Journal of Infectious Diseases Advance Access published March 6, 2015



# The Sordid Affair between Human Herpesvirus and Human Immunodeficiency Virus

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**Abstract**

Both human immunodeficiency virus (HIV) and human herpesvirus (HHV) infections persist lifelong, and almost all individuals infected with HIV are also infected with one or more HHV. These co-infections are not independent processes or benign. In this review, we discuss how HHV, and cytomegalovirus (CMV) in particular, interact with concurrent HIV infection, and we describe the next steps necessary to understand and address these connections.

## Research Strategy and Selection Criteria

References for this review were identified through searches of PubMed and Google Scholar with no date restriction using the term “HIV” in combination with “herpesviruses”, “cytomegalovirus”, “herpes simplex”, “immune activation”, “epidemiology”, among others. All included articles were published in English. To obtain the most relevant articles for the focus of our review, we chose articles that were recent and that provided the strongest evidence to support the statements in the review. Specifically, we concentrated on papers published in the past 5 years, but also cited older publications when appropriate. For some larger topics that could not be discussed in depth, we cited other reviews that were more specific to that topic. To present the most current level of the field’s understanding, we also included high-impact abstracts presented at recent conferences but not yet published.

## Introduction

The Herpesviridae family comprises more than 120 known viruses adapted to many vertebrate species, including humans [1]. Human herpesviruses (HHV) have been infecting their vertebrate hosts for hundreds of million years [2]. During this time, they have evolved a number of complex strategies to escape host immune responses allowing lifelong infection. During the infection, HHV cycle through latent and active stages with the active stage being important for producing viral particles that can infect new hosts. Most viral active stages are largely asymptomatic; however, in the setting of a weakened immune system especially decreased cellular immunity, like organ transplant or co-infection with human immunodeficiency virus (HIV), episodes of human HHV reactivation are increased and prolonged and can cause significant morbidity and mortality [3, 4]. Here, we review the literature on how HHV interact with concurrent HIV infection, focusing on cytomegalovirus (CMV), and we discuss the next steps necessary to further elucidate these connections.

## Epidemiology and Natural History of HHV

Herpesviridae are composed of a double-stranded DNA genome contained within a nucleocapsid surrounded by a lipid envelope [5]. There are eight characterized herpesviruses in human: herpes simplex

virus (HHV-1/2; HSV-1/2), varicella zoster virus (HHV-3; VZV), Epstein Barr virus (HHV-4; EBV), CMV (HHV-5), human herpesvirus-6 (HHV-6), human herpesvirus-7 (HHV-7) and Kaposi's sarcoma-associated herpesvirus (HHV-8; KSHV) [5, 6]. These eight HHV represent hundreds of millions of years of evolutionary diversification and innovation [2]. It appears as if many of these viruses have been infecting the human lineage since before the rise of *Homo sapiens* [7]. Across all three herpesvirus subfamilies ($\alpha$, $\beta$, and $\gamma$), the closest relatives of HHV seem to be found in other great ape species (e.g. chimpanzees and gorillas) [7, 8]. It appears that they have been diverging almost exclusively along the evolutionary lineages of their hosts. A notable exception to this pattern may explain why humans have two HSV, whereas other primate species have only a single simplex virus: HSV-2 appears to be the result of a recent cross-species transmission from the ancestor of modern chimpanzees to a precursor of modern humans (e.g. *Homo erectus,* etc.) [7].

Most HHV are often acquired during childhood or during sexual debut, and they infect most of the human population worldwide with some regional differences [5, 6]. One exception might be KSHV, which is typically contracted in adulthood in Europe and North America. However, it has a much higher incidence in equatorial Africa (up to 35% by age 21) in the so-called “KS-belt” [5]. Most HHV must come in contact with mucosal surfaces or abraded skin to initiate infection [6]. Clinical manifestations of HHV infections are diverse and range from mild or subclinical disease to encephalitis, pneumonia, and other potentially lethal infections and various types of cancer including lymphoma, sarcoma, or nasopharyngeal carcinoma [5]. Primary HHV infection in immunocompetent hosts is often asymptomatic or minimally symptomatic, but morbidity and mortality can be high when an immunocompromised person is infected, especially with CMV, HSV, and VZV [5, 6]. After primary infection, the virus becomes latent in neural ganglia or blood mononuclear cells in its episomal form [5, 6]. After latency is established, various stimuli can reactivate HHV with clinical manifestations, like skin vesicles or mucosal ulcers. More commonly, HHV reactivation with shedding is largely asymptomatic [9]. One very common site of HHV shedding is the genital tract. For example, Koelle *at al.* [10] found that immunologically normal hosts shed HSV-2 asymptomatically in their anogenital regions a quarter of the days sampled (range 2% to 75% of days). Another study of immunocompetent adults found that about half of such episodes lasted less than 12 hours and about a third lasted less than 6 hours [11]. The frequency of shedding of various HHV in the genital secretion varies substantially across different

