735$, $X_5 = 0.105$,

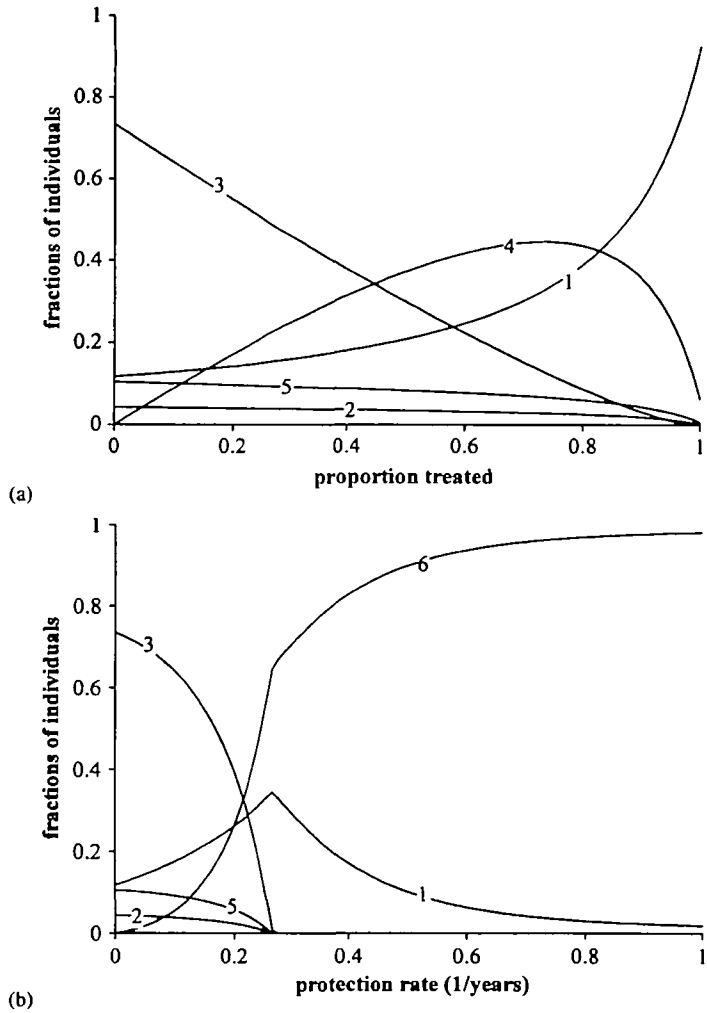


FIG. 6. The equilibrium proportions $X_i = x_i/x_7$ ($i = 1$–6) (whose curves are labelled by their respective numbers): (a) as a function of p ($\nu = 0$), and (b) as a function of ν ($p = 0$). For $\beta = 20.0$ years^{-1}.

and $X_4 = X_6 = 0.0$ when $p = 0$ and $\nu = 0$, as given in Table 1. Figure 6(a) shows the effect of the pure-treatment strategy. It can be noted that both susceptible individuals (X_1) and infectious individuals receiving treatment (X_4) increase as p increases up to about 80%. Afterwards X_4 decreases as X_1 increases rapidly, revealing that the treatment strategy becomes distinctively effective for higher values of p. The treatment does not prevent the development of the AIDS disease or the advent of new infections (X_2 and X_5 decrease slowly with p). Therefore, the overall transmission of HIV is strongly affected only when the treatment proportion is near unity. Figure 6(b) shows the eradication of the disease in the presence of the pure-protection strategy. Note that we have $\phi_0 > \mu$, then above the critical value ν^* almost all individuals are protected (X_6) by the education campaign

TABLE 1

The equilibrium proportions $X_i = x_i/x_7$ $(i = 1, \ldots, 6)$ given by equations (13) and (14) for cases a–e, with their respective threshold values

	Case				
	a	b	c	d	e
p	0	0.25	0.50	1.0	0
ν	0	0.15	0.25	0	0.3
β^{th}	2.351	8.963	31.82	18.53	26.23
ϕ_0^{th}	0.088	0.058	0.015	0.020	0.015
X_1	0.118	0.280	0.388	0.927	0.297
X_2	0.042	0.026	0	0.003	0
X_3	0.735	0.328	0	0	0
X_4	0	0.136	0	0.063	0
X_5	0.105	0.062	0	0.007	0
X_6	0	0.168	0.612	0	0.703
x_7	2636	5141	8750	8341	8750

in the presence of a low proportion of individuals at-risk. Consequently, we have a *herd immunization* due to the absence of HIV-infected persons.

The pure-treatment strategy, which is strongly dependent on public-health surveillance, has limited efficiency even when almost all HIV-infected individuals are found and are convinced they should follow the treatment. On the other hand, the protection strategy can lead to the eradication of the disease if an appropriate and feasible sex-education campaign takes place in the homosexual community.

Next we consider testing the model using some values for the parameters p and ν. Due to the absence of estimated data, we take those values representing a wide variation. In Table 1 we present the equilibrium and threshold values for five cases. In the following subsections, the analysis will concern Table 1.

4.2 *Dynamics analysis*

Equation (10) can be solved numerically using the fourth-order adaptive stepsize controlled Runge–Kutta method (Press *et al.*, 1989). The assumed initial values are $X_1(0) = 0.6$, $X_2(0) = 0.2$, $X_3(0) = X_5(0) = 0.1$, $X_4(0) = X_6(0) = 0.0$. In order to solve equation (10) with these initial conditions we set $x_7(0) = 1000$.

Figure 7 shows the numerical simulation for the five cases in Table 1. We will comment on each case separately.

