Modeling the synergy between HSV-2 and HIV and potential impact of HSV-2 therapy

Zhilan Feng\textsuperscript{a,c,*}, Zhipeng Qiu\textsuperscript{b,c}, Zi Sang\textsuperscript{b}, Christina Lorenzo\textsuperscript{c}, John Glasser\textsuperscript{d}

\textsuperscript{a} Department of Mathematics, Nanjing University of Information Science and Technology, Nanjing 210044, PR China
\textsuperscript{b} Department of Applied Mathematics, Nanjing University of Science and Technology, Nanjing 210094, PR China
\textsuperscript{c} Department of Mathematics, Purdue University, West Lafayette, IN 47907, USA
\textsuperscript{d} Population Biology, Ecology and Evolution, Emory University, 1462 Clifton Road, Atlanta, GA 30322, USA

\begin{abstract}
Mounting evidence indicates that genital HSV-2 infection may increase susceptibility to HIV infection and that co-infection may increase infectiousness. Accordingly, antiviral treatment of people with HSV-2 may mitigate the incidence of HIV in populations where both pathogens occur. To better understand the epidemiological synergy between HIV and HSV-2, we formulate a deterministic compartmental model that describes the transmission dynamics of these pathogens. Unlike earlier models, ours incorporates gender and heterogeneous mixing between activity groups. We derive explicit expressions for the reproduction numbers of HSV-2 and HIV, as well as the invasion reproduction numbers via next generation matrices. A qualitative analysis of the system includes the local and global behavior of the model. Simulations reinforce these analytical results and demonstrate epidemiological synergy between HSV-2 and HIV. In particular, numerical results show that HSV-2 favors the invasion of HIV, may dramatically increase the peak as well as reducing the time-to-peak of HIV prevalence, and almost certainly has exacerbated HIV epidemics. The potential population-level impact of HSV-2 on HIV is demonstrated by calculating the fraction of HIV infections attributable to HSV-2 and the difference between HIV prevalence in the presence and absence of HSV-2. The potential impact of treating people with HSV-2 on HIV control is demonstrated by comparing HIV prevalence with and without HSV-2 therapy. Most importantly, we illustrate that the aforementioned aspects of the population dynamics can be significantly influenced by the sexual structure of the population.
\end{abstract}

1. Introduction

\textit{Herpes simplex virus type 2} (HSV-2) and \textit{human immunodeficiency virus} (HIV) cause sexually-transmitted diseases (STDs) that are detrimental to human health. HIV is a retrovirus that infects cells of the immune system and leads to acquired immunodeficiency syndrome (AIDS). Since HIV was first identified in the United States in 1983, over 60 million people have been infected, and the WHO estimates that deaths due to AIDS exceed 25 million [1]. HSV-2 is a double-stranded DNA virus that almost exclusively infects the genital region, and has been recognized as the most common cause of genital ulcer disease [2]. HSV-2 seroprevalence is 16.2% in the United States, or about one in six Americans 14 to 49 years of age [3,4]. In developing countries, the prevalence of infection is 40–60\% [5]. Due to the high prevalence and lifelong infection, HSV-2 has a detrimental effect on human health globally [3]. Moreover, HSV-2 may facilitate HIV transmission [6–8].

Facilitation of HIV by HSV-2 is partly due to the enhanced susceptibility to HIV of HSV-2-infected individuals and partly to the enhanced HIV infectivity of individuals co-infected with HSV-2 and HIV. In HIV-uninfected individuals, HSV-2 causes genital ulceration and mucosal disruption, providing a direct portal for HIV entry [2]. A large number of CD4 + lymphocytes, HIV target cells, have been detected in herpetic lesions, and the presence of these cells could also increase susceptibility to HIV during sexual activity. The biological plausibility of this hypothesis is corroborated by epidemiological observations. A systematic review and meta-analysis of longitudinal studies by Freeman et al. [7] showed that HSV-2 seropositivity was a statistically significant risk factor for HIV acquisition in general population studies of men (summary adjusted risk ratio (RR), 2.7; 95\% confidence interval (CI), 1.9–3.9) and women (RR, 3.1; 95\% CI, 1.7–5.6). Another study [8] suggests that other STDs may affect susceptibility to HIV and that the extent of this effect may depend on specific population characteristics. Similarly, biological evidence and epidemiological observations

\* Corresponding author at: Department of Mathematics, Purdue University, West Lafayette, IN 47907, USA.

E-mail addresses: zfeng@math.purdue.edu (Z. Feng), mustqzp@mail.njust.edu.cn (Z. Qiu), clorenzo@math.purdue.edu (C. Lorenzo), jglasser@bellsouth.net (J. Glasser).

0025-5564/$ - see front matter \textcopyright 2013 Elsevier Inc. All rights reserved.

http://dx.doi.org/10.1016/j.mbs.2013.07.003