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Biologic interactions between HSV-2 and HIV-1 and possible implications for HSV vaccine development

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ABSTRACT

Development of a safe and effective vaccine against herpes simplex virus type 2 (HSV-2) has the potential to limit the global burden of HSV-2 infection and disease, including genital ulcer disease and neonatal herpes, and is a global sexual and reproductive health priority. Another important potential benefit of an HSV-2 vaccine would be to decrease HIV infections, as HSV-2 increases the risk of HIV-1 acquisition several-fold. Acute and chronic HSV-2 infection creates ulcerations and draws dendritic cells and activated CD4+ T cells into genital mucosa. These cells are targets for HIV entry and replication. Prophylactic HSV-2 vaccines (to prevent infection) and therapeutic vaccines (to modify or treat existing infections) are currently under development. By preventing or modifying infection, an effective HSV-2 vaccine could limit HSV-associated genital mucosal inflammation and thus HIV risk. However, a vaccine might have competing effects on HIV risk depending on its mechanism of action and cell populations generated in the genital mucosa. In this article, we review biologic interactions between HSV-2 and HIV-1, consider HSV-2 vaccine development in the context of HIV risk, and discuss implications and research needs for future HSV vaccine development.

1. Introduction

Herpes simplex virus type 2 (HSV-2) is the most common cause of recurrent genital ulcerative lesions; global HSV-2 prevalence is estimated at 11.3% (417 million people) among 15–49 year-olds, with 19.2 million new infections in 2012 [1]. Genital HSV-2 is lifelong, often stigmatizing, and can have profound effects on sexual relationships and quality of life. HSV-2 passage to the newborn occurs once in every 10,000 live births [2], and results in severe neurologic outcomes or death, even with antiviral therapy [3]. HSV-2 is also associated with viral meningitis and severe disseminated disease in immunocompromised hosts [4].

Moreover, HSV-2 infection plays a key role in the HIV-1 epidemic in many regions, as it is a risk factor for HIV-1 acquisition and transmission [5–7]. In addition to causing ulceration, lifelong HSV-2 shedding in the presence or absence of symptoms enhances CD4+ T-cell inflammation in the genital mucosa. These cells are the primary target for HIV and represent a plausible explanation for enhanced HIV-1 risk [8].

Development of an HSV-2 vaccine is a public health priority. The World Health Organization (WHO) outlined the need for new vaccines against sexually transmitted infections (STIs), given the large public health and financial burden imposed by STIs and limited existing prevention methods [9]. HSV-2 is an attractive target given high worldwide prevalence and significant advancement in the field relative to other STIs [10]. Prophylactic vaccines (to prevent infection) and therapeutic vaccines (to modify or treat existing infections) are in development. While an effective prophylactic vaccine is the ultimate goal, past trials were not successful [11,12]. A deeper understanding of the mucosal immune response to HSV-2 [8,13,14], and development of vaccine candidates eliciting broad immunologic responses [15–18], has stoked optimism that a prophylactic vaccine may be possible. In addition to benefits for those infected, therapeutic vaccines are a likely first step in the pathway towards a prophylactic vaccine and have shown partial efficacy in Phase II trials [18–21].

Prevention of new HSV-2 infections would reduce HSV-2 morbidity, but could also have an impact on HIV infection. To the extent that new HSV-2 infections are prevented among individuals

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receiving prophylactic vaccines, or among populations where HSV transmission is reduced through either prophylactic or therapeutic vaccination, the excess risk of HIV-1 associated with HSV-2 would be averted. Even for HSV-infected individuals receiving a therapeutic vaccine or who had breakthrough infection following prophylactic vaccination, the HSV-2 vaccine could theoretically limit CD4+ T-cell inflammation and thus HIV acquisition risk by reducing HSV-2 shedding. However, if a vaccine's mechanism of action against HSV-2 involves generating activated tissue-resident CD4+ T-cells in the genital tract, it could potentially enhance the risk of sexual HIV-1 acquisition to some degree. In order to explore these issues, we describe the link between HSV-2 and HIV-1 biology, review HSV-2 vaccine development as it pertains to HIV risk, and discuss implications for future HSV vaccine development.

