Can HIV invade a population which is already sick?

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Abstract. *It is known that an HIV infection when concomitant with another disease such as tuberculosis or pneumonia is a lot more lethal than HIV alone. We introduce two mathematical models for which if the concomitant diseases are prevalent enough in a given population and if double infections are lethal enough then HIV cannot take hold in this population. This provides an alternative (or a complement) to the theory that what determines whether a population will suffer an HIV epidemic is its sexual behavior. Our point of view may be relevant to the situation in Southeast Asia.*

1. Introduction. There are many infectious diseases that plague the poorest populations: tuberculosis, pneumonia, sexually transmitted diseases. The combination of one of these infectious diseases with HIV is known to be more lethal than HIV alone. For instance, it is thought that today at least one billion people are infected with tuberculosis. Of these, if they are not also infected with HIV, only a fraction (between 5% and 15%) will develop the disease during their lifetime, see Enarson and Rouillon (1998). The appearance of HIV in an individual infected with TB disrupts the balance between the tubercle bacillus and its human host. It is believed that more than 30% of people infected with both HIV and TB develop TB during their lifetime. Moreover, the response to TB treatment is much better in people who are HIV negative than in people who are HIV positive, see Enarson and Rouillon (1998), Rieder et al. (1989) and Chum et al. (1996).

The HIV pandemic has hit very hard some populations (in particular in Africa) while it has largely spared some other populations (in particular in some parts of Asia). A widely accepted explanation for that is the difference in sexual behavior in different populations (see UNAIDS (1998) and (1999)). In this paper we propose an alternative theory. If the double infection by HIV and a given concomitant infection is lethal enough and if a given population has a high enough density of the concomitant infection then HIV cannot take hold in the population. It is known that if a given disease is too virulent (such as Ebola, for instance) then it cannot spread. Our hypothesis is that many double infections such as TB/HIV are too virulent to spread. We are in particular interested in Southeast Asia where TB is highly prevalent (more than 50% of the population is infected in some countries) and which has been somewhat spared by the HIV pandemic so far, see Dye et al. (1999). We will use two simple mathematical models to make our point more precise. In the first model we will assume that all individuals mix together. In the second model there will be a spatial structure and the individuals will be able to mix only with their nearest neighbors. Our results will show that the two models have the same qualitative behavior. Since these two models are at opposite ends in terms of mixing and they show the same qualitative behavior we think this is a good indication that our results hold for

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a rather general class of models. The models used below are variations of models used in Schinazi (2001) for another question.

2. A model with total mixing. We consider a population for which there is at least one endemic disease such as TB, pneumonia or a sexually transmitted disease which is not HIV. An individual taken at random in the population is infected with the endemic disease with probability p. For each individual in the population there are three possible states: 0 (HIV negative), 1 (HIV positive, no concomitant infection) or 2 (HIV positive, concomitant infection). Our (very) simple minded model evolves as follows. An individual in state 0 is infected by HIV at a rate proportional to the density of HIV infected individuals in the population. A newly HIV infected individual is in state 2 with probability p or in state 1 with probability $1-p$, depending whether he was already infected by something else or not. Individuals in states 1 and 2 die at rate δ_1 and δ_2, respectively. We will assume the biologically meaningful hypothesis that

$$\delta_1 < \delta_2.$$

Let u_i, $i = 0, 1, 2$, be the density of individuals in state i. In particular, $u_0 + u_1 + u_2 = 1$. Assuming that all individuals mix with each other we get the following system of differential equations:

$$\begin{aligned}\frac{du_1}{dt} &= \lambda(1-p)u_0(u_1+u_2) - \delta_1 u_1\\ \frac{du_2}{dt} &= \lambda p u_0(u_1+u_2) - \delta_2 u_2\end{aligned}$$

where λ is the infection rate. It is clear that $(u_1, u_2) = (0, 0)$ is an equilibrium for the system above. This is the HIV free equilibrium. If this equilibrium is unstable we will say that an HIV epidemic is possible. If (0,0) is stable then we will say that an HIV epidemic is not possible. We know that an equilibrium is stable if and only if all eigenvalues of the Jacobian matrix have strictly negative real parts. For an elementary introduction to stability see for instance Boyce and DiPrima (1992). The Jacobian of the system of differential equations at (0,0) is

$$\begin{pmatrix} \lambda(1-p) - \delta_1 & \lambda(1-p) \\ \lambda p & \lambda p - \delta_2 \end{pmatrix}.$$

The determinant of this matrix is

$$Det = \lambda p(\delta_2 - \delta_1) - \delta_2(\lambda - \delta_1)$$

and its trace is

$$Tr = \lambda - (\delta_1 + \delta_2).$$

There are three cases to consider.

