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Infectious Co-factors in HIV-1 transmission Herpes Simplex Virus type-2 and HIV-1: New Insights and interventions

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Abstract

Over the last thirty years, epidemiologic and molecular studies indicate a strong and synergist relationship between the dual epidemics of herpes simplex type 2 (HSV-2) and HIV-1 infection. While prospective studies show that HSV-2 infection increases the risk for HIV-1 acquisition by two-three fold, HSV-2 suppression with standard prophylactic doses of HSV-2 therapy did not prevent HIV-1 acquisition. Reconciling these discrepancies requires understanding recent HSV-2 pathogenesis research, which indicates HSV-2 infection is not a latent infection with infrequent recurrence but a near constant state of reactivation and viral shedding which is not completely suppressed by standard antivirals. Because current antivirals do not prevent or fully suppress HSV-2 replication, priorities are HSV-2 vaccine development and antivirals that reach high concentrations in the genital mucosa and suppress the persistent genital inflammation associated with genital herpes reactivation in order to reduce the increased susceptibility to HIV-1 infection associated with HSV-2. HIV-1 and HSV-2 synergy is also seen among co-infected individuals who exhibit higher HIV-1 viral load compared to HSV-2 uninfected individuals. Standard HSV-2 therapy modestly lowers HIV-1 viral load and is associated with slower HIV-1 disease progression. A promising area of research is higher doses of HSV-2 suppressive therapy achieving a greater reduction in plasma HIV-1 RNA, which could translate to greater reductions in HIV-1 disease progression and infectiousness. However, many questions remain to be answered including potential effectiveness and cost-effectiveness of higher dose HSV-2 suppressive therapy. Mathematical models of HSV-2 and HIV-1 at a population level would be useful tools to estimate the potential impact and cost-effectiveness of higher dose HSV-2 suppressive therapy.

Keywords

HIV; HSV-2; HIV-1 viral load; HIV-1 RNA; epidemiologic synergy; valacyclovir

Introduction

Over the last 30 years, the global, intersecting epidemics of herpes simplex virus type 2 (HSV-2) and HIV-1 have demonstrated a complex relationship between pathogens. The synergy between these two sexually transmitted infections goes beyond similar risk factors for acquisition; they interact both in their epidemiologic niche and at a pathogenesis level driving viral replication and facilitating transmission (1). Moreover, exploiting this synergy

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for HIV-1 prevention interventions has not proved straight-forward due to both viral and host factors. Indeed, because trials of standard doses of HSV-2 suppressive therapy (i.e., acyclovir 400 mg twice daily) did not reduce acquisition or transmission of HIV-1, research in this area slowed. However, recent epidemiologic and laboratory studies have shed new light on the role of HSV-2 in transmission of HIV-1. Recent intervention trials have indicated that standard dose HSV-2 suppressive therapy for HIV-1 infected persons at intermediate CD4 T cell counts delays HIV-1 disease progression pre-ART initiation and higher doses of HSV-2 suppressive therapy achieve substantially greater reductions in plasma HIV-1 levels, potentially leading to greater clinical and prevention benefits which require further evaluation. Below we review the evidence for HSV-2 and HIV-1 synergy, describe new insights, and propose future research directions.

Epidemiology

HSV-2, the etiologic agent of genital herpes and the most common cause of genital ulcer disease (GUD), is a highly prevalent sexually transmitted infection (STI) globally. Sixteen percent of the world's population age 15 to 49 years, 536 million people, were estimated to be living with HSV-2 in 2003 (2). The prevalence of HSV-2 varies by geographic region, age, gender, study population (3) and HIV-1 serostatus. Sub-Saharan Africa has a higher reported HSV-2 seroprevalence compared to the Americas, Europe, Australia, Asia and the Middle East and North Africa (MENA). HSV-2 prevalence estimates among adults in the general population (HIV-1 uninfected) in sub-Saharan Africa range from 30% to 80% in women, and 10% to 50% in men (4). Women in Central and South America have HSV-2 prevalence ranges from about 20% to 40%, with lower prevalence seen in developing Asian countries (10–30%) (4). In the United States, HSV-2 seroprevalence was estimated to be 16% between 2005 and 2008 in a national survey of adults in the general population age 14 to 49 years--12% in men and 21% in women (5). Estimates from the MENA regions are some of the lowest seen for the general population (13% in women attending antenatal clinics and 9% for men in a HIV-1 sentinel surveillance study in Morocco (6)) with higher prevalence seen among risk groups (7). In all settings HSV-2 seropositivity is higher in women than in men, as seen in the data summarized above.

