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Review

# Non-CMV Viral Infections Following Solid-Organ Transplantation – Focus on Human T-Cell Lymphotropic Virus Type-1 and Human Herpesviruses-6,-7 and -8

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**Abstract**

In non-endemic regions of the world, human T-cell lymphotropic virus type-1 (HTLV-1) is an uncommon pathogen in the transplant host, but can be associated with significant morbidity and mortality. Careful assessment for risk factors, targeted screening and heightened awareness of the clinical presentation of HTLV-1 associated disease is necessary for timely recognition and management in the transplant host. The use of antiretroviral agents in the management of symptomatic disease due to HTLV-1 remains controversial. Human herpesvirus-6 (HHV-6) has long been recognized as a pathogen in the transplant host however, establishing pathogenicity remains a challenge in clinical situations. Chromosomally integrated HHV-6 has been reported in ~1% of the solid-organ and allogeneic stem cell transplant population; and is often mistaken for active infection. Increased recognition of this entity is needed to avoid unnecessary use of antiviral medications. Current guidelines recommend against screening and treatment of asymptomatic HHV-6 infection in the solid-organ transplant host. Human herpesvirus-7 (HHV-7) is often diagnosed as co-infection with other beta-herpesviruses, but pathogenicity is less clear. There continues to be no clinical syndrome solely attributable to HHV-7. Human

herpesvirus-8 (HHV-8) infection following organ transplantation can be due to primary acquisition from donor or non-donor derived exposures; or secondary to reactivation of latent infection in a seropositive recipient. Kaposi sarcoma is the most common HHV-8 associated post-transplant complication however, there is increasing recognition of non-neoplastic syndromes of febrile illness with bone marrow suppression and hemophagocytic syndrome. Lack of standardized laboratory assays for HHV-8 remains an impediment to targeted screening of high risk organ donors and recipients. A multi-disciplinary approach is needed for management of HHV-8 associated diseases.

**Keywords**
HTLV-1; HHV-6; HHV-7; HHV-8; solid-organ transplantation

## 1. Introduction

Human herpesvirus-6,-8 (HHV-6,-8) and human T-lymphotropic virus type-1 (HTLV-1) are associated with significant morbidity and mortality in the solid-organ transplant host. The role of HHV-7 as a sole pathogen remains unclear; but co-infection with other beta-herpesviruses is frequently encountered in the immunosuppressed host. There are unique challenges associated with each of these viruses as it pertains to the organ transplant recipient. In case of HHV-6 and HHV-7, it is their ubiquitous nature, and frequent clustering of infection with *Cytomegalovirus*, that continue to pose diagnostic and therapeutic challenges to the transplant practioner. HHV-8 and HTLV-1 on the other hand, are geographically uneven viruses; and while well-established pathogens in the transplant host, need greater recognition in non-endemic regions of the world. This review aims to enhance our understanding of the impact of HHV-6,-7,-8 and HTLV-1 on the solid-organ transplant host; and highlights the diagnostic and therapeutic challenges that continue to be associated with these infections.

## 2. Human T-Lymphotropic Virus Type-1

Human T-lymphotropic virus type-1 (HTLV-1) is an RNA retrovirus that was first described in the 1980s [1, 2]. An estimated 15 to 20 million individuals worldwide are infected with HTLV-1; which is endemic in parts of South America, the Caribbean, West Africa and Asia [3-6]. Based on data in blood donors, seroprevelance in the United States is less than 1% [7]. The most common mode of transmission of HTLV-1 in endemic areas is mother to child, most commonly through breast feeding [8]. Other modes of transmission include sexual intercourse, transfusion of cellular blood products and organ transplantation [9].

Following initial infection, HTLV-1 establishes a state of life-long latency in the lymphocytes. Most people remain asymptomatic but in an estimated 2%-5% of cases, symptomatic disease as HTLV-1 associated myelopathy tropical spastic paraparesis (HAM/TSP) or adult T-cell leukemia/lymphoma (ATL) can develop [4, 10]. HAM/TSP usually presents with gait disturbances, lower extremity weakness, urinary incontinence, decreased sensation and upper motor neuron

signs [11]. Some of the clinical manifestations of ATL are generalized lymphadenopathy, hypercalcemia and bone lesions.

### *2.1 HTLV-1 in Solid-Organ Transplantation: An Uncommon But Potent Pathogen*

While transmission through organ transplantation has been reported, there are only a few known cases of proven donor-derived HTLV-1 infection [12, 13]. The rate of HTLV-1 associated disease appears to be even lower in the transplant host [11, 13-16]; and this is evident in Organ Procurement Transplantation Network (OPTN)/United Network of Organ Sharing (UNOS) data that identified no cases of HTLV-1 infection among 162 recipients of 134 reactive HTLV-1/2-positive donors between 1999 and 2008 [17-19].

In SOT recipients, the clinical course of HTLV-1 disease can be different with shorter latency period and more rapid progression of disease [20, 21]. The natural history of HTLV-1 in the transplant host however, is not well understood due to lack of long-term cohort studies. The factors that promote disease in SOT patients are an increased pro-viral load, immunosuppression and association with host human leukocyte antigen (HLA) subtypes (B-5401, DRB1-0101). HTLV-1 antibodies usually develop 1-3 months after exposure and are positive lifelong [10, 12, 22, 23].

