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Special Article

Human Herpesvirus 6, 7 and 8 in Solid Organ Transplantation

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Abbreviations: CI, chromosomally integrated; CMV, cytomegalovirus; CNI, calcineurin inhibitor; HHV, human herpesvirus; IL, interleukin; KS, Kaposi sarcoma; MCD, multicentric Castleman disease; mTOR, mammalian target of rapamycin; NK, natural killer; PEL, primary effusion lymphoma.

Human Herpesviruses 6 and 7

Epidemiology and risk factors

Human herpesvirus (HHV)-6A, HHV-6B and HHV-7 arelymphotropicβ-herpesviruses that are almost universally acquired during the first few years of life and establish latency in mononuclear cells, which eventually serve as reservoirs for endogenous viral reactivation during times of immune suppression or as potential vectors of transmission to susceptible individuals (1). In less than 1% of infected individuals, HHV-6 persistence occurs as a result of integration of the virus into the host chromosome, a condition known as chromosomally integrated CI-HHV-6 (2,3), with as yet undefined clinical significance (4,5). Previously felt to be two variants of the same virus, HHV-6A and HHV-6B were recognized as two distinct viruses by the International Committee on Taxonomy of Viruses in 2012, due to increasing virologic and epidemiologic evidence to support this distinction (6). HHV-6B has been implicated in most primary infections in children (7,8) and reactivation events after transplantation (9), whereas HHV-6A predominates in the lymph nodes of HIV-infected adults (10). Compared to HHV-6, less is known about the clinical implications of HHV-7 infection.

Primary HHV-6 and HHV-7 infections in immunocompetent children range from asymptomatic to self-limited febrile illnesses with rash, diarrhea, respiratory symptoms, or seizures (7,11–13). Transmission of HHV-6 and HHV-7 are thought to occur through saliva (14–16) or perinatally (17,18). Seroconversion occurs within the first 6–24 months of age for HHV-6 (7,17) and by 3 years for HHV-7 (19,20). However, an HHV-6 mononucleosis-like illness has been reported in adults (21,22) and primary infections of HHV-6 and HHV-7 can also occur in solid organ transplant recipients through allograft-transmission (23) or as a result of natural transmission in the community (24,25). Because seroprevalence studies typically show that over 90% of adults are infected with both viruses (1,11,17,19), most infections after transplantation are thought to result from the reactivation of endogenous latent virus (26,27). The estimated rates of HHV-6 reactivation after solid organ transplantation have varied widely between 20–82% (9,28–30), due to the variation of the diagnostic assays used and the inability of some tests to distinguish active from latent infection. In one review, HHV-6 infections were mostly reported in heart and lung (66–91%), liver (22–54%) and kidney (23–55%) transplant recipients, with few reports in kidney–pancreas and intestinal transplant recipients (31). There is less information on the rate of active HHV-7 infection after solid organ transplantation, though it has been estimated to occur in 0–46% of patients (9). Reactivation of both viruses occurs relatively early, generally within the first 2–4 weeks after solid organ transplantation (9,28,29,32,33).

Active infection by HHV-6 and HHV-7 in solid organ transplant recipients is usually asymptomatic. Overt clinical disease directly due to HHV-6 is estimated to occur in less than 1% of solid organ transplant recipients (27,32), reportedly causing fever and rash (34), hepatitis (35), gastroduodenitis (36,37), colitis (38,39), pneumonitis (34,40,41), and encephalitis (42). It may also present as a CMV-like syndrome, with fever and some degree of bone marrow suppression (43,44). Acute HHV-6 infection has also developed in patients who received liver transplantation for HHV-6 associated acute fulminant liver failure (45). Although HHV-6B causes more infections in transplant recipients, HHV-6A has been associated with giant cell hepatitis (35) and fatal disease in two renal transplant recipients (23,46). Of all the reported cases thus far, CI-HHV-6B is seen more commonly in solid organ transplant recipients whereas CI-HHV-6A has been described in hematopoietic stem cell transplant recipients, but the clinical significance is unclear (47). In contrast to HHV-6, symptomatic disease

due solely to HHV-7 to date has not been documented in heart (48), intestinal (49) or renal (50) transplant recipients, and the clinical associations in liver transplant recipients are controversial (51,52).