(a) Assume that $\lambda < \delta_1 < \delta_2$. In this case the determinant is positive and the trace is negative for any p in [0,1] and $\delta_2 > \delta_1$. Thus, the eigenvalues of the Jacobian have negative real parts. The equilibrium (0,0) is stable and no epidemic can take place.

(b) Assume that $\delta_1 < \lambda < \delta_2$. Note that the determinant is negative if and only if

$$p < p_c$$

where

$$p_c = \frac{\delta_2}{\delta_2 - \delta_1}(1 - \delta_1/\lambda).$$

Observe that under the assumption $\delta_1 < \lambda < \delta_2$ the critical value p_c is strictly between 0 and 1.

If

$$p > p_c$$

then the determinant is positive and the trace is negative. Thus, no epidemic is possible.

In conclusion, under the assumption $\delta_1 < \lambda < \delta_2$ an epidemic is possible if and only if p is smaller than p_c.

(c) Assume that $\delta_1 < \delta_2 < \lambda$. In this case the determinant is negative for all p in [0,1]. For, using that $p \leq 1$ we get

$$Det = \lambda p(\delta_2 - \delta_1) - \delta_2(\lambda - \delta_1) \leq \lambda(\delta_2 - \delta_1) - \delta_2(\lambda - \delta_1) = \delta_1(-\lambda + \delta_2) < 0.$$

Thus, in this case an epidemic is always possible.

Case (b) is the most interesting one. There, we assume that $\delta_1 < \lambda < \delta_2$. That is, an HIV epidemic is possible in the absence of concomitant diseases ($p = 0$ and $\delta_1 < \lambda$) but is not possible in the case where the whole population is infected by a concomitant disease ($p = 1$ and $\lambda < \delta_2$). We have shown that an HIV epidemic is possible if and only if the proportion p of the population infected with a concomitant infection is above a certain threshold p_c. So, at least in theory, if the double infection is lethal enough (mathematically this is translated by $\lambda < \delta_2$) then an HIV epidemic is not possible in a population where other infections are highly prevalent (that is, if $p > p_c$).

3. A model with little mixing

We now consider a continuous time spatial stochastic model η_t on $\mathbf{Z}^d$ where each site may be in one of three states: 0, 1 or 2. If the model is in configuration η, let $n_1(x, \eta)$ and $n_2(x, \eta)$ be the number of nearest neighbors of x (among the $2d$ nearest neighbors of x) that are in state 1 and in state 2, respectively. Assume that the model is in configuration η, then the state at a given site x evolves as follows:

$$0 \to 1 \text{ at rate } \lambda(1-p)(n_1(x,\eta) + n_2(x,\eta))$$
$$0 \to 2 \text{ at rate } \lambda p(n_1(x,\eta) + n_2(x,\eta))$$
$$1 \to 0 \text{ at rate } \delta_1$$
$$2 \to 0 \text{ at rate } \delta_2$$

In words, 1's and 2's infect nearest neighbors that are in state 0 at rate λ. Newly infected individuals are 1 with probability $1-p$ or 2 with probability p. Infected individuals in state 1 and 2 die at rates δ_1 and δ_2, respectively. For this model we will say that an HIV epidemic is possible if there is a positive probability that the process never hits the configuration where all sites are in state 0.

In the absence of concomitant infection, i.e. $p = 0$, we have a population of 0's and 1's only. In this particular case, the system evolves as

$$0 \to 1 \text{ at rate } \lambda n_1(x, \eta)$$
$$1 \to 0 \text{ at rate } \delta_1$$

The model above is called a contact process. It is known that there is a critical value λ_c (that depends on the dimension d of the grid $\mathbf{Z}^d$) such that if $\lambda \leq \lambda_c$ then an epidemic is not possible (the 1's die out) while if $\lambda > \lambda_c$ then an epidemic is possible. For more on the contact process, see for instance Liggett (1999). We are now ready to state our result.

