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Published on: 01 Sep 2019 - Clinical Transplantation (John Wiley & Sons, Ltd)

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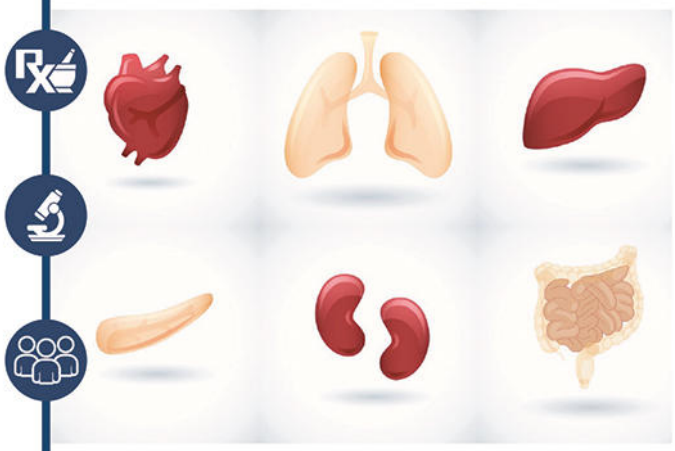

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Article type : Special Issue-Transplant Infectious Diseases

Human Herpesvirus 6, 7 and 8 in Solid Organ Transplantation- Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose.

Abstract

These updated guidelines from the Infectious Diseases Community of Practice of the American Society of Transplantation review the diagnosis, prevention and management of HHV-6A, HHV-6B, HHV-7, and HHV-8 in the pre- and post-transplant period. The majority of HHV-6 (A and B) and HHV-7 infections in transplant recipients are asymptomatic; symptomatic disease is reported infrequently across organs. Routine screening for HHV-6 and 7 DNAemia is not recommended in asymptomatic patients, nor are prophylaxis or

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ctr.13518
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preemptive therapy. Detection of viral nucleic acid by quantitative PCR in blood or CSF is the preferred method for diagnosis of HHV-6 and HHV-7 infection. The possibility of chromosomally-integrated HHV-6 DNA should be considered in individuals with persistently high viral loads. Antiviral therapy should be initiated for HHV-6 encephalitis and should be considered for other manifestations of disease. HHV-8 causes Kaposi's sarcoma, primary effusion lymphoma, and multicentric Castleman disease and is also associated with hemophagocytic syndrome and bone marrow failure. HHV-8 screening and monitoring may be indicated to prevent disease. Treatment of HHV-8 related disease centers on reduction of immunosuppression and conversion to sirolimus, while chemotherapy may be needed for unresponsive disease. The role of antiviral therapy for HHV-8 infection has not yet been defined.

Human Herpesviruses 6 and 7

Etiology and description of the pathogens

Human herpesvirus 6A (HHV-6A), HHV-6B, and HHV-7 are three closely related species within the subfamily *Betaherpesvirinae*. Like other herpesviruses, all three species establish lifelong latent infection in the host following primary infection and may then reactivate and undergo lytic replication in the setting of immunosuppression. HHV-6A and HHV-6B share approximately 90% amino acid identity but are two distinct species and utilize different host cell receptors (CD46 for HHV-6A and CD134 for HHV-6B) (1-3). Although some studies have suggested that HHV-6A exhibits relative neurotropism (4), little is known of how clinical presentation may differ between HHV-6A and HHV-6B, particularly in solid organ transplant (SOT) recipients. Epidemiological factors that differentiate HHV-6A from HHV-6B will be discussed below. However, the two viruses will be referred to under the collective name of HHV-6 when discussing studies in which the viruses were not analyzed separately or

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in areas where differentiation between the two viruses is not known to impact clinical management.

HHV-6A and HHV-6B are unique in their ability to covalently integrate into the subtelomeric region of human chromosomes, resulting in chromosomally-integrated HHV-6 (CIHHV-6) in germ cells (5, 6). When this occurs, HHV-6 DNA is then transmitted to offspring in a Mendelian manner via germ cell lines. Individuals with CIHHV-6 have at least one copy of HHV-6 DNA in every cell and therefore have exceedingly and persistently high levels of detectable HHV-6 DNA in blood and tissue samples, which may complicate interpretation of diagnostic studies (7). CIHHV-6 is estimated to occur in approximately 1% of the general population in the U.S. and Europe, with 2/3 of cases secondary to HHV-6B (8). The impact of CIHHV-6 on transplant remains an important area of study that is further discussed below.

Epidemiology and risk factors

HHV-6A, HHV-6B, and HHV-7 are presumed to be transmitted within the general population via contact with infected saliva (9-12). By adulthood, nearly 90% of individuals are seropositive for both HHV-6 and HHV-7 (12-16). Thus most infections after transplant are thought to result from the reactivation of latent virus; donor-derived transmission of HHV-6, including CIHHV-6, has been reported via hematopoietic stem cell transplant and SOT (17-23).