Figure 7(a) shows a population without any kind of intervention (case a); i.e., $x_4(t) \equiv 0$ and $x_6(t) \equiv 0$. The *basic reproduction ratio* R_0 $(= R(0, 0))$ is 8.51. In this case the contact rate at threshold (2.35 years^{-1}) is much lower than its actual value (20.0 years^{-1}), while the intrinsic input rate at threshold (0.088 years^{-1}) is lower than, but near, its actual value

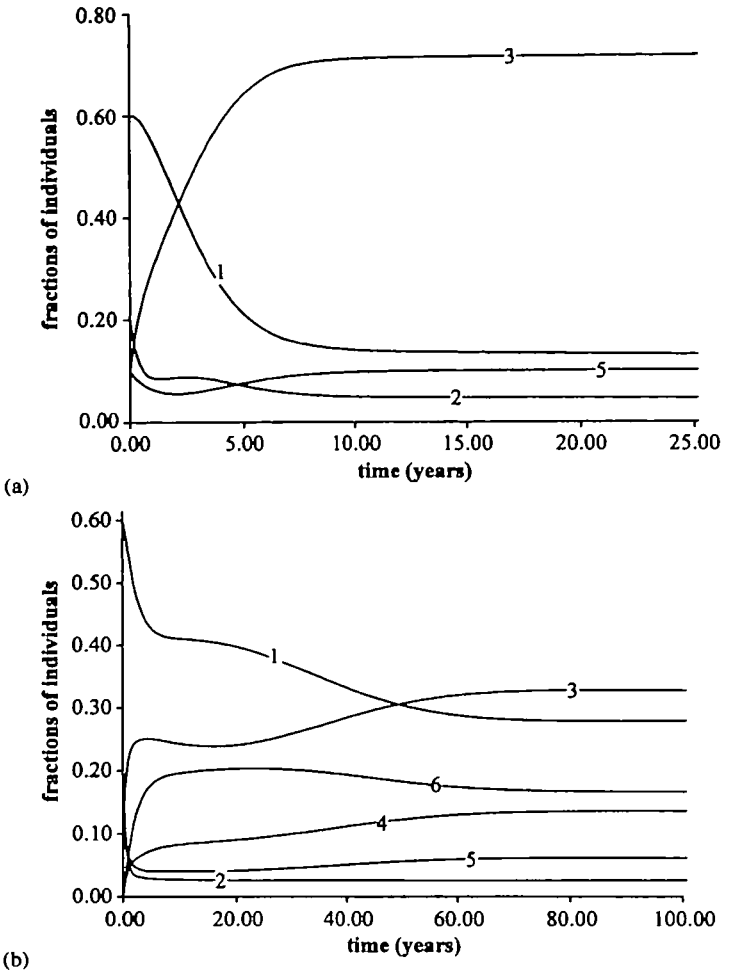


FIG. 7. Numerical simulation of the system dynamics in the cases: (a) $p = 0$ and $\nu = 0$, (b) $p = 0.25$ and $\nu = 0.15$

(0.12 years^{-1}). So we have a high prevalence in a small-sized population. It should be observed that when the infectious individuals are not treated (x_3) the equilibrium quickly attains its asymptote. Since the population size is very low (Table 1) a stochastic approach should be used. However, Fig. 7(a) can still be used as an insight into how the disease progresses.

Figure 7(b) shows a population under treatment and protection strategies (case b) that do not eradicate the disease. The *reproduction ratio* is 2.23, and so the disease is still at an endemic level. The susceptible (x_1) and latent (x_2) individuals are diminished to about one-half and one-eighth of their initial values. At equilibrium all individuals with HIV comprise about 65% of the population. The asymptotes are reached after a long time (100 years).

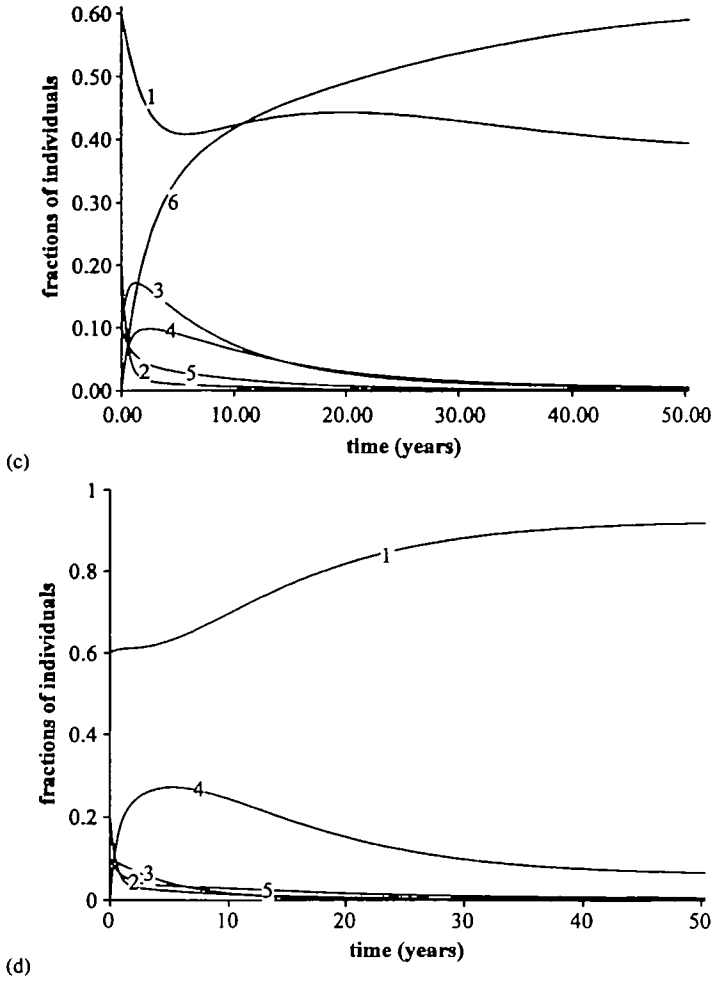
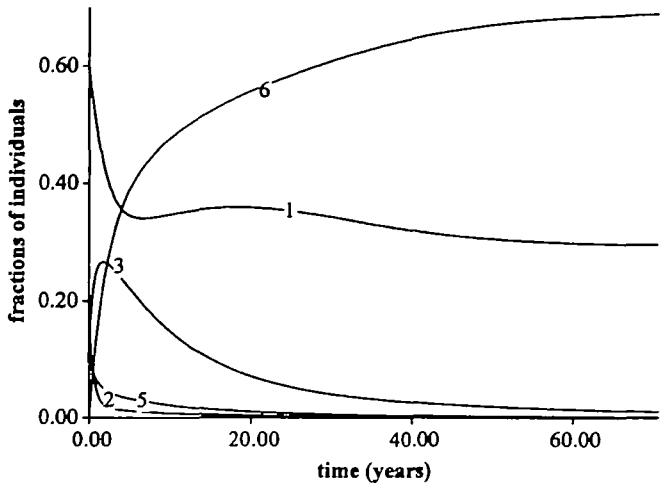


