Universidade de São Paulo
Faculdade de Saúde Pública

VOLUME 33
NÚMERO 4
AGOSTO 1999
p.329-33

Revista de Saúde Pública

Journal of Public Health

A theoretical model of the evolution of virulence in sexually transmitted HIV/AIDS

Modelo teórico da evolucão da virulência do HIV/AIDS transmitido sexualmente

FAB Coutinho, E Massad, RX Menezes and MN Burattini

Departamento de Patologia. Laboratórios de Investigação Médica 01. Faculdade de Medicina da Universidade de São Paulo. São Paulo, SP-Brasil

FAB Coutinho, E Massad, RX Menezes and MN Burattini *A theoretical model of the evolution of virulence in sexually transmitted HIV/AIDS* Rev. Saúde Pública, 33 (4), 329-33,1999 www.fsp.usp.br/rsp

A theoretical model of the evolution of virulence in sexually transmitted HIV/AIDS

Modelo teórico da evolucão da virulência do HIV/AIDS transmitido sexualmente

FAB Coutinho, E Massad, RX Menezes and MN Burattini

Departamento de Patologia. Laboratórios de Investigação Médica 01. Faculdade de Medicina da Universidade de São Paulo. São Paulo, SP-Brasil

Keywords
Acquired Inmunodeficiency 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.

Correspondence to:
Marcelo N. Burattini
Av. Dr. Arnaldo, 455
01246-903 São Paulo - Brasil
E-mail: mnburatt@usp.br

The publication of this article was supported by FAPESP (Process n. 98/13915-5).
Submitted on 10.10.1998. Reviewed on 13.1.1999.
Approved on 13.4.1999.

Rev. Saúde Pública, 33 (4), 1999
www.fsp.usp.br/rsp

Resultados

Os resultados indicam que, quando a probabilidade de aquisição da infecção pelo HIV é uma função tanto da atividade sexual da população humana quanto da virulência das cepas de HIV, a evolução da virulência do HIV correlaciona-se positivamente com a taxa de aquisição de novos parceiros sexuais.

Conclusão

Concluiu-se que no caso de uma população hospedeira com uma baixa (alta) taxa de troca de parceiros sexuais a evolução da virulência do HIV é tal que a cepa menos (mais) virulenta predomina.

INTRODUCTION

A recent paper by Lipstch and Nowak[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:

$$\begin{aligned} \frac{dX(t)}{dt} &= f(N) - (\lambda_1 + \lambda_2 + \mu) X(t) \\ \frac{dY_1(t)}{dt} &= \lambda_1 X(t) - (\nu_1 + \mu) Y_1(t) \\ \frac{dY_2(t)}{dt} &= \lambda_2 X(t) - (\nu_2 + \mu) Y_2(t) \end{aligned} \qquad (1)$$

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

$$\lambda_i = \frac{c\beta_i Y_i(t)}{N} \qquad (2)$$

where c is the rate of new partner acquisition, β_i (i = 1, 2) is the probability that a host with strain i will infect a single susceptible partner and ν_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[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

$$R_{0i} = \frac{c\beta_i}{\nu_i + \mu} \qquad (3)$$

Equation 3 shows that changing the rate of new partner acquisition c scales R_{0i} equally for all strains. Thus, the main conclusion of Lipstch and Nowak[10] that, in the long run, partner acquisition should have no effect on the evolution of virulence.

This conclusion depends crucially on β_i being independent of c and ν. 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 β, for sexually transmitted HIV, should be a function of both c and ν. In section 3 we propose a simple form for this dependence and we examine how R_0 depends on c and ν to conclude that low rates of acquisition of new partners favours a less virulent strain.

Epidemiological evidence for the dependence of β on c and ν.

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[4,13,17] that STD's 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[1].

Furthermore, the number of new sexual partners has been directly associated with the risk of HIV infection in a number of studies[3,8,16]. For instance, in the study by Burcham et al.[3] 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[15,18,19].

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 β on c and ν.

