Herpes simplex virus type 2 and syphilis infections with HIV: an evolving synergy in transmission and prevention

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Purpose of review

Herpes simplex virus type 2 (HSV-2) and syphilis are associated with HIV infection. The purpose of this review is to summarize the advances in the relationship of HSV-2 and syphilis with HIV, highlighting intervention trials to prevent HIV acquisition and transmission.

Recent findings

HIV acquisition has often been linked to genital ulcers due to HSV-2 and syphilis. The latest pathophysiological studies have continued to elucidate the relationship between HSV-2, syphilis and HIV, establishing that both syphilitic and HSV-2-infected tissue have increased numbers of chemokine receptor 5-expressing T cells, and several models have further emphasized the viral synergy between HSV-2 and HIV. In clinical trials, HSV suppressive therapy decreased HIV RNA levels that might affect transmission, but two trials have failed to prevent HIV acquisition. Male circumcision, however, prevents both HIV and HSV-2 acquisition.

Summary

Genital ulcers from HSV-2 and syphilis are associated with HIV acquisition. The exact role for these HIV cofactors is still unknown and exemplified by the failure of HSV suppressive therapy to decrease HIV acquisition. Male circumcision, however, reduces HSV-2 acquisition. With several HSV suppressive trials to prevent HIV transmission and disease progression currently ongoing, the future promises to provide more critical information for the control of HIV infection.

Keywords

genital ulcer disease, HIV, herpes simplex virus type 2, male circumcision, prevention trials, syphilis, *Treponema pallidum*

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Introduction

Herpes simplex virus type 2 (HSV-2) and syphilis are common sexually transmitted infections (STIs) [1–4]. HSV-2-seropositive individuals have a lifelong risk of infecting their sexual partners [5]. It is estimated that HSV-2 seroprevalence increased by almost one-third to 21.8% in the United States between 1976 and 1994 [6]. In Uganda, it is estimated that the HSV-2 seroprevalence in women and men is 74 and 57%, respectively [3]. *Treponema pallidum* infects at least 12 million individuals annually [4]. Genital ulcer disease (GUD) due to both syphilis and HSV-2 is also associated with an increased risk of acquiring HIV. Recent studies have continued to evaluate the pathophysiological relationship between HSV-2, syphilis and HIV and also explored potential interventions that could reduce HIV acquisition and transmission by suppressing HSV-2 infection. This review highlights recent advances in the synergy between HSV-2, syphilis and HIV.

Syphilis is associated with HIV acquisition

Multiple studies [7–9] have shown that syphilis infection is associated with an increased risk of acquiring HIV. The incidence of syphilis among HIV-positive individuals is increasing and disproportionately affects men who have sex with men (MSM) [7,10]. The association between syphilis and HIV acquisition may be partially mediated by the association between symptomatic GUD and HIV acquisition [11]. The pathophysiology behind this association has been further clarified recently by Sheffield *et al.* [12•] who showed that women with either syphilis, HSV-1 or HSV-2 infection have significantly higher numbers of $CD14^+$ cells that express chemokine receptor 5 (CCR5) within the genital ulcer. These authors also found that CCR5 mRNA expression is higher in syphilitic tissue [12•].

Although syphilis is associated with HIV acquisition, HIV also adversely affects the serologic response to syphilis. It has been recently demonstrated that HIV-infected

individuals with $CD4^+$ T-cell counts of less than 200 cells/μl are at higher risk of a lack of a serologic response to syphilis [13]. In addition, administration of highly active antiretroviral therapy (HAART) is also associated with a 60% reduction in the lack of a serologic response to syphilis [13]. Thus, HIV and syphilis are synergistically associated with one another, with syphilis enhancing transmission and acquisition of HIV, and HIV suppressing the serologic detection of syphilitic infection.

Herpes simplex virus type 2 risk factors

Although there have been numerous studies to evaluate HSV-2 prevalence, little is known about incident HSV-2 infection. Knowledge of HSV-2 risk factors is important for prevention of primary HSV-2 infection and potentially for trials of HSV-2 interventions aimed at reducing HIV transmission and progression. Several recent studies [14,15•,16•] evaluated both prevalent and incident risk factors in Peru, Tanzania and Uganda. One study [16•] in Rakai, Uganda demonstrated that HSV-2 incidence increases with alcohol use when combined with sexual intercourse [adjusted incidence rate ratios (adjIRR), 1.92; 95% confidence interval (CI), 1.46–2.53], and decreased with consistent condom use (adjIRR 0.56; 95% CI, 0.36–0.89), and was not significantly affected by enrolment HIV status. Thus, education on modifiable behavioral changes may reduce HSV-2 acquisition. Although the acquisition of HSV-2 is becoming more well defined, there is still limited research on HSV-2 transmission.