### *2.2 HTLV-1 - Pathogenesis and Diagnosis*

The first step in the diagnosis of HTLV-1 infection is screening with enzyme immunoassays (EIA). Positive screening tests can then be confirmed using line immunoassays or Western blot [24]. Currently available screening assays have high sensitivity but do not differentiate between HTLV-1 and 2; and have low positive predictive value in areas of low seroprevelance such as the United States. HTLV-1 is a highly cell bound with only small amounts of free virus present in the circulation. The virus infects lymphocytes and the pro-virus undergoes integration into the host genome. PCR testing for viral RNA on non-cellular specimens such as plasma is therefore of limited diagnostic utility [25]. Using PCR for measurement of HTLV-1 pro-viral DNA load in peripheral blood mononuclear cells appears to be a promising tool that may have a role in diagnosis of cases (particularly when standard confirmatory assays are indeterminate) and to assess risk of HTLV-1 associated disease [26-28]. This is an encouraging development but further research is needed to better understand the diagnostic role of pro-viral DNA measurement in the clinical care of patients.

### *2.3 Finding the Balance - Shift away from Universal Donor Screening*

In light of low positive predictive value of available testing and concern about preclusion of healthy donor organs based on false positive results, the policy of universal donor screening for HTLV-1/2 was put on the table for discussion. These concerns were further supported by analysis of universal HTLV-1/2 screening of deceased donors which revealed that the ratio of false positive to true positive screening was 40:1 [4, 29]; and that an estimated 167–227 uninfected organs were rejected each year due to false positive screening results [4, 17].

In 2009 mandatory, universal donor screening for HTLV-1, was eliminated by the OPTN/UNOS. However, further recommendations were made by the Organ Procurement Transplantation Network Ad Hoc Disease Transmission Advisory Committee (DTAC) that targeted screening of donors presumed to be at high risk for HTLV-1 infection should continue, and all positive donor

screening tests should be confirmed retrospectively to allow appropriate follow up of the recipients [17]. The American Society of Transplantation Infectious Disease Community of Practice (AST IDCOP) also recommends targeted screening of high risk donors and recipients [4]. Since organs from donors who screen positive for HTLV-1 can be used for transplantation, it is essential that the recipient is informed about the potential risks as part of the informed consent process required for transplantation. The optimal management and follow up of recipients receiving organs from donors proven or suspected to have HTLV-1 is unknown, and there are currently no established guidelines. The AST IDCOP recommends using a combination of laboratory tests and clinical monitoring for follow up of recipients with confirmed or high suspicion of donor infection. Transplant practioners must also be educated on clinical manifestations of HAM/TSP and ATL, and must maintain a heightened awareness in follow up of high risk organ recipients for timely diagnosis and management of HTLV-1 associated complications.

### *2.4 HTLV-1 Associated Disease: HAM/TSP and ATL*

The diagnosis of HAM/TSP can be particularly challenging and transplant practioners should be aware of the WHO criteria for timely recognition and appropriate work up [30]. Diagnosis can be missed or delayed due to rarity of the HTLV-1 infection outside of endemic areas, lack of pre-transplant serologic screening and low frequency of associated disease in infected SOT recipients. In patients developing ATL the treatment consists of chemotherapy; and steroids, interferon-alpha, and immunoglobulin therapy might be employed in cases of HAM/TSP. While sometimes employed, the role of antiviral medications in HTLV-1 associated disease remains controversial.

Antiretroviral medications including zidovudine and raltegravir have been shown to have in-vitro activity against HTLV-1 [31]; however the in-vivo results have been disappointing [32-34]. This lack of concordance is explained by the lack of continuous viral replication cycles in chronic carriers of the infection [4, 34, 35]. Limited clinical data suggest efficacy of prosultiamine with improved motor strength, urinary bladder function and pro-viral DNA in patients with HAM/TSP [35, 36]. Prosultiamine is a thiamine derivative has been found to have activity against HTLV-1 infected cells by inducing apoptosis [37]. While promising, these findings need investigation in larger randomized clinical trials to better understand the benefit to patients. Based on expert opinion, it has been suggested that post-exposure prophylaxis may be beneficial to prevent HTLV-1 infection following exposure through organ transplantation. There is however no data on the efficacy of this approach and it is currently not approved or recommended by the CDC [3].

## 3. Human Herpesvirus-6

Human herpesvirus-6 (HHV-6) is a lymphotropic beta (β)-herpesvirus, which was first isolated from peripheral blood lymphocytes of immunosuppressed patients in 1986 [38]. Initially classified as variants of the same virus, HHV-6A and B are now recognized as separate species [39]. In the vast majority of the population, HHV-6 exposure occurs during early childhood, and initial infection is followed by establishment of life long latency inside the mononuclear cells [40-42]. Majority of human infections are due to HHV-6B with an estimated prevalence of 97% [43]. In addition to blood mononuclear cells, a wide variety of body tissues are infected with HHV-6 including salivary glands, tonsils, brain, liver and kidney [44]. In a smaller percentage of the population, HHV-6 viral genome undergoes integration into the host chromosome [45-47]. The

ability to establish latency through integration into the host genome is a unique property of the HHV-6 virus. This entity is termed as chromosomally integrated HHV-6 (CIVVH-6), and is estimated to occur is 1% of the human population worldwide [46]. The clinical significance and diagnosis of CIHHV-6 in the transplant host will be discussed in detail later in this manuscript.

Since the vast majority of adults are seropositive, HHV-6 infection in the post-transplant setting most commonly is due to reactivation of endogenous virus [48, 49]. Primary infection through transmission from the community or the allograft itself has been reported but very uncommon [50, 51]. HHV-6B has been implicated as the cause of majority of infections in adult SOT recipients [39, 43, 52, 53]; with a much smaller percentage due to HHV-6A.