studies and is strongly dependent on the geographical location, cohort characteristics and detection methods. When an infected individual has a compromised immune system, shedding of HHV increases dramatically. For example, almost two-thirds of HIV-infected men asymptomatically shed at least one HHV in their genital tract, regardless of CD4+ T-cell count, geographical location or use of antiretroviral therapy (ART) [12, 13]; CMV and EBV were the most frequently detected during these shedding episodes and were found in about half of all tested semen samples, while the other HHV (HSV, VZV, HHV-6, -7, and -8) were found at lower frequencies, between 0-17% [12, 13]. Such asymptomatic shedding is likely important for the natural history and transmission dynamics of HHV and interplays with other co-infecting viruses (e.g. HIV). Table 1 provides a summary of prevalence and characteristics for the most common HHV infections.

**Epidemiology of HHV and HIV Co-infections**

Currently, there are over 35 million people living with HIV-1 worldwide (UNAIDS, Gap report 2014, accessed, accessed February 2015). Unlike HHV, which have been infecting humans since our species arose [7], HIV is a far younger virus, infecting humans for the past hundred years or so [14]. Whereas new HIV cases are reported in all regions of the world, 95% of new infections occur in individuals who reside in low- and middle-income countries, particularly in the sub-Saharan Africa [15]. In the absence of therapy, infection with HIV-1 results in a progressive loss of immune function marked by depletion of the CD4+ T-lymphocytes, leading to opportunistic infections and malignancies characteristic of AIDS. Although both host and viral determinants influence the rate of disease progression, the median time from initial infection to the development of AIDS among untreated individuals ranges from 8 to 10 years [5]. Clinical and immunological factors associated with disease progression have been extensively investigated including, CD4 T-cell count, HIV-1 subtype, markers of inflammation, HIV RNA levels, opportunistic infections, and co-infection with various HHV (more frequently CMV, but also HSV, KSHV and others) [3, 16].

Both HIV and HHV infections persist lifelong, and almost all individuals infected with HIV are also infected with one or more HHV. Since the first description of AIDS, co-infections with HHV have been part of the clinical presentation (and responsible for several AIDS-defining conditions) and are among the most common opportunistic infections observed in people with AIDS, including CMV, HHV-8, HSV, EBV and VZV [17]. For example, the considerable overlap between the HIV and the HHV epidemics does not appear to be happenstance: the synergy between these two largely sexually transmitted viral infections goes beyond similar risk factors for acquisition [9]. Accumulating data show that these two types of infections interact both in their epidemiologic niche and at a pathogenesis level by driving viral replication and facilitating transmission.

**HHV Shedding and Impact on HIV Transmission**

Several studies have provided convincing evidence that co-infection with some HHV (more frequently HSV-2 and CMV but also others) play a role in HIV-1 transmission and acquisition, independently from the level of immunosuppression [12, 17, 18]. Three main mechanisms are likely responsible: (i) physical disruption of the mucosal surface creating a portal for HIV entry (that's especially true for HSV-2), (ii) local inflammation with recruitment of activated CD4 T-cells targeted by HIV, (iii) enhanced HIV replication with increased level of genital HIV RNA shedding [1, 12, 19]. In fact, HHV, and particularly HSV and CMV, can up-regulate HIV replication directly through a complex interaction with the long terminal repeat region and transactivation of proviral HIV [20] and indirectly through release of inflammatory cytokines and chemokines [17]. A recent study suggested that CMV could also be responsible for up-regulation of CCR5 expression in central memory T cells, at least when looking at cord blood mononuclear cells exposure *in vitro* [21]. These conditions are often asymptomatic, with only minimal breaks in the mucosa or skin in the genital area. Such theoretical risk is also supported by seroepidemiological studies that have demonstrated associations between HSV-2 seropositivity and increased risk of HIV acquisition [22]. In the last decade, several clinical trials have investigated the effect of the anti-herpetic drug acyclovir on HIV RNA replication, transmission and disease progression [23, 24]. Interestingly, a mathematical model of HSV-2/HIV-1 co-infection in the high HSV-2 prevalence setting of Kisumu, Kenya estimated that more than a quarter of HIV-1 infections were attributable to HSV-2 [25]; however, a randomized trial with 400mg of acyclovir twice daily did not decrease HIV-1 despite