FIG. 7. (c) $p = 0.50$ and $\nu = 0.25$, (d) $p = 1.0$ and $\nu = 0$

Figure 7(c) shows a population under treatment and protection strategies (case c) which lead to the eradication of the disease. The *reproduction ratio* is 0.63, and we must have $x_2(\infty) = x_3(\infty) = x_4(\infty) = x_5(\infty) = 0$. The numbers of infectious individuals (x_3 and x_4) increase rapidly in the first moments followed by a slow decrease. The protected individuals (x_6) prevail in the equilibrium, which is attained after a relatively long period of time.

Figure 7(d) shows the effect of a pure-treatment strategy (case d) over all infectious individuals, which results in $x_6(t) \equiv 0$ and $x_3(\infty) = 0$. The *reproduction ratio* is 1.08. We can observe that $x_2(\infty)$, $x_4(\infty)$, and $x_5(\infty)$ have very low values and all the equilibrium values are reached after a long time.

Figure 7(e) shows the effects of an efficient pure-protection strategy (case e), with



(e)

FIG. 7. (e) $p = 0$ and $\nu = 0.3$. For $\beta = 20.0$ years^{-1}.

TABLE 2

The eigenvalues corresponding to cases a–e shown in Table 1. The symbol i *stands for the imaginary part*

	Case				
	a	b	c	d	e
ψ_1	−2.19	−2.14	−0.41	−2.11	−0.43
ψ_2	−0.66+i0.13	−0.70	−0.015	−0.01	−0.015
ψ_3	−0.66−i0.13	−0.47	−2.01	−0.015	−2.11
ψ_4	−0.04	−0.07+i0.05	−0.72	−0.72	−0.03
ψ_5	−0.015	−0.07−i0.05	−0.04	−0.09	−0.72
ψ_6	−0.52	−0.015	−0.09	−0.52	−0.11
ψ_7	−0.12	−0.09	−0.11	−0.12	−0.12

$x_4(t) \equiv 0$. The *reproduction ratio* is 0.76, and the disease is eradicated in a similar way to case c.

All the above cases were simulated up to $t = 1000$ years without any relevant changes after the range of time shown in Fig. 7. The stability and the asymptotic approach of the equilibrium points can be checked using the eigenvalues shown in Table 2. Cases a and b present a pair of complex eigenvalues.

4.3 *Sensitivity analysis*

The sensitivity of the model with respect to its parameters gives the scenario of the possible outcomes under feasible intervention strategies. The sensitivity of each x_i with respect to the model parameters is ranked according to their contributions to its variance. Setting

TABLE 3

The rank of parameters contributing to the sensitivity analysis for case c. When there are alterations in the rank, the actual rank is presented in parentheses. Note that the multiplying factor inside the parentheses applies to the whole column

	$\sigma^2_{x_1}$ ($\times 10^6$)	$\sigma^2_{x_2}$ ($\times 10^5$)	$\sigma^2_{x_3}$ ($\times 10^5$)	$\sigma^2_{x_4}$ ($\times 10^5$)	$\sigma^2_{x_5}$ ($\times 10^5$)	$\sigma^2_{x_6}$ ($\times 10^6$)
ν	1.83	0.95 (2)	0.84 (2)	8.29	12.9	3.23
n	1.41	5.03 (1)	33.4 (1)	1.58 (3)	3.20 (3)	1.15
ζ_1	0.52	0.27	0.24 (5)	2.34 (2)	3.63 (2)	0.91
ζ_0	0.33	0.17	0.15 (6)	1.50 (4)	2.32	0.58
μ	0.05	0.08 (6)	0.75 (3)	0.09	0.17	0.05
ϕ_0	0.03	0.10 (5)	0.68 (4)	0.03	0.07	0.02

a relative simultaneous error of 5% for all the parameters, we use equation (B.4) from Appendix B to perform the sensitivity analysis for the cases shown in Table 1.

In case c the disease is eradicated by protection ($p = 0.50$) and treatment ($\nu = 0.25$ years^{-1}) strategies (with $R = 0.63$). The sensitivity analysis is shown in Table 3.

We observe that a 5% variation of the parameters may dramatically change the scenario to a moderate-level endemic. This case corresponds to the disease eradication due to the protection strategy. Therefore, all contributions come from parameters related to protection (ν, ζ_1, and ζ_0) and vital dynamics (n, μ, and ϕ_0). The variance of each x_i is given by the column elements. The parameter ν (ϕ_0) occurs most frequently as the largest (least) contributor to the variation of the dynamic variables. However, for x_2 and x_3 the largest contributor is n. The most affected dynamic variable is x_6 (5.95×10^6), while x_2 (6.60×10^5) is the least affected. The parameters not shown in Table 3 are those presenting no contribution to the variance of dynamic variables.