### *3.1 Clinical Manifestations of HHV-6 in the Solid-Organ Transplant Host: Direct and Indirect Effects*

The reported incidence of symptomatic infection in the SOT recipients varies between clinical series but overall despite high seroprevelance, the incidence of symptomatic HHV-6 infection following organ transplantation is low [48, 49, 54]. Most HHV-6 infections represent reactivation of latent virus in the early post-transplant period (first 4-6 weeks) with fewer reports of late onset infections (months to years) [48, 55].

Clinical manifestations of HHV-6 can be attributed to direct and indirect effects. Among the direct effects, the most commonly reported include febrile illness with bone marrow suppression and encephalitis [56, 57]. Other reported manifestations are gastrointestinal (gastroduodenitis, colitis), pneumonitis, fulminant hepatic failure. Reported manifestations of HHV-6A in the transplant population include giant-cell hepatitis [58], hemophagocytic syndrome [50], and hepatitis with pancytopenia [51]. There are indirect effects of HHV-6 due to immunomodulatory properties which include recurrence of hepatitis C infection [59, 60], *Cytomegalovirus* (CMV) infection [61-63], allograft rejection [62, 64], and fungal infections [54, 62, 65]. The increased risk of CMV infection/disease in association with HHV-6 was clearly shown in a study by Kumar *et al* where risk of CMV disease increased by 3.59-fold in patients with HHV-6 infection (95% CI, 1.53-8.44; P=0.003) [54]. Limited data is suggestive of an association between HHV-6 and bronchiolitis obliterans syndrome but further research is warranted to better understand and validate these findings [66].

There are many reports of HHV-6 and CMV co-infection in SOT recipients. On genomic analysis, HHV-6 is most closely related to human CMV with 66% similarity in amino acid sequences [67]**.** In a study of liver transplant recipients who were found to be positive for both viruses, HHV-6 was on average activated earlier than CMV in most patients (HHV-6 activation: 19.8 ± 4.5 days vs. CMV activation: 28.4 ± 60.5 days - P = 0.001), with a 9-day time gap between the activation of the two viruses. Regression analysis of the time of CMV and HHV-6 activation revealed a linear relationship [68].

### *3.2 Diagnosis of HHV-6: Establishing Pathogenicity of a Ubiquitous Organism*

Over the years, HHV-6 has been recognized as a pathogen in the transplant host. However, establishing pathogenicity of HHV-6 in clinical situations remains a challenge. Clinical manifestations of HHV-6 overlap with other herpes viruses, particularly CMV; and it is not uncommon to find both viruses in the work up of patients with suspected infection. In these

scenarios, HHV-6 is often questioned as the true-pathogen in comparison to CMV. Other features of HHV-6 which make the diagnosis of active infection challenging, are the ubiquitous nature of the virus, high seroprevelance in humans, establishment of clinical latency and integration of viral genome into the human chromosome. Careful consideration must be given to the intrinsic properties of HHV-6 including CIHVV-6, and the limitations of current diagnostics to avoid unnecessary antiviral therapy [53].

Diagnostic approach to HHV-6 has been characterized broadly into indirect and direct [44, 69]. Indirect diagnostics are based on detection of HHV-6 antibodies, while direct diagnostics employ methods for detection of whole virions or viral components and include viral culture, HHV-6 antigen detection, and PCR.

### 3.2.1 Serologic Testing

Serology for HHV-6 is useful as a screening tool to determine risk of future infection in an immunosuppressed host but since seroprevelance in the adult population is high, it's utility in the diagnosis of active infection is limited. Furthermore, currently available serologic tests are species non-specific hence unable to differentiate between HHV-6A and B species and may have cross-reactivity with other β-herpes viruses [44, 69].

### 3.2.2 Polymerase Chain Reaction

Most commonly employed direct diagnostic testing is based on detection of viral nucleic acids by PCR. PCR testing for HHV-6 is commercially available for a broad range of clinical specimens and does provide differentiation between HHV-6A and B species however, standardization of testing methodology and measurement units is lacking [44, 69]. Active infection is often diagnosed based on quantitative PCR testing (Q-PCR) but there are no standardized thresholds for interpretation of active infection versus latent versus CIHHV-6. For diagnosis of active infection, reverse-transcriptase PCR can be employed that can differentiate between latent and actively replicating virus by detection of viral transcripts. This technique was described in 1999 where viral transcripts were detected by amplification of mRNA corresponding to major structural antigens in peripheral blood mononuclear cell samples taken from children with recent clinical illness suggestive of HHV-6. In comparison with DNA-PCR and viral culture performed on the same specimens, reverse-transcriptase PCR was found to have sensitivity of 95% and specificity of 98.8% [70].

### 3.2.3 Viral Antigen Based Testing

With the advent of Q-PCR testing for HHV-6, the role of antigenemia assays as screening tools for detected of viremia is limited. However, detection of viral antigens in tissue using monoclonal antibodies and immunohistochemical testing is still of benefit for the diagnosis of tissue invasive disease [55, 71].

