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Roseoloviruses in transplant recipients: clinical consequences and prospects for treatment and prevention trials

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Abstract

Roseoloviruses frequently reactivate in transplant recipients. We review the impact of Roseoloviruses in transplant recipients and highlight research priorities. Human herpesvirus 6A (HHV-6A) and HHV-6B were recently classified as distinct species with important differences. Both viruses can result in inherited chromosomally integrated HHV-6, which may cause complications after transplant. HHV-6B is the primary species associated with disease and appears to have pleiotropic effects on the central nervous system. Small preemptive and prophylactic studies have not shown a statistically significant impact on HHV-6 disease. Although Roseoloviruses are associated with diverse complications in transplant patients, studies providing strong evidence for a causal role are lacking. Trials focusing on prevention and treatment will be important to inform the significance of Roseolovirus reactivation.

Introduction

The *Roseolovirus* genus of the *Betaherpesvirinae* consists of three distinct but closely related species, human herpesvirus 6A (HHV-6A), HHV-6B, and HHV-7. Roseoloviruses cause ubiquitous human infection and have important differences in epidemiology and pathogenesis. They establish latency after primary infection, and viral reactivation is the usual cause of disease in immunocompromised patients, especially after allogeneic hematopoietic cell transplantation (HCT) and solid organ transplantation (SOT). This review highlights recent findings about the impact of Roseoloviruses in transplant recipients (Table 1), as well as research priorities to advance understanding of the clinical significance and management of these pathogens.

Inherited chromosomally integrated human herpesvirus 6A and B

An important consideration unique to HHV-6 is its ability to integrate into human chromosomal telomeres. When this occurs in germ-line cells, vertical transmission of chromosomally integrated HHV-6 (ciHHV-6) results in offspring with at least 1 copy of

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HHV-6 DNA in every nucleated cell of their body [1], independent of viral reactivation. Population-based studies have estimated this to occur in about 1% of people [2••], and inherited ciHHV-6 has been described in both HCT and SOT recipients [3]. Although characteristics of routine HHV-6 testing can indicate inherited ciHHV-6, a lack of appreciation for this condition has caused considerable confusion and misreporting in the literature [4].

Whether patients with inherited ciHHV-6 can develop HHV-6 reactivation with associated pathogenicity, or other indirect complications, is a topic of considerable controversy. However, an accumulating body of *in vitro* and *in vivo* evidence suggests that inherited ciHHV-6 can be the source of pathogenic viral reactivation or other complications [5–7]. A recent report detailed *in vivo* molecular and virological evidence of functional HHV-6A reactivation from inherited ciHHV-6A in an immunocompromised boy with X-linked severe combined immunodeficiency who underwent HCT [8••]. A study in liver transplantation recipients found that those with pre-transplant inherited ciHHV-6 had higher rates of bacterial infection [9]. However, a review of 21 reported cases of patients or recipients of donor cells with inherited ciHHV-6A and B found no clinical disease associations [3]. Novel approaches facilitating fast, cost-efficient, and clinically accessible testing for inherited ciHHV-6 [10•] will be important to broaden our understanding of this condition and whether routine pre-transplant screening is warranted. Inherited ciHHV-6 is reviewed in detail in this section by Kaufer *et al*.

Human herpesvirus 6A

The epidemiology of HHV-6A is not well described and appears to be geographically distinct from HHV-6B. Primary infection occurs later in life, usually without clinical symptoms, in the USA, Europe, and Japan [11], but it appears to be more common during infancy in Sub-Saharan Africa [12]. HHV-6A is found in about a third of individuals with inherited ciHHV-6 [2••].

No disease has been causally linked with HHV-6A, which is infrequently described in immunocompromised patients and only accounts for 0–3% of reactivation after transplantation [13••,14•]. There are a few case reports of HHV-6A encephalitis after HCT [15–17]. However, with a contemporary understanding of HHV-6, these cases were most likely due to unrecognized inherited ciHHV-6, and whether HHV-6A was contributory to the patients' illness is hard to know with the information provided. Ultimately, HHV-6A detection in the setting of transplantation is suggestive of inherited ciHHV-6. Due to the low incidence of HHV-6A reactivation in HCT and SOT patients, it remains unclear if it shares an association with the diversity of complications seen in the setting of HHV-6B reactivation.

Human herpesvirus 6B

HHV-6B infects most children within the first 3 years of life and is found in approximately 2/3 of patients with inherited ciHHV-6 [2••]. HHV-6B accounts for the majority of HHV-6 reactivation in transplant recipients and can be detected in plasma and/or serum samples from 30 to 50% of patients [13••,14•,18•,19••,20•]. HHV-6B reactivation typically occurs

during the first 2–4 weeks after transplantation and has been associated with a variety of complications (Table 1), which occur with greater frequency after HCT than SOT.

HHV-6B as a cause of encephalitis was first noted after HCT in 1994 [21]. A large body of literature has since convincingly described a distinct syndrome of limbic encephalitis after transplant as described in Table 2. These patients have detectable HHV-6B DNA in cerebrospinal fluid (CSF) [19••,20•,22–24], and studies have demonstrated viral protein expression in the mesial temporal lobes of affected patients [25,26]. HHV-6B-associated limbic encephalitis has significant morbidity and mortality despite antiviral treatment [23,24,27,28]. This syndrome occurs in approximately 1% of all HCT patients and as many as 10% of cord blood HCT recipients, who have an increased incidence of HHV-6 reactivation and disease [20•,23]. A recent meta-analysis of 19 papers found that HHV-6B encephalitis was significantly higher in CBT recipients (8.3%) than other allogeneic HCT recipients (0.5%) [19••]. In a prospective cohort of CBT recipients transplanted without antithymocyte globulin, reactivation was documented in 94% of patients [29]. The authors reported a low level (1.6%) of encephalitis and no association with clinical outcomes, but almost 1/3 of patients received preemptive antiviral therapy. This syndrome has also been described after SOT but is much less common [14•,30].

