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

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1. Introduction

Herpes simplex virus type 2 (HSV-2) and 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 [9] 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...