### 3.2.4 Plasma versus Whole Blood PCR

Q-PCR testing for diagnosis of HHV-6 infection is most often performed on non-cellular specimens such as plasma despite the fact that the virus is highly cell associated. This has raised questions about the adequacy of plasma as a sample for HHV-6 testing. In fact, recent data

revealed that the source of HHV-6 DNA detected in plasma infact corresponds with lysis of blood cells rather than active virus production due to infection of lymphoid tissue or organs [72]. Further research on patients samples with various stages of HHV-6 infection (primary, past, congenital, no infection, CIHHV-6) revealed that in comparison with virus isolation by culture, plasma HHV-6 real time-PCR had a sensitivity of 92% for identification of primary infection and specificity of 84% [73]. All patients in this study with CIHHV-6 had detectable virus by plasma HHV-6 real time PCR but only 5.6% had detection of active viral transcripts by reverse-transcriptase PCR [73]. This data suggests that Q-PCR testing on plasma is not a reliable marker of active infection and in order to distinguish active infection from CIHHV-6, testing on whole blood might be more specific [73, 74]. Q- PCR testing on whole blood is available commercially but data are limited. As with testing on plasma, there are no standardized cut-offs for interpretation of active versus latent infection.

It is important to recognize the differences between the currently available diagnostic tests for HHV-6, to choose the test appropriate for the clinical question at hand. Clinicians must also bear in mind, that current testing for HHV-6 is limited not only by the lack of clinically meaningful cut-offs for active infection, but also by the lack standardized WHO units of IU/mL; contributing to inter-laboratory variation in results. We make the following recommendations in this regard.

- Serologic testing is not of utility in the diagnosis of active infections. A positive serology with negative Q-PCR testing indicates latent HHV-6 infection.
- In a patient with clinical signs and symptoms attributable to HHV-6, positive Q-PCR testing can be indicative of active infection however; important to remember that Q-PCR testing does not distinguish CIHHV-6 from active viral replication.
- CIHHV-6 is typically an asymptomatic patient with a very high HHV-6 viral load. To distinguish CIHHV-6 from active infection, reverse-transcriptase PCR testing can be employed.
- The current role of viral antigen based tests in the diagnosis of active HHV-6 infection is largely limited to immunohistochemistry for detection of viral antigen in tissue specimens.

### *3.3 Chromosomally Integrated HHV-6: Clinical Significance and Diagnosis*

Based on the work of multiple investigators, CIHHV-6 is defined as the presence of ≥1 HHV-6 DNA copies/cell [46, 75, 76]. Clinical significance of CIHHV-6 in the immunosuppressed host is an area of active research. The prevalence of CIHHV-6 in the solid-organ and allogeneic stem cell transplantation appears to be low (~ 1%) [77]. Study of the integrated HHV-6 viral genome has shown that these viruses differ greatly from their non-integrated counterparts. These integrated genomes however, in majority (CIHHV-6B 95% and CIHHV-A 72%), do contain a complete complement of intact viral genes and appear to be capable of reactivation from the latent state [78]. While the clinical significance of CIHHV-6 in the organ transplant host remains undefined, limited data suggest that the rate of clinical disease due to CIHHV-6 is low [53]. A review by Lee *et al* of 9 SOT patients with CIHHV-6 [53], showed that the median HHV-6 DNA copies per ml of whole blood in LT recipients was $2.7 \times 10^6$ ($1.1 \times 10^6$ - $18.3 \times 10^6$) and in kidney transplant patients was $5.1 \times 10^6$ genomes per ml of whole blood. In the same series, a small bowel recipient had HHV-6 DNA PCR done on hair follicles which revealed DNA concentration of $11 \times 10^6/10^6$ cells, consistent with CIHHV-6 [76]. None of these patients developed clinical disease due to HHV-6 infection and 2 patients were treated with antiviral agents for mistaken diagnosis of active infection [53, 79]. heightened awareness of this entity is therefore needed and a suggested

approach by experts is that in patients with suspected CIHHV-6 (typically DNA load of > 5.5 $\log^{10}$ copies per ml of whole blood), reverse-transcriptase PCR be considered to rule out active infection due to HHV-6 and avoid unnecessary use of antiviral agents [47, 73].

### *3.4 Treatment of HHV-6: Indications for Antiviral Therapy*

Acyclovir and valacyclovir have no significant activity against HHV-6 at doses used in patient care. It is however susceptible to ganciclovir, foscarnet and cidofovir [44, 80], at doses similar to those used for treatment of CMV. HHV-6 genes which are of relevance to antiviral treatment include U69 and U38. U69 encodes a protein kinase, which is involved in the initial phosphorylation of ganciclovir that is subsequently tri-phosphorylated to its active form by cellular kinases. U38 encodes the viral DNA polymerase [80] which is the site of action of ganciclovir, foscarnet and cidofovir.

Successful use of ganciclovir and foscarnet for symptomatic HHV-6 infection has been reported in transplant recipients, but no controlled trials have been performed to prove efficacy [81-84]. A study in hematopoietic stem-cell transplant recipients looked at the effects of antivirals on serum and cerebrospinal fluid HHV-6 viral load in patients diagnosed with encephalitis [85]. They found decrease in HHV-6 VL in both sites, concurrent with use of antiviral therapy (ganciclovir and/or foscarnet). However, this study did not provide perspective on possible differences in efficacy between the 2 agents [85]. In light of current available data, use of either agent appears appropriate for treatment of HHV-6 associated disease, including encephalitis. The AST IDCOP recommends treatment of HHV-6 associated encephalitis or other clinical syndrome attributed to HHV-6 but treatment of asymptomatic infections of the organ transplant host is not recommended [86]. Data on impact of current post-transplant antiviral prophylaxis on non-CMV viruses is limited. Available data suggests that the incidence of HHV-6, HHV-8, *Varicella zoster virus* (VZV) and *Epstein-Barr virus* (EBV) may be reduced but HHV-7 may not be impacted [87] Since most HHV-6 infections are asymptomatic and self-limited, and antiviral prophylaxis for HHV-6 following organ transplantation is currently not recommended [86]. Limited data suggests HHV-6 viremia threshold $\geq 10^4$ copies/ml is predictive of encephalitis in hematopoietic stem-cell transplant recipients, however similar data is lacking in SOT [88]. If data were to emerge on the impact of asymptomatic HHV-6 infection in the organ transplant host, the recommendation for antiviral prophylaxis and/or preemptive treatment of asymptomatic infection may change. However, any such approach would need to take into account the risk from toxicity of currently available antiviral agents.