2. Epidemiology of genital HSV

HSV-2 spreads efficiently through populations via sexual transmission. Most infected people are asymptomatic and unaware of their infection [22]. However, HSV-2 shedding is common regardless of symptoms [23,24]. Subclinical shedding is responsible for most transmissions [25]. HSV-2 risk starts with sexual debut and prevalence increases with age [22]. Women have a twofold higher risk for prevalent HSV-2 infection [1]: a potential biologic explanation is that women have a larger surface area of at-risk genital mucosa, though sexual network structures may also contribute to enhanced risk [26]. HSV-2 incidence is low in the Americas, Europe, Australia, and Asia, necessitating large sample sizes for vaccine trials; women in sub-Saharan Africa have a higher incidence (3–23 per 100 person-years) [1,27]. Variability in HSV-2 incidence amongst populations is attributable to prevalence in the community, age of sexual debut and number of partners [27]. HSV-2 prevalence exceeds 80% amongst HIV-1 infected heterosexuals in sub-Saharan Africa [28], and men who have sex with men (MSM) [29]. In contrast to HIV-1, HSV-2 infection is nearly universal amongst female sex workers with repeated exposures [30], suggesting a genetic phenotype of complete protection is rare or absent.

HSV-1 has significant genetic homology to HSV-2, is primarily transmitted orally and is the leading cause of recurrent oral-labial ulcers. HSV-1 is also transmitted through oral-genital contact and is an increasingly common cause of genital herpes in Europe, North America and East Asia, accounting for an estimated 140 million cases [31]. HSV-1 is the leading cause of infectious blindness and encephalitis in the United States and may be more readily passed to the newborn than HSV-2, particularly with incident genital infection during the third trimester [3]. A vaccine eliciting protection against HSV-1 and HSV-2 would have additional benefit relative to a product protective against only HSV-2. Genital HSV-1 has a milder natural history than HSV-2, with less frequent shedding [24,32]. It is unknown whether genital HSV-1 influences HIV incidence or whether an HSV-1 vaccine would impact HIV risk.

3. Epidemiologic evidence for HSV-2 infection enhancing HIV acquisition risk

For an HSV-2 vaccine to affect HIV-1 acquisition risk, a causal relationship between HSV-2 infection and enhanced HIV-1 risk must exist. A classic framework for proving causality is the Bradford Hill criteria, which include strength and specificity of associations, consistency of findings, temporal sequence, dose-response gradient, biologic plausibility and definitive experimental proof. Most but not all of these criteria have been established in human studies [33].

A strong association between prevalent HSV-2 infection and enhanced HIV-1 risk was demonstrated in multiple clinical sites spanning four continents [6]. Three systematic reviews and meta-analyses revealed a 2–3-fold enhancement of HIV risk in men and women with HSV-2 infection, which persists when adjusting for age and sexual risk [6,7]. Temporal sequence, in which HIV-1 infection follows HSV-2 infection, is inherent to these studies. Several observations suggest a dose-response relationship. In the most recent meta-analysis including 57 studies, HIV acquisition risk was 4.7-fold higher after incident HSV-2 infection, when HSV ulceration, shedding rate, and inflammation are highest, compared with 2.7-fold during chronic HSV-2 infection [7]. These factors are linked to the proposed biologic mechanisms of enhanced HIV risk, as described below.

An area of debate is specificity: whether non-biologic factors explain enhanced HIV-1 risk amongst HSV-2 infected persons. If the association lies in a non-causal pathway, then intervening upon HSV-2 would not impact HIV incidence. The association linking HSV-2 and HIV acquisition persists after controlling for confounding variables including demographics, sexual behavior, HIV vaccination and circumcision [34]. Meta-analyses only included studies with adequate control of confounders [2,5,6]. However, confounding is challenging to eliminate entirely. HIV and HSV-2 share a route of transmission, study participants can misreport sexual behaviors, and individual sexual behavior may be less important than community sexual networks. Sexual concurrency, having multiple overlapping sexual partners, is not measured in most studies but might promote spread of both viruses [35].