HHV-6B may have protean effects on the central nervous system (CNS) beyond encephalitis. A large prospective study of 315 allogeneic HCT recipients that systematically assessed for CNS dysfunction found an independent and temporal association of HHV-6B reactivation with delirium and neurocognitive decline after HCT [31]. Two other studies show that HHV-6B DNA detection in CSF in the absence of other explanatory etiologies may be associated with a spectrum of disease, ranging from headache alone to fulminant encephalitis [32,33•]. Our understanding of the significance of HHV-6B DNA detection in the CSF continues to evolve but is limited by the lack of routine CSF sampling in asymptomatic controls. Although previous reports suggest that HHV-6B detection in the CSF in the absence of CNS symptoms is very unusual (<1%) [24,34], a recent study found that this may occur with greater frequency [33•].

HHV-6B reactivation has been associated with many other conditions in transplant patients (Table 1), although its role is less clearly defined. There is an association of HHV-6B reactivation with myelosuppression and delayed engraftment, particularly involving platelets [35]. A recent large prospective trial in 235 consecutive allogeneic HCT recipients showed delayed platelet engraftment among the 48% of patients who developed HHV-6B viremia within 100 days [18•]. This study also showed an association between HHV-6B reactivation and acute graft-versus-host disease (aGVHD) in univariate and multivariable models, a finding corroborated in more detail in another large prospective trial [13••] as well as other recent studies [23,36]. Interestingly, a retrospective study found that either initial HHV-6 reactivation or aGVHD predisposed patients to subsequent development of the other [37•]. They also show that HHV-6B reactivation was associated with rash that imitated skin aGVHD in 17 patients; histopathology revealed a lymphoid infiltrate but no evidence of aGVHD. These patients were treated with steroids for presumptive aGVHD, which may have been unnecessary. Given that fever and rash are the most frequent manifestation of

HHV-6B reactivation after HCT [38], study of the causal pathways connecting these manifestations with HHV-6 and aGHVD is warranted.

Increased risk for cytomegalovirus (CMV) reactivation and disease has been variably demonstrated in HCT [39] and SOT [40,41] recipients. In a large prospective study of 315 allogeneic HCT patients, HHV-6 reactivation was independently and quantitatively associated with increased risk of subsequent CMV reactivation [13••]. A small study of 9 CMV seropositive and negative patients undergoing kidney transplantation showed that both groups had increased risk for HHV-6 viremia when the donor was CMV seropositive [42]. Additionally, HHV-6 viremia was a sign of impending primary CMV infection in CMV sero-discordant transplantations. A recent study of 41 liver transplant patients found that recipients of liver allografts with detectable HHV-6 DNA in pre-transplantation samples had increased risk for post-transplantation CMV disease and allograft loss [43•].

Allograft dysfunction and rejection is gaining more traction as a serious complication of HHV-6B reactivation [44] or primary infection [45], particularly in liver transplantation. Retrospective testing for HHV-6 DNA in 26 liver biopsies was positive in 39% of patients with graft hepatitis of unclear etiology, and confluent periportal necrosis was associated with high viral loads in 4 patients who responded to antiviral therapy [46]. After lung transplantation, HHV-6 testing of transbronchial biopsies found a significant association between HHV-6 detection and interstitial pneumonia, although there was no association with graft rejection [47].

Cases of what appear to be HHV-6B directly affecting organs other than the brain have been reported in the HCT population as well. A case of HHV-6B-associated hepatitis in an allogeneic HCT recipient established the link between HHV-6B and clinical hepatitis. This report demonstrated temporally associated HHV-6B reactivation in blood and liver samples, along with immunohistochemical evidence of active viral replication in the liver [48•]. A number of studies have attempted to address a potential association between HHV-6 and pneumonitis. Findings have been conflicting and the issue remains unresolved. While additional studies are clearly needed, HHV-6 may be an underappreciated cause of hepatic and pulmonary disease in HCT and SOT patients.

The importance of attaining a better understanding of the significance of HHV-6 detection in end organ diseases is underscored by an association between HHV-6 reactivation and increased mortality after HCT [13••,18•,49]. However, whether HHV-6 directly contributes to this and other clinical outcomes or is simply an indirect marker of the severity of patient illness and immunologic deficiency remains unclear.

Human herpesvirus 7

Infection with HHV-7 typically occurs in childhood, and most adults are seropositive. Primary infection rarely comes to clinical attention and is less well understood than with HHV-6B. HHV-7 DNA detection in blood samples after transplantation is primarily due to reactivation and is found in approximately 40–60% of patients [50–52]. This typically occurs within the first 2–4 weeks after transplant. In contrast to HHV-6B, there is no obvious peak time of reactivation, and the vast majority of reactivation events are transient,

low-level, and not associated with any clinical manifestations. However, HHV-7 is not as well studied in immunocompromised patients, and most reports are small, often with conflicting results.

HHV-7 reactivation has been associated with a variety of diseases in a few case reports. These include CNS disease [53], myelosuppression [54], aGVHD [55], and allograft dysfunction and rejection [56]. Data from a number of studies suggest a potential indirect effect of HHV-7 to increase rates of CMV reactivation and disease in HCT [57] and SOT [58,59] recipients, but this is not a consistent finding [52]. Future studies of HHV-6B should incorporate testing for HHV-7 to advance our understanding of its possible significance in transplantation.