In addition to the direct effects described above, HHV-6 and HHV-7 appear to have immunomodulatory properties that result in important indirect effects on viral co-infections, fungal infections and allograft rejection. Both HHV-6 and HHV-7 have been associated with an increased risk of CMV disease (40,48,53–60). HHV-6 has also been associated with fungal and other opportunistic infections (61–63), early fibrosis due to hepatitis C virus recurrence after liver transplantation (64,65), and a higher mortality rate after liver (62,66) and heart–lung transplantation (63). HHV-6 and HHV-7 infections have been associated with allograft rejection and dysfunction (51,56,67,68), but the presence of CMV may confound the association. In addition, both HHV-6 and HHV-7 have been detected in bronchoalveolar lavage fluid (69), though the association between virus detection and bronchiolitis obliterans syndrome after lung transplantation is controversial (70,71). Although CI-HHV-6 has not been clearly associated with a clinical syndrome, there are data suggesting indirect effects. For example, a significantly higher rate of bacterial infections in liver transplant recipients (71.4% vs. 31.4%; $p = 0.04$) was noted among those with CI-HHV-6 than in the HHV-6 negative group, with a corresponding nonsignificantly higher rate of allograft rejection in the CI-HHV-6 group (72).

As with other herpesviruses transmitted through saliva, risk of infection with HHV-6 is associated with lower socioeconomic status and having more than one sibling, whereas seasonality and black race are associated with a higher prevalence of HHV-7 infection (73). Though data are limited, it is assumed that the intensity of pharmacologic immunosuppression is a risk factor for HHV-6 and HHV-7 reactivation and disease (74), potentially through prolonged suppression of memory responses (75). Certain agents, including muromunab-CD3 (49) and alemtuzumab have been associated with active HHV-6 infection after transplantation (76).

Diagnosis

Several factors complicate the diagnosis of clinically relevant HHV-6 infection. Diagnostic tests to detect HHV-6 and HHV-7 include serology, culture, antigenemia, immunohistochemistry and nucleic acid amplification assays. In general, these tests are not well standardized. In addition, many tests are unable to differentiate latent versus active infection or to distinguish between HHV-6A and HHV-6B, and there may also be cross-reactivity between HHV-6 and HHV-7. Specific testing for HHV-7 is mainly performed for research purposes, as there have not been any clear clinical syndromes associated with HHV-7 infection. Perhaps the most difficult aspect of interpreting HHV-6 and HHV-7 testing, however, is determining whether detection of the virus implies causality in a given clinical syndrome; the diagnosis of symptoms directly related to HHV-6 or HHV-7 infection typically requires the exclusion of other more likely etiologies.

Due to high HHV-6 and HHV-7 seroprevalence rates in adults, serology is of limited benefit for the diagnosis of active infection in solid organ transplant recipients (III; Ref. 9). Viral culture of HHV-6 is laborious and not routinely used. HHV-6 antigenemia assays can detect HHV-6 viral antigens in peripheral blood mononuclear cells using monoclonal antibodies (33) and can distinguish between HHV-6A and HHV-6B. Antigen-based assays are also rapid, relatively easy to perform, and may discriminate between active and latent infection. However in one study of adult liver transplant recipients, HHV-6 and HHV-7 active infection were detected in up to 39.2% and 14.2% of patients, respectively, at a median of 9 days posttransplantation, usually preceding CMV antigenemia; however, the cut-off level to determine clinically significant active infection is unknown (77). Further studies are needed to determine clinically significant levels of antigenemia posttransplantation. Polymerase chain reaction (PCR) may be preferred for the detection of HHV-6 and HHV-7 viremia after solid organ transplantation (II-2; Ref. 78). PCR assays can distinguish between HHV-6A, HHV-6B and HHV-7, but they may not differentiate active from latent infection (79,80). Quantitative real-time PCR assays on noncellular samples are often used for the diagnosis of active HHV-6 and HHV-7 infection (81–85); however, recent evidence suggests that HHV-6 DNA in plasma reflects the presence of infected blood cells (86). Therefore, quantification of viral DNA in whole blood, reverse transcriptase PCR on whole blood, or methods to detect messenger mRNA may be more specific for the diagnosis of active HHV-6 infection (III; Refs. 86–88). However, there are limited data linking reactivation of HHV-6 using whole blood clinical samples with clinical disease. It is also important to consider the potential detection of CI-HHV-6 in blood samples, characterized by persistent HHV-6 viral loads of over a million copies per mL of whole blood, which may be misinterpreted as substantial active infection leading to unnecessary treatment (4,72). Recent guidelines suggest that HHV-6 levels in whole blood exceeding 5.5 $\log_{10}$ copies/mL are strongly suggestive of CI-HHV-6, which is confirmed by the ratio of viral to human genomes of 1:1 (3). Qualitative or quantitative HHV-6 PCR of the cerebrospinal fluid is useful to diagnose HHV-6 encephalitis in patients with the appropriate clinical signs (42). Immunohistochemistry to detect viral antigens in biopsy specimens may be more informative than viremia in cases where tissue-invasive HHV-6 disease is suspected (34,89,90). However, HHV-6 antigen may be found commonly in tissue in the absence of symptoms (91,92). Because of the apparent low rate of clinical disease and the relatively high rate of subclinical viral reactivations, routine monitoring for HHV-6 or HHV-7 infection after solid organ transplantation