reducing levels of HIV RNA in blood and genital secretions [24]. This suggests that such treatment may not be enough to completely suppress replication of HSV-2 or that other viruses that are not susceptible to acyclovir, like CMV, also contribute to HIV transmission. Additionally, activated T cells persist at mucosal surfaces for months after cessation of active HSV replication and represent a residual pool of target cells for HIV-infection and replication [26]. Some studies suggest that the observed effect of acyclovir on HIV RNA levels might not be mediated by suppression of HSV (or other HHV) but rather a consequence of direct drug inhibition of acyclovir on HIV replication [27]. This direct drug effect is controversial since acyclovir-associated mutations are typically not observed in HIV isolates from HIV-infected people treated with acyclovir [23]. In the same direction, male circumcision, which is associated with lower inflammation environment in the genital area, was repeatedly associated with reduced risk of sexual HIV and HSV-2 transmission, especially in the heterosexual population [28].

Although the effect of HSV-2 shedding on HIV co-infection is widely documented, it is not the only HHV infection that is common worldwide and might facilitate HIV-1 transmission [13]. All viruses that co-infect and reside in the genital tract may influence each other's virologic dynamics [13]. For example, the genital shedding of HHV (especially HSV, EBV and CMV) among ART-naïve HIV-infected individuals has been associated with increased genital shedding of HIV RNA [12, 13, 18, 19, 23, 29] and with increased HIV transmission [9, 18]. These connections were also observed among co-infected men receiving ART, where high-level seminal CMV shedding, but not presence of asymptomatic bacterial co-infections, was associated with HIV RNA shedding, conferring a potential risk for HIV transmission [29]. Along these lines, a study from our group on HIV infected and uninfected MSM, found that over one third of HIV transmissions among MSM in San Diego could potentially be attributable to CMV shedding, compared to 21% for bacterial STI and 17% for HSV-2 [30]. Together, these observations highlight the importance of considering the prevalence of HHV shedding across populations and geographical locations to design effective HIV prevention strategies. In any case, a clinical trial is needed to definitively assess the degree to which CMV is causally associated with the shedding and transmission of HIV.

**CMV, Inflammation and Immunosenescence**

Among all HHV, CMV infection has one of the most dynamic and fierce interactions with the human immune system. In this complex host-virus relationship the virus elicits and maintains high frequency of CMV-specific T-cells that is engaged in a life-long fight to restrain CMV replication and prevent life-threating disease [31]. On the other side, CMV developed effective immune evasion strategies preventing this immune response to clear infection or interfere with viral transmission. In fact, CMV is among the largest of the known viruses to infect humans (with a 230-kb genome) with presumably a large number of T-cell epitopes [31, 32]. Specifically, approximately 10% of both the CD4+ and CD8+ memory T cells circulating in blood are targeted towards CMV, and this percentage can increase up to 50% of CD8+ and 30% of CD4+ T cells in older individuals. As people age with their CMV infection, the continual immune activation and response to CMV replication basically drive the T-cell repertoire towards a more differentiate T-cell phenotype with indication of replicative exhaustion and senescence [33]. Therefore, CMV infection may compromise the response to other antigens by both shrinking the remaining T-cell repertoire (in favor of expansion of CMV-specific T-cells) and by decreasing T-cell diversity. As such, senescent T-cells frequently bear antigen specificity towards CMV [34], and the abundance of senescent T-cells correlates with a variety of negative outcomes, like decreased vaccine responsiveness, autoimmunity, frailty, reduction in the T-cell receptor repertoire, cardiovascular disease and poor responsiveness to new infections [35]. Additionally, persistent and intermittent CMV replication is associated with a large bystander activation of non-CMV specific T cells [36], likely secondary to the production of several chemokines at the site of CMV replication. Further, CMV encodes both viral homologue chemokines and chemokine-like receptors, which also activate immune cells through a non-antigen specific mechanism [17, 37, 38]. Moreover, a recent study demonstrated that CMV might have the ability to divert CD8+ T cell responses away from canonical CMV epitopes that likely constitute the most efficient targets for cytolysis [39]. Therefore, recurrent CMV shedding may further stress the immune resources in HIV infected individuals and accelerate progression to AIDS [3, 4].

