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Keywords
Acquired Immunodeficiency Syndrome.
Virulence. Models, statistical.

Abstract

Introduction
The evolution of virulence in host-parasite relationships has been the subject of several publications. In the case of HIV virulence, some authors suggest that the evolution of HIV virulence correlates with the rate of acquisition of new sexual partners. In contrast some other authors argue that the level of HIV virulence is independent of the sexual activity of the host population.

Methods
Provide a mathematical model for the study of the potential influence of human sexual behaviour on the evolution of virulence of HIV is provided.

Results
The results indicated that, when the probability of acquisition of infection is a function both of the sexual activity and of the virulence level of HIV strains, the evolution of HIV virulence correlates positively with the rate of acquisition of new sexual partners.

Conclusion
It is concluded that in the case of a host population with a low (high) rate of exchange of sexual partners the evolution of HIV virulence is such that the less (more) virulent strain prevails.

Descritores
Síndrome de Imunodeficiência Adquirida.
Virulência. Modelos estatísticos.

Resumo

Introdução
A evolução da virulência na relação hospedeiro-parasita tem sido objeto de várias publicações. No caso do HIV, alguns autores sugerem que a evolução da virulência do HIV correlaciona-se com a taxa de aquisição de novos parceiros sexuais. Por outro lado, outros autores argumentam que o nível de virulência do HIV é independente da atividade sexual da população hospedeira.

Métodos
Propõe-se um modelo matemático para estudar a influência potencial que o comportamento sexual humano possa ter na evolução da virulência do HIV.
INTRODUCTION

A recent paper by Lipstch and Nowak\(^\text{10}\) investigates the evolution of virulence in sexually transmitted HIV/AIDS. Assuming a population with a constant supply of new susceptibles they conclude that, in the long run, new partner acquisition rates should have no effect on the evolution of pathogen virulence. We summarise their arguments below.

They consider the competition of two different strains of virus. Strain 1, called more virulent is more pathogenic to its hosts and more transmissible during the course of a single partnership. Strain 2, called less virulent for its ability to remain longer in the host without producing AIDS, is therefore less pathogenic to its host but is also assumed to be less transmissible. The rate of new partner infection is assumed to be independent of the total population density or size.

Let \(X\) be the number of susceptibles in the population, \(Y_1\) and \(Y_2\) represent the number of hosts infected, respectively, with strain 1 and strain 2. \(N = X + Y_1 + Y_2\) is the total population minus the individuals with AIDS which are assumed to be too ill. The spread of the two strains can be modelled by the following system of differential equations:

\[
\begin{align*}
\frac{dX(t)}{dt} &= f(N) - (\lambda_1 + \lambda_2 + \mu) X(t) \\
\frac{dY_1(t)}{dt} &= \lambda_1 X(t) - (\nu_1 + \mu) Y_1(t) \\
\frac{dY_2(t)}{dt} &= \lambda_2 X(t) - (\nu_2 + \mu) Y_2(t)
\end{align*}
\]

The force of infection \(\lambda_i (i = 1, 2)\) is assumed to be

\[
\lambda_i = \frac{c \beta_i Y_i(t)}{N}
\]

where \(c\) is the rate of new partner acquisition, \(\beta_i (i = 1, 2)\) is the probability that a host with strain \(i\) will infect a single susceptible partner and \(\nu_i\) is the rate individuals infected with each strain develop full-blown AIDS (in the present paper this parameter is called virulence).

As shown by Brenmerman and Thieme\(^\text{2}\) one of the pathogen strains will drive the other to extinction. The winning strain will be the one with the greatest reproductive number \(R_0\). For strain \(i\), we have

\[
R_0 = \frac{c \beta_i}{\nu_i + \mu}
\]

Equation 3 shows that changing the rate of new partner acquisition \(c\) scales \(R_0\) equally for all strains. Thus, the main conclusion of Lipstch and Nowak\(^\text{10}\) that, in the long run, partner acquisition should have no effect on the evolution of virulence.

This conclusion depends crucially on \(\beta\) being independent of \(c\) and \(\nu\). This assumption is, however, contradicted by a number of studies on HIV transmission. In section 2, we summarise the biological studies that show that in fact \(\beta\), for sexually transmitted HIV, should be a function of both \(c\) and \(\nu\). In section 3 we propose a simple form for this dependence and we examine how \(R_0\) depends on \(c\) and \(\nu\) to conclude that low rates of acquisition of new partners favours a less virulent strain.

Epidemiological evidence for the dependence of \(\beta\) on \(c\) and \(\nu\).