HSV-2 seroprevalence increases steadily after sexual debut and with age. In the United States, the seroprevalence of HSV-2 rose steadily from 1.4% among 14 to 19 year olds to 26.1% among 40 to 49 year olds (5); a trend that has not changed since the inception of the national health surveys with HSV-2 testing in 1976. In sub-Saharan Africa, 50% of HIV-1 uninfected persons are HSV-2 seropositive by age 25 years (4). Sexual network structures contribute to higher HSV-2 prevalence seen among STI clinic clients and commercial sex workers (4). HIV-1 infected individuals have higher rates of HSV-2 antibodies compared to HIV-1 uninfected persons; 85% among HSV-2 and HIV-1 co-infected individuals in sub-Saharan Africa (4), 65% among men who have sex with men (MSM) in San Francisco (8) and 80% of HIV-1 infected men in combined data from a US national survey (9).

A recent household serosurvey in Kenya, notable as the first nationally representative estimate of HSV-2 prevalence and risk factors for that country, clearly demonstrated these epidemiologic patterns. Of the 17,940 participants who consented, 15,707 individuals (87.5%) were tested for HSV-2 and HIV-1 (10). They found a HSV-2 seroprevalence of 35% with 42% HSV-2 seropositivity among women and 26% among men. For women and men age 15 to 24 years, HSV-2 prevalence increased from 7% to 30% and 3% to 14% respectively. The seroprevalence of HSV-2 among HIV-1 co-infected individuals was 81%. Among HSV-2 seropositive persons, HIV-1 prevalence was 16% and 2% among HSV-2 seronegative individuals. The synergy between HSV-2 and HIV-1 seen in these epidemiologic patterns is supported by the pathogenesis of both infections.

Pathogenesis

HSV-2, a neurotropic virus, gains entry either at the mucosal skin or through skin abrasions and replicates in the epidermal or dermal cells (3). Primary infection can be asymptomatic, but can also cause ulcer disease accompanied by systemic symptoms and rarely manifests as disseminated disease. Following initial infection, the virus travels down the nerve axon and establishes latency within the dorsal root ganglia. Viral replication initiates reactivation which occurs as either new blister formation or, more frequently, asymptomatic shedding (11). Recent studies have illustrated that the major burden of HSV-2 infection lies in frequent recurrences – 80% of which are asymptomatic or unrecognized. Studies that use daily self-collected anogenital swabs to detect HSV-2 reactivation demonstrated that the median shedding rate was 25% of days (range 2% to 75% of days) (12). A study that used six hourly swabbing found that 49% of episodes lasted less than 12 hours and 29% lasted less than 6 hours (13). Even these short bursts of HSV-2 replication have viral copy numbers sufficient for HSV-2 transmission. An intra-host model of HSV-2 pathogenesis estimated that the dorsal root ganglion releases small amounts of virus in a near constant pattern to replicate the shedding patterns seen in clinical studies (14). A key characteristic of HSV-2 infection is now understood to be near-constant viral shedding--not at all the quiescent latent phase previously ascribed to HSV-2 between episodes of symptomatic genital ulcer disease, which were described to be infrequent (11).

Impact of HSV-2 therapy on HSV-2 natural history

Acyclovir and its pro-drug, valacyclovir, treat herpes outbreaks and suppress HSV-2 shedding. Valacyclovir achieves higher plasma concentrations, has 3 – 5 times higher bioavailability and a longer half-life than acyclovir, which makes less frequent valacyclovir dosing possible compared to acyclovir (15). Valacyclovir is converted to acyclovir *in vivo*. Acyclovir is an HSV-specific drug, which requires HSV thymidine kinase for phosphorylation. This intracellular phosphorylation step activates acyclovir, which is incorporated by HSV DNA polymerase, triggering chain termination and ending HSV replication. Acyclovir and valacyclovir decrease the severity of genital lesions in immunocompetent and immunosuppressed individuals, if given early in the disease course. Suppressive therapy at low doses (acyclovir 400mg twice daily and valacyclovir 500mg daily) in HIV-uninfected persons decreases genital ulcer rates by ~75% and shedding rates by 80% (16). No further decrease in the shedding rate was seen when high dose therapy (valacyclovir 1g thrice daily) was compared to standard dose HSV-2 suppressive therapy (acyclovir 400mg twice daily and valacyclovir 500mg daily) (17). Regardless of HSV-2 suppressive therapy dose, breakthrough episodes had a median length of 7–10 hours and 80% were subclinical (17).