is not recommended based on the current evidence. Diagnostic testing should be limited to scenarios where symptomatic HHV-6 infection is plausible, and to assist in guiding treatment decisions, including response to therapy (III; Ref. 93).

Treatment

The majority of HHV-6 and HHV-7 infections are subclinical and transient, and therefore treatment of asymptomatic viral reactivation is not recommended (II-2). However, treatment directed against HHV-6 should be initiated in the setting of HHV-6 encephalitis and should be considered for other clinical syndromes attributable to HHV-6 (III). Especially in cases of moderate or severe disease, antiviral treatment may be complemented by a reduction in the degree of pharmacologic immunosuppression (III). Furthermore, HHV-6 and HHV-7 co-infections with CMV generally do not require therapy in addition to the treatment given for CMV infection and disease (III; Ref. 94). Currently, no antiviral compounds have been approved for the treatment of HHV-6 and HHV-7 infections in solid organ transplant recipients, though foscarnet, ganciclovir and cidofovir have been used clinically, based on *in vitro* data and anecdotal clinical reports in stem cell transplant recipients (30,95–97). However, there are no randomized controlled trials demonstrating antiviral efficacy in the treatment of HHV-6 or HHV-7 infections. *In vitro*, HHV-6 is sensitive to achievable concentrations of ganciclovir, foscarnet and cidofovir, though HHV-6A and HHV-6B demonstrate different susceptibilities (95). HHV6-B is usually susceptible to both ganciclovir and foscarnet, whereas HHV6-A is more resistant to ganciclovir though mutations in U69 and U28 genes (98,99). Of note, a cidofovir-resistant isolate of HHV-6 has been reported (100). HHV-7 appears resistant to ganciclovir *in vitro*, and may not be inhibited with achievable concentrations of ganciclovir (95). Both HHV-6 and HHV-7 are resistant to acyclovir and penciclovir (95).

Prevention

Specific antiviral prophylaxis or pre-emptive therapy for HHV-6 infection is not recommended due to insufficient evidence, and because the vast majority of HHV-6 and HHV-7 infections after solid organ transplantation are subclinical (III). Antiviral prophylaxis for CMV with ganciclovir or valganciclovir does appear to reduce the incidence of HHV-6 viremia in solid organ transplant recipients (101,102), though a similar effect has not been observed for HHV-7 (94).

Research issues

A full understanding of the clinical impact of HHV-6 and HHV-7, including the direct effects as well as interactions with CMV, impact on allograft dysfunction, and other immunomodulatory effects, requires large prospective clinical studies. A comprehensive assessment of the magnitude of their clinical impact would be required to estimate the potential benefits of interventions such as routine monitoring for these viruses after transplantation. Standardization of diagnostic methods to allow for more precise determination of the burden of active infection and association with clinical disease is warranted, along with further characterization of CIHHV-6 and its association with disease. Finally, determining the *in vivo* efficacy of currently available antiviral compounds against HHV-6 and HHV-7, preferably through randomized controlled trials, would be beneficial.