While most evidence suggests a causal link, direct causality has not been explicitly proven. The multicenter HPTN 039 study [36], and the London School of Hygiene and Tropical Medicine trial in Tanzania [37], assessed whether limiting HSV-2 shedding with 400 mg acyclovir twice daily would decrease HIV-1 acquisition. In both trials, there was no impact on HIV-1 incidence. However, this intervention did not sufficiently suppress the biologic factors linking HSV-2 to increased HIV-1 risk (described below) [38]. A more potent therapy or therapeutic vaccine might still protect against HIV-1 over time.

Overall, there is compelling evidence for a strong association between HSV-2 infection and enhanced HIV acquisition risk. A mathematical model applied to empiric HSV-2 and HIV prevalence data from Kenya best fit the data when synergy between these two viruses was assumed [39]. The model suggests that enhanced HIV risk due to HSV-2 extends beyond individuals or couples and that a quarter of new HIV infections are due to prevalent HSV-2 in certain sub-Saharan settings [39].

4. Biologic interactions between HSV-2 infection and HIV infection

4.1. HSV-2 pathophysiology

HSV-2 is efficiently transmitted during sexual encounters. The virus replicates and spreads amongst genital keratinocytes, often resulting in painful ulcers. HSV-2 spreads to nerve endings and is transported to dorsal root ganglia, where latency is established for the lifetime of the infected host. HSV-2 reactivates within ganglia almost constantly [40], and travels back to the genital tract via axons where it again spreads among keratinocytes. Replicating HSV-2 is detected by PCR every 1–2 weeks in most infected people [23,24]. Most reactivations are subclinical (no visible lesions), have low peak viral load and are cleared in fewer than 12 h. A fraction of reactivations persist for weeks, are associated with high viral loads and generate crops of erosions and vesicles. The percentage of specimens positive for HSV DNA measured with repeated genital

sampling, termed the shedding rate, is approximately 20%, with notable heterogeneity amongst study participants.

The mechanisms underlying viral clearance in mucosa involve early innate recognition, a coordinated cytolytic immune response, and perhaps local antibody production. During primary HSV-2 infection, the role of innate immunity is likely to be particularly critical as a local resident T cell population has yet to be established in mucosa or ganglia. Innate immune cells and antigen presenting cells represent early immune responders in biopsies of active lesions [41,42]. Langerhans cells are infected, undergo apoptosis and are taken up by dermal dendritic cells for antigen presentation [43]. Given their interactions with epidermal cells and CD4+ T cells, Langerhans cells may help augment transmission of both HIV and HSV-2 [44,45]. Distinct monocyte subsets help orchestrate the subsequent T cell response during different stages of HSV-2 infection [46,47]. The cyclic hormonal milieu in women may also impact dendritic cell and CD4+ T cell mediated protection against HSV-2 infection [48].

During reactivating infection, the critical role of persistent, tissue resident CD4+ and CD8+ T-cells (T_{rm}) in HSV-infected cells is increasingly recognized. CD4+ T cells appear to lodge in the dermis while CD8+ T cells reside more superficially at the dermal-epidermal junction and in the lower epidermis, precisely where nerve endings terminate [8,49]. CD8+ T_{rm} have been studied at the single cell level, and maintain an activated state following HSV-2 clearance by persistently expressing antiviral cytokines and lodging at neuron endings where HSV-2 is released into mucosa [8,14,49]. A central determinant of whether reactivation is asymptomatic and rapidly cleared may be T_{rm} density at the precise reactivation site. T_{rm} are spatially aggregated and remain for months after viral clearance [50]. Heterogeneous T_{rm} distribution may explain variability in viral loads across time and space [51].

While CD4+ and CD8+ T_{rm} alone can clear HSV-2 in mouse models [13,52–54], the degree of synergy and co-dependence between these cells remains unknown in humans. It is also unknown whether bystander CD4+ and CD8+ T cells, which are not pathogen specific but retain effector function, play a role in eliminating HSV-2 infected cells [55]. There is indirect evidence for the importance of CD4+ T cells in orchestrating a local immune response, as persons with AIDS have considerably higher shedding rates and longer average shedding episode duration than HIV uninfected persons [56]. Herpes-specific CD4+ and CD8+ T-cell responses as measured in blood appear to be impaired in this population [57]. Antiretroviral therapy for HIV-1 progressively reduces HSV-2 shedding [58], suggesting that virus-specific immune reconstitution is possible.