Diagnostic considerations

Studies have used a variety of non-standardized techniques to detect Roseoloviruses in a wide range of specimens, making direct comparisons problematic. This, along with the challenge implicit in attributing disease to commensal viruses, has led to many questions about the actual role Roseoloviruses play in many associated clinical conditions following transplantation. The historical lack of a clear distinction between HHV-6A and HHV-6B in the literature further limits a comprehensive understanding of their epidemiologic differences and etiologic associations. Notably, HHV-6A and HHV-6B were only recently classified as distinct species in 2012 [60], so previous reports lacked a scientific imperative to distinguish between them. Differentiating HHV-6A from HHV-6B has also been hampered by the lack of specificity of serologic assays [11]; distinguishing between the two viruses is best accomplished at this time with polymerase chain reaction assays and sequencing [61•]. Unfortunately, these tests continue to be expensive and are not widely available. Diagnosis of Roseolovirus infections is reviewed in this section by Hill *et al*.

Treatment

Early diagnosis, treatment, and prevention are important concepts when considering Betaherpesviruses in immunocompromised transplant patients. Although some recommendations exist for diagnosis and management of specific HHV-6-associated diseases [62,63], there are no widely adopted standard practice guidelines. Furthermore, there are no FDA approved medications for treating Roseoloviruses, and optimal treatment approaches (i.e. single or combination antivirals, dose, duration) have not been rigorously studied. Although a detailed review of treatment is beyond the scope of this review, studies attempting to screen for and prevent HHV-6-associated diseases merit brief discussion.

The use of prophylactic ganciclovir in HCT and SOT patients can reduce HHV-6B reactivation [40,64] and may reduce associated morbidity in high-risk patients [65,66], but large scale adoption is limited by ganciclovir-induced myelosuppression. The use of low dose foscarnet for 10 days post-engraftment to prevent HHV-6B reactivation was recently explored in a retrospective cohort study of 118 allogeneic HCT recipients (unrelated or cord blood donors) [67••]. High-level HHV-6B reactivation (>10,000 copies/ml) occurred in 19.4% of patients receiving foscarnet versus 33.8% of those not, and HHV-6B encephalitis occurred in 4.5% of patients receiving foscarnet versus 9.9% of those not; neither finding

was statistically significant. Two small prospective studies of preemptive foscarnet in HCT recipients [68,69] did not significantly reduce the complications of HHV-6B reactivation and highlight the challenge of initiating preemptive therapy after a viral threshold has been reached but prior to onset of HHV-6-associated disease. The development of HHV-6 specific cytotoxic T cells for adoptive immunotherapy has been encouraging [70•] but is in early stages of development. These topics are reviewed in detail by Prichard *et al*. and Becerra *et al*. in this section.

Research priorities

This review highlights the recent findings and continued deficiencies in our clinical understanding of the significance of Roseoloviruses in transplant recipients. To advance our ability to quickly and accurately assess patients who will be or are adversely affected by these pathogens, future studies should focus on strategies to diagnose HHV-6B-associated end organ diseases, determine an optimal treatment approach for HHV-6B encephalitis, identify possible HHV-6A or B disease in the setting of inherited ciHHV-6, and determine whether prevention of HHV-6B reactivation improves outcomes (Table 1). Testing should distinguish between species in all cases. Clinical trials of new antivirals (i.e. brincidofovir, previously CMX001) [71] and immunotherapeutic treatments with less toxicity will be imperative to establish support for a causal role of Roseolovirus pathogenicity in immunocompromised patients and to potentially improve outcomes. The clinical understanding of HHV-7 is much less developed, and additional large, well-designed prospective studies are warranted. Ultimately, a more complete understanding of the clinical impact of Roseoloviruses requires large, multicenter prospective studies using well-defined disease criteria and standardized viral assays capable of discriminating between species.

Conclusion

HHV-6B reactivation from latency is a frequent occurrence after transplantation, and a preponderance of evidence suggests a causal association between HHV-6B and encephalitis. Although a growing body of literature supports the involvement of Roseoloviruses, especially HHV-6B, in additional diseases, potential pathways of pathogenesis are not well defined. Thus, the precise role that Roseoloviruses play in causing these clinical outcomes in immunocompromised transplant recipients remains unclear. The widespread prevalence of Roseoloviruses in diverse human cell types complicates an understanding of its role in this myriad of associated diseases, and there is significant controversy regarding whether viral infection and replication cause, or merely correlate with, associated pathologies. Complex interactions between these viruses and the host immune system further confound attempts to implicate them in pathologic processes. Further study is needed to establish causality and explore prevention and treatment options.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

• of special interest

•• of outstanding interest

1. Hall CB, Caserta MT, Schnabel K, Shelley LM, Marino AS, Carnahan JA, Yoo C, Lofthus GK, McDermott MP. Chromosomal integration of human herpesvirus 6 is the major mode of congenital human herpesvirus 6 infection. Pediatrics. 2008; 122:513–520. [Internet]. [PubMed: 18762520]

2 ••. Pellett, P.; Ablashi, D. Chromosomally integrated human herpesvirus 6: questions and answers. Rev Med Virol. 2012. http://dx.doi.org/10.1002/rmv. [Internet]. A review article that details the clinical features of patients with chromosomally integrated HHV-6 and its significance

3. Lee S-O, Brown RA, Razonable RR. Chromosomally integrated human herpesvirus-6 in transplant recipients. Transplant Infect Dis: Off J Transplant Soc. 2012; 14:346–354. [Internet].