Human Herpesvirus 8

Epidemiology and risk factors

Human herpesvirus8 (HHV-8) is a γ-herpesvirus that causes Kaposi sarcoma (KS) and, much less commonly, primary effusion lymphoma (PEL) and multicentric Castleman disease (MCD; Refs.103–106). HHV-8 has also been reported as a cause of fever and other constitutional symptoms, bone marrow suppression, hemophagocytic syndrome and clonal gammopathy after transplantation (106–109). HHV-8 infects B cells, oral epithelial cells, as well as cells of endothelial origin ("spindle cells") present in KS lesions (110). As with all herpesviruses, HHV-8 infection is lifelong, and the virus alternates between latency and active lytic replication, during which infectious virus is produced. Natural transmission of HHV-8 primarily occurs through saliva, but infection may also be acquired via sexual intercourse, blood transfusion and organ transplantation (111,112).

The prevalence of HHV-8 infection varies widely depending on the geographic region; seroprevalence is estimated to be between 0–5% in North America, northern Europe, and Asia, between 5–20% in the Mediterranean and Middle East, and >50% in parts of Africa (111,112). In high-prevalence areas, acquisition of HHV-8 frequently occurs during early childhood, in contrast to low-prevalence areas where seropositivity of children is extremely rare (113,114). The incidence of active HHV-8 infection and disease after solid organ transplantation reflect these geographic differences in seroprevalence. Between 23 and 68% of HHV-8 seropositive transplant recipients develop KS (115–117). As such, the cumulative risk of KS in transplant recipients has been reported to range from as low as 0.4% of patients in North America to 6% in the Mediterranean and Middle East (112,115–124). Furthermore, in Saudi Arabia, KS accounted for 87.5% of all tumors detected in kidney transplant recipients, compared to only approximately 3–6% in North America (118,124). The onset of KS is most often within the first 1–2 years after transplantation, though it may occur as early as a few weeks to as late as 18 years after transplantation (103,106,124–127).

The risk and manifestations of symptomatic HHV-8 infection in transplant recipients are likely dependent on the presence of pretransplant HHV-8 immunity, level of immunosuppression and type of organ. KS and other

HHV-8-related diseases may occur as a result of either primary infection in recipients of allografts from HHV-8-infected donors (106,107,128–132), or viral reactivation in recipients infected with HHV-8 before transplant (132–134). Primary HHV-8 infection in liver transplant recipients may result in particularly high rates of disease and death, based on a recent prospective Italian cohort study in which three of five patients who acquired HHV-8 posttransplant died from multiorgan failure or MCD, and a fourth developed KS (106).

The risk of HHV-8-related disease is greatly increased by pharmacologic immunosuppression or HIV infection, likely due to impaired control of HHV-8 replication (110,135). The intensity of immunosuppression, including use of antilymphocyte agents, has been associated with the risk of KS after transplantation (115). HHV-8 T cell responses were notably absent in a case series of transplant patients at the onset of KS, but became detectable following reduction in immunosuppression, which coincided with remission of KS (136). NK cells (137) and B cells may also be protective against KS; low levels of HHV-8 neutralizing antibodies have been associated with KS in HIV infection (138,139), and treatment of MCD with rituximab has been reported to increase HHV-8 reactivation and exacerbate KS (140). Use of calcineurin inhibitors (CNIs) for immunosuppression has been indirectly implicated as a risk factor for KS, since regression of KS lesions has occurred after reduction of CNIs or switching to the mTOR inhibitor sirolimus (also known as rapamycin; Refs.136,141). Older age and male gender have also been identified as risk factors for KS (117,120,124). Risk factors for less common clinical manifestations of HHV-8 infection in transplant recipients have not been well defined.

Diagnosis

A variety of serological assays are available to test for HHV-8 infection. However, use of these assays, which are based on a variety of viral antigens, is not standardized, and their sensitivity ranges from approximately 80% to greater than 90% (142,143). Although donor and recipient serological screening prior to solid organ transplantation may help stratify the risk of HHV-8-related disease after transplantation, how this information should be used is poorly understood at present (II-2). Similarly, the value of testing for seroconversion or an IgM response to HHV-8 post-transplantation is uncertain (III). For the detection of active HHV-8 infection, quantitative PCR testing of peripheral blood may be informative (II-2; Ref. 135). As HHV-8 viremia is associated with the development of KS, PCR could be used to monitor for risk of disease as a part of a preemptive strategy (see below; Refs.135,144,145). In addition, the use of HHV-8 viral load measurements to follow patients with KS and to assess response to therapy has also been suggested (115,142,146), though studies are needed to determine the clinical utility of these approaches (III).