The estimated prevalence of HHV-6 reactivation among SOT recipients varies widely from 20-82% (17, 24-27), due in part to the variability of diagnostic assays and the inability of some tests to distinguish active from latent infection. The majority of reactivation events in SOT recipients are secondary to HHV-6B (24, 25, 27, 28), although not all prevalence studies

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utilized diagnostic assays that discriminated between HHV-6A and HHV-6B (17, 29, 30). There is less information on the rate of active HHV-7 infection after SOT, with reported rates of reactivation varying widely between 0-46% of recipients (24, 31-33). Reactivation of both HHV-6 and HHV-7 has been reported to first occur most frequently within the first 2-4 weeks SOT (17, 24, 25, 27-29, 34, 35).

Clinical manifestations

The majority of HHV-6 and HHV-7 reactivation events in both pediatric and adult SOT recipients are asymptomatic (28-30, 35). In the context of presumed symptomatic infection, a wide range of clinical signs and symptoms have been attributed to HHV-6 in SOT recipients, including fever, rash, bone marrow suppression, hepatitis, gastroduodenitis, colitis, and pneumonitis (28, 30, 31, 34-42), with fever and bone marrow suppression reported most commonly (43). Limbic encephalitis secondary to HHV-6 is a well-described entity in the stem cell transplant population (44) but seems to be less common in the SOT population (35, 45, 46). CIHHV-6 does have the potential to reactivate and result in symptomatic disease (6, 47-50). However the limited data available from SOT populations suggest that clinically apparent disease secondary to CIHHV6 is uncommon in these patients (51, 52). Clinically-apparent HHV-7 disease seems to be infrequent among SOT recipients and has been reported to result in non-specific febrile syndrome with thrombocytopenia and bone marrow suppression (53-55).

Pediatric patients who undergo transplant during the first few years of life are theoretically more likely to acquire primary HHV-6 or HHV-7 infection post transplant. 24% of children were diagnosed with primary HHV-6 infection in one study of 80 young pediatric heart, kidney, and liver recipients; only three children in the entire study cohort were presumed to

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be HHV-6 uninfected by the end of the study period (35). Although mean peak HHV-6 viral load (utilizing quantitative polymerase chain reaction [PCR] that did not differentiate HHV-6A from HHV-6B) was significantly higher among children with primary infection, children with primary infection were no more likely to have symptoms attributable to HHV-6 compared to children with reactivation. The duration of HHV-6 DNAemia did not differ significantly between children with primary infection compared to those wtih viral reactivation (35). Signs and symptoms attributed to primary or reactivated HHV-6 infection in this study included fever, diarrhea, rash, seizures, lymphopenia, and elevated alanine aminotransferase level. A study of HHV-6 DNAemia among pediatric liver transplant recipients reported symptoms attributable to HHV-6 to be infrequent and included vomiting, lethargy, splenomegaly, and bone marrow suppression (30). Limited data from pediatric liver transplant recipients suggest that both HHV-7 DNAemia and symptomatic HHV-7 disease, either secondary to primary infection or reactivation, is uncommon among transplanted children (33).

Several studies have attempted to investigate immunomodulatory properties of HHV-6 and HHV-7 that may potentiate risk of opportunistic infection and allograft rejection. Epidemiological associations have been reported between HHV-6 and fungal infections (56-58), early fibrosis due to hepatitis C virus recurrence after liver transplant (59, 60), and greater risk of mortality rate after liver (57, 61) and heart-lung transplant (58). Both HHV-6 and HHV-7 have been detected in bronchoalveolar lavage fluid, although it is not clear if viral detection contributes to bronchiolitis obliterans syndrome after lung transplant (62, 63). HHV-6 and HHV-7 infections have also been associated with allograft rejection and dysfunction (26, 64, 65), but the presence of CMV may confound the reported associations.

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Studies have suggested an association between HHV-6 and HHV-7 reactivation and increased risk of CMV disease among adult kidney and liver recipients (31, 32, 64, 66-69), but it is unclear if HHV-6 and 7 infection truly potentiates CMV disease or if the presence of these viruses instead represents more intensive immunosuppression and its attendant risk of CMV. Among a subset of adult SOT recipients with CMV disease who received CMV-directed antiviral therapy as part of a multicenter, prospective clinical trial, HHV-6 and HHV-7 infections were detected among nearly 17% of subjects (70). HHV-6 and HHV-7 infections were not associated with time to CMV disease resolution or risk of CMV recurrence and in general did not seem to impact the clinical course of CMV disease. These results suggest that evaluation for HHV-6 or HHV-7 infection in the setting of CMV disease is not routinely indicated, and detection of co-infection is unlikely to impact CMV clinical course or management. HHV-6 DNAemia was not associated with increased risk of subsequent CMV DNAemia in pediatric liver transplant recipients (28, 30) and was not associated with increased risk of CMV DNAemia or graft rejection in a cohort of pediatric heart, kidney, and liver transplant recipients (35).

Limited data suggest that CIHHV-6 may exert indirect effects post transplant. Liver transplant recipients who were known to have CIHHV6 prior to transplant were subsequently at greater risk for bacterial infection when compared to a cohort without CIHHV6 but were not at significantly greater risk for other opportunistic infections graft rejection (52).