T-cells congregate around infected neurons within trigeminal ganglia in persons with chronic oral HSV-1 [59], and perhaps in dorsal root ganglia during HSV-2. However, mechanisms of immune containment of HSV-2 in latent infection sites are poorly characterized in humans, likely multifactorial, and may operate independently from control of lytic infection in genital mucosa. Correlates of immune protection may be tissue-specific but are not established based on the difficulty of concurrently sampling neuronal and mucosal compartments.

4.2. Biology of early HIV-1 mucosal infection

During early HIV-1 infection, a bottleneck occurs during transition from mucosal to systemic infection when viremia and sustained infection are inevitable [60]. The genital mucosa represents a challenging environment for HIV based on CD4+ T-cell limitation relative to sites of persistent infection in CD4+ T-cell-rich lymphatic tissues. HIV may delay initiation of replication during early infection to remain viable within these sparsely available mucosal cells [61]. Prior to amplification within mucosal CD4+ T-cells, HIV also may achieve initial cellular uptake into vaginal or foreskin epidermal Langerhans cells via viral synapses [62–65]. Following transport to regional lymph nodes, the virus more easily maintains cell-to-cell spread. An increase in the number and proportion of activated, mucosal CD4+ T_{rm} due to HSV-2 might increase the probability that early infection survives long enough to foster persistent infection.

4.3. HIV-1 and HSV-2 co-infection

A multifaceted synergistic relationship between genital HSV-2 and HIV-1 infections is established. HSV-2 shedding rate, drug resistance, genital viral load, and disease severity increase during late-stage HIV-1 infection, due to decreasing CD4+ T-cell functionality [66]. HSV-2/HIV-1 co-infected persons are also more likely to transmit HIV due to higher genital and plasma HIV viral loads [67,68]. The mechanism underlying this effect may be that HSV-2 and HIV co-replicate in permissive cells [69]: indeed, acyclovir partially inhibits HIV-1 replication and induces specific replication mutations [70]. A more attractive hypothesis is that HSV-2 may create a field effect in which diffused cytokines allow infiltration of a higher density of HIV-1 target cells with enhanced CCR5 expression [71]. HSV-2 may contribute to the HIV epidemic due to enhanced transmission via higher HIV viral load [72,73].

4.4. HSV-2 infection and HIV acquisition

There is biologic evidence for enhanced HIV-1 acquisition in the context of HSV-2 infection. HSV-2 infection may relax the bottleneck of HIV-1 acquisition: remarkably, multi-strain primary HIV infection occurs more commonly in the context of chronic genital inflammation, implying greater host susceptibility to HIV-1 [74,75].

Several plausible biologic explanations exist for enhanced risk of HIV-1 acquisition on a per-coital basis in HSV-2 infected people. By causing recurrent breaches in genital skin and mucosa, HSV-2 enhances accessibility of CD4+ T-cells, which reside in the deeper dermis. HSV-2 also increases the number of activated CD4+ T-cells for HIV entry and spread within the genital tract at prior sites of reactivation [8,14,49,50]. These cellular infiltrates persist for months after lesions heal, even with suppressive antiviral treatment [8,49]. The local half-life of genital CD4+ and CD8+ T_{rm} is unknown but is estimated to be at least many months [50,76]. Importantly, asymptomatic shedding of HSV-2 induces persistent infiltrates of HIV susceptible CCR5+ CD4+ T cells in the female genital tract [77], an effect not reversed by 2 months of valacyclovir therapy [38].

Aside from mucosal breaches in the epidermis, it remains unknown how HIV-1 is able to access CD4+ T cells, which reside in the mid and upper dermis. Recent work in murine systems demonstrates that tissue resident T cells are motile and express dendritic arms to enhance the number of contacts with antigen presenting cells [78,79]: this strategy may also increase exposure to HIV virions. Alternatively, dendritic cells may first be infected with HIV and then passage the virus to mucosal CD4+ T cells [45].