Herpes simplex virus type 2 is associated with HIV acquisition

HSV-2 is associated with a three-fold increased risk for acquiring HIV in observational studies [1–3,5]. It has been estimated that there is a 2.6-fold increased risk of HIV acquisition per coital act associated with genital ulceration [17]. As HSV-2 is the main cause of genital ulceration worldwide [1–3], this fact underscores the importance of the association between HSV-2 and HIV. A recent study [18] in Tanzania found an increased HIV incidence among women with either prevalent HSV-2, incident HSV-2 or active GUD.

The pathophysiology between HSV-2 and HIV has also been further elucidated recently. It was previously accepted that the association between symptomatic GUD and HIV transmission might be related to higher HIV RNA levels in genital ulcers of those individuals with HSV-2 [19]. In addition to the breaches of the mucosal barrier, it has been proposed that the increased risk of HIV acquisition associated with HSV-2 infection may be due to recruitment of $CD4^+$ T cells expressing CCR5 and immature dendritic cells into areas of HSV replication with both clinical and subclinical reactivation of mucosal lesions [20–22]. Individuals coinfected with HIV and HSV-2 also have higher numbers of $CD4^+$ T cells compared with HIV-positive individuals after adjusting for HIV viral load [23•], but HIV-specific $CD8^+$ T-cell responses and systemic inflammation are reduced [24]. Thus, it has been hypothesized that HSV-2 enhances HIV acquisition by creating mucocutaneous lesions that permit HIV entry while simultaneously recruiting HIV-susceptible cells to the mucosa [25].

Herpes simplex virus type 2 and HIV viral synergy

Powers *et al.* [26•] recently conducted a meta-analysis of 27 studies that provided heterosexual infectivity estimates to determine transmission cofactors that affect HIV heterosexual infectivity. The authors found that HIV infectivity is significantly greater among uncircumcised men, individuals with GUD and individuals with early-stage or late-stage (compared with mid-stage) HIV infection [26•]. Although there were limited data that prevented meta-regression analyses, the authors also determined that infectivity is higher for individuals with any STI [26•]. The increased infectivity among individuals with STIs and GUD suggests that HSV-2 may play a role in HIV transmission.

Although it is often difficult to fully and accurately incorporate timing of HIV and HSV-2 infections, durations of viral infection stages, viral shedding and other key transmission factors, Abu-Raddad *et al.* [27•] created a model of HIV and HSV-2 dynamics and interactions to evaluate the synergy between these two viruses compared with other STIs. The authors estimate that in areas of high HSV-2 prevalence (such as Africa), HSV-2 may contribute to more than 25% of incident HIV infections [27•]. It is proposed that HSV-2 makes individuals more at risk for HIV infection or more infectious for those individuals that are coinfected with HIV and HSV-2 [27•]. Consequently, the authors believe that HSV-2 infection is a critical initiator for the global spread of HIV [27•]. Although this model has plausibility and biological factors to support this synergy in transmission, it does not control for the confounding factor of behavior that invariably is linked to acquisition of both infections.

Herpes simplex virus suppressive therapy decreases HIV RNA levels

A study [28] from Rakai, Uganda previously demonstrated that HSV-2-positive individuals who experience HIV seroconversion have significantly higher HIV viral load set points when compared with HSV-2-seronegative individuals. In addition, three studies [29–31] showed that HSV-2-seropositive individuals have increased levels of genital or plasma HIV-1 RNA levels, whereas

several studies [23•,32,33] showed no association. Nagot *et al.* [34•] extended these finding using multiple longitudinal samples. They found that both genital and plasma HIV-1 viral loads are higher among women with at least one GUD or genital HSV-2 DNA shedding [34•]. Overall, the findings suggest that HSV suppression might decrease HIV shedding.