In case e the disease is eradicated by a pure-protection ($\nu = 0.3$ years^{-1}) strategy (with $R = 0.76$). Table 4 shows the sensitivity analysis. Similar to case c, the parameters related to protection are among the most sensitive. Contrary to case c, the rank of the population carrying capacity of the homosexual population is followed by ζ_1 and ζ_0. Still, ϕ_0 remains the least sensitive parameter. The most affected dynamic variable is x_6 (1.29×10^7), while x_2 (3.22×10^6) is the least affected. In the absence of treatment, as expected, the variance of the number of incubated (x_2) and diseased (x_5) individuals increased, as did x_6, compared to case c.

The strategy without any kind of intervention (case a, with the *basic reproduction ratio* $R_0 = 8.51$) is shown in Table 5. In this case, the rank is preserved for almost all the dynamic variables, except for x_4 and x_5 where the carrying capacity and the incubating rate exchange their positions. As expected, in such an endemic situation, the parameters related to the disease (σ, β, and α) also contribute to the variance. The parameter ϕ_0 (ε_3) is always the largest (least) contributor to the variance variation of the dynamic variables. The most affected dynamic variable is x_5 (1.42×10^7), while x_6 (9.77×10^6) is the least affected.

The strategy where all the infectious individuals are treated (case d, with $p = 1.0$ and $R = 1.08$) is shown in Table 6. In this case, all contributions come from treatment (p, γ^*,

TABLE 4

The rank of parameters contributing to the sensitivity analysis for case e. When there are alterations in the rank, the actual rank is presented in parentheses

	$\sigma^2_{x_1}$ ($\times 10^6$)	$\sigma^2_{x_2}$ ($\times 10^6$)	$\sigma^2_{x_3}$ ($\times 10^6$)	$\sigma^2_{x_4}$ ($\times 10^6$)	$\sigma^2_{x_5}$ ($\times 10^6$)	$\sigma^2_{x_6}$ ($\times 10^6$)
ν	6.01	0.14 (2)	0.14 (2)	3.04	4.22	8.27
ζ_1	1.95	0.05 (5)	0.05 (5)	0.98	1.37	2.68
ζ_0	0.87	0.02 (6)	0.02 (6)	0.44	0.61	1.19
n	0.83	2.88 (1)	2.93 (1)	0.06	0.11	0.64
μ	0.06	0.07 (3)	0.07 (3)	0.02	0.023	0.07
ϕ_0	0.02	0.06 (4)	0.06 (4)	0.001	0.022	0.01

TABLE 5

The rank of parameters contributing to the sensitivity analysis for case a. When there are alterations in the rank, the actual rank is presented in parentheses. The dagger symbol stands for the number not being multiplied by the factor

	$\sigma^2_{x_1}$ ($\times 10^6$)	$\sigma^2_{x_2}$ ($\times 10^6$)	$\sigma^2_{x_3}$ ($\times 10^6$)	$\sigma^2_{x_4}$ ($\times 10^6$)	$\sigma^2_{x_5}$ ($\times 10^6$)	$\sigma^2_{x_6}$ ($\times 10^6$)
ϕ_0	5.20	5.49	5.57	5.31	6.95	4.90
α	3.22	3.36	3.41	3.23	4.30	3.04
n	0.67	0.70	0.71	0.68 (4)	0.89 (4)	0.63
σ	0.61	0.64	0.64	0.77 (3)	1.01 (3)	0.57
γ_0	0.38	0.40	0.41	0.50	0.66	0.36
μ	0.21	0.22	0.22	0.23	0.30	0.20
β	0.035	0.042	0.041	0.034	0.044	0.033
ε_1	0.034	0.041	0.040	0.033	0.043	0.032
ε_3	$0.28^\dagger$	$0.34^\dagger$	$0.31^\dagger$	$0.27^\dagger$	$0.35^\dagger$	$0.26^\dagger$

ε_2, and ε_3) and vital dynamics (n, ϕ_0, and μ) parameters, and parameters related to the disease (σ, β, and α). The variance of each x_i is given by the sum of the column elements. The vital dynamics parameters always occur as the great contributors to all the dynamic variables. The rank is preserved for x_1 and x_6. The parameter n (ε_3) is always the largest (least) contributor to the variation of the dynamic variables. The most affected dynamic variable is x_3 (1.55×10^{10}), while x_6 (1.29×10^7) is the least affected. The present case shows the largest variation in the dynamic variables.

The sensitivity of an endemic situation under the protection ($p = 0.25$) and treatment ($\nu = 0.15$ years^{-1}) strategies (case b, with $R = 2.23$) is more uniformly dependent on all the parameters in the model, as shown in Table 7. The parameter n (ε_3) is always the largest (least) contributor to the variation of the dynamic variables. The most affected dynamic variable is x_3 (1.08×10^7), while x_6 (6.08×10^6) is the least affected.

5. Discussion

The model presented in this paper gives insights into AIDS epidemics among homosexual communities considering some kinds of protection and/or treatment strategies. The main

TABLE 6

The rank of parameters contributing to the sensitivity analysis for case d. When there are alterations in the rank, the actual rank is presented in parentheses. The dagger symbol stands for the number not being multiplied by the factor

	$\sigma^2_{x_1}$ ($\times 10^6$)	$\sigma^2_{x_2}$ ($\times 10^6$)	$\sigma^2_{x_3}$ ($\times 10^7$)	$\sigma^2_{x_4}$ ($\times 10^6$)	$\sigma^2_{x_5}$ ($\times 10^6$)	$\sigma^2_{x_6}$ ($\times 10^6$)
n	12.8	335	1455	340	21.8	12.1
ϕ_0	0.51	13.2	57.6	13.4	0.86	0.48
μ	0.25	6.43	28.0	6.53	0.42	0.23
p	0.019	0.20 (6)	0.67 (6)	0.21 (6)	0.020 (6)	0.017
σ	0.017	0.19 (7)	0.62 (7)	0.19 (7)	0.018 (7)	0.016
β	0.012	0.56 (4)	2.70 (4)	0.60 (4)	0.022 (4)	0.011
ε_2	0.011	0.54 (5)	2.59 (5)	0.55 (5)	0.021 (5)	0.010
γ^*	0.010	0.11	0.38	0.12	0.010	0.009
α	0.006	0.07	0.23	0.07	0.009	0.006
ε_3	$5.6^\dagger$	$263^\dagger$	$12636^\dagger$	$266^\dagger$	$10^\dagger$	$5.3^\dagger$