T-cells induced by chronic HSV-2 infection are classified as T_{rm} based on specific cell-surface homing and activation markers. T_{rm} remain activated in the absence of replicating pathogen, are in disequilibrium from central memory and effector memory T-cells in blood and lymphatic organs, and are specialized for early pathogen recognition and elimination [80,81]. CD4+ T_{rm} may promote HIV acquisition at reproductive sites that are not common for HSV-2 reactivation. Approximately 5% of cervical CD4+ T-cells were HSV-2 specific in infected women, and were often directed at the same HSV antigen over time [82]. HSV-specific T_{rm} also reside in trigeminal ganglia during HSV-1 infection [59]. While these cells will not impact HIV acquisition risk, the degree of control they

exert on reactivation may indirectly impact HIV risk because limiting HSV-2 release into the genital tract may decrease mucosal inflammation. Immune activation of T-cells in blood correlates with enhanced HIV acquisition risk [83], though it is unknown if these findings can be extrapolated to T_{rm}.

The presence of CD4+ T_{rm} may be more important in geographic regions where these two overlapping epidemics are most intense. Regardless of HIV-1 status, HSV-2 shedding rate may be higher in Ugandan men [84] than North American men [23], which is consistent with higher levels of genital inflammation documented in regions of Africa [85]. Despite their importance in clearance of HSV-2 infected cells, T_{rm} are reactive to infection: mathematical models suggest that high HSV-2 shedding rate is a predictor of genital tract inflammation, rather than inflammation predicting lower shedding. This is in keeping with increased HIV risk early after HSV-2 acquisition [86].

4.5. Antiviral therapy for HSV-2 to limit HIV-1 acquisition

Standard antiviral therapy for HSV-2 did not decrease HIV-1 acquisition risk in clinical trials, which may be explained by several factors [36,37]. First, the dose of acyclovir used does not completely suppress HSV-2 shedding [87]. In fact, no licensed dose of acyclovir, famciclovir or valacyclovir completely eliminates HSV-2 shedding [87]. Second, the T_{rm} inflammatory footprint established by HSV-2 infection persists despite months of treatment [8,14,49,50], even in the absence of herpetic ulcers [77]. An optimal time to test for HIV acquisition may be more than 12 months into HSV-2 antiviral treatment. To this end, ART-treated men did not have a decrease in immune activation markers when acyclovir was added to their regimen [38], and valacyclovir had no effect on CD4+ T-cell activation in HIV/HSV-2 co-infected women in Kenya [88]. Third, drug levels were lower in black African women than in American women from prior studies [89].

5. HSV vaccine development and HSV-HIV interactions

5.1. Therapeutic vaccine development

An effective therapeutic HSV vaccine is needed because current licensed antiviral agents, while clinically effective, do not completely suppress shedding or recurrent ulcers [87]. Antiviral agents require daily dosing, which may be less desirable than a therapeutic vaccine that may be given every year. Valacyclovir only prevented 50% of HSV-2 transmission from seropositive persons to their partners [90]; a therapeutic vaccine that has a more potent effect on HSV-2 shedding may be more effective for this indication. In certain practical respects, therapeutic vaccines are also a logical first step in HSV prophylactic vaccine development. Clinical trials for therapeutic vaccines are less expensive and can be performed much more rapidly and with considerably smaller samples sizes than prophylactic vaccine trials, with study participants serving as their own controls [91]. Patients perform daily self-sampling for 30–60 days, followed by vaccination and then another 30–60-day self-sampling period. HSV-2 shedding rate is an accepted surrogate outcome for disease severity and transmission risk [90,92]. This approach limits sample size and study duration, while maximizing statistical power.