Natural history of HSV-2 in HIV-1 co-infected individuals

Deficits in host innate or cellular immunity result in more frequent clinical disease, which can be persistent or disseminated. Indeed, persistent HSV-2 is a common presentation of advanced HIV-1 infection; low CD4 counts and high viral load are associated with increased frequency of HSV-2 shedding (18, 19). Use of antiretroviral therapy with subsequent increases in CD4 cells does not completely eliminate the effect of HIV-1 infection on HSV-2 shedding and GUD (19, 20). The synergy between HIV-1 and HSV-2 goes beyond increased severity of clinical HSV-2 disease among HIV-1 infected individuals; HSV-2 infection is associated with both increased risk of HIV-1 transmission and acquisition; mechanisms of which are addressed below.

HSV-2 and HIV-1 synergy

Multiple observational studies from 4 continents suggest a 2–3 fold increased risk of HIV-1 acquisition associated with prevalent HSV-2 infection and an up to 7-fold increased risk with incident HSV-2 infection (21–23). A meta-analysis of prospective studies, adjusted for age and sexual behavior, found an increased risk of HIV-1 acquisition among HSV-2 seropositive individuals for women (relative risk (RR) =3.4; 95% CI: 2.4, 4.8), men (RR =2.8; 95% CI: 2.1, 3.7), and MSM (RR =1.6; 95% CI: 1.2, 2.0) (23). Re-enforcing this synergy, HIV-1 infection increases acquisition of HSV-2 approximately 3 to 5-fold for the minority of HIV-1 infected persons who are HSV-2 seronegative when they acquire HIV-1 (24, 25). At the population level, a mathematical model of HSV-2/HIV-1 co-infection in a high HSV-2 prevalence setting (Kisumu, Kenya) estimated that more than 25% of HIV-1 infections were attributable to HSV-2 and that HSV-2 facilitated the spread of HIV-1 into low-risk populations (26). Further, modeling studies that examined the relationship between HSV-2 and HIV-1 suggested that an HSV-2 prevalence of >20% would be necessary to amplify an HIV-1 epidemic (7).

Mechanisms through which HSV-2 increases HIV-1 incidence

Three biological mechanisms likely contribute to increased HIV-1 incidence among HSV-2 seropositive individuals: (1) physical disruption of the epithelial surface by HSV-2, (2) recruitment and persistence of inflammatory cells in the genital tract during HSV-2 reactivation at mucosal surfaces, and (3) increase in plasma HIV-1 RNA with HSV-2 co-infection (Table 1). Macro and micro HSV-2 ulceration create a portal of entry for HIV-1 (27). Further, HSV-2 reactivation increases the recruitment and persistence of inflammatory cells targeted by HIV-1 (28, 29). Recent studies have demonstrated an increase and persistence of HIV-1 target cells (CCR-5-expressing CD4 T cells and CD-SIGN-expressing dendritic cells) that are present after ulcer healing in normal skin, are minimally affected by antiviral therapy, and increase susceptibility for HIV-1 (29).

In addition to increasing the risk of HIV-1 acquisition, herpetic lesions are accompanied by HIV-1 shedding from the genital mucosal surface of co-infected individuals (30), thereby increasing the risk of HIV-1 transmission. Higher HIV-1 titers are found in genital secretions during episodes of HSV-2 reactivation (30, 31). HSV-2 up-regulates HIV-1 replication at the cellular level through different pathways including transactivation of the HIV-1 long terminal repeat by HSV-1-infected cell protein (ICP)0, ICP4, ICP27 and US11 gene products and cytokine release and antigen presentation from HSV-2 infected cells (32–34). This up-regulation increases HIV-1 viral load, the primary determinant of HIV-1 transmission (35, 36). Plasma HIV-1 RNA levels in HIV-1/HSV-2 co-infected individuals pre-ART are 0.20–0.55 log₁₀ copies/ml higher than those without HSV-2 co-infection (37–40), which may translate to more rapid progression to AIDS and/or increased HIV-1 infectiousness for sexual partners (36, 41, 42). Recently we reviewed studies that adjusted for CD4 count or time since HIV-1 infection and found that HSV-2 infection was associated with increased plasma HIV-1 RNA by a mean of 0.18 log₁₀ copies/mL (95% CI: 0.01, 0.34), and HSV suppressive therapy decreased plasma HIV-1 levels by -0.28 log₁₀ copies/mL (95% CI: -0.36, -0.19) (43).