In non-HIV-infected populations there are associations between CMV IgG levels and increased carotid artery stiffness and ischemic heart disease. One of the largest of these studies was the Sacramento Area Latino Study on Aging (SALSA). In this population-based study of 1,468 adults aged 60–101 years [40],

individuals with the highest anti-CMV IgG titers had the greatest hazard of mortality (all-cause and cardiovascular). In another SALSA analysis, 1,204 subjects were screened annually over 4 years with a modified mini-mental status exam and a word list-learning test of delayed recall. Again, those individuals with the highest anti-CMV IgG concentrations had worse neurocognitive outcomes [40]. In a separate analysis of HIV seronegative individuals older than 65, higher CMV IgG levels and larger numbers of CMV-specific CD4+ T cells were both independently associated with worse neurocognitive performance and worse functional status [41]. Interestingly, a recent study among HIV/CMV co-infected individuals demonstrated that higher levels of CMV IgG were associated with *lower* levels of CMV replication, suggesting that increased CMV IgG levels do not primarily reflect frequent CMV reactivations, but more likely are the consequence of a stronger immune response to CMV leading to less reactivation [42]. Therefore, caution should be used when considering CMV IgG as a surrogate marker of CMV activity and burden and it is likely the immune response to CMV that may be, at least partly, to blame for observed pathology.

**CMV, Activation/Inflammation and Endorgan Disease in the Setting of HIV-infection**

Immune activation is a hallmark of HIV-1 infection, and plays an important role in the CD4+ T-cell depletion, immune dysfunction and a variety of clinical conditions [35]. Suppressive ART reduces the levels of T-cell activation and inflammation, but it does not normalize it and the mechanisms of this persistent immune activation remain unknown. Also, CMV infection induces systemic inflammation not only during primary infection but also during the chronic phase [35]. Indeed both viruses, HIV and CMV, are associated with increased immune activation and inflammation-related morbidities including neurocognitive impairment, cancer and cardiovascular disease [35, 43-46]. Since almost all HIV-infected individuals are co-infected with CMV, it is hard to distinguish HIV versus CMV versus combined effects on inflammation and disease progression [17]. Since the beginning of the HIV epidemic, the connections between HIV and CMV have been recognized, and many studies have suggested that CMV accelerates the development of HIV-dependent immunological abnormalities [34, 43, 44].

Even asymptomatic shedding of CMV in the genital tract has been associated with increased T-cell immune activation and proliferation in peripheral blood [19, 47]. Interestingly, this CMV-associated immune activation occurs even when HIV replication is suppressed with ART [47]. To clarify some of the mechanistic underpinnings of these observations, we recently investigated associations between asymptomatic CMV replication in the genital tract and PD-1 expression on circulating CD4 T-cells during suppressive ART and found that PD-1 expression was increased during CMV shedding [48]. Since increased PD-1 expression on T cells has been implicated in the maintenance of the HIV reservoir, HIV disease progression and the inability of the immune system to adequately control HIV infection [49], the mechanisms connecting CMV, HIV and PD-1 expression deserves further attention. The links between CMV shedding and systemic inflammation during HIV infection was has examined in a randomized control study that showed a reduction in T-cell immune activation when HIV-infected individuals were treated with the anti-CMV drug valganciclovir [50]. While this study was limited in that only 70% of the subjects had HIV RNA suppression with ART and the sample size was small (n=30), it did show a sustained reduction in CMV shedding and immune activation 4 weeks after stopping valganciclovir. This suggests that reducing immune activation might also reduce CMV shedding, and if such a circular feedback is true, then the anti-inflammatory benefit of reducing CMV replication could be greatly compounded with multiple cycles of anti-CMV therapy (see figure 1). In contrast, a more recent randomized trial of valacyclovir in ART-suppressed HSV-2/HIV co-infected individuals failed to decrease systemic immune activation suggesting that HSV-1/2 are not likely to be responsible for the decrease in immune activation we observed in the valganciclovir trial, further increasing the likelihood that the effect was mediated by CMV and not other HHV [51].