Several phase II therapeutic HSV vaccine trials have been performed. GEN003/MM-2 consists of HSV-2 glycoprotein D2, a truncated infected cell polypeptide 4, and Matrix M-2 adjuvant, and is designed to elicit humoral and cellular responses. This vaccine demonstrated reduction of shedding and lesion rate in a guinea pig model [16]. In a Phase II trial, the 30 and 100 μg doses induced persistent reductions in shedding rate at 3, 6 and 12 months following vaccination, with concurrent reductions in lesion rates [18,20], though shedding returned to baseline at 12 months in the 30 μg arm and 6 months in the 100 μg arm. The vaccine was well tolerated. GEN003 elicited HSV-2 specific persistent antibody and T-cell responses [20]. A DNA plasmid vaccine candidate encoding glycoprotein D, several tegument proteins, and a cationic lipid-based adjuvant (Vaxfectin®), provided complete protection against primary and recurrent genital skin disease following intravaginal HSV-2 challenge in guinea pigs, and reduced shedding and disease [17,93]. Vaxfectin was formulated with gD, and gD +UL46, in a phase 1/2 human study: there was no reduction in shedding rate despite a significant decrease in lesion rate and viral load. HerpV is 32 HSV-2 peptides formulated with heat shock protein 70 and a QS-21 saponin adjuvant. It elicits broad CD4+ and CD8+ T-cell responses [15]. In a Phase II study, there was a modest decrease in shedding rate and a decrease in viral load.

The preclinical pipeline includes a broad array of subunit, whole virus, DNA and mutated live virus platforms. Licensure of a therapeutic vaccine will depend on whether improvements can be made in vaccine design or dosing strategies, but also on the competitive landscape for other HSV-2 interventions. Novel antiviral agents are in development. Recently, a helicase primase inhibitor pritelivir demonstrated highly potent suppression of shedding [91], though attempts to license this agent for chronic HSV-2 infection are currently on hold. Amenamevir is another helicase inhibitor with some promise for HSV-2 suppression [94]. Brincidofovir is a promising agent with activity against multiple DNA viruses, though its side effect profile may prohibit use on a chronic suppressive basis [95]. HSV-2 cure is also being pursued with a focus on gene therapy approaches [96]. If a completely suppressive antiviral therapy or cure is developed for HSV-2, the marketplace for a therapeutic vaccine may be altered.

5.2. Therapeutic vaccines and HIV infection

It is unknown how current therapeutic HSV-2 vaccine candidates might impact HIV-1 acquisition risk. If decreased HSV shedding translates into decreased HSV transmission, then there may be a cumulative decrease in HIV-1 infection risk due to population-wide prevention of new HSV infections. However, there is not adequate data to understand whether there will be vaccine-induced protection against HIV-1 or risk for an HSV-infected person who is vaccinated. The vaccine products that have been studied in humans elicit both humoral and cellular responses [18–21,97]. Yet, no studies to date assess whether these vaccines only induce these responses in blood, or also in the genital mucosa.

While such studies are needed, there will be significant challenges with study design. Presumably, initial studies will be conducted on individuals with symptomatic infection to address the primary clinical need of decreasing recurrences. The impact on shedding rate in asymptomatic persons will therefore be challenging to assess initially. Moreover, because biopsies sample limited micro-environments which represent only a fraction of the total at-risk area, it may be impossible to measure total mucosal T_{rm} in humans. Single biopsies may misrepresent T_{rm} abundance and phenotype across all infected tissue. The T_{rm} response may be highly focal within genital mucosa [49], but perhaps less so in cervical tissues [82]. Areas of HSV-2 reactivation are notable for dense sheets of T_{rm} infiltrates, which taper rapidly over millimeters [50]. Mathematical models suggest that spatial heterogeneity in T-cell density is the driver of variable duration and viral loads of HSV-2 genital tract reactivations [50]. Murine investigations demonstrate that T_{rm} rarely migrate from prior regions of infection [78].

One potential method to assess whether a therapeutic vaccine elicits a meaningful T_{rm} response is to interrogate these cells for vaccine epitope specificity [98], and to assess whether a vaccine

alters the landscape of T cell receptor sequences. While it is possible and routine to quantitatively measure PBMCs for vaccine specific T-cell responses, the T_{rm} response might be independent of the systemic response. Measurement of PBMCs may not serve as an adequate surrogate of HIV risk.