Diagnostic strategies

Diagnostic tests for HHV-6 and HHV-7 include serology, culture, histopathology with immunohistochemistry, antigenemia, and nucleic acid amplification tests (typically PCR). Given the ubiquitous nature of infection and the limitations of serological assays in

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immunocompromised hosts, serology is minimally informative in SOT recipients (24, 55, 71). Viral isolation in cell culture is highly specific for active infection (72, 73) but is not widely available through most laboratories and thus is not routinely recommended.

For suspected HHV-6 disease, tissue biopsy may be performed where possible to confirm the diagnosis or rule out other etiologies. Immunohistochemistry to detect viral antigens in biopsy specimens (26, 37, 74) is of minimal clinical utility as it is not widely available, and HHV6 antigens may be detected in tissue in the absence of symptoms (75, 76).

Antigenemia assays have largely been supplanted by quantitative PCR (71, 72), which is the preferred assay for the detection of HHV-6 and HHV-7 DNAemia and presumed active infection after SOT**.** Quantitative PCR may be helpful in diagnosing active infection and in monitoring response to intervention. PCR can be used to quantify HHV-6 and HHV-7 DNA from peripheral blood mononuclear cells (PBMC), plasma, serum, and whole blood. PCR may also be used to detect HHV-6 and HHV-7 DNA from tissue, bronchoalveolar lavage fluid, and cerebrospinal fluid. Many clinical and translational studies have utilized PCR for the U38 gene common to both HHV-6A and HHV-6B to diagnose HHV-6 DNAemia without differentiating between the two variants (29, 30, 35, 72), but variant-specific PCR is available as well (73, 77, 78). Quantitative PCR is preferred over qualitative for both HHV-6 and HHV-7, as a single test result with a low viral load may indicate a false positive result (72), and very high, sustained HHV-6 viral loads may suggest CIHHV6 (8). Quantitative PCR from plasma or serum is widely available and is preferred over whole blood or PBMC for diagnosis of active infection; these fluids are relatively cell-free but may still contain viral DNA from lysed cells (79). Quantitative HHV-6 DNA PCR from plasma is reported to be approximately 84% specific for actively replicating virus (72).

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It is important to note that PCR assays available for both HHV-6 and HHV-7 are limited by a lack of standardization and validation. A study using serum samples spiked with known concentrations of HHV-6A DNA found significant variability of viral loads among different PCR assays (80). Data are also insufficient to determine the level of detectable HHV-6 or HHV-7 DNA in a biological sample that should be considered clinically significant in SOT recipients.

Interpretation of PCR assays is also complicated by the fact that detection of HHV-6 or HHV-7 DNA does not confirm causality in a given clinical syndrome (81) and may occur even in otherwise immunocompetent patients in the setting of sepsis or other severe disease (82). HHV-6 DNA has been detected in CSF from both immunocompromised and immunocompetent patients in the absence of neurological dysfunction (83, 84), thus the diagnosis of HHV-6 encephalitis should be considered in the context of both clinically-compatible symptoms and detection of HHV-6 DNA in CSF. Characteristic changes observed by magnetic resonance imaging (MRI) may also support the diagnosis (85). Although at least one study as reported higher HHV-6 CSF viral loads among SCT recipients with HHV-6 encephalitis, the threshold CSF viral load that best correlates with diagnosis is unknown (84). In general, diagnostic testing for HHV-6 or HHV-7 should be limited to scenarios where symptomatic infection is plausible, and to assist in guiding treatment decisions. The diagnosis of symptoms directly related to HHV-6 or HHV-7 requires the careful exclusion of other etiologies.

The infrequent but well-described phenomenon of CIHHV6 should also be considered when interpreting HHV-6 viral loads. Recognition of CIHHV is important in order to avoid unnecessary antiviral therapy among individuals who have persistently elevated HHV6 viral

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loads but no clearly attributable symptoms (51). CIHHV6 is suggested by extremely and persistently elevated HHV-6 viral loads that show minimal fluctuation when followed over time (8). Although persistent elevation of plasma or serum viral load may suggest the possibility of CIHHV, the diagnosis is more certain when the viral load is assayed in whole blood or isolated PBMC (8). Because individuals with CIHHV have at least one HHV-6 genomic copy per white blood cell, these individuals typically have HHV6 viral loads in whole blood or PBMC of at least 5.5 $\log_{10}$ copies/ml (7, 8, 86, 87). Testing of hair follicles or nails or use of fluorescence *in situ* hybridization (FISH) have been used to confirm CIHHV (87, 88) but are labor intensive and typically not necessary for establishing the diagnosis (8). Thus individuals with CIHHV may be identified by persistent elevation of viral load from whole blood or PBMC (8) or through use of droplet digital PCR (89-91), with testing of family members or other more specific diagnostic modalities as needed.

Treatment

The majority of HHV-6 and HHV-7 infections are subclinical and transient, thus treatment of asymptomatic DNAemia is not recommended. Treatment directed against HHV-6 should be initiated in the setting of HHV-6 encephalitis. Treatment should be considered for other clinical syndromes attributable to HHV-6 and HHV-7. Especially in cases of moderate or severe disease attributed to HHV-6 or HHV-7, antiviral treatment may be complemented by reduction in pharmacologic immunosuppression.