**Possible Benefit of HHV/HIV Co-infection**

Even if HHV and HIV have many pathogenic co-dynamics, virus-to-virus interactions are not always negative for the human host. For example, HHV-6 can suppress the replication of CCR5-tropic HIV, which is predominant form of transmitted HIV, and HHV-7 replication can down-regulate the CD4 receptor on T cells consequently reducing the infection of CD4+ T cells by HIV [17]. Further, one recent study observed that ART naïve, recently HIV-1 infected adults co-infected with HSV-2 at the time of HIV-1 acquisition had higher CD4+ T-cell counts over time compared to individuals infected with HIV alone, and this was independent of

HIV RNA levels in blood [52]. Similarly, increased rate of HSV shedding has also been associated with higher CD4+ T-cell count among HIV-infected persons [12]. Similarly, one study showed that mice latently infected with either murine γ-herpesvirus 68 or murine cytomegalovirus (which are genetically similar to the human pathogens EBV and CMV) are resistant to some bacterial infections [53]. Taken together, interactions between HIV and HHV are complex and HHV-associated immune stimulation could have both positive and negative effects.

**CMV and HIV DNA Reservoir**

There is convincing evidence that chronic inflammation and immune activation helps to maintain the HIV reservoir during ART [35]. To draw the link between CMV shedding, systemic inflammation and maintenance of the HIV reservoir, recent studies have demonstrated that asymptomatic CMV seminal shedding is associated with increased levels of total HIV DNA in both ART naïve individuals [54] and in individuals suppressed on long-term ART [47]. Further, in a large longitudinal study of 108 individuals followed since the earliest phase of HIV infection, there was a significant positive association between longitudinal levels of CD4+ T-cell associated HIV DNA in blood and the frequency of detectable CMV DNA in blood cells [55]. Also, *in vitro* studies demonstrated that CMV infection may facilitate HIV DNA entry in cells that are ordinarily non-permissive, as fibroblasts [56]. Although the observational design of these studies does not allow causality to be inferred and they didn't specifically evaluate the replication competent HIV DNA subset, it does support the theory that asymptomatic CMV replication could drive local and systemic immune activation with a subsequent increase in the HIV reservoir. It may follow that targeting drivers of chronic inflammation, like CMV, might be an important factor to consider in HIV curative strategies. Confirming this hypothesis will require a large randomized placebo controlled clinical trial of antiviral therapy aimed at stopping CMV shedding in the male genital tract as a way to reduce the HIV reservoir. Such a trial will be difficult with currently approved anti-CMV therapies given their inherent toxicities [45] but newer anti-CMV therapies may hold such promise.

## Conclusions

The virologic and immunologic connections between HHV and HIV are close and complex. A detailed knowledge of host-mediated interactions between HHV and HIV is necessary, not only to understand the complex mechanisms of HIV infection, but also for the development of new anti-HIV therapies. Interactions between HHV (especially CMV) and HIV will be difficult to address with available technologies. Current anti-CMV therapies are toxic and not applicable on a large scale and for prolonged periods of time. Newer and less toxic anti-CMV drugs (e.g., Brincidofovir [57], or Letermovir [58]) are in development and should be evaluated as part of future clinical trials. Of course none of these drugs will eradicate HHV and prolonged course of therapy will be necessary and might still not be enough to reverse the inflammatory process initiated with cellular infection. Therapeutic or prophylactic vaccines against CMV (and other HHV) are also in development but it is unclear if an additional (vaccine-induced) stimulation of the immune system might further enhance the inflammatory process. Therefore, more interventional studies are needed to determine if suppression of HHV replication (not just HSV) will have a positive effect on HIV disease progression and transmission. In particular, considering the strong association between CMV and HIV-1, such trials should test the effect of anti-CMV drugs to fully understand if anti-CMV therapies can help in the fight of HIV related disease and perhaps in the HIV cure effort.