Episodic therapy for GUD, which was evaluated in three randomized control trials (RCTs) in Ghana, Central African Republic, South Africa (acyclovir 400mg thrice daily) and Malawi (acyclovir 800mg twice daily), can shorten the disease course of GUD but is often started late (median duration of symptoms at presentation was 6 days) (44–46). Analysis of pooled data from all three trials among 1,478 participants with GUD found 63% of ulcers were herpetic, based on laboratory testing (47). Among 726 HIV-1 infected participants randomized to episodic acyclovir, 92% had HIV-1 RNA detected from genital ulcers at

study entry, and those on acyclovir had lower levels of lesional HIV-1 RNA on day seven of follow-up compared to participants receiving placebo (adjusted risk ratio (aRR)= 0.73, 95% CI: 0.55,0.98) (47). Thus, the reduction in HIV-1 shedding from genital lesions after short course episodic acyclovir showed a marginal benefit. Further, our meta-analysis found that episodic therapy for GUD was not associated with a change in plasma HIV-1 RNA (43). In summary, short course episodic treatment for HSV-2 GUD and suppressive therapy of acyclovir 400mg twice daily have been found to be insufficient to reduce the persistent genital inflammation associated with HSV-2 reactivation.

Higher HIV-1 viral load in the setting of HSV-2 co-infection translated to increase risk of transmission: a study among HIV-1 serodiscordant couples in Uganda estimated that the per-coital act transmission probability of HIV-1 was higher for participants reporting GUD history than those without (48). Also, studies indicate that HSV-2 increases mother to child transmission (MTCT) of HIV-1 (49, 50). Among 307 HIV-1 infected pregnant Thai women, HSV-2 shedding was associated with higher HIV-1 RNA (4.2 vs. 4.1 log₁₀ copies/mL; p=0.05) and increased risk of intrapartum transmission (adjusted odds ratio (aOR) = 2.9; 95% CI: 1.0, 8.5) (51). This increase in both genital HSV-2 shedding and HIV-1 viral load during late pregnancy would support the increased risk of MTCT of HIV-1 associated with HSV-2.

Impact of HSV-2 suppressive therapy on HIV-1 transmission

Supported by evidence of the role of HSV-2 infection in HIV-1 acquisition and transmission, three RCTs evaluated the impact of acyclovir suppressive therapy 400 mg twice daily, two RCTs on HIV-1 acquisition (the multicenter HPTN 039 trial and the London School of Hygiene and Tropical Medicine trial in Mwanza, Tanzania) and one RCT (the Partners in Prevention HSV-2/HIV-1 Transmission Study) on HIV-1 transmission; no significant effect was found on HIV-1 incidence (52–54) despite modest reductions in genital ulcer incidence, and an average 0.25 log₁₀ reduction in plasma HIV-1 RNA in the Partners in Prevention HSV-2/HIV-1 Transmission Study. The reasons for these null findings have been better understood since the trials reported their results. First, as described above, HSV-2 pathogenesis studies have demonstrated a near constant state of HSV-2 reactivation with shedding not completely suppressed by even high doses of HSV-2 suppressive therapy (11, 17). Second, persistence of HIV-1 susceptible T cells (i.e., CCR5+ cells) in the genital epithelium even after lesion healing and prolonged acyclovir therapy increases available target cells for HIV-1 attachment and cell entry (29). Third, while we found that episodic acyclovir initiated promptly after GUD recognition had similar virologic and clinical response as in previous episodic GUD studies (55), we also observed lower acyclovir levels in a pharmacokinetic study in black African women compared to historical non-Africans, which requires further study (56). The fourth possible reason for the findings was suboptimal adherence; adherence has been shown to be challenging for HIV-1 prevention trials requiring daily or coitally dependent dosing and the HSV-2 suppression trials required twice daily dosing.