Theorem. *(a) If $\frac{\lambda}{\delta_1} < \lambda_c$ then no HIV epidemic can take place for any p in [0,1] and any $\delta_2 > \delta_1$.*

(b) If $\frac{\lambda}{\delta_2} < \lambda_c$ then for any $\delta_1 < \delta_2$ there is a $p_c(\lambda, \delta_1, \delta_2)$ in (0,1) such that no HIV epidemic can take place for any $p > p_c$.

(c) If $\frac{\lambda}{\delta_2} > \lambda_c$ then for any $\delta_1 < \delta_2$ and any p in [0,1] an epidemic is possible.

Observe that the spatial stochastic model has the same qualitative behavior as the mean field model. We see again in (b) that if a large proportion of a population is already sick and if the double infection with HIV is lethal enough then HIV will not be able to invade this population. This might be one explanation why Southeast Asia has been largely spared (so far) by the HIV pandemic: this is one of the regions in the world where TB prevalence is the highest (see Dye et al. (1999)). However, there are certainly other explanations why some populations have been hit harder than others by the HIV pandemic. In particular, sexual practices such as the number of partners per individual seem to play a pivotal role, see Rotello (1997), UNAIDS (1998) and (1999). It might be the case that the proportion in the population of concomitant infection is useful as a secondary explanatory variable (after sexual practices) to predict whether HIV will invade a given population.

4. Proof of the Theorem. We now give the explicit graphical construction for the process η_t. The graphical construction takes place in the space-time region $\mathbf{Z}^d \times (0, \infty)$. Consider a collection of independent Poisson processes: $\{N^{x,y}, D^x : x, y \in \mathbf{Z}^d, ||x-y|| = 1\}$. For x and y in $\mathbf{Z}^d$ such that $||x - y|| = 1$ let the intensities of $N^{x,y}$, D^x be λ and δ_2, respectively. For each x in $\mathbf{Z}^d$, at each arrival time of the Poisson process D^x, if there is a 2 at x it is replaced by a 0. If there is a 1 at x then it is replaced by a 0 with probability δ_1/δ_2. With this recipe deaths of 2's occur at rate δ_2 and deaths of 1's occur at rate δ_1. Moreover, the deaths are coupled in a way that will be useful in our proof. At an arrival time of $N^{x,y}$ if there is a 1 or a 2 at x and a 0 at y we put a 1 at y with probability $1-p$ or a 2 at y with probability p. In this way we obtain a version of our spatial stochastic process. We construct the process *restricted* to a space-time region $\mathcal{A}$ if we only use the

arrival times of the Poisson processes $N^{x,y}$ and D^x for x and y inside $\mathcal{A}$. For more on graphical constructions, see p 32 in Liggett (1999).

Proofs of Theorem (a) and (c)

Consider the contact process ξ_t with only states 0 and 1 and rates:

$$0 \to 1 \text{ at rate } \lambda n_1(x, \xi)$$
$$1 \to 0 \text{ at rate } \delta_1$$

We construct the process ξ_t with the same Poisson processes $N^{x,y}$ and D^x that we use for η_t. However, for ξ_t we take $p = 0$ in this construction. It is easy to check that if we take initial configurations ξ_0 and η_0 such that if there is a 1 or 2 at x for the configuration η_0 then there is a 1 at x for the configuration ξ_0 then the same is true at any time t for configurations η_t and ξ_t. This is due to the fact that birth rates for ξ_t and η_t are the same but death rates are lower for ξ_t than for η_t. Under the assumption $\frac{\lambda}{\delta_1} < \lambda_c$, the 1's in ξ_t die out for any initial configuration thus the 1's and 2's in η_t must die out as well. An epidemic is not possible. This completes the proof of (a).

