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

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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.

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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 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.

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.

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