4. Clark DA, Nacheva EP, Leong HN, Brazma D, Li YT, Tsao EHF, Buyck HCE, Atkinson CE, Lawson HM, Potter MN, et al. Transmission of integrated human herpesvirus 6 through stem cell transplantation: implications for laboratory diagnosis. J Infect Dis. 2006; 193:912–916. [Internet]. [PubMed: 16518751]

5. Arbuckle JH, Medveczky MM, Luka J, Hadley SH, Luegmayr A, Ablashi D, Lund TC, Tolar J, De Meirleir K, Montoya JG, et al. The latent human herpesvirus-6A genome specifically integrates in telomeres of human chromosomes *in vivo* and *in vitro*. Proc Natl Acad Sci U S A. 2010; 107:5563–5568. [Internet]. [PubMed: 20212114]

6. Pantry SN, Medveczky MM, Arbuckle JH, Luka J, Montoya JG, Hu J, Renne R, Peterson D, Pritchett JC, Ablashi DV, et al. Persistent human herpesvirus-6 infection in patients with an inherited form of the virus. J Med Virol. 2013; 85:1940–1946. [Internet]. [PubMed: 23893753]

7. Gravel, A.; Hall, CB.; Flamand, L. Sequence analysis of transplacentally-acquired human herpesvirus 6 DNA is consistent with the transmission of a chromosomally-integrated reactivated virus. J Infect Dis. 2013. http://dx.doi.org/10.1093/infdis/jit060. [Internet].

8 ••. Endo, A.; Watanabe, K.; Ohye, T.; Suzuki, K.; Matsubara, T.; Shimizu, N.; Kurahashi, H.; Yoshikawa, T.; Katano, H.; Inoue, N., et al. Molecular and virological evidence of viral activation from chromosomally integrated HHV-6A in a patient with X-SCID. Clin Infect Dis: Off Publ Infect Dis Soc Am. 2014. http://dx.doi.org/10.1093/cid/ciu323. [Internet]. A case report that presents molecular and virological evidence for HHV-6 reactivation and associated complications in an immunocompromised patient with chromosomally integrated HHV-6A

9. Lee S-O, Brown RA, Razonable RR. Clinical significance of pretransplant chromosomally integrated human herpesvirus-6 in liver transplant recipients. Transplantation. 2011; 92:224–229. [Internet]. [PubMed: 21629177]

10 •. Sedlak RH, Cook L, Huang M-L, Magaret A, Zerr DM, Boeckh M, Jerome KR. Identification of chromosomally integrated human herpesvirus 6 by droplet digital PCR. Clin Chem. 2014; 60:765–772. [Internet]. A methodological paper describing the development of a clinical assay using droplet digital PCR to rapidly and accurately identify chromosomally integrated HHV-6 in blood and tissue samples. [PubMed: 24594780]

11. De Bolle L, Naesens L, De Clercq E. Update on human herpesvirus 6 biology, clinical features, and therapy. Clin Microbiol Rev. 2005; 18:217–245. [Internet]. [PubMed: 15653828]

12. Bates M, Monze M, Bima H, Kapambwe M, Clark D, Kasolo FC, Gompels UA. Predominant human herpesvirus 6 variant A infant infections in an HIV-1 endemic region of Sub-Saharan Africa. J Med Virol. 2009; 81:779–789. [Internet]. [PubMed: 19319952]

13 ••. Zerr DM, Boeckh M, Delaney C, Martin PJ, Xie H, Adler AL, Huang M-L, Corey L, Leisenring WM. HHV-6 reactivation and associated sequelae after hematopoietic cell transplant. Biol Blood Marrow Transplant: J Am Soc Blood Marrow Transplant. 2012; 18:1700–1708. [Internet]. A prospective study of 315 allogeneic HCT recipients that tested plasma for HHV-6 DNA twice-weekly over 12 weeks and evaluated the association between HHV-6 reactivation and various clinical outcomes.

14 •. Razonable RR. Human herpesviruses 6, 7 and 8 in solid organ transplant recipients. Am J Transplant: Off J Am Soc Transplant Am Soc Transplant Surg. 2013; 13:67–78. [Internet]. A review of the clinical significance of HHV-6, HHV-7, and HHV-8 in SOT.

15. Zerr DM, Gupta D, Huang M-L, Carter R, Corey L. Effect of antivirals on human herpesvirus 6 replication in hematopoietic stem cell transplant recipients. Clin Infect Dis: Off Publ Infect Dis Soc Am. 2002; 34:309–317. [Internet].

16. Bosi A, Zazzi M, Amantini A, Cellerini M, Vannucchi AM, De Milito A, Guidi S, Saccardi R, Lombardini L, Laszlo D, et al. Fatal herpesvirus 6 encephalitis after unrelated bone marrow transplant. Bone Marrow Transplant. 1998; 22:285–288. [Internet]. [PubMed: 9720744]

17. De Labarthe A, Gauthert-Dejean A, Bossi P, Vernant J-P, Dhedin N. HHV-6 variant A meningoencephalitis after allogeneic hematopoietic stem cell transplantation diagnosed by quantitative real-time polymerase chain reaction. Transplantation. 2005; 80:539. [Internet]. [PubMed: 16123732]

18 •. Dulery R, Salleron J, Dewilde A, Rossignol J, Boyle EM, Gay J, de Berranger E, Coiteux V, Jouet J-P, Duhamel A, et al. Early human herpesvirus type 6 reactivation after allogeneic stem cell transplantation: a large-scale clinical study. Biol Blood Marrow Transplant: J Am Soc Blood Marrow Transplant. 2012; 18:1080–1089. [Internet]. A prospective study of 235 consecutive allogeneic HCT recipients that investigated the impact of HHV-6 reactivation on outcomes by performing weekly plasma HHV-6 PCR through day 100.