5.3. Prophylactic vaccine development

There are no currently licensed prophylactic HSV-2 vaccines [97]. Previous trials have not yielded an efficacious candidate against HSV-2. The Herpevac study tested an adjuvanted glycoprotein D-based subunit vaccine (gD-2) for protection against HSV-1 and HSV-2 genital disease in double seronegative women. This population was selected based on 73–74% protection in two trials of a gD-2 vaccine [12]. The Herpevac study demonstrated no efficacy against HSV-2 infection, 35% protection against HSV-1 infection and 58% protection against HSV-1 genital disease [11]. These results were recapitulated in a cotton rat model based on a more potent antibody response against HSV-1 [99]. Higher titers of neutralizing antibodies against HSV-1 relative to HSV-2 were noted in trial participants [100]. Post vaccination anti-gD-2 antibodies were predictive of efficacy against HSV-2 in a dose response fashion [101].

One concern with an antibody vaccine, demonstrated experimentally in a guinea pig model, is diminished protection against HSV-2 infection in HSV-1 seropositive persons [102]. Vaccines are being developed to induce a focused and potent antibody response. In mice, antibody but not cell-mediated responses are required to provide early and rapid protection against HSV-2 challenge following vaccination with a live attenuated HSV-2 ICP0-mutant [103]. An HSV-2 virus in which gD-2 was deleted provided protection against lethal infection and establishment of latency in mice, via induction of antibody-dependent cell-mediated cytotoxicity [104], highlighting that prior vaccines may have targeted inappropriate entry glycoproteins. Addition of gC to gD subunit vaccines enhances protection in mice and reduces recurrences in guinea pigs [102]. Addition of gE2 limits HSV-2 immune evasion and provides more comprehensive protection [105]. These developments underlie the continued interest in developing vaccines that protect entirely via generation of neutralizing antibodies, and would not increase HIV-1 infection risk.

There is concurrent excitement for development of a T-cell based vaccine. Recognition of certain T-cell epitopes may provide superior protection during established infection [106]. Numerous animal studies highlight the ability of T-cells to patrol and contain HSV, in latent ganglionic sites of infection [107], and in genital mucosa [13,52]. Broadly reactive antigen specific tissue resident T-cells exist in proximity to infected cells in human ganglia [59,108] and genital mucosa [8,49]. Novel methods have been developed to scan for T-cell reactivity to the entire HSV proteome [89], which may allow accurate detection of immunologic correlates of protection. Intranasal vaccination induces a partially protective intra-vaginal tissue-resident CD4+ T-cell response: in mice, CD4+ T-cells are sufficient for protection [109], which may be relevant for enhancing HIV risk.

Preclinical studies of subunit and DNA vaccines designed to elicit antibody and CD4+/CD8+ T-cell responses demonstrate enhanced protection against lethal infection in mice relative to antibody vaccine alone [110]. Replication deficient HSV-2 mutants show promise in various animal models and elicit both cellular and humoral immunity [111]. The addition of chemokine ligands as vaccine immunogens induces balanced mucosal antibody and Th1 and Th2 cellular responses [112]. There is focus on developing interventions that favor induction of a potent T_{RM} response. Topically applying chemokines to vaginal tissue draws activated T-cells to the periphery and provides protection against HSV-2 challenge [113]. These cells are sustained in memory lymphocyte clusters via local secretion of chemokines by macrophages [13]. Indeed, vaccine adjuvants that target dendritic cells, NK cells and macrophages are under intense study [114]. Given that the many preclinical vaccines are tested under different protocols and animal models, it is difficult to compare the promise of each approach.

5.4. Prophylactic vaccines and HIV infection

A prophylactic HSV-2 vaccine would likely limit HIV-1 at the population level by preventing new HSV-2 infections and the associated excess risk of HIV-1. Change in HIV-1 risk following HSV-2 vaccination would likely be amplified beyond vaccine recipients. For instance, if an HSV-2 vaccine decreases incident HIV-1, then indirect protection may occur due to less ongoing HIV-1 transmission. The potential effects of an HSV-2 vaccine at the population level have been modeled. Depending on degree of implementation, vaccine efficacy, and study population, HSV-2 incidence may decrease 5–70% over 10 years with widespread implementation, while population prevalence would take longer to decrease (IHL Spicknall, personal communication). It has also been estimated that an HSV-2 vaccine campaign that achieved 70% population coverage, 75% reduction in HSV-2 susceptibility and 75% reduction in HSV-2 shedding among those with incident infection, would reduce HIV-1 incidence by 30–40% over two decades [115].