Given the challenges of HSV-2 suppression for HIV-1 prevention, key areas of further research are HSV-2 vaccine development and microbicides that inhibit both HIV-1 and HSV-2. An HSV-2 vaccine would be of benefit by reducing the excess HIV-1 incident cases associated with HSV-2 infection, estimated to be up to one third of HIV-1 cases in sub-Saharan Africa (26). Vaccine candidates to date have not demonstrated efficacy; initial recombinant vaccine candidates were thought to protect HSV-1 and HSV-2 negative women (57) but that finding was not borne out by a RCT (58). New strategies, including live attenuated HSV-2 virus (59), are in early development. A better understanding of the T cell response needed to clear initial HSV-2 infection would bolster HSV-2 vaccine development (60). In addition to HSV-2 vaccines, 1% vaginal tenofovir-based gel reduced the incidence

of HIV-1 by 39% and HSV-2 by 51% among women in a study by the Centre for the AIDS Programme of Research in South Africa (CAPRISA) (61). Further, tenofovir gel was shown to achieve high intra-vaginal levels when applied topically (compared with oral administration) with direct anti-herpetic effects (inhibiting HSV DNA polymerase) (62). Recently, daily vaginal 1% tenofovir gel was reported to have no efficacy against HIV-1 acquisition in the Microbicide Trial Network VOICE trial; efficacy against HSV-2 in the daily 1% tenofovir gel has not yet been analyzed (63).

Impact of HSV-2 suppressive therapy on HIV-1 disease progression

Mediated through decreases in HIV-1 viral load, the key determinant of HIV-1 disease progression (64), HSV-2 suppressive therapy slows the clinical course of HIV-1. Longstanding evidence has demonstrated a survival advantage with HSV-2 suppressive therapy across high, moderate and low resource populations: First seen in early studies of HIV-1 treatment almost 20 years ago, high dose acyclovir added to zidovudine monotherapy was found to reduce the risk of HIV-related mortality (65). Further, in a meta-analysis of randomized trials from North America and Europe, high dose acyclovir prophylaxis (>3,200mg per day) demonstrated a reduction in the risk of mortality (66). A systematic review found that a 1 log₁₀ increase in viral load was associated with a 2-fold increase in HIV-1 disease progression (67). The Partners in Prevention HSV-2/HIV-1 Transmission Study of acyclovir suppressive therapy (400mg bid) among HIV-1 serodiscordant couples in East and southern Africa found a 16% (95% CI: 2%, 29%) reduction in disease progression (using a composite endpoint of CD4 count <200, ART initiation and non-trauma related death) and 0.25 log₁₀ copies/mL decrease in viral load (68). Further, among the HIV-1 infected participants with a CD4 count >350 cells/μL at study entry, a 19% (95% CI: 7%, 29%) reduction in time to CD4<350 cells/μL was seen (68).

Similarly, a recent randomized placebo controlled study among 440 HIV-1 and HSV-2 co-infected individuals with CD4 counts 300–400 cells/μL in Uganda found 400mg of acyclovir twice daily decreased HIV-1 disease progression by 27% (aHR 0.73, 95% CI: 0.56, 0.97). When stratified by baseline viral load quintile, a stronger treatment effect of 36% (HR 0.64, 95% CI: 0.43, 0.96) was seen among the highest two baseline plasma viral load quintiles (i.e., HIV-1 RNA > 50 000 copies/mL), while the lowest two lowest viral load quintiles showed no efficacy (HR 0.90, 95% CI: 0.54, 1.50) (69). Across all study participants, plasma HIV-1 viral load was 0.46 log₁₀ copies/mL lower in the acyclovir group compared to the placebo group.