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

$$\beta(c,\nu) = \kappa_1 c^{k_2}\left[1 - \exp - \left(\kappa_3 \frac{\nu^2}{c^{k_2}}\right)\right] \qquad (4)$$

saturates when c and ν increase to a finite value. A simple function satisfying the above requirements could be:

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

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

It should be noted that R_0 is maximised by certain values of ν (ν_{max}) and its peaks increase with c

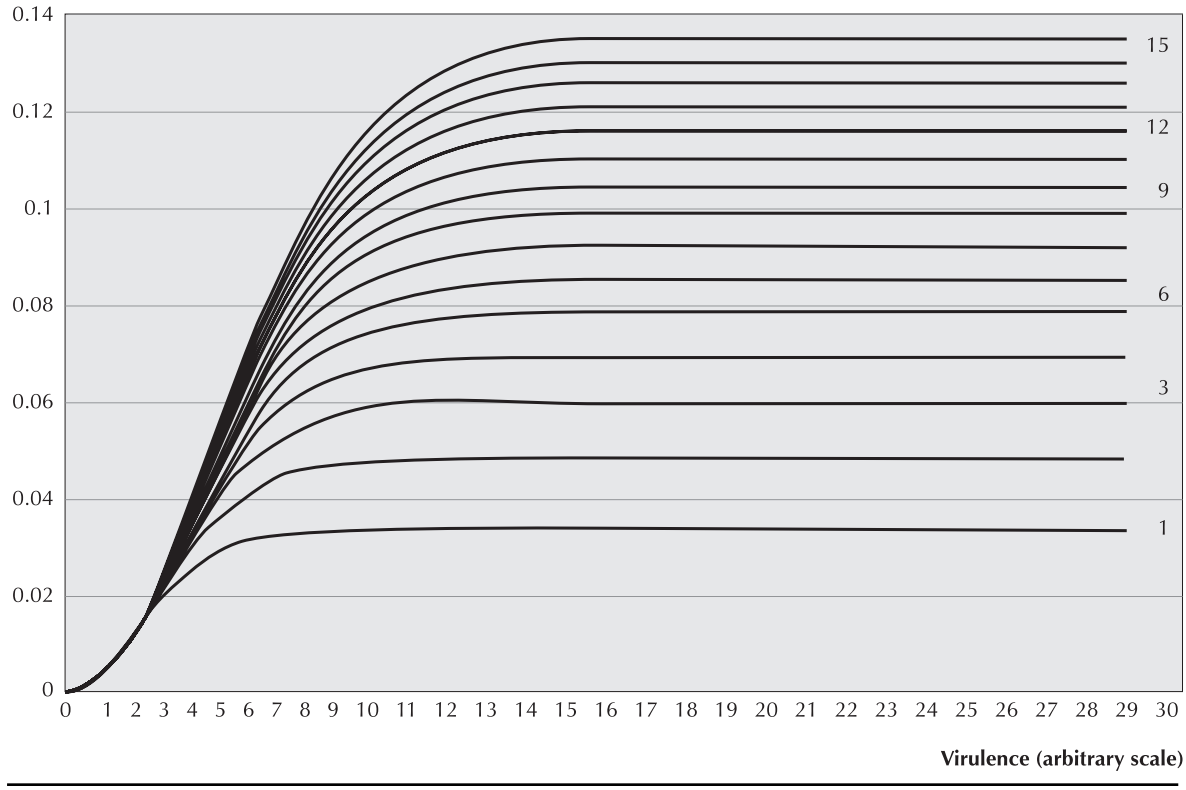

Figure 1 - Transmission probability β (c, ν) for several values of c. The abscissa represents the virulence of HIV on an arbitrary scale.