19 ••. Scheurer ME, Pritchett JC, Amirian ES, Zemke NR, Lusso P, Ljungman P. HHV-6 encephalitis in umbilical cord blood transplantation: a systematic review and meta-analysis. Bone Marrow Transplant. 2013; 48:574–580. [Internet]. A systematic literature review and meta-analysis of 19 studies to compare the prevalence of HHV-6 reactivation and HHV-6 encephalitis in cord blood and non-cord blood HCT recipients. [PubMed: 23000642]

20 •. Ogata M, Satou T, Kadota J-I, Saito N, Yoshida T, Okumura H, Ueki T, Nagafuji K, Kako S, Uoshima N, et al. Human herpesvirus 6 (HHV-6) reactivation and HHV-6 encephalitis after allogeneic hematopoietic cell transplantation: a multicenter, prospective study. Clin Infect Dis: Off Publ Infect Dis Soc Am. 2013; 57:671–681. [Internet]. A multicenter, prospective trial of 230 allogeneic HCT recipients in Japan to determine the epidemiology of HHV-6 encephalitis and its relationship with HHV-6 reactivation.

21. Drobyski WR, Knox KK, Majewski D, Carrigan DR. Brief report: fatal encephalitis due to variant B human herpesvirus-6 infection in a bone marrow-transplant recipient. N Engl J Med. 1994; 330:1356–1360. [Internet]. [PubMed: 8152447]

22. Ward KN. Child and adult forms of human herpesvirus 6 encephalitis: looking back, looking forward. Curr Opin Neurol. 2014; 27:349–355. [Internet]. A review of HHV-6 encephalitis to update the current state of knowledge given the recent classification of HHV-6A and HHV-6B as distinct species, as well as advances in the understanding of chromosomally integrated HHV-6. [PubMed: 24792343]

23. Hill JA, Koo S, Guzman Suarez BB, Ho VT, Cutler C, Koreth J, Armand P, Alyea EP, Baden LR, Antin JH, et al. Cord-blood hematopoietic stem cell transplant confers an increased risk for human herpesvirus-6-associated acute limbic encephalitis: a cohort analysis. Biol Blood Marrow Transplant: J Am Soc Blood Marrow Transplant. 2012; 18:1638–1648. [Internet].

24. Seeley WW, Marty FM, Holmes TM, Upchurch K, Soiffer RJ, Antin JH, Baden LR, Bromfield EB. Post-transplant acute limbic encephalitis: clinical features and relationship to HHV6. Neurology. 2007; 69:156–165. [Internet]. [PubMed: 17620548]

25. Wainwright MS, Martin PL, Morse RP, Lacaze M, Provenzale JM, Coleman RE, Morgan MA, Hulette C, Kurtzberg J, Bushnell C, et al. Human herpesvirus 6 limbic encephalitis after stem cell transplantation. Ann Neurol. 2001; 50:612–619. [Internet]. [PubMed: 11706967]

26. Fotheringham J, Akhyani N, Vortmeyer A, Donati D, Williams E, Oh U, Bishop M, Barrett J, Gea-Banacloche J, Jacobson S. Detection of active human herpesvirus-6 infection in the brain: correlation with polymerase chain reaction detection in cerebrospinal fluid. J Infect Dis. 2007; 195:450–454. [Internet]. [PubMed: 17205485]

27. Shimazu Y, Kondo T, Ishikawa T, Yamashita K, Takaori-Kondo A. Human herpesvirus-6 encephalitis during hematopoietic stem cell transplantation leads to poor prognosis. Transplant Infect Dis: Off J Transplant Soc. 2013; 15:195–201. [Internet].

28. Sakai R, Kanamori H, Motohashi K, Yamamoto W, Matsuura S, Fujita A, Ohshima R, Kuwabara H, Tanaka M, Fujita H, et al. Long-term outcome of human herpesvirus-6 encephalitis after allogeneic stem cell transplantation. Biol Blood Marrow Transplant: J Am Soc Blood Marrow Transplant. 2011; 17:1389–1394. [Internet].

29. Olson, AL.; Dahi, PB.; Zheng, J.; Devlin, SM.; Lubin, M.; Gonzales, AM.; Giralt, SA.; Perales, M-A.; Papadopoulos, EB.; Ponce, DM., et al. Frequent human herpesvirus-6 viremia but low

incidence of encephalitis in double-unit cord blood recipients transplanted without antithymocyte globulin. Biol Blood Marrow Transplant: J Am Soc Blood Marrow Transplant. 2014. http://dx.doi.org/10.1016/j.bbmt.2014.02.010. [Internet]