KS presents in transplant patients as red or violaceous lesions of the skin or oral mucosa, but may also involve the lymph nodes or visceral organs, including the transplanted allograft (130,134,147,148). Presenting symptoms of PEL are dependent on the location (primarily the pleural, peritoneal or pericardial spaces) and size of the effusion. MCD is characterized by fever and other systemic symptoms of inflammation, lymphadenopathy, and anemia. Histopathology is required for definitive diagnosis of HHV-8-related tumors, and should be performed whenever possible. Testing for the presence of HHV-8 in biopsy or fluid samples (e.g. tumor tissue for KS, lymph node for MCD, pleural or ascitic fluid for PEL) using immunohistochemistry, in situ hybridization, or PCR is also valuable (II-2; Refs. 103,135).

Treatment

A multidisciplinary approach is recommended, including early consultation with oncology, infectious disease, and dermatology specialists, as appropriate. Cautious reduction or cessation of pharmacologic immunosuppression is the first line therapy for the treatment of KS if feasible (II-3; Refs. 136,149–151). The degree to which immunosuppression is reduced should be individualized based on the type of organ transplanted and the severity of KS in each case. For patients receiving a CNI as a part of their immunosuppression regimen, switching to sirolimus should also be considered (II-3). In addition to its ability to block T cell activation through inhibition of IL-2 response, sirolimus has antitumor properties, and conversion to sirolimus has led to regression of KS lesions in some patients (130,134,141,152,153). In addition, sirolimus blocks HHV-8 replication, which may provide additional clinical benefits (154).

Patients whose KS lesions do not regress with reduction in immunosuppression or change to sirolimus may require intralesional chemotherapy, surgical excision or radiation therapy or other local treatment for isolated lesions, or systemic chemotherapy for visceral or severe disease, using liposomal doxorubicin, paclitaxel, or other agents (II-2; Ref. 155). Chemotherapy may also ameliorate the risk of allograft rejection due to reduction of immunosuppression (148,156). It should be noted that no controlled KS treatment trials have been performed in transplant recipients. Data regarding treatment of MCD and PEL in transplantation is even more limited. As such, decisions regarding systemic chemotherapy may benefit from evaluation of evidence from the HIV literature (104,111,157,158). The benefits of antiviral therapy in transplant recipients with established KS or other manifestations of HHV-8 infection are not defined (135). However, numerous case reports suggest a benefit of antivirals for HHV-8 related diseases, including one in which foscarnet was used successfully for the treatment of bone marrow suppression and hemophagocytosis related to primary HHV-8 infection after kidney transplantation (108,135).

Table 1: Summary of recommendations for the diagnosis, prevention and treatment of human herpes viruses 6, 7 and 8 after solid organ transplantation