TABLE 7

The rank of parameters contributing to the sensitivity analysis for case b

	$\sigma^2_{x_1}$	$\sigma^2_{x_2}$	$\sigma^2_{x_3}$	$\sigma^2_{x_4}$	$\sigma^2_{x_5}$	$\sigma^2_{x_6}$
n	3.0×10^6	4.1×10^6	4.7×10^6	2.9×10^6	4.0×10^6	2.6×10^6
ϕ_0	2.6×10^6	3.7×10^6	4.2×10^6	2.6×10^6	3.6×10^6	2.3×10^6
α	8.5×10^5	1.1×10^6	1.2×10^6	8.3×10^5	1.1×10^6	7.5×10^5
μ	1.2×10^5	1.6×10^5	1.7×10^5	1.2×10^5	1.7×10^5	1.0×10^5
β	1.1×10^5	2.0×10^5	2.3×10^5	1.1×10^5	1.4×10^5	9.5×10^4
ε_1	1.0×10^5	1.9×10^5	2.2×10^5	1.0×10^5	1.3×10^5	9.1×10^4
ε_1^*	3.7×10^4	6.7×10^4	7.9×10^4	3.6×10^4	4.8×10^4	3.3×10^4
σ	1.5×10^4	1.9×10^4	2.6×10^4	8.2×10^3	4.2×10^3	1.3×10^4
ζ_0	9.5×10^3	1.8×10^4	2.1×10^4	9.6×10^3	1.3×10^4	1.7×10^4
γ_0	6.8×10^3	8.9×10^3	1.2×10^4	7.8×10^2	1.0×10^3	6.0×10^3
ζ_1	5.3×10^3	9.9×10^3	1.3×10^4	5.4×10^3	7.3×10^3	9.8×10^3
ν	5.6×10^2	9.3×10^2	8.4×10^2	3.9×10^2	5.3×10^2	2.6×10^3
p	5.2×10^2	6.6×10^2	1.8×10^3	6.0×10^2	1.5×10^2	4.6×10^2
ε_2^*	6.3×10^1	1.2×10^2	1.3×10^2	6.2×10^1	8.3×10^1	5.6×10^1
γ^*	5.5×10^1	7.0×10^1	1.9	8.8×10^2	1.3×10^{-2}	4.8×10^1
ε_2	2.9×10^1	5.3×10^1	6.2×10^1	2.9×10^1	3.8×10^1	2.6×10^1
ε_1^0	2.8×10^{-1}	5.1×10^{-1}	5.9×10^{-1}	2.7×10^{-1}	3.6×10^{-1}	2.5×10^{-1}
ε_2^0	1.4×10^{-1}	2.6×10^{-1}	3.0×10^{-1}	1.4×10^{-1}	1.9×10^{-1}	1.3×10^{-1}
ε_3^*	8.8×10^{-2}	1.6×10^{-1}	1.9×10^{-1}	8.5×10^{-2}	1.1×10^{-1}	7.8×10^{-2}
ε_3^0	4.4×10^{-2}	8.0×10^{-2}	9.4×10^{-2}	4.3×10^{-2}	5.7×10^{-2}	3.9×10^{-2}
ε_3	1.2×10^{-2}	2.2×10^{-2}	2.6×10^{-2}	1.2×10^{-2}	1.6×10^{-2}	1.1×10^{-2}

TABLE 8

The actual equilibrium values and their deviations (in parentheses) induced by the variations in the parameters

	Case				
	a	b	c	d	e
x_1	310 (3220)	1442 (2620)	3392 (2042)	7729 (3693)	2596 (3119)
x_2	113 (3300)	132 (3093)	0 (812)	25 (18873)	0 (1794)
x_3	1937 (3322)	1687 (3288)	0 (1898)	0 (124424)	0 (1807)
x_4	0 (3294)	700 (2598)	0 (1176)	529 (19014)	0 (2129)
x_5	276 (3769)	318 (3051)	0 (1492)	58 (4819)	0 (2517)
x_6	0 (3126)	861 (2466)	5358 (2440)	0 (3585)	6154 (3586)

goal is to show that a well-chosen mixture of protection and treatment strategies might offer useful options for health policies.

A sex-education strategy (and/or vaccination, when available) is shown to be much more efficient than a treatment strategy. We observe that a pure-protection strategy, when correctly applied, can eradicate the disease, while a pure-treatment strategy, for reasonably large values of β, can be only partially successful (Fig. 2). On the other hand, the protection strategy based on a sex-education campaign has a limited value due to a kind of social Weber–Fechner effect (Stevens, 1970) and is very difficult to assess. However, the treatment strategy depends heavily on the HIV vigilant testing and case tracing, which must be almost total to have some efficacy as a controlling strategy, making it an extremely expensive procedure.

We describe next in detail some strategy scenarios through the results of a sensitivity analysis.

In endemic situations (Tables 5–7) we observe the following descending rank trend: vital dynamics parameters (μ, ϕ_0, and n), disease transmission parameters (σ, β, and α), controlling parameters (p, ν, $\zeta(\nu)$, and $\varepsilon_i(\nu)$), and the other parameters. The treatment parameters (p and, γ^*) are, in general, less sensitive than the protection parameters (ν, ζ_0, and ζ_1). This can also be seen from Fig. 6. The dynamical variables x_1 and x_6 are more sensitive to variations in ν, while x_4 is more sensitive to variations in p, in a joint strategy, as expected.