It should be noted that there are no antiviral compounds licensed for HHV-6 or HHV-7 infections, and there are no randomized, controlled trials demonstrating antiviral efficacy for the treatment of HHV-6 or HHV-7-related disease in SOT recipients. Recommendations for use of antivirals in the setting of HHV-6 and HHV-7 are based on *in vitro* data and limited

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clinical reports. *In vitro* data suggest similar antiviral susceptibility patterns for HHV-6A and HHV-6B (92). Ganciclovir, foscarnet, cidofovir, and brincidofovir all inhibit HHV-6 replication *in vitro* at clinically-achievable concentrations (91, 93, 94); cidofovir and foscarnet seem to exhibit more potent activity *in vitro* (91). HHV-6 appears resistant to acyclovir (93). Ganciclovir resistance may occur through mutations of the U69 and U28 HHV-6 genes (95, 96), and a mutation of the HHV-6 U38 gene resulting in cidofovir resistance has also been reported (97). Ganciclovir, foscarnet, and cidofovir have all been utilized in SOT recipients in the setting of HHV-6 infection (22, 28, 98-100) and may be used for treatment of HHV-6 disease. Use of both ganciclovir and foscarnet has been associated with reduction of HHV-6 viral load in both serum and cerebrospinal fluid in SCT recipients with HHV-6 encephalitis, although response to antivirals was not universal in this study (44). Valganciclovir has been used in adult liver transplant recipients with HHV-6 DNAemia (29), but data are insufficient to support its use in severe disease such as encephalitis.

Cidofovir and foscarnet inhibit HHV-7 replication *in vitro* (91). HHV-7 appears resistant to ganciclovir and acyclovir *in vitro* and does not seem to be inhibited by clinically achievable concentrations of ganciclovir (93, 101). Foscarnet and cidofovir have been used for treatment of HHV-7 infection in SOT recipients and may be used for treatment of HHV-7 disease.

Adoptive immunotherapy for severe HHV-6 disease with cytotoxic T-lymphocytes has been used in an investigational setting, primarily among the stem cell transplant and primary immune deficiency populations (102, 103).

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Prevention: prophylaxis and pre-emptive therapy

Specific antiviral prophylaxis or pre-emptive therapy directed against HHV-6 and HHV-7 is not recommended, nor is routine monitoring for HHV-6 and HHV-7 DNAemia post transplant, as the vast majority of infections after SOT are subclinical, even among pediatric patients who are suspected to have primary infection (28-30, 35). Although some studies have suggested a decreased risk of HHV-6 infection in the setting of CMV prophylaxis (54, 104), other studies in both adult and pediatric SOT recipients found that both HHV-6 and HHV-7 DNAemia occur frequently with doses of ganciclovir and valganciclovir typically used for both CMV prophylaxis and treatment (29, 35, 54, 70, 101).

Research and future areas of investigation

Large, prospective, and ideally multicenter studies are needed to accurately quantify the burden of disease that is truly attributable to HHV-6 (including CIHHV-6) and HHV-7 in SOT recipients and to elucidate the underlying host-viral mechanisms that may contribute to indirect effects on patient outcomes and graft function. These studies could also provide further evidence to support or disprove the need for preemptive monitoring after transplant. Randomized, controlled trials are needed to assess the efficacy of various antivirals and to evaluate the safety and efficacy of immunomodulatory therapies, including adoptive immunotherapy.

HHV-6 and HHV-7 recommendations and level of evidence

Diagnosis

Serological studies for HHV-6 and HHV-7 are not recommended in the evaluation of SOT candidates or recipients **(strong, low).**

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Culture, while highly specific for active infection, is not widely available and is not routinely recommended **(strong, low)**.

For suspected HHV-6 disease, tissue biopsy may be performed where possible to confirm the diagnosis or rule out other etiologies **(weak, low).**

Detection of viral nucleic acid by quantitative PCR in blood or CSF is the preferred method for diagnosis of HHV-6 and HHV-7 infection and is recommended over antigenemia assays **(strong, moderate)**.

Viral nucleic acid may also be detected from bronchoalveolar lavage fluid and tissue by PCR and may be informative performed in the appropriate clinical context **(weak, low).**

Diagnostic testing for HHV-6 or HHV-7 should be limited to scenarios where symptomatic infection is plausible, as detection of viral nucleic acid or antigen may be insufficient evidence of disease in the absence of clinically compatible symptoms **(strong, moderate)**.

CIHHV6 should be a consideration in individuals with persistent, high grade DNAemia and may be diagnosed by serial monitoring of viral load by PCR of whole blood or PBMC or by droplet digital PCR **(strong, low)**.

Treatment

The majority of HHV-6 and HHV-7 infections are asymptomatic, transient, and do not require antiviral treatment **(strong, moderate)**.

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Antiviral treatment with foscarnet, ganciclovir, or cidofovir should be initiated in the setting of HHV-6 encephalitis **(strong, moderate).**

Treatment should be considered for other syndromes attributable to HHV-6 or HHV-7 **(weak, low)**.

Especially in cases of moderate or severe disease, antiviral treatment may be complemented by reduction of immunosuppression **(strong, low)**.