The proof of (c) is quite similar to the proof of (a). We consider a contact process ζ_t that evolves according to the following rates:

$$0 \to 2 \text{ at rate } \lambda n_2(x, \zeta)$$
$$2 \to 0 \text{ at rate } \delta_2$$

We also construct ζ_t in the same probability space as η_t by using the same Poisson processes to construct both processes. However, for ζ_t we take $p = 1$ in this construction. This time ζ_t is below η_t in the following sense. If we take initial configurations ζ_0 and η_0 such that if there is a 2 at x for the configuration ζ_0 then there is a 1 or a 2 at x for the configuration η_0 then the same is true at any time t for configurations ζ_t and η_t. This is due to the fact that birth rates are the same for both processes but death rates are higher for ζ_t than for η_t. Under the assumption $\frac{\lambda}{\delta_2} > \lambda_c$, starting with at least one 2, the 2's in ζ_t have a positive probability of surviving forever. The same must be true for η_t. An epidemic is possible. This completes the proof of (c).

Proof of Theorem (b)

This has essentially been proved in Schinazi (2001). However, the 1's there correspond to the 2's here, p near 0 there corresponds to p near 1 here. Since the proof is not that long we decided to give a complete proof with the necessary modifications.

We prove (b) under the assumption $d = 2$, in order to avoid more cumbersome notation. The same ideas work in any $d \geq 1$.

We define two space–time regions:

$$\mathcal{A} = [-2L, 2L]^2 \times [0, 2L], \qquad \mathcal{B} = [-L, L]^2 \times [L, 2L]$$

where L is an integer to be chosen later. Define $\mathcal{C}$ to be part of the 'boundary' of the box $\mathcal{A}$:

$$\mathcal{C} = \Big\{(m, n, t) \in \mathcal{A} : |m| = 2L \text{ or } |n| = 2L \text{ or } t = 0\Big\}$$

We will compare our spatial stochastic model to a certain dependent percolation process on the set $\mathcal{L} = \mathbf{Z}^2 \times \mathbf{Z}_+$, where $\mathbf{Z}_+ = \{0, 1, 2, \ldots\}$. For a short introduction to oriented percolation, see p 13 in Liggett (1999). We say that the site (k, m, n) in $\mathcal{L}$ is *wet* if there are no 1's and no 2's in $(kL, mL, nL) + \mathcal{B}$ whatever the configuration in $(kL, mL, nL) + \mathcal{C}$ is for the process restricted to $(kL, mL, nL) + \mathcal{A}$. Sites which are not wet are called *dry*.

For any $\epsilon > 0$, given $\frac{\lambda}{\delta_2} < \lambda_c$ and $\delta_1 < \delta_2$ we will show that there is an integer L and a proportion p_c such that:

$$P\big((k, m, n) \text{ is wet}\big) \geq 1 - \epsilon \text{ if } p > p_c.$$

We start by showing the above property when $p = 1$. Then, using a continuity argument, we will deduce that the inequality remains true for p close to but smaller than 1. By translation-invariance, it suffices to consider the site $(0, 0, 0) \in \mathcal{L}$. Note that if $p = 1$ then 1's and 2's do not give birth to 1's in the space-time region $\mathcal{A}$ and the 1's that are in $[-2L, 2L]^2$ at time 0 will rapidly disappear. Let E be the event that there are no 1's left at time $L/2$ in $[-2L, 2L]^2$. Because there are $(4L + 1)^2$ sites in $\mathcal{A}$ and since the death rate of 1's is δ_1 we have that

$$P(E) \geq (1 - e^{-\delta_1 L/2})^{(4L+1)^2}.$$

By taking L large enough, the r.h.s. may be made larger than $1 - \epsilon/4$ for an arbitrarily small $\epsilon > 0$.