The emergence of ganciclovir-resistant HHV-6 strains during treatment has been reported which correlates with U69 and U38 mutations [89, 90]. Cidofovir resistance in HHV-6 has also been shown through in-vitro selection and is associated with mutation in U38 [91]. The emergence of drug-resistance HHV-6 strain should be considered if indicated clinically, during antiviral prophylaxis or treatment for other herpes viruses such as CMV. Further study is however, required to better understand the clinical significance of these drug resistant strains.

## 4. Human Herpesvirus-7

HHV-7 is a member of the herpesvirinae family and β -herpesvirus sub-family. It was discovered in 1990 from human CD4 T-cells [92]. HHV-7 is a ubiquitous virus that exhibits similar cellular tropism to HHV-6 viruses but appears to be less pathogenic. Similar to HHV-6B, over 90% of the adult population is estimated to be seropositive. Infection due to HHV-7 occurs in early childhood but tends to occur later than HHV-6B [93]. The clinical manifestations of primary HHV-7 infection are not as well-defined but it has been described as a cause of exanthem subitum and febrile illness with seizures [94, 95]. Primary HHV-7 infection is followed by the establishment life-long latency in host-peripheral blood mononuclear cells [96].

### *4.1 Clustering of Beta-Herpesviruses - Co-Pathogens with CMV or 'Innocent Bystanders'*

Reactivation of HHV-7 following organ transplantation has been well-documented however, as is the case with HHV-6, search for direct pathogenicity has been challenging due to overlapping clinical manifestations, clustering of viral reactivation with CMV, and correlation with occurrence of CMV disease [97]. Many authors have described HHV-6 and 7 as co-pathogens with CMV. Interaction between the 3 β-herpesviruses has been postulated to play a role in both the direct and indirect viral effects attributed to CMV [52]. Contrary to this, more recent prospective data while showing high prevalence of herpesvirus co-infection in SOT recipients with CMV disease, failed to show significant impact of HHV-6/7 co-infection [98]. In this study by Human *et al*, response to CMV antiviral therapy, baseline CMV viral load, time to viral eradication and risk of recurrence in patients with HHV-6 or7 co-infection and in those without, were similar [98]. The findings of this study put into question the clinical impact of HHV-6/7 co-infections on CMV infection/disease in organ transplant recipients and hence despite high prevalence, routine post-transplant monitoring for these viruses in not recommended [86]. There continue to be no reliable reports of clinical syndromes solely attributable to HHV-7 in organ transplant recipients.

### *4.2 Impact of Routine Antiviral Prophylaxis on HHV-7*

Antiviral prophylaxis with oral ganciclovir or valganciclovir does not appear to have an impact on HHV-7 [87, 98]. In-vitro measurement of end-point inhibitory concentrations (EC-50) for antivirals against β-herpesviruses revealed that HHV-7 was most susceptible to cidofovir but the EC-50 was higher than for HHV-6A/B (0.3 μg/ml for HHV-6A, 1.2 μg/ml for HHV-6B and 3.0 μg/ml for HHV-7) [99]. The clinical relevance of this data is unclear and there are no clinical interpretative breakpoints for such antiviral susceptibility testing.

## 5. Human Herpesvirus-8

Human herpesvirus-8 (HHV-8) is a gamma-herpesvirus [100]. As with all herpesviruses, HHV-8 establishes a lifelong state of latency following initial infection, and in the presence of certain host factors can enter the lytic phase producing actively infective virions which can kill the host cell. HHV-8 has a broad range of cellular tropism and natural reservoir for infection includes lymphoid, epithelial and endothelial cells [100].

HHV-8 seroprevelance in the world varies greatly by geographic region, with the highest rates of infection found in the Africa (up to 58%), Mediterranean (14%-25%), and the Middle East [101-107].

In endemic areas infection is acquired in childhood, in comparison to areas of low seroprevelance where it appears to be acquired later in life [102, 108]. HHV-8 transmission occurs through saliva, blood, sexual contact and organ transplantation [109-111]. In non-endemic areas, high seroprevelance has been found among men who have sex with men (MSM) [112-114], and migrants from endemic areas [115]. Global seroprevelance of HHV-8 among MSM has been estimated in a recent meta-analysis at 33.0% (95%CI 29.2%-37.1%) [116]. In the setting of organ transplantation, infection can develop due to secondary reactivation in a seropositive recipient but primary HHV-8 infection due to donor and non-donor derived exposures has been well-described [110, 111].

### *5.1 Clinical Manifestations of HHV-8: Oncogenic and Non-Oncogenic Properties*

HHV-8 remains best known as an oncogenic virus and the causal agent of Kaposi's sarcoma (KS), multi-centric Castleman's disease (MCD) and primary effusion lymphoma (PEL).