Prevention

Antiviral prophylaxis and preemptive antiviral therapy for HHV-6 or HHV-7 infections are not recommended after transplant **(strong, low)**.

Routine monitoring for HHV-6 and HHV-7 infections after SOT is not recommended **(strong, low).**

HHV-8

Etiology and description of the pathogen

Human herpesvirus 8 (HHV-8), or Kaposi's sarcoma herpesvirus (KSHV), gained increased attention in the height of the acquired immune deficiency syndrome (AIDS) epidemic as Chang et al first discovered it as the etiologic agent of Kaposi's sarcoma (KS) in 1994(105). Four variants have been described: classic, endemic, iatrogenic or immunosuppression-associated, and epidemic or AIDS-associated(106). Soon after, HHV-8 was found to be the causative agent of primary effusion lymphoma (PEL) and forms of multicentric Castleman disease (MCD)(107, 108). HHV-8 has also been associated with severe, non-neoplastic

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complications such as hemophagocytic syndrome, pancytopenia, hepatitis and KS-associated herpesvirus inflammatory cytokine syndrome in SOT recipients(109, 110).

HHV-8, a DNA gammaherpesvirus, exhibits both latent and lytic phases. Primarily infecting B-cells, macrophages, endothelial ("spindle cells" in KS lesions) and epithelial cells, the virus can establish lifelong latency after acute infection. The viral and host complexities influencing lytic replication, ultimately resulting in production of infectious virions, have not been fully elucidated. However, lytic activation by inflammatory cytokines, coinfecting viruses, oxidative stress and tissue hypoxia have been described(111), (112). Host immunity, mediated through CD4+ and CD8+ T-cell responses, plays a critical role in controlling HHV-8 replication and is necessary for post-transplant KS (PT-KS) regression, (113), (114). Clinically, the role of this cellular mediated immune control of HHV-8 has been supported by observed regression of KS after immune-reconstitution with antiretroviral therapy in AIDS patients and after reduction of T-cell specific immunosuppression in SOT recipients(106, 114-116). The virus encodes for specific gene products such as latency associated nuclear antigen 1 (LANA-1), a viral analogue of human interleukin-6 (vIL-6), and microRNAs which help the virus evade host innate and adaptive immune responses. Eventually this interferes with cell cycle and apoptosis control creating an inflammatory milieu supporting tumor growth and angiogenesis(117). Though latently-infected cells contribute to a majority of HHV-8 associated cancers, lytic replication is also suspected to promote tumorigenesis and is indirectly supported by observed decreased risk of KS development among patients receiving antiviral therapy(118-121). Transmission of virus occurs primarily through saliva but may be transmitted sexually through semen and cervicovaginal secretions, vertically through breast milk, by intravenous drug use or blood transfusion, and through transplant (122-124).

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Epidemiology and risk factors

Rates of HHV-8 infection and seropositivity demonstrate significant geographic diversity as well as subgroup and transmission pattern heterogeneity. Furthermore, lack of a standard serological test obfuscates true seroprevalence estimates. In the United States (US) an estimated 3-7% of blood donors are seropositive but with minimal rates of HHV-8 DNA detected(125). Similarly low seroprevalence has been reported in northern European, southeast Asian, and Caribbean countries(126). Higher rates of HHV-8 seropositivity are found in the Middle East, Mediterranean (5-20%) and sub-Saharan Africa (>50%)(127, 128). Globally, the pooled seroprevalence among men who have sex with men (MSM) has recently been estimated to be 33% and over 40% among MSM who are infected with human immunodeficiency virus (HIV) (129).

Unsurprisingly, rates of KS mirror global HHV-8 seroprevalence. The incidence of KS among the general population is low(130). World-wide, the incidence of PT-KS appears to have risen in the modern era though a recent registry study suggests an overall decrease in incidence in the US specifically(130, 131). In endemic regions, PT-KS comprises 35-87.5% of all post-transplant neoplasms but accounts for less than 10-15% in parts of Europe and the US(132-134). Cumulative incidence of PT-KS ranges from 0.3-0.8% in non-endemic regions to 3.2-5.3% in endemic regions(132-138). Geographic areas within countries with diverse subpopulations and varied donor and recipient HHV-8 seroprevalence, such as Italy and Spain, may demonstrate different transplant center-specific PT-KS rates(136, 137, 139). Further, as the US foreign-born population grows, donors and recipients from HHV-8 endemic areas may become more common. The reported incidence per 100,000 person years is highest in kidney recipients than liver or heart recipients with cases in lung transplant recipients being least common (130).

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Post-transplant HHV-8 seroconversion in endemic areas may be seen in 14-33% of patients, with DNAemia detected in a minority of patients(140, 141). Similarly, a recent study from north central Italy prospectively screening donors and recipients found that 4% of donors and 18% of recipients were HHV-8 seropositive, and 25% of serologically mismatched recipients seroconverted within 6 months. Reactivated HHV-8 post-transplant was seen in 2.1%, and one individual developed PT-KS(136). Though donor transmission has been well described, and serologic mismatch is a known risk for primary recipient disease, HHV-8 DNAemia in the post-transplant setting is most commonly from reactivated virus(136, 142-144). Among liver allograft recipients, donor transmission events are more frequent and may present earlier with more aggressive disease when compared to recipients of other organs. (124, 137, 140, 144, 145). This may relate to the liver's size and vascularity or suggest the presence of a larger hepatic reservoir of infected cells.