30. Vinnard C, Barton T, Jerud E, Blumberg E. A report of human herpesvirus 6-associated encephalitis in a solid organ transplant recipient and a review of previously published cases. Liver Transplant: Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc. 2009; 15:1242–1246.
31. Zerr DM, Fann JR, Breiger D, Boeckh M, Adler AL, Xie H, Delaney C, Huang M-L, Corey L, Leisenring WM. HHV-6 reactivation and its effect on delirium and cognitive functioning in hematopoietic cell transplantation recipients. Blood. 2011; 117:5243–5249. [Internet]. [PubMed: 21389320]
32. Bhanushali MJ, Kranick SM, Freeman AF, Cuellar-Rodriguez JM, Battiwalla M, Gea-Banacloche JC, Hickstein DD, Pavletic S, Fahle G, Nath A. Human herpes 6 virus encephalitis complicating allogeneic hematopoietic stem cell transplantation. Neurology. 2013; 80:1494–1500. [Internet]. [PubMed: 23516318]
33 •. Hill, JA.; Boeckh, MJ.; Sedlak, RH.; Jerome, KR.; Zerr, DM. Human herpesvirus 6 can be detected in cerebrospinal fluid without associated symptoms after allogeneic hematopoietic cell transplantation. J Clin Virol: Off Publ Pan Am Soc Clin Virol. 2014. http://dx.doi.org/10.1016/j.jcv.2014.07.001. [Internet]. A study investigating the clinical significance of HHV-6 DNA detection in the cerebrospinal fluid of 51 allogeneic HCT recipients
34. Wang FZ, Linde A, Hägglund H, Testa M, Locasciulli A, Ljungman P. Human herpesvirus 6 DNA in cerebrospinal fluid specimens from allogeneic bone marrow transplant patients: does it have clinical significance? Clin Infect Dis: Off Publ Infect Dis Soc Am. 1999; 28:562–568. [Internet].
35. Zerr DM, Corey L, Kim HW, Huang M-L, Nguy L, Boeckh M. Clinical outcomes of human herpesvirus 6 reactivation after hematopoietic stem cell transplantation. Clin Infect Dis: Off Publ Infect Dis Soc Am. 2005; 40:932–940. [Internet].
36. Gotoh M, Yoshizawa S, Katagiri S, Suguro T, Asano M, Kitahara T, Akahane D, Okabe S, Tauchi T, Ito Y, et al. Human herpesvirus 6 reactivation on the 30th day after allogeneic hematopoietic stem cell transplantation can predict grade 2-4 acute graft-versus-host disease. Transplant Infect Dis: Off J Transplant Soc. 2014; 16:440–449. [Internet].
37 •. Pichereau C, Desseaux K, Janin A, Scieux C, Peffault de Latour R, Xhaard A, Robin M, Ribaud P, Agbalika F, Chevret S, et al. The complex relationship between human herpesvirus 6 and acute graft-versus-host disease. Biol Blood Marrow Transplant: J Am Soc Blood Marrow Transplant. 2012; 18:141–144. [Internet]. A retrospective analysis of 365 allogeneic HCT recipients to determine the relationship between HHV-6 reactivation and graft-versus-host disease.
38. Roux J, Battistella M, Fornecker L, Legoff J, Deau B, Houhou N, Bouaziz J-D, Thieblemont C, Janin A. Human Herpesvirus-6 cytopathic inclusions: an exceptional and recognizable finding on skin biopsy during HHV6 reactivation after autologous stem-cell transplantation. Am J Dermatopathol. 2012; 34:e73–e76. [Internet]. [PubMed: 22576078]
39. Tormo N, Solano C, de la Cámara R, Garcia-Noblejas A, Cardeñoso L, Clari MA, Nieto J, López J, Hernández-Boluda JC, Remigia MJ, et al. An assessment of the effect of human herpesvirus-6 replication on active cytomegalovirus infection after allogeneic stem cell transplantation. Biol Blood Marrow Transplant: J Am Soc Blood Marrow Transplant. 2010; 16:653–661. [Internet].
40. Razonable RR, Brown RA, Humar A, Covington E, Alecock E, Paya CV. Herpesvirus infections in solid organ transplant patients at high risk of primary cytomegalovirus disease. J Infect Dis. 2005; 192:1331–1339. [Internet]. [PubMed: 16170749]
41. Humar A, Malkan G, Moussa G, Greig P, Levy G, Mazzulli T. Human herpesvirus-6 is associated with cytomegalovirus reactivation in liver transplant recipients. J Infect Dis. 2000; 181:1450–1453. [Internet]. [PubMed: 10762575]
42. Van Leer-Buter, CC.; Sanders, JSF.; Vroom, HEJ.; Riezebos-Brilman, A.; Niesters, HGM. Human herpesvirus-6 DNAemia is a sign of impending primary CMV infection in CMV serodiscordant renal transplantations. J Clin Virol: Off Publ Pan Am Soc Clin Virol. 2013. http://dx.doi.org/10.1016/j.jcv.2013.07.014. [Internet]
43 •. Guardia AC, Stucchi RSB, Sampaio AM, Milan A, Costa SCB, Pavan CR, Boin I, de FSF. Human herpesvirus 6 in donor biopsies associated with the incidence of clinical cytomegalovirus

disease and hepatitis C virus recurrence. Int J Infect Dis: IJID: Off Publ Int Soc Infect Dis. 2012; 16:e124–e129. [Internet]. A study of 41 liver transplant recipients to determine if the presence of CMV or HHV-6 DNA in pre or post-transplant liver graft biopsies was associated with post-transplant CMV disease and hepatitis C virus recurrence.