The impact of an effective HSV-2 prophylactic vaccine will depend on vaccine mechanism. Antibody-inducing products are unlikely to enhance HIV-1 per-coital acquisition probability. Future products that are tested as prophylactic vaccines may first demonstrate effectiveness as therapeutic vaccines. Many current platforms are designed to induce a T_{rm} response. Other vaccines are derived from live attenuated strains that induce humoral and cell-mediated responses [116,117], regardless of the mechanism of actual protection. Modern subunit approaches elicit broad antibody, CD4+ T-cell and CD8+ T-cell responses against HSV-2 while providing rapid resolution of infection in mice and guinea pigs [118]. These approaches could theoretically decrease or increase HIV-1 risk.

The concern for enhanced HIV-1 acquisition following vaccination is not simply theoretical. The STEP trial, an HIV vaccine trial, which utilized an adenoviral vector to express HIV-1 *gag*, *pol* and *nef*, was stopped early based on increased HIV-1 incidence in the vaccine arm relative to controls [119]. Increased risk was isolated to uncircumcised men with serologic evidence of past exposure to adenovirus. This enhanced risk waned with time suggesting a vaccine related effect [120]. Data is conflicting on whether activated CD4+ T-cell expansion to the adenoviral vector explains enhanced HIV-1 susceptibility [121,122]. However, dense infiltrates of CD4+ T-cells are observed in the foreskin of HSV-2 infected men [123,124] and these cells are up-regulated for the HIV-1 CCR5 entry co-receptor [125]. A biologically active vaccine might enhance this effect.

Finally, while the goal of a prophylactic vaccine is to prevent seroconversion and establishment of latency, the more modest goals of limiting post-infection burden of latency, HSV-2 shedding rate and lesion rate were achieved in murine systems and should also be considered in regards to HIV risk [126]. A vaccine that attenuates primary infection may be adequate for licensure in humans, because maintenance of viral load below a certain threshold may prevent transmissions [92] and ulcers. At the population level, a vaccine that decreased shedding by 75% would slowly but substantially reduce HSV-2 prevalence. For these reasons, the effect of an attenuating HSV-2 vaccine on HIV-1 risk could be substantial.

6. Implications for HSV vaccine development and future directions

Development and licensure of an HSV vaccine within a decade is possible. Prevention of new HSV-2 infections will likely reduce the excess risk of HIV, and this prevention benefit could be substantial [112]. However, there are theoretical reasons that a vaccine might limit or enhance HIV-1 acquisition risk for an individual with HSV infection who has been vaccinated, depending on the vaccine's mechanism of action. Currently, there are inadequate data to weigh these possibilities. Therefore, during and following development and licensure of therapeutic or prophylactic HSV-2 vaccines, several steps should be considered to assess HIV-1 risk and ensure vaccine safety. When possible, studies should be performed to identify vaccine mechanisms and surrogates of protection. Basic studies of mucosal antibody and T-cell responses to vaccines can be performed using modern tissue-based cell culture models of early HSV-2 and HIV mucosal infection [127] and relevant animal models [128]. These studies would provide reassurance if an effective vaccine does not induce a mucosal CD4+ T-cell response, or increase acquisition risk in validated HIV challenge models [129].

Early in vaccine development, it will be important to build consensus across a wide range of stakeholders on the safety data requirements and optimal strategies for evaluating and implementing HSV-2 vaccines in high HIV-1-prevalence areas. Depending on the supporting data, populations that will be targeted for therapeutic or prophylactic HSV-2 vaccination programs, but have high theoretical risk of HIV-1 should be considered for prospective, controlled vaccine studies with HIV-1 incidence as an endpoint. Appropriate ethics and safety input will be essential in guiding study design and implementation. Mathematical model projections may assist in situations where HIV-1 incidence data are only available for certain populations. An HSV-2 vaccine would be of enormous benefit and could represent an important tool to fight HIV-1 infection, particularly in high incidence regions. Steps should be taken to ensure vaccine safety as a priority in the face of even a small theoretical risk of enhanced HIV infection for some vaccine mechanisms.

Conflict of interest

JTS receives research support from Genocea, a developer of therapeutic HSV-2 vaccines. SG reports no conflicts of interest.

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