A recent study evaluated the role of valacyclovir to reduce plasma and breast milk HIV-1 shedding among HIV-1, HSV-2 co-infected women post-partum; Roxby and colleagues conducted a randomized, double-blind, placebo controlled trial of HSV-2 suppression with 500 mg valacyclovir twice daily among 148 pregnant Kenyan women from 34 weeks gestation to 12 months postpartum. At 12 months, plasma HIV-1 RNA in the valacyclovir arm was 0.4 log₁₀ copies/ml lower in the valacyclovir arm compared to placebo at 12 months postpartum. CD4 count increased from prenatal baseline levels in both groups due to post-pregnancy effects, but the CD4 count increased by 73 cells/μL more in the valacyclovir arm than in the placebo arm (p=0.03) (70). Valacyclovir reduced risk of breast milk HIV-1 RNA detection by 30% (RR 0.70, 95% CI: 0.49, 0.99) at 6 weeks postpartum, compared to placebo (71). Mean plasma HIV-1 RNA levels were 0.51 log₁₀ copies/mL lower (95% CI: 0.73 to 0.30, p<.001) in the valacyclovir arm compared to the placebo arm between 6 weeks and twelve months postpartum. The study was too small to assess the impact of valacyclovir on MTCT of HIV-1. Thus, post-partum valacyclovir suppressive therapy could be evaluated for reduction of maternal to child HIV-1 transmission in countries that have high breastfeeding rates for HIV-1 infected women who do not continue ART post-partum.

To evaluate whether HSV-2 suppressive dose is associated with different magnitude of plasma HIV-1 reduction, two studies recently investigated high dose valacyclovir. Perti and colleagues reported valacyclovir 1g twice daily decreased HIV-1 RNA by 0.40 log₁₀ copies/mL (95% CI: -0.64 to -0.21 log₁₀ copies/mL) among HIV-1, HSV-2 dually infected persons in Seattle who were not on ART (72). Mugwanya and colleagues reported the results of a randomized cross over trial of higher dose HSV-2 suppressive therapy, valacyclovir 1.5g compared to acyclovir 400mg (both twice daily) among 32 HIV-1-HSV-2 co-infected participants in Kenya (73). They found mean plasma HIV-1 viral load was significantly lower on valacyclovir compared to acyclovir by 0.62 log₁₀ copies/mL (95% CI: -0.68, -0.55 log₁₀ copies/mL) and compared to baseline by 1.23 log₁₀ copies/mL (95% CI: -1.38, -1.07 log₁₀ copies/mL). Also, CD4 cell counts increased by a median of 86 cells/μL (Mann-Whitney *U* test: *P* = 0.3 vs. baseline) and 69 cells/μL (Mann-Whitney *U* test: *P* = 0.7 vs. baseline) over the 12 weeks of therapy for valacyclovir and acyclovir respectively. These studies suggest that higher-dose suppression may have substantially greater clinical HIV-1 benefits and reduce risk of HIV-1 transmission, based on a modeled 50% reduction in HIV-1 transmission risk with an average of 0.74 log₁₀ reduction in plasma HIV-1 RNA (74). Based on the 1 log₁₀ reduction in plasma viral load observed in the high dose valacyclovir arm in the Mugwanya study, this is estimated to reduce HIV-1 incidence by 55% in a high HSV-2 prevalence region (75).

The impact of acyclovir on disease progression is mediated through decreases in HIV-1 viral load, the key determinant of HIV-1 disease progression (64). Standard doses of acyclovir have been demonstrated to modestly decrease HIV-1 RNA by 0.2 – 0.25 log₁₀ copies/mL (43) and slow HIV-1 disease progression 16% to 27% (68, 76). Since our initial meta-analysis, four more studies (described above) demonstrate the impact of HSV-2 suppressive therapy on HIV-1 viral load. In total, there are now 12 published studies which enrolled a total of 4,969 participants that have assessed the impact of acyclovir or valacyclovir HSV-2 suppressive therapy on plasma HIV-1 RNA (41, 53, 70, 72, 73, 76–82); the updated summary estimate for decrease in plasma HIV-1 RNA associated with HSV-2 suppressive therapy is 0.40 log₁₀ copies/mL, (95% CI: -0.51 to -0.28) (Figure 1).

A clear dose-dependent effect of suppressive regimens on plasma HIV-1 viral load is evident with higher-dose HSV-2 suppression (Figure 2). At the lowest dose (acyclovir 400 mg twice daily), two randomized trials have recently demonstrated statistically significant delays in HIV-1 disease progression (68, 76), although this dose has not been adopted into clinical practice given the perception that a greater magnitude of effect is needed to warrant the cost (83). A recent study shows that dose of HSV-2 suppression is important; high-dose valacyclovir suppressive therapy (1.5g twice daily) decreased HIV-1 RNA by 1.23 log₁₀ copies/mL (95% CI: -1.38 to -0.96 log₁₀ copies/mL) compared to the baseline plasma HIV-1 RNA in HIV-1/HSV-2 dually infected persons with CD4>250 who were not eligible for ART based on national guidelines (73). Higher-dose suppression should be evaluated for HIV-1 disease progression and infectiousness outcomes now that valacyclovir is generic and drug costs are decreasing significantly.