Pre-existing HHV-8 seropositivity in the transplant population in endemic areas has been reported in the range of 4.9% to 16% [117-119]. The frequency of KS in solid-organ transplant recipients parallels the seroprevelance of HHV-8 infection in different regions of the world. In areas where HHV-8 infection is endemic, KS is a commonly seen malignancy in the transplant host; in one report from Saudi Arabia accounting for nearly 88% of all post-transplant cancers [120]. In a more recent report from Turkey during 1997 to 2017, KS was identified as the second most common post-transplant malignancy accounting for 18% of the cases, following squamous and basal cell carcinoma which were the most common at 29% [121]. The overall KS risk following solid-organ transplantation has been shown to be 125.3-fold higher (95% CI, 98.2–157.6) than in the general Italian population, reflecting the risk conferred by HHV-8 infection in endemic areas [122]. In contrast, in areas of low seroprevelance such as the United States, the prevalence of post-transplant KS is much lower; and the most common malignancies in solid-organ transplant recipients are non-Hodgkin lymphoma, lung, liver and kidney cancer [123]. Analysis of United States solid-organ transplant and population based cancer registries, identified 163 cases of KS among 264,624 transplant recipients from 1987-2014; with incidence rate of 12.4 per 100,000 person-years [124]. The same study also showed a decreasing incidence rate of KS with passage of time post-transplant (<1 year post-transplant: 35.1, <3: 15.6, <5: 5.0 and ≥ 5: 2.6 per 100, 000 person years); and a decrease in incidence rate during more recent years (1997-2003: 13.8 and 2004-2014: 9.6 per 100,000 person years) [124].

HHV-8 infection at the time of transplant is the most important risk factor for post-transplant KS [119, 122, 125, 126]. There appears to be a difference in the KS risk conferred by preexisting/pre-transplant versus acquired/post-transplant HHV-8 infection; with higher risk in patients with pre-transplant HHV-8 infection [119, 126]. The rates of post-transplant KS among HHV-8 seropositive kidney transplant recipients and seronegative recipients with positive donors (D+/R-), are 13% and 4.6% respectively [126]. These findings suggests that reactivation of latent HHV-8 infection plays a greater role in the development of post-transplant KS than incident infection. Other risk factors identified in majority of studies include increased recipient age at

transplant, male sex, country of birth and ethnicity [127]. The role of induction and maintenance immunosuppressives with risk of KS remains unclear [127]. Some studies have shown a significant association with total amount of calcineurin inhibitor and use of anti-thymocyte globulin or IL-2 receptor antibody induction [127]; however the same has not been seen in other studies [124, 127, 128]. Similar to previous data, a more recent study by Cahoon *et al* showed increased risk of KS among males, non-white race, non-US citizenship, lung transplantation (versus kidney) and older age at the time of transplant (>65 years old = 28.6, 50-64 = 16.4, 35-49=7.7 and 15-34= 5.7 per 100, 000 person-years); and no association with specific induction or maintenance immunosuppressive medications [124].

KS is the most frequent manifestation of HHV-8 infection in the transplant host which presents in 90% of the cases as mucocutaneous lesions. According to Israel Penn International Transplant Tumor Registry (IPITTR) data, in 60% disease was limited to the skin, oropharyngeal mucosa and conjunctiva. Visceral disease has been reported in about 40% of cases with concomitant cutaneous KS in majority of patients [129, 130]. More recently published OPTN data on US transplant recipients (1987-2003) identified 65 cases of KS, 80% of which were cutaneous-only and 20% with reported visceral disease [131]. Further analysis of the IPTTIR (1982 to 2001) was carried out to determine if there are clinical differences between post-transplant KS among international and US cases. This analysis revealed a higher rate of visceral KS among international patients in comparison to US patients who presented primarily with cutaneous-only disease (47% versus 27%, $P < 0.01$) [132]. Among international patients, median time to presentation with post-transplant KS was shorter than among US patients and visceral KS was associated with significantly reduced 1-year patient survival in comparison with cutaneous-only disease (90% versus 70%, $P < 0.01$). Therapeutic approach was similar and in both groups most commonly consisted of minimization of immunosuppression with either surgery and/or radiation therapy [132]. Limited data suggests that the clinical manifestations and treatment outcomes SOT recipients with KS is similar between those who have HIV infection and those without [133].

Less common oncologic manifestations of HHV-8 infection include multi-centric Castleman's disease (MCD) and primary effusion lymphoma (PEL) [86, 134, 135]. Common clinical manifestations of MCD include fevers, pancytopenia, lymphadenopathy, elevated inflammatory markers and splenomegaly [136]. The diagnosis of PEL should be considered in a patient presenting with effusions in relation to serosal surfaces of the body (pericardium, pleural, peritoneal) [137, 138]. Concomitant occurrence of multiple disease manifestations of HHV-8 has also been reported in transplant recipients including KS and MCD [139-141], and KS, MCD and HLH [142]. While HHV-8 remains best known as an oncogenic virus, there is increasing recognition of non-neoplastic disease manifestations including severe bone marrow suppression, multi-organ failure and hemophagocytic syndrome (HLH) [142-147].

### *5.2 Laboratory Testing for HHV-8: Role of Viral Testing in Screening, Diagnosis and Prognosis of HHV-8-Associated Diseases*

Most cells in HHV-8 associated disease are latently infected however, a proportion of cells do enter lytic replication (highest in MCD and lowest in KS); and both latent and lytic proteins play a role in tumorigenesis and inflammation [148, 149]. Current diagnostics are based on detection of latent and/or lytic gene products through molecular or serologic methodology. In addition,

immunohistochemical staining on tissue is available for diagnostic confirmation of HHV-8 associated disease. Below we outline the potential indications for HHV-8 serology and PCR in the organ transplant population.