On E there are only 0's and 2's left in $[-2L, 2L]^2$ by time $L/2$. Thereafter the 2's evolve as a subcritical contact process in $\mathcal{A}$. Let F be the event that there are no 2's in the space time region $\mathcal{B}$. On E, if there is a 2 in $\mathcal{B}$ there must be an infection path from $[-2L, 2L]^2 \times L/2$ into $\mathcal{B}$ or from one of the sides of the box $\mathcal{A}$ into $\mathcal{B}$. Let $\mathcal{D}$ be

$$\mathcal{D} = \{(m, n) \in \mathbf{Z}^2 : |m| = 2L \text{ or } |n| = 2L\}.$$

Let $\{(x, t) \to \mathcal{B}\}$ denote the event that there is an infection path from (x, t) to $\mathcal{B}$ inside $\mathcal{A}$. We have that

$$P(\exists x \in \mathcal{D}, \exists t \in [0, 2L] : (x, t) \to \mathcal{B}) \leq \int_0^{2L} \sum_{x \in \mathcal{D}} P((x, t) \to \mathcal{B}) dt.$$

An infection path from x in $\mathcal{D}$ to $\mathcal{B}$ has length at least L. Bezuidenhout and Grimmett (1991) have shown, for the subcritical contact process, that the probability that an infection path is at least L long is less than $Ce^{-\gamma L}$ where C and γ are strictly positive constants. Thus,

$$P(\exists x \in \mathcal{D}, \exists t \in [0, 2L] : (x, t) \to \mathcal{B}) \leq \int_0^{2L} \sum_{x \in \mathcal{D}} Ce^{-\gamma L} dt = 2L \times 4(4L + 1)Ce^{-\gamma L}.$$

Similarly the probability of an infection path from $[-2L, 2L]^2 \times L/2$ to $\mathcal{B}$ is less than $(4L + 1)^2 Ce^{-\gamma L/2}$. Therefore, we have

$$P(F|E) \geq 1 - 8L(4L + 1)Ce^{-\gamma L} - (4L + 1)^2 Ce^{-\gamma L/2}.$$

By taking L large enough the probability above may be made larger than $1-\epsilon/4$. We have

$$P\big((0,0,0) \text{ is wet}\big) \geq P(EF) = P(E)P(F|E) \geq 1 - \epsilon/2 \text{ if } p = 1.$$

Since $\mathcal{A}$ is a finite box there is $p_c < 1$ such that with probability at least $1-\epsilon/2$ there are no arrivals inside $\mathcal{A}$ of Poisson processes with rate $\lambda(1-p)$. That is, by picking p close enough to one there will be no birth of 1 inside $\mathcal{A}$, with high probability. Therefore, we get

$$P\big((0,0,0) \text{ is wet}\big) \geq 1 - \epsilon \text{ if } p > p_c.$$

We define a percolation process on $\mathcal{L}$ for which the probability that a given site is wet is $1-\epsilon$. We position oriented edges between sites in $\mathcal{L}$ in order to obtain a percolation model. For (k,m,n) and (x,y,z) in $\mathcal{L}$, we draw an oriented edge from (k,m,n) to (x,y,z) if $n \leq z$ and if the intersection between $(kL,mL,nL)+\mathcal{A}$ and $(xL,yL,zL)+\mathcal{A}$ is not empty. Note that the event $\{(k,m,n) \text{ is wet}\}$ depends only on the graphical construction within $(kL,mL,nL)+\mathcal{A}$. Given (k,m,n) in $\mathcal{L}$ there is only a fixed number of sites (j,r,s) in $\mathcal{L}$ such that $(kL,mL,nL)+\mathcal{A}$ and $(jL,rL,sL)+\mathcal{A}$ intersect. Given that events that depend on disjoint regions of the graphical construction are independent, the percolation process we have defined in $\mathcal{L}$ although dependent, has an interaction with only finite range.

A path of dry sites for this model is a connected oriented path which moves along oriented edges (in the direction of the edge) and through dry sites only.

Since $\epsilon > 0$ can be taken arbitrarily small, it is not difficult to see that the probability of a path of dry sites between sites x and y in the percolation process decreases exponentially fast with $||x-y||$, see (8.2) in Berg et al. (1998). Notice that a 1 or 2 at x at time t implies an infection path from time 0 to time t. This infection path for the spatial stochastic process corresponds to a path of dry sites for the percolation process. But long dry paths for the percolation process are very unlikely. By using this comparison it is possible to show that for any fixed site, after a finite random time, there will never be a 1 or a 2 at that site if $p > p_c$ for the spatial stochastic process. See the proof of Theorem 4.4 in Berg et al. (1998) for more details. This completes the proof of Theorem (b).

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