The risk of KS in the SOT population is also low but is still at least 200 to 500-fold greater than that observed in the general population (146-148). Though HHV-8 seropositivity is the key risk factor for PT-KS, other factors include HLA-B mismatching, African or Middle Eastern origin, lung transplant, older age at transplant and receipt of antilymphocyte agents(113, 114, 131, 143, 146, 149). As more HIV positive recipients are being transplanted worldwide, and as HIV positive donor organs are being recovered more frequently in the setting of the HIV Organ Policy Equity (HOPE) Act, the epidemiology of HHV-8 related diseases may evolve and further risk factors may be identified. Recent case reports of PT-KS and other HHV-8 related diseases in HIV positive transplant recipients have been described(150, 151). The ongoing opioid epidemic in the United States has contributed to an increase in donors classified as Public Health Service (PHS) increased

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risk (152). Though donors defined as PHS increased risk, particularly those who inject drugs, may have an increased risk of HHV-8 infection, the actual prevalence and subsequent transmission risk amongst this donor group is unknown.

KS after a kidney transplant does not automatically preclude re-transplant. A recent retrospective review from France found a 25% (2/8) KS recurrence rate after a second kidney transplant in those patients who had PT-KS after their first transplant. This was similar to the rate of primary KS among first-time transplants, and disease resolved in both recipients with tapering of immunosuppressive medications. A longer delay from KS remission to second transplant may be associated with a lower recurrence risk(153).

Clinical manifestations

Patients infected with HHV-8 can present with both neoplastic and non-neoplastic manifestations concomitantly, and associated DNAemia may be infrequent(113, 114, 141, 154, 155). The severity, timing and type of HHV-8 related disease may differ by organ transplanted, with thoracic and liver transplant recipients more commonly presenting with more severe signs and symptoms(140, 156). Patients may present with mild signs and symptoms of fever, maculopapular rash, lymphadenopathy, and cytopenias(157). However, HHV-8 associated lymphoproliferative B-cell disorders, clonal gammopathies, hepatitis, fatal bone marrow failure, and hemophagocytic syndromes have been reported(144, 154, 155, 158-161). Recently Mularoni et al. described a case of KS-associated inflammatory cytokine syndrome (KICS) in a liver-kidney transplant recipient(109). Proposed clinical criteria for this syndrome, which is recognized in HIV positive patients, include a constellation of clinical symptoms, radiographic and histologic abnormalities, cytokine profiles,

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inflammatory biomarkers and other laboratory abnormalities and can result in fatal organ damage(109).

PT-KS is the most commonly reported HHV-8 related disease and neoplastic manifestation after SOT. On average, PT-KS presents within 13 months (3 – 16 months) after transplant and peaks within one year but may present many years after transplant(131, 146, 148). Onset also varies by organ transplanted, with earlier presentation seen after liver transplant when compared to kidney transplant(137). A majority of PT-KS lesions involve skin of the extremities and trunk and mucosal surfaces of gingiva, and hard and soft palates and has been associated with cutaneous squamous cell carcinoma(131, 132, 162). Visceral involvement occurs in 10% of PT-KS, with 50% occurring in liver transplant recipients which may directly involve the allograft(163). Mortality rates up to 60% have been described(164).

MCD is characterized by B-cell transformation to plasmablasts, which subsequently infiltrate multiple lymph nodes and distort their architecture. It can be seen after primary HHV-8 infection or reactivation and typically presents with fevers, lymphadenopathy, hepato-splenomegaly, and cytopenias. MCD is commonly associated with increased IL-6 and IL-10 production(165, 166). Less commonly, primary effusion lymphoma, an HHV-8 driven, non-Hodgkin, body cavity lymphoma, has been reported after SOT. PEL can involve the serosal surfaces of the pleura, pericardium and peritoneum and carries a significant 1-year mortality(167).

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Diagnostic Strategies

Historically, serologic testing with indirect immunofluorescence assays (IFA), enzyme-linked immunosorbent assays (ELISA) and Western blot assays targeting both HHV-8 latent and lytic viral antigens have variable sensitivity and specificity ranging from 60-100%, with poorer performance seen in lower seroprevalence populations(168, 169). In a recent multicenter, prospective evaluation of six HHV-8 serological assays (four IFAs and two ELISAs), only two of six lytic antigen-based IFAs demonstrated agreement with the predefined reference standard(136). Given the lack of standardization, as well as variable sensitivity and specificity, serological assays are of limited utility for the diagnosis of HHV-8 related disease **.**

Globally, HHV-8 serologic testing is not routinely included in pre-transplant screening, with low rates of donor and recipient screening reported (27.3% and 11.4% respectively) even in endemic areas(170). In endemic areas, universal donor and recipient screening may be useful to assess the risk of post-transplant HHV-8 disease but is not recommended in regions with low seroprevalence. Targeted screening of at-risk donors and recipients or those from endemic regions may be considered in low seroprevalence areas though seropositivity is not a routine contraindication to transplant. All pre-transplant HHV-8 serologic tests should be cautiously interpreted as performance may vary widely depending on assay characteristics and antigen preparations (136, 168).