### 5.2.1 Organ Donor and Recipient Screening

A number of commercial assays are available for HHV-8 serologic testing. These can be used to screen for latent HHV-8 infection in organ donors and recipients, but are not diagnostic of active infection. Certainly, such an approach appears attractive especially in HHV-8 endemic regions of the world, and could be utilized to risk stratify donors and recipients prior to transplantation. This approach is in fact, utilized by some transplant centers in endemic regions however; wider implementation of this practice continues to be impacted by lack of standardization in testing methodology and inter-laboratory variability in results. The continued lack of a gold-standard HHV-8 serologic assay was shown nicely in a recent multi-center prospective study which found, that out of 6 commercial serologic assays (both LANA and lytic antigen based), only 2 assays (both based on lytic antigen) showed perfect agreement with the reference standard [150]. In this study, the investigators also looked for baseline (pre-transplant) HHV-8 viremia using peripheral whole blood or plasma PCR testing. The correlation between baseline PCR and serologic test results was poor, both for donors and recipients; only 3 out 10 seropositive donors had detectable viremia at baseline, and only 1 out of 93 among seropositive recipients [150].

### 5.2.2 Diagnosis of HHV-8 Associated Disease (KS/PEL/MCD)

When HHV-8 associated disease is suspected, every effort must be made to obtain tissue specimens for diagnosis. Viral testing of tissue specimens using PCR and/or immunohistochemistry appears to carry the greatest diagnostic accuracy. The role of both peripheral blood PCR and serology in the diagnosis of HHV-8 associated disease remains controversial [149, 151].

HHV-8 replication precedes the development of KS but the level of viremia is typically low. Blood PCR testing for diagnosis of KS therefore, in most studies has shown poor sensitivity and specificity [126, 149, 150, 152, 153]. Data on HIV/AIDS patients has shown that only ~ 10%-60% of patients with KS will have HHV-8 viremia [148, 154, 155]. Specific to SOT, data are limited but similar. A prospective investigation of HHV-8 associated complications in kidney transplant recipients reported that PCR had a sensitivity of only 23.8% in HHV-8 seropositive recipients. Among the 3 patients in this study who developed HHV-8 associated disease (2 KS and 1 non-neoplastic primary infection), but significant viremia was seen only in 1 patient supporting the low diagnostic yield of blood HHV-8 PCR in patients with KS [126].

Blood levels for HHV-8 are higher in PEL and MCD, and peripheral blood testing for viremia may have greater yield in diagnosis. In the absence of histopathology, HHV-8 viremia can be supportive however; histopathology remains the gold standard for diagnosis [148]. A recent study compared the degree of HHV-8 viremia between KS, PEL and MCD [156]. Similar to results from prior studies, patients with KS had the lowest levels of viremia. Among patients with KS, higher level viremia was seen in patients who had advanced stage KS and clinical progression of disease. Blood levels for HHV-8 were higher for patients with PEL and MCD and overall, the highest level of detectable virus was seen in effusion fluid in patients with PEL [156]. Based on these results, the authors

postulated that there might be a role for HHV-8 viral load monitoring in patients with KS who are suspected of developing concomitant PEL and/or MCD [156].

#### 5.2.3 Viral Load Monitoring

Detection of HHV-8 viremia in the blood however, has been shown to be helpful in predicting the risk of incident KS by providing a quantitative measure of lytic replication [154, 155]; and has shown correlation with disease progression and regression in patients on treatment for KS [157]. Pellet *et al* reported results of quantitative HHV-8 PCR testing in 43 cases of post-transplant KS. In their cohort, 40% of patients were found to have significant HHV-8 viremia (> 100 copies per microgram of DNA) [157]. The authors conducted an analysis of factors associated with viremia and identified progressive disease due to KS as an independent predictor of viremia, suggesting a role of HHV-8 viral load testing as a prognostic marker in patients with post-transplant KS [157].

Available data on HHV-8 diagnostics must be reviewed bearing in mind that current testing modalities are not standardized. There continues to be significant variability in sensitivity and specificity between different HHV-8 blood assays and the clinical application of these in diagnosis of HHV-8 associated diseases is not clear in the absence of histopathology. Based on published literature, we make the following recommendations in regards to current state of HHV-8 diagnostics.

- Peripheral blood HHV-8 serologic testing can be utilized to screen for asymptomatic infection and risk stratification in the transplant setting; however its utility in the diagnosis of HHV-8 associated disease is unclear.
- Peripheral blood PCR for HHV-8 viremia appears to have greater yield in PEL/MCD and non-neoplastic HHV-8 related disease due to higher viral load in these conditions. Its role in the diagnosis of KS is limited due to typically low viral loads.
- The current literature suggests that detection of HHV-8 viremia by blood PCR is most useful in predicting risk of incident disease and prognosis of patients with known HHV-8 associated diseases.
- Diagnosis of HHV-8 associated disease must rely on histopathology with use of molecular and immunohistochemical testing for detection of HHV-8.