Due to the association between HSV-2 and genital HIV shedding, several studies evaluated the role for HSV suppressive therapy to decrease genital and plasma HIV RNA levels. Among 140 HSV-2 and HIV coinfected women in Burkina Faso that received either 500 mg valacyclovir twice daily or placebo, those in the intervention group had significantly lower genital (0.29 $\log_{10}$-copies/ml decrease) and plasma (0.53 $\log_{10}$ copies/ml decrease) HIV RNA levels [35••]. In addition, among 20 HSV-2 and HIV-positive MSM in Lima, Peru with CD4 cell counts of more than 200 cells/μl that received either 500 mg valacyclovir twice daily or placebo, those in the intervention group also had significantly lower rectal (0.16 $\log_{10}$ copies/ml decrease) and plasma (0.33 $\log_{10}$ copies/ml decrease) HIV RNA levels [36••]. The same group of researchers also evaluated 20 HSV-2 and HIV-positive women in Lima, Peru who received either 500 mg valacyclovir twice daily or placebo and then the alternative therapy for 8 weeks after a 2-week washout period. Those in the intervention group had significantly lower cervical and plasma HIV RNA levels [37••]. These findings helped to lay the groundwork for several clinical trials to determine whether HSV suppression can decrease HIV acquisition, HIV transmission or HIV disease progression.

Herpes simplex virus suppressive therapy to prevent HIV acquisition

Due to the ability of HSV suppressive therapy to decrease plasma, genital and rectal HIV RNA levels, it had been hypothesized that HSV suppressive therapy may decrease HIV acquisition, transmission or disease progression. Two randomized control trials [38••,39••] were completed in 2008 to evaluate whether HSV-2 suppressive therapy could prevent HIV acquisition among HIV-negative, HSV-2-seropositive individuals (Table 1). Watson-Jones *et al.* [38••] enrolled female workers at recreational facilities in Tanzania to receive 400 mg acyclovir twice daily ($n = 400$) or placebo ($n = 421$). The HIV incidence was 4.1 per 100 person-years in the placebo group and 4.4 per 100 person-years in the acyclovir group. The trial by Celum *et al.* [39••] evaluated women in Africa and MSM in Peru and USA and assigned participants to twice daily 400 mg acyclovir ($n = 1637$) or placebo ($n = 1640$). Although the incidence of genital ulcers decreased by 47% and HSV-2-positive genital ulcers decreased by 63% in the acyclovir group, the HIV incidence was nonsignificantly higher in the acyclovir group (3.9 per 100 person-years) compared with the placebo group (3.3 per 100 person-years) [39••].

It is hypothesized that the failure of these two clinical trials to prevent HIV acquisition with HSV suppression may be due to insufficient drug concentration or that HSV-2 does not increase HIV susceptibility. Acyclovir does not have good absorption and has a short half-life. Thus, the plasma concentrations may be deficient to prevent HIV acquisition. Although a recently published

Table 1 Summary of two randomized trials of herpes simplex virus suppression therapy to prevent HIV acquisition

	Watson-Jones *et al.* [38••]	Celum *et al.* [39••]
Location and participant sex	Tanzanian females	African females (multiple countries) Peruvian and American MSM
Age range (years)	16–35	18–75
Number enrolled	821	3277
Intervention arm	400	1637
Control arm	421	1640
Acyclovir dose (mg, b.i.d.)	400	400
Follow-up schedule (months)	Every 3	Every 3
Participant follow-up (months)	12–30	12–18
Retention rate (%)	83	85
Drug adherence (by pill count, %)	90	94
Number of GUDs detected by examination		
Intervention arm	9	574
Control arm	6	1090
GUD ratio (95% CI)[a]	1.69 (0.61–4.70)	0.53 (0.46–0.62)
Number of incident HIV events		
Intervention arm	27	75
Control arm	28	64
Cumulative HIV incidence/100 person-years		
Intervention arm	4.4	3.9
Control arm	4.1	3.3
HIV ratio[b]	1.08 (0.64–1.83)	1.16 (0.83–1.62)

b.i.d., twice daily; CI, confidence interval; GUD, genital ulcer disease; HR, hazard ratio; MSM, men who have sex with men; OR, odds ratio; RR, relative risk.
[a] GUD ratio is an OR for Watson-Jones *et al.* [38••] and RR for Celum *et al.* [39••].
[b] HIV ratio is an RR for Watson-Jones *et al.* [38••] and HR for Celum *et al.* [39••].

meta-analysis demonstrated that HSV-2-positive status is a significant risk factor for HIV acquisition, this association is not present among high-risk women [40]. Therefore, it is possible that HSV-2 suppression trials failed to prevent HIV acquisition, as risk factors other than HSV-2 seropositivity may play a more important role for HIV acquisition.