In eradication states due to the joint strategy (Table 3) and the pure-protection strategy (Table 4), dynamic variables show a nonsensitivity to variations in p and rank alterations with respect to the ν and n parameters. This can be shown from Fig. 3, where we observe that the minimum *reproduction ratio* value is always higher than one for the pure-treatment strategy. Interestingly, treatment strongly influences the saturation level n, which might be interpreted as a behavioural change induced by social intervention.

Table 8 shows the actual equilibrium values and their deviation (the square root of the variance) for the cases a–e induced by the relative 5% variation in all parameters. Table 8 shows the very remarkable consequences for the epidemic dynamics resulting from health policies. For instance, consider the situation where all parameters vary in the worst direction. We observe that cases c and e show relatively small variations in the equilibrium values and behave quite similarly when compared to the whole picture. In case e the disease

is controlled solely by the protection strategy, while in case c both strategies are present, resulting in a more robust health policy. On the other hand, case d, which includes a treatment strategy only (however, it reaches all infectious individuals), shows the appearance of a highly endemic-level situation.

Summarizing the above discussion, we conclude that the protection and treatment strategies are complementary. Consequently, according to the model, the desirable strategy consists of efficient HIV vigilance testing encouraging infectious individuals to participate in a treatment programme, together with preventive education reaching effectively both kinds of individuals: at-risk and in-treatment. In this situation, susceptible individuals are protected by the so-called herd immunization.

The dynamics analysis also shows that the protection strategy is much more efficient than the treatment strategy, although it must be carefully used since there is a quick return to the prior endemic situation when this strategy is interrupted.

Finally, the logistic density-dependent recruitment rate was chosen with the aim of attaining a realistic nonexploding homosexual population, which would not be the case with a Malthusian vital dynamics. Lipsitch & Nowak (1995) considered constant and Malthusian recruitment rates to analyse the evolution of HIV virulence. Indeed, they have referred to, but not considered, a density-dependent saturation in order to obtain analytical results (Lipsitch *et al.*, 1996). By using a logistic input we could calculate the thresholds and equilibria values and follow up the dynamics through its steady state. From Table 1 we observe that the contact-rate threshold depends strongly on the protection rate rather than on the treatment proportion.

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REFERENCES

ANDERSON, R. M. & MAY, R. M. 1991 *Infectious Diseases of Humans: Dynamics and Control.* Oxford University Press.

ANDERSON, R. M., JACKSON, H. C., MAY, R. M., & SMITH, A. M. 1981 Population dynamics of fox rabies in Europe. *Nature* **289**, 765–771.

ANDERSON, R. M., MAY, R. M., & MCLEAN, A. R. 1988 Possible demographic consequences of AIDS in developing countries. *Nature* **332**, 228–234.

ANDERSON, R. M., BLYTHE, S. P., GUPTA, S., & KONINGS, E. 1989 The transmission dynamics of the human immunodeficiency virus type 1 in the male homosexual community in the United Kingdom: The influence of changes in sexual behaviour. *Phil. Trans. R. Soc. Lond. B* **325**, 45–98.

ARROWSMITH, D. K. & PLACE, C. M. 1986 *Ordinary Differential Equations: A Qualitative Approach with Applications.* London: Chapman and Hall.

AZEVEDO NETO, R. S., SILVEIRA, A. S. B., NOKES, D. J., YANG, H. M., PASSOS, S. D., CARDOSO, M. R. D., & MASSAD, E. 1994 Rubella seroepidemiology in a non-immunized population of São Paulo State, Brazil. *Epidemiol. Infect.* **113**, 161–173.

BERMAN, A., NEUMANN, M., & STERN, R. 1989 *Nonnegative Matrices in Dynamic Systems.* New York: Wiley.

DIETZ, K. 1975 Transmission and control of arbovirus diseases. In: *Epidemiology*, (D. Ludwig & K. L. Cooke, eds.) pp. 104–121. Philadelphia, PA: Society for Industrial and Applied Mathematics.

FRANK, P. M. 1978 *Introduction to System Sensitivity Theory.* New York: Academic Press.

GAO, L. Q. & HETHCOTE, H. W. 1992 Disease transmission models with density dependent demographics. *J. Math. Biol.* **30**, 717–731.

GREENHALGH, D. 1990 Vaccination campaign for measles. *Math. Biosci.* **100**, 201–240.

GREENHALGH, D. 1992a Some results for an SEIR epidemic model with density dependence in the death rate. *IMA J. Math. Appl. Med. Biol.* **9**, 67–106.

GREENHALGH, D. 1992b Vaccination in density-dependent epidemic models. *Bull. Math. Biol.* **54**, 733–758.

GREENHALGH, D. & DAS, R. 1995 Modelling epidemics with variable contact rates. *Theor. Pop. Biol.* **47**, 129–179.

GRIMSHAW, R. 1990 *Nonlinear Ordinary Differential Equations.* Oxford: Blackwell Scientific.

HESSOL, N. A., BYERS, R. H., LIFSON, A. R., O'MALLEY, P. M., CANNON, L., BARNHART, J. L., HARRISON, J. S., & RUTHERFORD, G. W. 1990 Relationship between AIDS latency period and AIDS survival time in homosexual and bisexual men. *J. AIDS* **3**, 1078–1085.

HETHCOTE, H. W. 1988 Optimal ages of vaccination for measles. *Math. Biosci.* **89**, 29–52.

HYMAN, J. M. & STANLEY, E. A. 1988 Using mathematical models to understand the AIDS epidemic. *Math. Biosci.* **90**, 415–473.

LIPSITCH, M. & NOWAK, M. A. 1995 The evolution of virulence in sexually transmitted HIV/AIDS. *J. Theor. Biol.* **174**, 427–440.