## Financial Disclosure

This work was supported by the Department of Veterans Affairs and grants from the National Institutes of Health: AI43638, AI100665, MH097520, DA034978, AI036214, AI007384, AI027763, AI106039, AI074621, AI110181, 7-UM1 AI068636-07, P30-AI027763, amfAR grant 108537 with support from FAIR, UL1TR000100, the James B. Pendleton Charitable Trust.

## Competing Interests

SG, MM, JOW and DMS do not have any commercial or other associations that might pose a conflict of interest.

## Acknowledgment

We are very thankful to Peter Hunt, Leonid Margolis and Christophe Vanpouille for their useful comments and feedback.

# Figure Legend

**Figure 1: Theoretical Model connecting asymptomatic CMV replication with HIV transmission (blue line), larger HIV DNA reservoir (green line) and endorgan disease (purple line).**

We hypothesize a circular feedback loop between CMV and HIV replication – immune activation and proliferation – T cell dysfunction (Senescence and Exhaustion) (red circular loop). In other word, CMV and HIV replication are likely responsible for increasing Immune activation and T cell dysfunction, which in turn further enhance CMV and HIV replication. This persistent immune activation has been repeatedly associated with neurocognitive and cardiovascular disease, aging and increased viral reservoir, and CMV is likely part of that mechanism.

| HHV | Name | Type | Estimated Prevalence | | | | Primary target cells | Site of latency | Route of Transmission | Acute Syndromes | Chronic syndromes and other rare manifestations |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Children | Adults (US) | Adult (dev world) | HIV infection | | | | | |
| 1 | HSV-1 | Alpha | 20-40 | 50-70 | 50- >90 | 90-100 | Mucoepithelial | Neuro4n | Close contact (oral or STD) | Mostly oral (gingivostomatitis) | Episodic reactivation, encephalitis, Keratitis, mucocutaneous disease |
| 2 | HSV-2 | Alpha | 0-5 | 20-50 | 20-60 | 50-90 | Mucoepithelial | Neuron | Close contact (STD) | Mostly genital | Episodic reactivation, encephalitis, Keratitis, mucocutaneous disease |
| 3 | VZV | Alpha | 50-75 | 85-95 | 50-80 | 90-100 | Mucoepithelial | Neuron | Respiratory and close contact (also STD) | Chickenpock | Episodic reactivation (shingles) |
| 4 | EBV | Gamma | 10-50 | 80-95 | 90-100 | 90-100 | B cells and epithelial cells | B cells | Close contact, saliva, STD, transfusions/transplant, congenital | Infectious mononucleosis | Burkitt's lymphoma, CNS lymphoma, posttransplant lymphoproliferative syndrom, nasopharyngeal carcinoma, HIV-associated hairy leukoplakia |
| 5 | CMV | Beta | 10-30 | 40-70 | 40-80 | 90-100 | Monocytes, lymphocytes and epithelial cells | Monocytes, lymphocytes, secretory glands and possibly others | Close contact, saliva, STD, transfusions/transplant, congenital | Infectious mononucleosis-like syndrom, retinitis and other organ diseases | Reactivation and organ diseases in immunocompromised host |
| 6 | HHV-6 | Beta | 80-100 | 60-100 | 60-100 | 80-100 | T-lymphoctes and others | T-lymphoctes, monocytes and others | Close contact (oral) | Roseola infantum | Meningitis, Encephalitis and possibly multiple sclerosis |
| 7 | HHV-7 | Beta | 50-80 | 60-100 | 40-100 | 80-100 | T-lymphoctes and others | T-lymphoctes, monocytes and others | Close contact (oral) | Roseola infantum | Hepatitis, post-infectious myeloradiculoneuropathy, pitydiasis rosea (?) |
| 8 | HHV-8 | Gamma | <3 | 3-5 | 10-50 | 50-90 | Endothelial cells | Monocytes, dendritic cells, B lymphocytes, and endothelial cells | Close contact (oral or STD) | Lymphadenopathy, diarrhea, rash, fatigue | Kaposi's sarcoma, primary effusion lymphoma, Multicentric Castleman's disease |

**Table 1:** Summary of prevalence and characteristics for the most common HHV infections

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