Mechanism of action of acyclovir and resistance

The mechanism of action of acyclovir and related drugs on HIV-1 viral load, thought initially to be indirect, is still to be elucidated. It was hypothesized that acyclovir acted indirectly on HIV-1 viral load by decreasing the overall levels of T cell activation by limiting HSV-2 reactivation. However, in vitro studies have suggested that acyclovir may act directly on HIV-1 reverse transcriptase, and that the effects of acyclovir on reducing HIV-1 viral load could be in part through direct inhibitory effects on HIV-1 replication as well as through indirect effects through HSV-2 suppression (84, 85). Clinical studies of acyclovir or valacyclovir suppression on plasma HIV-1 reduction in HSV-seronegative,

HIV-1 infected persons would be informative in terms of confirming these in vitro observations, but are challenging to conduct, given the high rate of HIV-1 and HSV co-infection. Importantly, while the in-vitro studies identified a HIV-1 resistance mutation, V75I, which was selected after high doses of acyclovir in vitro, the V75I mutation was not seen in clinical studies over two years of HSV-2 suppressive therapy with acyclovir (86, 87).

Cost-effectiveness of valacyclovir suppressive therapy

Using the Partners in Prevention HSV-2/HIV-1 Transmission Study results of delayed disease progression, a cost-effectiveness analysis (from the perspective of an intervention to delay HIV-1 disease progression in South Africa) found that suppressive acyclovir therapy could be an affordable strategy for reducing HIV-1 disease progression. At the lowest international pricing for acyclovir (US \$ 0.026 per day for 400mg acyclovir twice daily), the cost per life year gained (LYG) was US \$737 (95% CI: US \$ 373/LYG, US \$ 2,489/LYG) under ART eligibility criteria of CD4<350 cell/ μ L. This estimate is cost saving compared to ART, for which the cost-effectiveness is estimated to be US \$12,000/LYG. However, under South African pricing for acyclovir (US \$ 0.14 per day for 400mg acyclovir twice daily) suppressive acyclovir costs US \$ 1130/LYG (95% CI: US \$ 616/LYG, US \$ 3,785/LYG) (88). Given the greater impact on HIV-1 disease progression recently reported from the Rakai trial with the same dose of acyclovir (400 mg twice daily), the cost-effectiveness would be modestly greater. However, the marked variability of acyclovir and valacyclovir costs substantially impacts the cost-effectiveness of HSV-2 suppressive therapy for HIV-1, HSV-2 dually infected persons for clinical and potentially public benefits.

Corbell and colleagues reviewed the access to acyclovir in 8 African countries. They found that while the country-specific (government) purchasing price of acyclovir was 1 to 2 times the median international reference price, the retail cost in the private sector was 6 to 10 times the median international reference price (89). Drug pricing is highly variable depending on the underlying cost of production, volume required (demand) and supply. Transparency in drug pricing would help cost-effectiveness analyses better balance the effectiveness of interventions against their true costs; particularly for a drug like valacyclovir which is no longer under patent. The Clinton Health Access Initiative (CHAI) is helping to bridge the gap between pharmaceutical companies and drugs for public health use, including valacyclovir

Future directions

Valacyclovir is an excellent candidate for HIV-1 treatment pre-ART to delay disease progression, given its safety, tolerability and lack of evidence of selection of HIV-1 resistance *in vivo* (86, 87). In addition, daily medication (e.g., co-trimoxazole prophylaxis) has been shown to improve retention in care (90) and may facilitate transition to ART and good ART adherence. Adding choice to our HIV-1 treatment armamentarium is important; HIV-1 infected persons who are not ready to start antiretroviral therapy could use valacyclovir therapy as a means to engage in care, reduce plasma HIV-1 levels and delay disease progression, and learn strategies for adherence until they are ready to start ART. For patients in low resource settings who are diagnosed before they are ART eligible, valacyclovir would provide a valuable intervention pre-ART. Currently there are >12 million HIV+ individuals in low resource countries who are not yet ART eligible by current WHO guidelines (91); valacyclovir could delay their disease progression and engage them in pre-ART care, providing clinical benefits and facilitating their linkage to ART when they become eligible for ART.