LIPSITCH, M., SILLER, S., & NOWAK, M. A. 1996 The evolution of virulence in pathogens with vertical and horizontal transmission. *Evolution* **50**, 1729–1741.

LONGINI JR, I. M., CLARK, W. S., BYERS, R. H., WARD, J. W., DARROW, W. W., LEMP, G. F., & HETHCOTE, H. W. 1989 Statistical analysis of the stages of HIV infection using a Markov model. *Statist. Med.* **8**, 831–843.

LONGINI JR, I. M., BYERS, R. H., HESSOL, N. A., & TAN, W. Y. 1992 Estimating the stage-specific numbers of HIV infection using a Markov model and back-calculation. *Statist. Med.* **11**, 831–843.

MASSAD, E., AZEVEDO NETO, R. S., BURATTINI, M. N., ZANETTA, D. M. T., COUTINHO, F. A. B., YANG, H. M., MORAES, J. C., PANNUTI, C. S., SOUZA, V. A. U. F., SILVEIRA, A. S. B., STRUCHINER, C. J., OSELKA, G. W., CAMARGO, M. C. C., OMOTO, T. M., & PASSOS, S. D. 1995 Assessing the efficacy of a mixed vaccination strategy against rubella in São Paulo, Brazil. *Int. J. Epidemiol.* **24**, 842–850.

MENA-LORCA, J. & HETHCOTE, H. W. 1992 Dynamic models of infectious diseases as regulators of population size. *J. Math. Biol.* **30**, 693–716.

MORTON, O. 1992 Achievements in research. In: *A Global Report: AIDS in the World* (J. Mann *et al.*, eds.), pp. 229–377. Cambridge, MA: Harvard University Press.

MURRAY, J. D. 1989 *Mathematical Biology.* In: Biomathematics Texts, Vol. 19. Berlin. Springer-Verlag.

POWER, R. 1990 Drug-using trends and HIV risk behaviour. In: *AIDS and Drug Misuse: The Challenge for Policy and Practice in The 1990s* (J. Strang & G. Stimson, eds.), pp. 67–76. London: Routledge.

PRESS, W. H., FLANNERY, B. P., TEUKOLSKY, S. A., & VETTERLING, W. T. 1989 *Numerical Recipes: The Art of Scientific Computing (FORTRAN Version).* Cambridge University Press.

PUGLIESE, A. 1990 Population models for diseases with no recovery. *J. Math. Biol.* **28**, 65–82.

STEVENS, S. S. 1970 Neural events and psychophysical law. *Science* **170**, 1043–1050.

STRANG, J. & STIMSON, G. 1990 The impact of HIV: Forcing the process of change. In: *AIDS and Drug Misuse: The Challenge for Policy and Practice in The 1990s* (J. Strang & G. Stimson, eds.), pp. 3–15. London: Routledge.

THIEME, H. R. 1992 Epidemic and demographic interaction in the spread of potentialy fatal diseases in growing populations. *Math. Biosci.* **111**, 99–130.

YANG, H. M. 1998 Modelling vaccination strategy against directly transmitted diseases using a series of pulses. *J. Biol. Systems* **6**, 187–212.

YANG, H. M., CARVALHO, H. B., & MASSAD, E. 1999 Modelling HIV transmission among injecting drug users, with implications for control strategies. *Math. Model. Scient. Comp.* To appear.

Appendix A: Stability analysis

The equilibrium point $\mathbf{x}^1$ (= **0**) needs a special approach since the force of infection λ is indeterminate. Applying the Gronwall inequality (Grimshaw, 1990) to equation (11), we conclude that $x_7 \to 0$ as $t \to \infty$ if

$$\phi_0 \leqslant \mu. \tag{A.1}$$

Therefore, the stability of $\mathbf{x}^1$ is guaranteed if (A.1) is obeyed. Otherwise, from the same equation we have

$$\frac{\mathrm{d}}{\mathrm{d}t} x_7 = (\phi_0 - \mu)\, x_7 - \frac{\phi_0}{n} (x_7)^2 > 0 \tag{A.2}$$

if $x_7 \sim 0$. Hence the origin is unstable. Thieme (1992) and Greenhalgh & Das (1995) obtained similar results for related models.

The stability of the other two equilibrium states are analysed through the eigenequation (Grimshaw, 1990),

$$\Psi(\psi) = \det\left[\mathbf{J}^* - \psi \mathbf{I}_{7\times 7}\right] = 0, \tag{A.3}$$

where $\mathbf{I}_{7\times 7}$ is the identity matrix, and

$$\mathbf{J}^* = \left.\frac{\partial \mathbf{F}[\mathbf{x}, \theta]}{\partial \mathbf{x}}\right|_{\mathbf{x}^i, \theta} \quad (i = 2, 3) \tag{A.4}$$

is the Jacobian matrix calculated at the equilibrium values. If all the eigenvalues ψ of an equilibrium state have negative real parts (Arrowsmith & Place, 1986), then it is stable.

In case of a disease-free population, substituting $\mathbf{x}^2$ in equation (A.3) results in the eigenvalues

$$\begin{cases} \psi_1 = -\mu, \\ \psi_2 = -[\mu + \nu + \zeta(\nu)], \\ \psi_3 = -(\phi_0 - \mu), \end{cases}$$