	Recommendations	Level of evidence
HHV-6 and HHV-7		
Diagnosis	Viral serologies are not helpful in the diagnosis of HHV-6 and HHV-7 infections after solid organ transplantation	III
	Direct methods, such as the detection of viral nucleic acids in blood or CSF by PCR, or viral antigen in tissue by immunohistochemistry, are preferred methods for diagnosis of HHV-6 and HHV-7	II-2
	Quantitative PCR on whole blood, reverse transcriptase PCR on whole blood, or methods to detect mRNA may be more specific for the diagnosis of active HHV-6 and HHV-7 infection	III
	Routine monitoring for HHV-6 and HHV-7 infections after solid organ transplantation is not recommended, except to assist in guiding decisions regarding treatment of symptomatic HHV-6 infection, including response to therapy	III
Treatment	The majority of HHV-6 and HHV-7 infections are asymptomatic, transient, and do not require antiviral treatment	II-2
	Antiviral treatment with ganciclovir, foscarnet or cidofovir should be initiated in the setting of HHV-6 encephalitis and should be considered for other syndromes attributable to HHV-6	III
	Treatment of symptomatic HHV-6 and HHV-7 infections should include reduction in the degree of immunosuppression, especially for moderate or severe disease	III
	HHV-6 and HHV-7 co-infections with CMV do not require additional therapy	III
Prevention	Antiviral prophylaxis or preemptive antiviral therapy for HHV-6 or HHV-7 infections is not recommended after transplantation	III
HHV-8		
Diagnosis	Serology is of limited utility in the diagnosis of HHV-8 after solid organ transplantation	III
	Pretransplant donor and recipient HHV-8 serology may stratify the risk of disease after transplantation in endemic areas	II-2
	Immunohistochemistry using monoclonal antibodies against HHV-8 antigens is useful for the pathological diagnosis of KS and other angiogenic proliferative diseases	II-2
	Nucleic acid amplification assays to quantitate HHV-8 load in clinical samples is preferred for the diagnosis of active HHV-8 replication	II-2
	Quantification of HHV-8 load could be used for monitoring transplant patients with KS	III
Treatment	Reduction or cessation of immunosuppression should be a first line therapy, especially for moderate or severe disease	II-3
	Conversion of immunosuppressive regimen from calcineurin inhibitors to sirolimus (rapamycin) should be considered	II-3
	Current evidence does not support the use of antivirals for the treatment of KS	II-2
	Patients whose lesions do no not regress despite reduction in immunosuppression or conversion to sirolimus may require local interventions or systemic chemotherapy	II-2
Prevention	HHV-8 serologic screening of donors and recipients may be considered to assess risk, especially in geographic regions with high rates of infection	II-2
	In HHV-8 seropositive recipients or those who receive an organ from HHV-8 seropositive donor, monitoring of HHV-8 load after transplantation may be useful to determine the risk of disease	III
	Avoidance of over-immunosuppression in high risk individuals and in those with detectable HHV-8 viremia may be beneficial	III
	The use of antivirals with activity against HHV-8 (e.g. valganciclovir) to prevent KS in selected high risk transplant recipients with detectable HHV-8 viremia may be beneficial based on studies in HIV-infected patients	III

PCR= polymerase chain reaction; HHV= human herpesvirus; CSF= cerebrospinal fluid; CMV= cytomegalovirus; KS= Kaposi sarcoma.

Prevention

Although serologic screening of donors and recipients is not routinely performed, it may be considered, especially in those from geographic regions with high rates of infection (II-2). However, seropositivity in either the donor or the recipient is not typically regarded as a contraindication to transplantation (132). In recipients who are seropositive for HHV-8 or receive an organ from a seropositive donor, monitoring of HHV-8 viral load after transplantation may be a useful strategy to determine the risk of clinical disease (III). Avoidance of over-immunosuppression in high-risk individuals and in those with detectable HHV-8 viremia is advisable (III). However, the frequency and duration of monitoring or the level of clinically relevant HHV-8

replication has yet to be determined. Moreover, once HHV-8 is detected, current data are insufficient to define a beneficial preemptive strategy (135). *In vitro* studies demonstrate that HHV-8 replication is inhibited by ganciclovir, foscarnet and cidofovir at concentrations achieved in plasma (135). Furthermore, clinical trials have reported that valganciclovir can suppress HHV-8 replication *in vivo*, and that ganciclovir reduces the incidence of KS by 75–93% in people infected with HIV (159,160). Although these antivirals are effective prophylaxis in organ transplant recipients at risk for HHV-8-related disease or as preemptive treatment of a patient with active HHV-8 replication has not been studied. Use of immunosuppression regimens containing sirolimus rather than a CNI might theoretically lower the risk of KS because of the anti-proliferative properties of mTOR inhibitors and their association with lower overall risk of malignancy in some studies (161,162). However, adequately powered studies have not been performed to determine whether sirolimus prevents KS, and incident KS cases have been reported in patients receiving sirolimus (153,163).

Research issues

Additional prospective studies are needed to evaluate the use of pretransplant donor and recipient serology to stratify risk among recipient of different organ types in regions of HHV-8 endemicity. The use of HHV-8 viral load monitoring after transplantation to predict individuals at high risk of disease should be evaluated, with the goal of assessing the optimal frequency of testing and viral load threshold that accurately predict disease. The potential clinical utility of antiviral drugs for targeted prophylaxis, or as preemptive treatment of asymptomatic HHV-8 reactivation or replication, should be subjected to prospective controlled clinical trials. The benefits of immunosuppression regimens containing sirolimus or other mTOR inhibitors for the prevention and treatment of KS after transplantation should be investigated in randomized clinical trials. Conducting these trials in regions where HHV-8 infection is prevalent has obvious advantages, and should therefore be encouraged and supported (Table 1).

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Disclosure

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