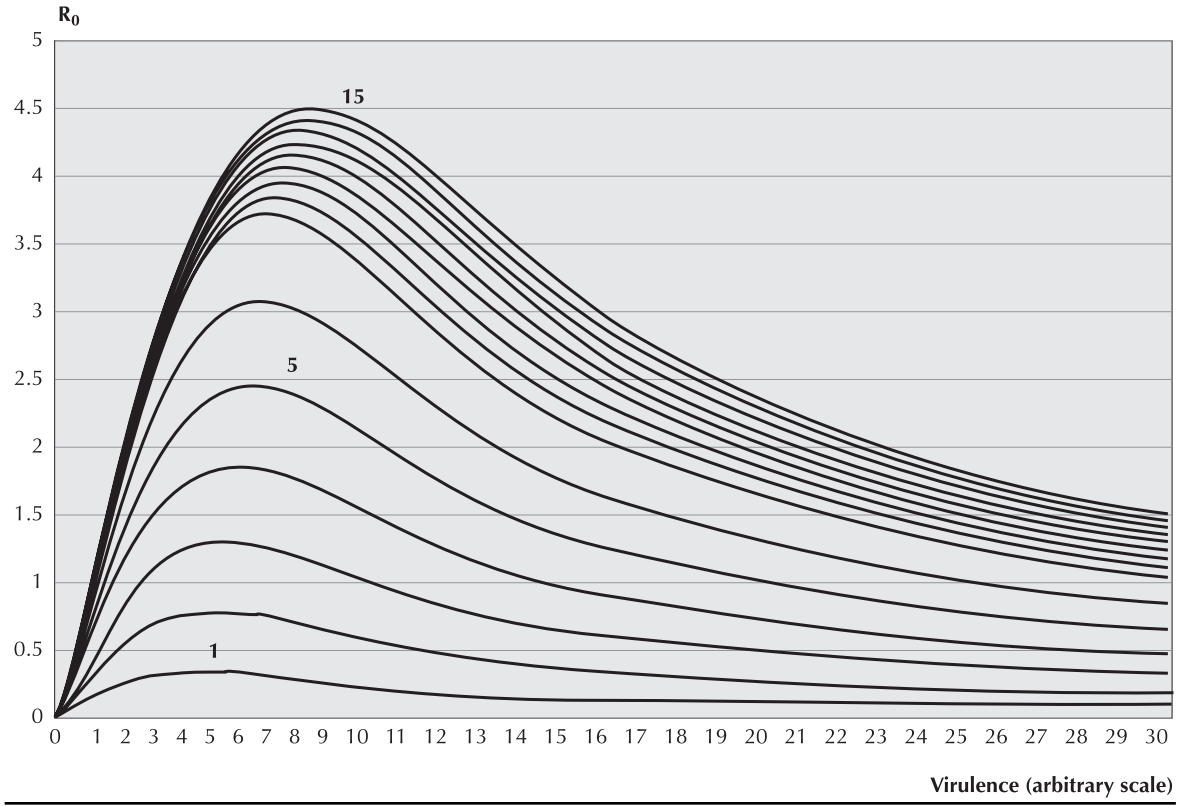

Figure 2 - The basic reproductive number (R_0) for several values of *c*. The abscissa represents the virulence of HIV in on an arbitrary scale.

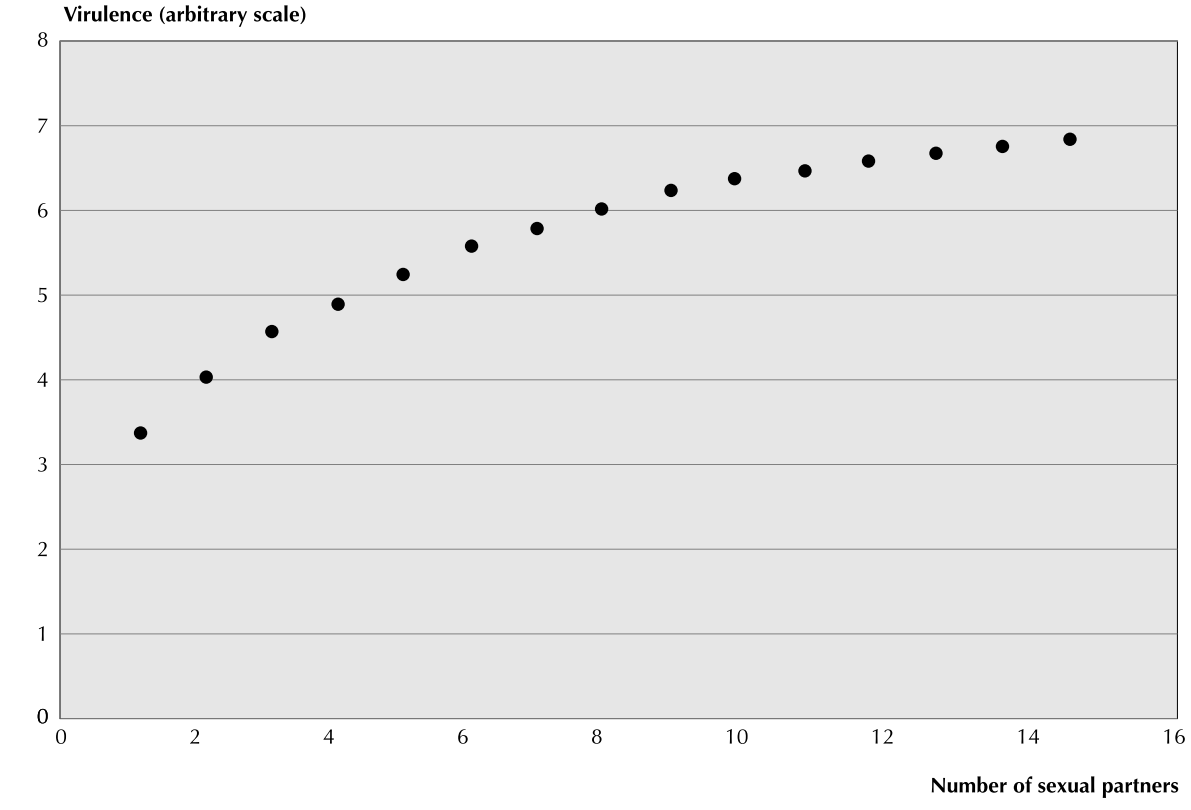

Figure 3 - Values of the virulence (on an arbitrary scale) that maximize R_0 *c*.