HSV-2 is an excellent candidate as a highly prevalent co-infection among HIV-1 infected persons for which we have antivirals that can reduce their frequency of subclinical and

clinical HSV-2 reactivation and delay HIV-1 disease progression. The potential impact of co-infections on total community viral load over time is a function not only of the magnitude of the increase in HIV-1 viral load observed in co-infected individuals, but also of the prevalence and the average duration of the co-infection among HIV-positive individuals. The magnitude of the increase in HIV-1 viral load seen with HSV-2 is modest (0.18 log(10) copies/ml) compared to other HIV co-infections such as acute malaria and active TB, which have an observed 2–3 times higher increase in HIV viral load (43). However, because HSV-2 is highly prevalent (80% – 90% among HIV-1 infected individuals) and infection is life-long, the potential impact of HSV-2 co-infection on total community viral load over time is likely to be greater than that of other HIV co-infections.

An ongoing multicenter, randomized double blind trial in the Americas is evaluating the impact of valacyclovir 500mg twice daily versus placebo on HIV-1 disease progression, defined as CD4 <350 cell/ μ L or ART initiation for any reason (92). While this study will provide further data, questions remain regarding what valacyclovir dose should be used, cost-effectiveness and epidemiologic context in which valacyclovir therapy will be a useful approach to pre-ART HIV-1 treatment. In addition, the net effect of HSV-2 suppression on achieving partial viral suppression and the population-level impact on HIV-1 transmission needs to be explored. The potential role of valacyclovir suppression as a novel HIV-1 treatment and prevention strategy warrants study.

Statistical and mathematical models are powerful tools that could be used to estimate effectiveness and cost-effectiveness of valacyclovir as pre-ART HIV-1 treatment and identify highest priority populations for evaluation of this strategy. Careful modeling analysis could identify the price point at which valacyclovir therapy would be cost-effective and would contribute to clinical trial design. Integrating cost-effectiveness analyses into effectiveness modeling also can speed the translation from clinical trial results to implementation with costing data available for decision makers (93–95).

In summary, over the last three decades a substantial body of epidemiologic and molecular evidence has demonstrated the epidemiologic synergy between HSV-2 and HIV-1. Recent studies have expanded our understanding of HSV-2 pathogenesis and provided a paradigm shift about HSV-2 pathogenesis--from a latent infection with infrequent recurrence to a near constant state of reactivation and viral shedding, which is not completely suppressed by current antivirals. In the absence of interventions that suppress HSV-2 replication, HSV-2 vaccine development is a priority to reduce the increased risk of HIV-1 infection associated with HSV-2. A second priority is to obtain confirmatory data on tenofovir gel for prevention of HSV-2. Lastly, a promising area of research that warrants further research is higher doses of valacyclovir for HSV-2 suppressive therapy on HIV-1 disease progression and infectiousness, given the higher reduction in plasma HIV-1 viral load compared to lower doses of HSV-2 suppression. However, many questions remain to be answered including potential effectiveness and cost-effectiveness of valacyclovir interventions.

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Figure 1. Forest plot of association between HSV-2 suppressive therapy and plasma HIV-1 RNA (log₁₀ copies/mL)

CI, confidence interval; ES, effect size; References (41, 53, 70, 72, 73, 76–82)

Fig. 2. Forest plot of association between HSV-2 suppressive therapy at different doses and change in plasma HIV-1 RNA ($\log_{10}$ copies/mL). CI, confidence interval; ES, effect size
 *Summary estimates of published studies; ACV – acyclovir; VAL – valacyclovir; 400mg ACV twice daily (53, 76, 78, 81); 500mg VAL twice daily (70, 77, 80, 82); VAL 1000mg twice daily (72); VAL 1500mg twice daily (73)

Table 1

Mechanisms through which HSV-2 increases HIV-1 incidence

HSV-2 mechanism	HIV-1 transmission	HIV-1 acquisition
Genital shedding, micro- ulcerations, and GUD	x	x
Increase in HIV-1 target cells in the genital mucosa	x	x
Increase HIV-1 replication and genital and plasma viral load	x	