### *5.3 Monitoring and Treatment of HHV-8 Associated Diseases in Transplant Recipients*

In the absence of robust data in SOT, current guidance regarding management of post-transplant HHV-8 associated diseases is based largely on expert opinion [86, 149, 158]. Riva *et al* proposed a comprehensive algorithm for monitoring and treatment of HHV-8 associated complications in the transplant recipient. They propose pre-transplant serologic screening of donors and recipients for stratification of risk, followed by monitoring of high risk recipients (D+/R- and R+) for viremia, virus-specific cell mediated immunity and clinical manifestations of HHV-8 associated disease [149]. Currently, donor and recipient HHV-8 serologic screening is performed in some centers mostly in endemic areas [149, 159, 160]. While such a practice seems useful as a tool for risk stratification and post-transplant surveillance, the lack of standardized testing has prevented this from being implemented on a larger scale. Nevertheless, recognition of HHV-8 risk in both the donor and recipient is essential for monitoring and timely recognition of related disease. Transplant practioners must therefore, obtain detailed history of risk factors for infection

and perform targeted screening in individuals at high risk, such as those from regions endemic for HHV-8. In the event that clinical signs and symptoms of HHV-8 associated disease complications do occur, confirmation of diagnosis must be made by histopathology and a multi-disciplinary management approach including consultation with oncology should be pursued.

For all post-transplant HHV-8 associated, neoplastic and non-neoplastic diseases, the mainstay of treatment is reduction of immunosuppression and change to an mTOR inhibitor based regimen (sirolimus or everolimus) [149, 158]. Study of patients with post-transplant KS has shown that the T-cell mediated immune response to HHV-8 is nearly absent at the onset of disease, with clinical regression occurring with reconstitution of virus-specific T-cell mediated immunity [161]. Over a decade now, data has been accumulating on the benefits of mTOR inhibitors in the management of post-transplant HHV-8 associated diseases [162-165]. Most case reports and series pertain to sirolimus; however successful management of post-transplant KS with switch to an everolimus based regimen has also been reported [162, 163]. Sirolimus serves as a therapeutic agent in post-transplant KS due to direct anti-tumor activity (through inhibition of the mTOR pathway) and anti-angiogenetic activity (through inhibition of vascular endothelial growth factor) [166, 167]. Rapamycin also has antiviral properties and is able to significantly inhibit HHV-8 lytic replication, providing further insight into the clinical benefit of these agents in patients with KS [168]. Reduction in immunosuppression alone is successful in many cases of post-transplant KS however, patients must be carefully followed for allograft rejection and need for chemotherapy (especially in cases of advanced disease) [158].

It is well-established that viral replication plays a key role in the pathogenesis of HHV-8 associated diseases. A number of antiviral agents have been found to have in-vitro activity against HHV-8 including, herpesvirus DNA synthesis inhibitors ganciclovir, valganciclovir, foscarnet and cidofovir [148, 169]. However, a direct role of antiviral agents in the prevention and treatment of HHV-8 associated diseases is yet to be defined. Among antiviral agents with HHV-8 activity, valganciclovir is the only one that has been studied in a clinical trial [170]. In this study, the investigators studied the impact of valganciclovir on viral replication by measuring HHV-8 viral load in oropharyngeal specimens, in a cohort of 26 HHV-8 seropositive men. Of these, 16 were also HIV infected. In the valganciclovir arm, significant reduction in HHV-8 viral load was detected in comparison to the placebo arm (44% in placebo group versus 23% in valganciclovir group- RR 0.54 [95% CI 0.33–0.90]; P 0.02), establishing the efficacy of valganciclovir in reducing HHV-8 viral replication. Based on the findings of this study, one can postulate that suppression of HHV-8 viral replication using antiviral agents may have a role in prevention and/or treatment of KS, however larger scale clinical trials are needed. Beyond this study, data on these agents is limited to small observational studies which reports benefits of antiviral therapy in prevention and regression of KS [148].

In addition to herpesvirus DNA synthesis inhibitors, there has been considerable interest in the role of HIV protease inhibitors which have been associated with reduction in incidence and improving outcomes in patients with HIV/AIDS associated KS [171]. Further research into the mechanism behind these observations has shown anti-tumor activity independent of HIV protease inhibition through a broad range of cellular pathways [172, 173]. Among the protease inhibitors, nelfinavir appears to be most promising agent due to direct antiviral activity against HHV-8 in addition to anti-neoplastic properties [174, 175].

Based on currently available data, it is safe to conclude that no firm recommendations can be made in regards to use of antiviral agents in the management of HHV-8 associated disease in post-transplant patients. Data is limited in general, and mostly pertain to HIV/AIDS patients. The demonstration of valganciclovir efficacy in reducing HHV-8 replication in a clinical trial, and the discovery of novel anti-tumor property of nelfinavir, is certainly exciting; and hopefully future research will pave the path towards a defined role of these agents in the management of HHV-8 associated disease. Till then, current standard of care consisting of reduction in immunosuppression, use of a rapamycin based regimen, and chemotherapy in consultation with oncology should be pursued.

## 6. Conclusion

HHV-6,-7,-8 and HTLV-1 each pose unique challenges to the transplant host. Diagnosis of true infection due to HHV-6 and -7 remains challenging. In particular, clinical scenarios where HHV-6 and HHV-7 are detected with other beta-herpesviruses such as CMV; it is hard to know whether these are innocent bystanders or co-pathogens. Additionally, CIHHV-6 is often misdiagnosed as active HHV-6 infection. Education of transplant practioners on CIHHV-6, can help avoid unnecessary use of antivirals in patients. HHV-8 and HTLV-1 are well-recognized pathogens in the transplant host, but the uneven global distribution of these contributes to failed recognition of infection and associated complications; especially in non-endemic regions of the world. Development of standardized laboratory assays for HHV-8 and HTLV-1 is needed for accurate diagnosis and targeted screening of high risk organ donors and recipients.

## Author Contributions

K.O. wrote the manuscript. S.T. reviewed, wrote, revised and formatted the manuscript.

## Competing Interests

The authors declare no competing interests in regards to this manuscript.

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