When HHV-8 syndromes are suspected, biopsy tissue of involved sites (e.g. tumor tissue for KS, lymph node for MCD, pleural or ascitic fluid for PEL) should be obtained for histopathology with HHV-8 immunohistochemical staining and *in situ* hybridization or viral PCR testing to aide in diagnosis(171). Characteristic spindle-shaped cells along with latency

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associated nuclear antigen (LANA) and CD34 positive staining are common features of PT-KS lesions(172, 173).

Quantitative PCR from clinical samples may be useful for the diagnosis of HHV-8 related disease and is the preferred method to detect actively replicating virus(171). HHV-8 DNA testing has been performed on plasma and peripheral blood mononuclear cells (174). However, performance characteristics of different nucleic acid amplification assays can be limited by inconsistent standardization and varied testing modalities and may not be directly comparable across laboratories(136)(130, 157, 164). Though quantitative viral load is not a sensitive method to diagnose KS, MCD or PEL, it may be used in conjunction with the clinical-pathologic presentation to support the diagnosis and management of these HHV-8 related diseases (143, 175) (109, 165, 176-179).

When PT-KS is diagnosed, further workup including imaging and invasive investigative procedures (e.g. bronchoscopy, esophagogastroduodenoscopy, colonoscopy) may be warranted for disease staging. Two staging strategies have been proposed(180, 181). Non-neoplastic clinical syndromes similarly rely on clinical-pathologic patterns including DNAemia and detection of virus in involved tissues, as well as the exclusion of other mimickers and co-infections.

Treatment

The initial approach to management of neoplastic and non-neoplastic HHV-8 associated disease relies on careful reduction or cessation of pharmacologic immunosuppression, though evidence to support efficacy in MCD or PEL is limited to case reports(114, 144, 165, 182-184). Decreasing immunosuppression alone can result in complete remission in up to 30% of

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patients with PT-KS(182). Severity of disease, organ transplanted, and risk of rejection should be used to guide the extent to which immunosuppressive therapy is tapered. When possible, immunosuppressive regimens containing calcineurin inhibitors (CNI) should be switched to mammalian target of rapamycin (mTOR) inhibitors such as sirolimus in the setting of HHV-8 related disease, particularly PT-KS. Though KS regression has been routinely described with mTOR inhibitors, their use may also be associated with a decreased risk of post-transplant malignancy(185, 186). In addition to their role in inhibiting T-cell proliferation in transplant recipients, mTOR inhibitors promote antiangiogenic effects by impairing the expression and function of vascular endothelial growth factor (VEGF) and interfere with virus-specific pathways needed for viral replication(139, 187-191). Interestingly, conversion of CNI to sirolimus has also been associated with simultaneous HHV-8 specific cytotoxic T-cell recovery(110, 114). Though antiproliferative effects of mTOR inhibitors may be beneficial, cases of PT-KS while on sirolimus have been reported(192).

Though ganciclovir, foscarnet, cidofovir, may exhibit antiviral activity *in vitro*, and successful use of these agents for HHV-8 related disease has been reported, no prospective, controlled trials have been performed to demonstrate efficacy in the post-transplant setting(155, 193-195). Therefore, antivirals should not be routinely used for HHV-8 related disease.

Oncology consultation should be pursued for patients with lesions that do not respond to immunosuppression reduction or conversion to sirolimus. Topical or intralesional chemotherapy, and radiation may be used, as well as cytotoxic chemotherapy for severe or visceral disease. Most commonly liposomal anthracyclines, doxorubicin or daunorubicin, are

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used as first line systemic chemotherapeutic agents in AIDS-related KS. Other agents such as paclitaxel, vincristine, vinblastine, bleomycin and etoposide have been used and promising studies evaluating pomalidomide, bevacizumab, sorafenib and imatinib are ongoing(196). Treatments for MCD and PEL are even more limited by the lack of robust, quality studies. Rituximab, an anti-CD20 agent, used for MCD treatment in non-transplant patients, has shown promise and may improve survival(197). Given the rarity of PEL, limited treatment studies exist. However, chemotherapy remains the first-line therapy as permitted by functional status and comorbid conditions(198). Case reports using antiviral medications (both systemic and intracavitary in PEL) coupled with immunosuppression reduction or CNI to mTOR inhibitor conversion have reported successful outcomes in MCD and PEL(165, 167, 197). Also, treatment of HHV-8 DNAemia and non-neoplastic manifestations using different antiviral agents as well as rituximab has been described and may be effective(109, 157, 160).

HHV-8 specific T-cell mediated immunity (CMI) monitoring in the setting of resultant neoplastic and non-neoplastic disease presentations may allow more precise and personalized immunosuppressive management and dynamics may correspond with disease progression or resolution(109, 113, 114). Though data aiming to define the role of the HHV-8 CMI are promising, there is no compelling evidence at this time to support the use of adoptive immunotherapy for the treatment or prevention of HHV-8 related diseases. Recent studies have suggested a role for therapeutic autologous cytomegalovirus (CMV) specific T-cells for the treatment of resistant or refractory CMV infections, providing hope for similar precision therapy for viruses such as HHV-8(199).