It is an already well established fact that the likelihood of sexually related HIV transmission is influenced, among other things, by the presence of coadjuvant factors, in particular other sexually transmitted diseases (STDs), including chlamydia, gonorrhea, herpes and syphilis. The later, in turn, have incidence rates which are directly dependent on the level of sexual activity. In fact, it has been reported by a number of authors\(^\text{6,13,17}\) that STDs can increase the risk of HIV transmission by a factor of up to nine...
times. In addition, the relationship between HIV and other STDs has been suggested as a possible explanation for the higher prevalence of heterosexually transmitted HIV observed in Africa as compared to the rates observed in western countries.

Furthermore, the number of new sexual partners has been directly associated with the risk of HIV infection in a number of studies. For instance, in the study by Burcham et al. it has been shown that the relative risk for HIV infection increases by a factor of 1.02 per new sexual partner. It is, therefore, valid to assume the level of sexual activity as a determining factor of the likelihood of HIV transmission.

As for the influence of the viral load on the natural course and transmissibility of HIV infection, several direct and indirect evidences, mainly related to maternal-fetal transmission, point to a positive relationship between the level of viremia and the speed of disease progression and/or the transmission likelihood.

In what follows we consider likelihood of transmission as dependent both on the rate of partner exchange and on the level of virulence of HIV, as defined above.

A simple model for the dependence of $\beta$ on $c$ and $v$.

It is reasonable to assume a function for $\beta$ that is a logistic-like curve for both $c$ and $v$. This function should assume a zero value when either $c$ or $v$ were zero, and should

$$\beta(c, v) = \kappa_1 e^{\kappa_2 \left[ 1 - \exp\left( -\kappa_3 \frac{v^2}{c^{\kappa_4}} \right) \right]}$$

(4)
saturates when $c$ and $v$ increase to a finite value. A simple function satisfying the above requirements could be:

$$\beta(c, v) = \kappa_1 e^{\kappa_2 \left[ 1 - \exp\left( -\kappa_3 \frac{v^2}{c^{\kappa_4}} \right) \right]}$$

where $\kappa_i$ are positive constants. Figure 1 shows the shape of the function $\beta(c, v)$, for $\kappa_1 = 0.0333$, $\kappa_2 = 0.5$ and $\kappa_3 = 0.1$. The values for the parameters $\kappa_i$ were arbitrarily chosen to make the function $\beta(c, v)$ reproduce accepted epidemiological data.

The basic reproductive ratio, $R_0$, is calculated according to equation 3 replacing $\beta$ with $\beta(c, v)$ given by equation 4. Figure 2 shows its shape as a function of $v$ for several values of $c$.

It should be noted that $R_0$ is maximised by certain values of $v$ ($v_{\text{max}}$) and its peaks increase with $c$.

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**Figure 1** - Transmission probability $\beta(c, v)$ for several values of $c$. The abscissa represents the virulence of HIV on an arbitrary scale.
Figure 2 - The basic reproductive number ($R_0$) for several values of $c$. The abscissa represents the virulence of HIV on an arbitrary scale.

Figure 3 - Values of the virulence (on an arbitrary scale) that maximize $R_0 \cdot c$. 

References:
and always shift to the right, indicating that, for the assumed $\beta$, in the sub-population with a lower level of sexual activity, HIV evolves towards a less virulent state. In figure 3 is shown $v_{\text{max}}$ as a function of $c$.

These results are in agreement with the findings of Ewald and Massad et al.\textsuperscript{11,12}

**DISCUSSION**

The evolution of virulence in host-parasite relationships has been the subject of several publications in the past two decades (see the review by Levin\textsuperscript{8} for details). The paradigm of commensalism as a final end in the evolution of host-parasite interactions has been challenged by some theoretical\textsuperscript{14} and experimental works\textsuperscript{6-7}. In the case of HIV virulence, some authors have been addressing the subject with basically two opposite points of view with regard to the importance of sexual activity level. In a seminal paper, Ewald\textsuperscript{5} concludes that the fraction of the host population with the lowest level of sexual activity ends up infected with a less virulent HIV strain, in the sense that it causes disease (AIDS) after a longer period of time. Attempts to provide a mathematical treatment of Ewald’s arguments is provided in Massad et al.\textsuperscript{12}, indicating that the rate of acquisition of new sexual partners may influence the evolution of HIV virulence.

On the other hand, as mentioned above, Lipsitch and Nowak\textsuperscript{10} argue against this, demonstrating that when of $\beta$, is independent of $c$ and $v$, the level of virulence at equilibrium is independent of sexual activity. In this paper we show that when $\beta$ is considered as a function of $c$ and $v$ it turns out that the evolution of HIV virulence correlates with the rate of acquisition of new sexual partners in the sense that the greater this rate is, the greater the virulence of the HIV strain selected.

This debate is of extreme importance from the point of view of the epidemiology of HIV/AIDS. For such an infection, for which the only effective control measure is education with changing habits and attitudes towards sex, any conclusion regarding the role of sexual activity on the evolution of virulence can constitute an argument for or against such a measure.

**REFERENCES**