Herpes simplex virus suppressive therapy to prevent HIV transmission or disease progression

In addition to the two trials that evaluated whether HSV suppressive therapy prevents HIV acquisition, the Partners in Prevention trial is currently evaluating whether HSV suppressive therapy could reduce HIV transmission from HIV, HSV-2 coinfected individuals to the HIV-negative partner. Due to the evidence demonstrating that HIV and HSV-2 coinfected individuals have a higher HIV viral load set point than singly HIV-infected individuals [28–31,34•], another randomized clinical trial is evaluating whether HSV suppressive therapy can limit HIV disease progression. Results of these two trials on HIV and HSV-2 viral synergy will be available sometime during the next 2 years.

Male circumcision for HIV prevention and associated sexually transmitted infections

Three large randomized controlled trials and multiple observational studies demonstrated that male circumcision significantly decreases HIV acquisition in men [41–43]. Self-reported GUD was decreased in circumcised men in the trial conducted in Rakai, Uganda, suggesting that male circumcision may reduce other STIs [41]. Additionally, two observational studies [44,45] suggested that male circumcision significantly decreases HSV-2 infection, whereas others showed no association between male circumcision and HSV-2 infection [46–52]. Similarly, two observational studies [53,54] reported that male circumcision decreases syphilis infection, whereas others showed no association [51,55]. A meta-analysis of cross-sectional and prospective studies that estimated the decreased risk of HSV-2 and syphilis infection associated with circumcision is of borderline statistical significance with a relative risk of 0.88 (95% CI, 0.77–1.01) and 0.67 (95% CI, 0.54–0.83), respectively [56].

In a predefined analysis of secondary endpoints of a randomized control trial of uncircumcised men aged 15–49 years that were HIV and HSV-2 antibody negative at enrolment and were randomized to receive immediate circumcision ($n = 1684$) or circumcision after 24 months ($n = 1709$), male circumcision significantly reduced HSV-2 acquisition. The cumulative probability of HSV-2 seroconversion over 2 years was 7.8% in the intervention group and 10.3% in the control group (adjusted hazard ratio, 0.72; 95% CI, 0.56–0.92; $P = 0.008$) [57••]. HSV-2 incidence was lower in the intervention group than the control group in almost all sociodemographic, behavioral and sexually transmitted disease symptom subgroups. However, no significant difference was observed in syphilis acquisition or prevention by study arm (adjusted hazard ratio, 1.10; 95% CI, 0.75–1.65; $P = 0.44$) [57••].

It is possible that protection against HIV acquisition due to male circumcision could in part be mediated by decreased GUD-associated and HSV-2-associated genital ulcers. Thus, male circumcision prevents HSV-2 acquisition, and consequently the HSV-2 reduction may contribute to the efficacy of circumcision for prevention of HIV infection in men. However, the exact contribution of protection from HIV acquisition that is due to HSV-2 protection remains unknown.

Conclusion

There have been many advances recently in evaluating the association between HSV-2 and syphilis infections with HIV for both transmission and prevention. The mechanisms responsible for the synergistic association of HSV-2 and syphilis have been further elucidated demonstrating that both syphilitic and HSV-2-infected tissue have increased number of CCR5-expressing T cells, theoretically increasing HIV susceptibility in active GUD due to these infections. HSV-2 and HIV coinfections also result in higher HIV viral loads, and conversely HSV-2 suppression decreases plasma and genital viral load. Male circumcision decreases both HSV-2 and HIV acquisition, and models of HIV and HSV-2 dynamics have stressed the importance of HSV-2 infections in the spread of HIV.

The possibility of confounding due to correlated sexual risk behaviors cannot be excluded in most of these studies, and two trials of HSV-2 suppression in HSV-2-positive and HIV-negative men failed to show protection against HIV acquisition. It is still unknown, however, whether HSV suppressive therapy can prevent HSV-2 transmission or HIV disease progression. With these trials currently underway, it is evident that there is significant synergy between these two major STIs and HIV, and additional data on the relative roles of these infections with each other will be forthcoming in the near future.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 344).

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