plus the eigenequation

$$\Psi(\psi) = a_4\psi^4 + a_3\psi^3 + a_2\psi^2 + a_1\psi + a_0, \tag{A.5}$$

with

$$\left.\begin{aligned} a_4 &= 1, \\ a_3 &= (\mu+\sigma) + (\mu+\gamma_0) + (\mu+\gamma^*) + (\mu+\alpha), \\ a_2 &= \left\{(\mu+\sigma)(\mu+\alpha) + (\mu+\gamma_0)\left[\mu+\gamma^*\right]\right. \\ &\quad \left. + [(\mu+\sigma) + (\mu+\alpha)]\left[(\mu+\gamma_0) + (\mu+\gamma^*)\right]\right\}\left[1 - \frac{\beta}{\beta_2^{th}(\nu, p)}\right], \\ a_1 &= \left\{(\mu+\sigma)(\mu+\alpha)\left[(\mu+\gamma_0) + (\mu+\gamma^*)\right]\right. \\ &\quad \left. + (\mu+\gamma_0)\left[\mu+\gamma^*\right][(\mu+\sigma) + (\mu+\alpha)]\right\}\left[1 - \frac{\beta}{\beta_1^{th}(\nu, p)}\right], \\ a_0 &= (\mu+\sigma)(\mu+\gamma_0)\left[\mu+\gamma^*\right](\mu+\alpha)\left[1 - \frac{\beta}{\beta^{th}(\nu, p)}\right], \end{aligned}\right\} \tag{A.6}$$

where

$$\beta_1^{th}(\nu, p) = \frac{\{(\mu+\sigma)(\mu+\alpha)[(\mu+\gamma_0)+(\mu+\gamma^*)]+(\mu+\gamma_0)[\mu+\gamma^*][(\mu+\sigma)+(\mu+\alpha)]\}\dfrac{\mu+\nu+\zeta(\nu)}{\mu+\zeta(\nu)}}{\sigma\{[(\mu+\gamma^*)+(\mu+\alpha)]\varepsilon_1(\nu)+\gamma_0\varepsilon_3(\nu)](1-p)+[\{(\mu+\gamma_0)+(\mu+\alpha)\}\varepsilon_2(\nu)+\gamma^*\varepsilon_3(\nu)]p\}},$$

$$\beta_2^{th}(\nu, p) = \frac{\{(\mu+\sigma)(\mu+\alpha)+(\mu+\gamma_0)[\mu+\gamma^*]+[(\mu+\sigma)+(\mu+\alpha)][(\mu+\gamma_0)+(\mu+\gamma^*)]\}\dfrac{\mu+\nu+\zeta(\nu)}{\mu+\zeta(\nu)}}{\sigma[\varepsilon_1(\nu)(1-p)+\varepsilon_2(\nu)p]}. \tag{A.7}$$

and the threshold contact rate $\beta^{th}(\nu, p)$ is given by (16).

The disease-free population is a stable equilibrium point if

$$\phi_0 > \mu \tag{A.8}$$

and the fourth-order algebraic equation of (A.5) obeys the Routh–Hurwitz conditions (Murray, 1989). The eigenequation (A.5) comes out from the Jacobian matrix $\mathbf{J}_4^*$ given by

$$\mathbf{J}_4^* = \begin{bmatrix} -(\mu+\sigma) & \beta\varepsilon_1(\nu)\dfrac{\mu+\zeta(\nu)}{\mu+\nu+\zeta(\nu)} & \beta\varepsilon_2(\nu)\dfrac{\mu+\zeta(\nu)}{\mu+\nu+\zeta(\nu)} & \beta\varepsilon_3(\nu)\dfrac{\mu+\zeta(\nu)}{\mu+\nu+\zeta(\nu)} \\ \sigma(1-p) & -(\mu+\gamma_0) & 0 & 0 \\ \sigma p & 0 & -(\mu+\gamma^*) & 0 \\ 0 & \gamma_0 & \gamma^* & -(\mu+\alpha) \end{bmatrix}.$$

Note that the diagonal elements of $-\mathbf{J}_4^*$ are positive and their off-diagonal elements are nonpositive. Hence $-\mathbf{J}_4^*$ is an M-matrix (Berman *et al.*, 1989), and, therefore, if and only if $a_0 > 0$, that is,

$$\beta < \beta^{th}(\nu, p), \tag{A.9}$$

then the trivial equilibrium point is stable. Note that the condition (A.9), due to the relations

$$\begin{aligned} \beta^{th}(\nu, p) &< \beta_1^{th}(\nu, p), \\ \beta^{th}(\nu, p) &< \beta_2^{th}(\nu, p), \end{aligned} \tag{A.10}$$

implies that $a_i > 0$ ($i = 1$ and 2).

The equilibrium points were evaluated numerically by the Newton–Raphson method and the dynamic trajectories were obtained by a fourth-order stepsize-controlled Runge–Kutta method (Press *et al.*, 1989).

Appendix B: Sensitivity analysis

Using the absolute sensitivity function (Frank, 1978), we have the covariance matrix for the dynamic variables $\mathbf{x}$

$$\mathbf{V}_\mathbf{x} = \mathbf{H}\mathbf{V}_\theta\mathbf{H}^\mathsf{T}, \tag{B.1}$$

where $\mathbf{V}_\theta$ is the covariance matrix for the 21 parameters of θ stated in (9) and $\mathbf{H}$ is the sensitivity matrix given by

$$\mathbf{H} = \mathbf{J}^{-1}\mathbf{P}, \tag{B.2}$$

where $\mathbf{P}$ is given by

$$\mathbf{P} = \left.\frac{\partial F[\mathbf{x}, \theta]}{\partial\theta}\right|_{\mathbf{x}^i, \theta} \quad (i = 2, 3), \tag{B.3}$$

and the Jacobian $\mathbf{J}$ is given by (A.4), also evaluated only for $\mathbf{x}^2$ and $\mathbf{x}^3$.

If we consider $\mathbf{V}_\theta$ to be diagonal, with its diagonal elements given by $\sigma_{\theta_j}^2$, where $j = 1$–21, then

the variances related to the dynamic variables (the diagonal elements of $\mathbf{V}_{\mathbf{x}}$) are given by

$$\sigma_{x_k}^2 = \sum_{j=1}^{21} h_{kj}^2 \sigma_{\theta_j}^2 \quad \text{with } k = 1, 2, \ldots, 7. \tag{B.4}$$

This expression also gives the contribution of each parameter to the dynamic-variables sensitivity.