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Prevention

Post-transplant HHV-8 viral load testing may be used as part of a disease monitoring and prevention strategy in seropositive recipients or seronegative recipients with seropositive donors in high seroprevalence areas (136, 141, 175)**.** However, a clinically relevant quantitative viral load "cut off", optimal testing frequency and surveillance period duration post-transplant have not been defined. More frequent monitoring in mismatched recipients (D+/R-) in the first 3-6 months can be considered(136). In HIV-infected patients ganciclovir and valganciclovir have been shown to inhibit HHV-8 replication and decrease KS incidence(193, 200). However, using prophylactic or pre-emptive antivirals to prevent HHV-8 related disease in SOT recipients has not been well studied. Lowering immunosuppression in the setting of viral reactivations or primary infection is recommended to encourage recovery of HHV-8 specific T-cell immunity. Additionally, given mTOR inhibitors' association with lower post-transplant malignancy, antiangiogenic effects, inhibition of viral replication, and HHV-8 specific cytotoxic T-cell recovery, conversion to sirolimus may be helpful in high risk patients with HHV-8 DNAemia, though no evidence of efficacy currently exists(114, 139, 187, 188). Generally, monitoring of skin and mucosal surfaces through meticulous physical examination should also be routine in high risk patients.

Research and future areas of investigation

Further prospective trials are required to more carefully evaluate the specific role of HHV-8 donor and recipient screening in endemic areas. Additionally, determining the need for screening and defining such strategies outside of endemic regions will become more important as global population migration expands and HIV infected donors are recovered and recipients transplanted. Similar evolution of the PHS increased risk donor landscape in the

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United States and potential HHV-8 transmission risk remain to be explored. Optimal serologic screening relies on development of accurate, precise, and cost-effective tests. Though recent studies have demonstrated progress continued study is needed. In at-risk transplant recipients, strategic approaches to post-transplant viral load monitoring including validation of clinically significant viral load thresholds, monitoring intervals and surveillance durations are needed to understand the role in preventing and predicting HHV-8 disease manifestations. The utility of antiviral drugs and mTOR inhibitors for prevention and treatment HHV-8 after SOT needs prospective evaluation in large trials. As our understanding of dynamic HHV-8 CMI develops, studies evaluating the function of immune-monitoring strategies are necessary. These studies should further investigate alteration of immunosuppression and influence of mTOR inhibitors on HHV-8 CMI and disease correlation. Similar to recent use for CMV therapy, the feasibility and safety of HHV-8 viral-specific T-cells used for HHV-8 disease in SOT needs further study.

HHV-8 recommendations and level of evidence

Diagnosis

Serology is of limited utility in the diagnosis of acute HHV-8 related disease post-transplant **(strong, low)**.

In endemic regions pre-transplant donor and recipient HHV-8 serologic screening may be helpful to stratify disease risk after transplant **(weak, low)**.

Targeted pre-transplant HHV-8 serologic screening of at-risk donors and recipients or those from endemic regions may be considered in low seroprevalence regions **(weak, very low)**.

Direct detection of HHV-8 from involved sites using immunohistochemical testing, in situ hybridization, or viral PCR is useful for diagnosis of HHV-8 related disease **(strong, moderate)**.

Quantitative PCR from clinical samples can detect active HHV-8 replication and may be useful for the diagnosis of HHV-8 related disease **(strong, low)**.

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Quantitative PCR can be used to monitor treatment response in post-transplant patients with HHV-8 related diseases (KS, MCD, PEL) **(weak, very low)**.

PT-KS disease staging including imaging and invasive investigative procedures (e.g. bronchoscopy, esophagogastroduodenoscopy, colonoscopy) should be considered **(weak, low)**.

Treatment

Judicious reduction or cessation of immunosuppressive therapy should be first line therapy for patients with HHV-8 related disease **(strong, low)**.

Calcineurin inhibitor containing immunosuppressive regimens should be converted to mTOR inhibitors (mainly sirolimus) **(strong, low)**.

Antivirals should not be routinely used to treat HHV-8 related disease **(weak, low)**.

PT-KS unresponsive to reduction of immunosuppression or CNI to sirolimus conversion and severe or visceral disease may benefit from chemotherapy **(strong, low)**.

Prevention

In HHV-8 seropositive recipients or those who receive an organ from a seropositive donor, viral load monitoring may be useful to predict clinical HHV-8 disease **(weak, low)**.

Reduction of immunosuppression in the setting of viral reactivations or primary infection and avoiding over immunosuppression in at risk recipients may be beneficial **(weak, low)**.

Acknowledgement: This manuscript was modified from the Guideline included in the 3rd Edition of the AST Infectious Diseases Guidelines written by Jade Le and Soren Gantt published in the American Journal of Transplantation 2013;13 (Suppl 4): 128-137, and endorsed by the American Society of Transplantation.

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