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

These results are in agreement with the findings of Ewald[5] and Massad et al.[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[9] for details). The paradigm of commensalism as a final end in the evolution of host-parasite interactions has been challenged by some theoretical[14] and experimental works[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[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.[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[10] argue against this, demonstrating that when of β_i is independent of c and ν, the level of virulence at equilibrium is independent of sexual activity. In this paper we show that when β_i is considered as a function of c and ν 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

1. Berkley SF, Widy-Wirski R, Okware SI, Downing R, Linnand MJ, White KE, Sempala S. Risk factors associated with HIV infection in Uganda. *J Infect Dis* 1989; 160:22-30.
2. Bremermann HJ, Thieme HR. A competitive exclusion principle for pathogen virulence. *J Math Biol* 1989; 27:179-90.
3. Burcham JL, Tindall B, Marmor M, Cooper DA, Berry G, Penny R. Incidence and risk factors for human immunodeficiency virus seroconversion in a cohort of Sidney homosexual men. *Med J Aust* 1989; 150:634-9.
4. Cameron DW, Simonsen JN, D'Costa LJ, Ronald AR, Maitha GM. Gakinya MN et al. Female to male transmission of human immunodeficiency virus type 1: risk factors for seroconversion in men. *Lancet* 1989; 2(8660):403-7.
5. Ewald PW. Evolution of infectious disease. Oxford: Oxford University Press; 1994.
6. Fenner F, Marshall ID. A comparison of the virulence for European rabbits Oryctolagus cuniculus of strains of myxoma virus recovered in the fields of Australia, Europe and America. *J Hyg* 1957; 55:149-91.
7. Fenner F, Ratcliff FN. *Myxomatosis.* Cambridge (UK): Cambridge University Press; 1965.
8. Latif AS, Katzenstein DA, Bassett MT, Houston S, Emmanuel JC, Marowa E. Genital ulcers and transmission of HIV among couples in Zimbabwe. *AIDS* 1989; 3:519-23.
9. Levin BR. The evolution and maintanance of virulence in micro parasites. *Emerg Infect Dis* 1996; 2:93-102.
10. Lipsitch M, Nowak MA. The evolution of virulence in sexually transmitted HIV/AIDS. *J Theor Biol* 1995; 174:427-40.
11. Massad E. Transmission rates and the evolution of pathogenicity. *Evolution* 1987; 41:1127-30.
12. Massad E, Burattini MN, Menezes RX, Coutinho FAB. Modelling the role of sexual activity on the evolution of HIV virulence. *Math Model Sci Comput* 1995; 26:810-5.
13. Mastro TD, Satten GA, Nopkerso T, Sanguekharomyo S, Longini Jr IM. Probability of female to male transmission of HIV-1 in Thayland. *Lancet* 1994; 343:204.
14. May RM, Anderson RM. Parasite hosts coevolution. In: Futuyama DJ, Slatikin, M, editors. *Coevolution*. Sunderland (MA): Sinauer Associates; 1983. p. 186-206.
15. Mellors JW, Rinaldo Jr CR, Gupta P, White RM, Todd JA, Kingsley LA. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. *Science* 1996; 272:1167-70.
16. Pape JW, Stanback ME, Pamphile M, Bonsy M, Deschamps MM, Verdier RI et al. Prevalence of HIV infection and high risk activities in Haiti. *JAIDS* 1990; 3:995-1001.
17. Plummer FA, Simonsen JN, Cameron DW et al. Cofactors in male-female sexual transmission of human immunodeficiency virus type 1. *J Infec Dis* 1991; 163:233.
18. Simmonds P. Variation in HIV virus load of individuals at different stages in infection: possible relationship with risk of transmission. *AIDS* 1990; 4(Suppl. 1):S77-S83.
19. Weiser B, Nachman S, Tropper P, Viscosi KH, Grimson, R, Baxter G et al. Quantitation of human immunodeficiency virus type 1 during pregnancy: relationship of viral titer and mother to child transmission and stability of viral load. *Proc Natl Acad Sci USA* 1994; 91:8037-41.