44. Pischke S, Gösling J, Engelmann I, Schlue J, Wölk B, Jäckel E, Meyer-Heithuis C, Lehmann U, Strassburg CP, Barg-Hock H, et al. High intrahepatic HHV-6 virus loads but neither CMV nor EBV are associated with decreased graft survival after diagnosis of graft hepatitis. J Hepatol. 2012; 56:1063–1069. [Internet]. [PubMed: 22245897]
45. Dohna-Schwake C, Fiedler M, Gierenz N, Gerner P, Ballauf A, Breddemann A, Läer S, Baba HA, Hoyer PF. Primary HHV 6 infection after liver transplantation with acute graft rejection and multi-organ failure: successful treatment with a 2.5-fold dose of cidofovir and reduction of immunosuppression. Pediatr Transplant. 2011; 15:E126–E129. [Internet]. [PubMed: 20331520]
46. Buyse S, Roque-Afonso A-M, Vaghefi P, Gigou M, Dussaix E, Duclos-Vallée J-C, Samuel D, Guettier C. Acute hepatitis with periportal confluent necrosis associated with human herpesvirus 6 infection in liver transplant patients. Am J Clin Pathol. 2013; 140:403–409. [Internet]. [PubMed: 23955460]
47. Costa C, Curtoni A, Bergallo M, Solidoro P, Lorusso M, Delsedime L, Sapino A, Cavallo R. Quantitative detection of HHV-6 and HHV-7 in transbronchial biopsies from lung transplant recipients. New Microbiol. 2011; 34:275–280. [Internet]. [PubMed: 21811747]
48 •. Hill JA, Myerson D, Sedlak RH, Jerome KR, Zerr DM. Hepatitis due to human herpesvirus 6B after hematopoietic cell transplantation and a review of the literature. Transplant Infect Dis: Off J Transplant Soc. 2014; 16:477–483. [Internet]. A study investigating the clinical significance of HHV-6 DNA detection in the cerebrospinal fluid of 51 allogeneic HCT recipients.
49. De Pagter PJA, Schuurman R, Visscher H, de Vos M, Bierings M, van Loon AM, Uiterwaal CSPM, van Baarle D, Sanders EAM, Boelens J. Human herpes virus 6 plasma DNA positivity after hematopoietic stem cell transplantation in children: an important risk factor for clinical outcome. Biol Blood Marrow Transplant: J Am Soc Blood Marrow Transplant. 2008; 14:831–839. [Internet].
50. Peigo MF, Thomasini RL, Puglia ALP, Costa SCB, Bonon SHA, Boin IFS, Leonardi M, Mota NGS. Human herpesvirus-7 in Brazilian liver transplant recipients: a follow-up comparison between molecular and immunological assays. Transplant Infect Dis: Off J Transplant Soc. 2009; 11:497–502. [Internet].
51. Lehto JT, Halme M, Tukiainen P, Harjula A, Sipponen J, Lautenschlager I. Human herpesvirus-6 and -7 after lung and heart-lung transplantation. J Heart Lung Transplant: Off Publ Int Soc Heart Transplant. 2007; 26:41–47. [Internet].
52. Chan PKS, Li CK, Chik KW, Lee V, Shing MMK, Ng KC, Cheung JLK, Fok TF, Cheng AF. Risk factors and clinical consequences of human herpesvirus 7 infection in paediatric haematopoietic stem cell transplant recipients. J Med Virol. 2004; 72:668–674. [Internet]. [PubMed: 14981771]
53. Yoshikawa T, Yoshida J, Hamaguchi M, Kubota T, Akimoto S, Ihira M, Nishiyama Y, Asano Y. Human herpesvirus 7-associated meningitis and optic neuritis in a patient after allogeneic stem cell transplantation. J Med Virol. 2003; 70:440–443. [Internet]. [PubMed: 12767008]
54. Savolainen H, Lautenschlager I, Piiparinen H, Saarinen-Pihkala U, Hovi L, Vettenranta K. Human herpesvirus-6 and -7 in pediatric stem cell transplantation. Pediatric Blood Cancer. 2005; 45:820–825. [Internet]. [PubMed: 15700258]
55. Khanani M, Al-Ahmari A, Tellier R, Allen U, Richardson S, Doyle JJ, Gassas A. Human herpesvirus 7 in pediatric hematopoietic stem cell transplantation. Pediatric Blood Cancer. 2007; 48:567–570. [Internet]. [PubMed: 16544299]
56. Chapenko S, Folkmane I, Ziedina I, Chistyakovs M, Rozentals R, Krumina A, Murovska M. Association of HHV-6 and HHV-7 reactivation with the development of chronic allograft nephropathy. J Clin Virol: Off Publ Pan Am Soc Clin Virol. 2009; 46:29–32. [Internet].
57. Zawilinska B, Kopec J, Szostek S, Piatkowska-Jakubas B, Skotnicki AB, Kosz-Vnenchak M. Lymphotropic herpesvirus DNA detection in patients with active CMV infection – a possible role in the course of CMV infection after hematopoietic stem cell transplantation. Med Sci Monitor: Int Med J Exp Clin Res. 2011; 17:CR432–CR441. [Internet].

58. Kidd IM, Clark DA, Sabin CA, Andrew D, Hassan-Walker AF, Sweny P, Griffiths PD, Emery VC. Prospective study of human betaherpesviruses after renal transplantation: association of human herpesvirus 7 and cytomegalovirus co-infection with cytomegalovirus disease and increased rejection. Transplantation. 2000; 69:2400–2404. [Internet]. [PubMed: 10868648]

59. Lautenschlager I, Lappalainen M, Linnavuori K, Suni J, Höckerstedt K. CMV infection is usually associated with concurrent HHV-6 and HHV-7 antigenemia in liver transplant patients. J Clin Virol: Off Publ Pan Am Soc Clin Virol. 2002; 25(Suppl. 2):S57–S61. [Internet].

60. Adams MJ, Carstens EB. Ratification vote on taxonomic proposals to the International Committee on Taxonomy of Viruses (2012). Arch Virol. 2012; 157:1411–1422. [Internet]. [PubMed: 22481600]

61 •. Cassina G, Russo D, De Battista D, Broccolo F, Lusso P, Malnati MS. Calibrated real-time polymerase chain reaction for specific quantitation of HHV-6A and HHV-6B in clinical samples. J Virol Methods. 2013; 189:172–179. [Internet]. A methodological paper describing the development of two highly senstive PCR assays to discriminate between and quantify HHV-6A and HHV-6B in blood and tissue samples, even in the presence of mixed infections. [PubMed: 23391825]

62. Ljungman P, de la Camara R, Cordonnier C, Einsele H, Engelhard D, Reusser P, Styczynski J, Ward K. Management of CMV, HHV-6, HHV-7 and Kaposi-sarcoma herpesvirus (HHV-8) infections in patients with hematological malignancies and after SCT. Bone Marrow Transplant. 2008; 42:227–240. [Internet]. [PubMed: 18587440]

63. Tomblyn M, Chiller T, Einsele H, Gress R, Sepkowitz K, Storek J, Wingard JR, Young J-AH, Boeckh MJ, Boeckh MA. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant: J Am Soc Blood Marrow Transplant. 2009; 15:1143–1238. [Internet].

64. Galarraga MC, Gomez E, de Oña M, Rodriguez A, Laures A, Boga JA, Melon S. Influence of ganciclovir prophylaxis on citomegalovirus, human herpesvirus 6, and human herpesvirus 7 viremia in renal transplant recipients. Transplant Proc. 2005; 37:2124–2126. [Internet]. [PubMed: 15964357]

65. Tokimasa S, Hara J, Osugi Y, Ohta H, Matsuda Y, Fujisaki H, Sawada A, Kim JY, Sashihara J, Amou K, et al. Ganciclovir is effective for prophylaxis and treatment of human herpesvirus-6 in allogeneic stem cell transplantation. Bone Marrow Transplant. 2002; 29:595–598. [Internet]. [PubMed: 11979309]

66. Cheng FWT, Lee V, Leung WK, Chan PKS, Leung TF, Shing MK, Li CK. HHV-6 encephalitis in pediatric unrelated umbilical cord transplantation: a role for ganciclovir prophylaxis? Pediatr Transplant. 2010; 14:483–487. [Internet]. [PubMed: 19843234]

67 ••. Ogata M, Satou T, Inoue Y, Takano K, Ikebe T, Ando T, Ikewaki J, Kohno K, Nishida A, Saburi M, et al. Foscarnet against human herpesvirus (HHV)-6 reactivation after allo-SCT: breakthrough HHV-6 encephalitis following antiviral prophylaxis. Bone Marrow Transplant. 2012; 48:257–264. [Internet]. A prospective study of 118 allogeneic HCT recipients to explore the utility of low-dose foscarnet prophylaxis in reducing HHV-6 reactivation and associated complications. [PubMed: 22750998]

68. Ishiyama K, Katagiri T, Hoshino T, Yoshida T, Yamaguchi M, Nakao S. Preemptive therapy of human herpesvirus-6 encephalitis with foscarnet sodium for high-risk patients after hematopoietic SCT. Bone Marrow Transplant. 2011; 46:863–869. [Internet]. [PubMed: 20838386]

69. Ogata M, Satou T, Kawano R, Goto K, Ikewaki J, Kohno K, Ando T, Miyazaki Y, Ohtsuka E, Saburi Y, et al. Plasma HHV-6 viral load-guided preemptive therapy against HHV-6 encephalopathy after allogeneic stem cell transplantation: a prospective evaluation. Bone Marrow Transplant. 2008; 41:279–285. [Internet]. [PubMed: 18037945]

70 •. Papadopoulou A, Gerdemann U, Katari UL, Tzannou I, Liu H, Martinez C, Leung K, Carrum G, Gee AP, Vera JF, et al. Activity of broad-spectrum T cells as treatment for AdV, EBV, CMV, BKV, and HHV6 infections after HSCT. Sci Transl Med. 2014; 6:242ra83. [Internet]. A proof-of-concept study to demonstrate that generation of HHV-6 specific T cells for adoptive immunotherapy is feasible for clinical use.

71. Marty FM, Winston DJ, Rowley SD, Vance E, Papanicolaou GA, Mullane KM, Brundage TM, Robertson AT, Godkin S, Momméja-Marin H, et al. CMX001 to prevent cytomegalovirus disease

in hematopoietic-cell transplantation. N Engl J Med. 2013; 369:1227–1236. [Internet]. [PubMed: 24066743]

Table 1

Clinical characteristics of Roseoloviruses in immunocompromised transplantation recipients

	HHV-6A	HHV-6B	HHV-7
Incidence of reactivation	Infrequent (0–3%), consider ciHHV-6	Frequent (30–50%), more common after cord blood HCT	Frequent (40–60%)
Disease associations	Rare case reports, consider ciHHV-6	More frequent after HCT than SOT CNS dysfunction (especially encephalitis, where evidence supports causal association) Fever and rash Myelosuppression Acute GVHD Allograft dysfunction, rejection CMV reactivation Pneumonitis Hepatitis All-cause mortality	Rare case reports of disease but not well studied
Treatment and prevention	Not well studied	Antiviral treatment recommended for encephalitis (expert opinion) Prevention not shown to be beneficial in small studies	Not well studied
Research priorities	Significance of ciHHV-6	Optimal treatment for encephalitis Diagnosis of end-organ disease Significance of ciHHV-6 Clinical trials of treatment and prevention strategies	Large, prospective study of HHV-7 epidemiology, disease associations, and relationship to HHV-6 and CMV

HHV, human herpesvirus; ciHHV-6, inherited chromosomally integrated HHV-6; HCT, hematopoietic cell transplantation; SOT, solid organ transplantation; CNS, central nervous system; GVHD, graft-versus-host disease; CMV, cytomegalovirus.

Table 2

Clinical features of HHV-6B encephalitis

	Typical findings
Incidence	~1% in all allogeneic HCT recipients, rare case reports in SOT recipients ~8% in cord blood HCT recipients
Disease onset	~2–6 weeks after HCT
Symptoms/signs	Confusion, encephalopathy, anterograde amnesia, SIADH, seizures, insomnia
Brain MRI[a]	Circumscribed, non-enhancing, hyperintense lesions in the medial temporal lobes (especially the hippocampus and amygdala)
Cerebrospinal fluid	HHV-6B DNA, +/− mild protein elevation, +/− mild lymphocytic pleocytosis
Diagnosis	HHV-6B DNA detection in cerebrospinal fluid, consistent clinical findings, exclusion of inherited ciHHV-6 and other causes
Prognosis	Memory deficits and neuropsychological sequelae in up to 50%
	Death due to progressive encephalitis in up to 25% of all HCT recipients and 50% of cord blood HCT recipients

HHV-6B, human herpesvirus 6B; HCT, hematopoietic cell transplantation; SOT, solid organ transplantation; SIADH, syndrome of inappropriate antidiuretic hormone secretion; MRI, magnetic resonance imaging.

[a]Features of T2, fluid attenuation inversion recovery (FLAIR) and diffusion weighted-imaging (DWI) sequences.