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American Society for Transplantation and Cellular Therapy Series #9: Management of HHV-6B After Hematopoietic Cell Transplantation and Chimeric Antigen Receptor (CAR)-T-Cell Therapy

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Abstract

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The Practice Guidelines Committee and the Transplant Infectious Disease Special Interest Group of the American Society for Transplantation and Cellular Therapy developed guidelines focusing on human herpes virus 6B (HHV-6B). A compendium-style approach was used to address a series of standalone frequently asked questions (FAQs), supported by tables and figures to spotlight key concepts. Adult and pediatric infectious disease and hematopoietic cell transplantation (HCT) content experts developed these FAQs, and finalized recommendations after consensus was reached. This ninth topic in the series focuses on the relevant risk factors, diagnostic considerations, prophylaxis, and treatment approaches relevant to HHV-6B infections after HCT and Chimeric Antigen Receptor (CAR)-T-Cell Therapy.

Keywords/Topics:

HHV-6; encephalitis; inherited chromosomally integrated HHV-6; allogeneic hematopoietic cell transplant; CAR-T-cell therapy

Introduction

Human herpesvirus 6B (HHV-6B) is a ubiquitous beta-herpesvirus that infects virtually all children early in life, typically causing a transient febrile illness often with a rash (*exanthema subitum*)¹. After primary infection, HHV-6B establishes life-long latency with the potential to reactivate and cause disease in the setting of immunosuppression, particularly after allogeneic hematopoietic cell transplantation (HCT)¹. While often asymptomatic, HHV-6B is the leading cause of post-transplant infectious encephalitis and has been associated with pleiotropic manifestations^{2–4}. The epidemiology of HHV-6A infection is less clear⁵. The diagnosis of HHV-6 reactivation and disease can be complicated by inherited chromosomally integrated HHV-6 (iciHHV-6), and failure to consider this possibility may result in unnecessary treatments.

The American Society for Transplantation and Cellular Therapy (ASTCT) Committee on Practice Guidelines (CoPG) and the ASTCT Transplant Infectious Disease Special Interest Group (TID-SIG) assembled an expert opinion panel to identify key challenges in the management of HHV-6B reactivation and disease after HCT and chimeric antigen receptor T-cell (CAR-T-cell) therapy. Key clinical practice questions were developed, and best practice recommendations were formulated for relevant sections. Answers are based on a literature review and were discussed amongst the expert panel to reach consensus. Evidence-based grading was applied to guidelines regarding management⁶ and these are summarized in the appendix (Table S1). The recommendations also apply to the pediatric population.

I. Definitions and diagnosis of HHV-6 reactivation and inherited chromosomally integrated HHV-6

FAQ1: How do we define HHV-6 reactivation?: Reactivation is defined as new detection of HHV-6 DNA, messenger RNA (mRNA) or viral proteins in blood or other samples, like cerebrospinal fluid (CSF), following primary infection (which is assumed beyond infancy). HHV-6 DNA detection is primarily identified by real-time polymerase chain reaction (PCR) assays^{7–9}, but determining whether a positive result represents

viral replication (especially in cell-free samples, e.g., plasma) or latently integrated DNA (especially in cellular samples, e.g., whole blood or tissue) can be challenging. Inherited chromosomally integrated HHV-6 (iciHHV-6) results in detection of latent viral DNA in all biologic samples, further complicating diagnosis^{9–12}.

FAQ2: What diagnostic methods and specimens should be used to detect HHV-6B?: Quantitative PCR (qPCR) in blood, preferably on cell-free plasma or serum, is recommended for diagnosing systemic HHV-6B reactivation (**AII**). Testing in the absence of clinical manifestations is not recommended (**DII**). Although viral load thresholds for predicting end-organ disease have been proposed, significant inter-assay variability limits their generalizability and utility in clinical practice¹³. The recently implemented World Health Organization (WHO) international standard for HHV-6B PCR is recommended to improve standardization of results and comparability between studies (**AII**)¹⁴.

Localized HHV-6B reactivation may occur (e.g., CNS¹⁵ and lung^{16,17}) without detectable viral DNA in the blood, so PCR testing in biopsy or other specific fluid (bronchoalveolar lavage [BAL] fluid) can be considered in parallel with plasma testing, in appropriate clinical contexts and after excluding alternative causes (**CIII**). Viral antigens can be detected via immunohistochemistry of formalin-fixed, paraffin-embedded (FFPE) tissue biopsy samples, but these methods are not routinely available (available at Coppe Laboratories [Waukesha, Wisconsin, USA])⁷. An algorithm on HHV-6B disease evaluation is depicted in Figure 1.

FAQ3: What is inherited chromosomally integrated HHV-6 and how common is it?: While most herpesviruses maintain latency through episomal formation, HHV-6 can also integrate into host DNA as a mechanism of latency^{18–21}. When this occurs in germline cells, an individual can vertically transmit iciHHV-6 to their offspring in a Mendelian fashion, which results in the presence of ≥ 1 copies of the HHV-6 genome in all of the offspring's nucleated cells^{11,22,23}. HHV-6B accounts for >70% of iciHHV-6 cases and HHV-6A accounts for the remainder; when species testing is available and HHV-6A is detected, it is almost universally associated with iciHHV6^{10,11}. The prevalence of iciHHV-6 is typically ~1% in the general population but may be up to double in allogeneic HCT recipients as the host or donor may have iciHHV-6^{24,25}.

Individuals with iciHHV-6 have characteristically elevated viral loads $>5.5\log_{10}$ copies/mL in whole blood and other cellular samples, which can lead to an incorrect diagnosis of reactivation and precipitate unnecessary invasive workups and antiviral administration²⁶ (see also **FAQ4**). Although iciHHV-6 is typically transcriptionally silent^{27,28}, the potential for active replication of host or donor-derived integrated virus with subsequent and sometimes fatal disease has been documented, although this is likely rare^{24,25,29–33}. Inherited ciHHV-6 has been associated with an increased risk for acute graft-versus-host disease (GVHD) and cytomegalovirus^{10,26}, but the causality is unclear³⁴.

FAQ4: When to suspect and how to diagnose chromosomally integrated HHV-6?: IciHHV-6 should be suspected if:

- a. Persistent HHV-6B viremia despite antiviral therapy, or

- b. HHV-6B viremia is detected at viral loads exceeding $>5.5 \log_{10}$ (~315,000) copies/mL in whole blood (in the absence of leukopenia), or
- c. HHV-6A viremia is detected at any level (Figure 2) (**AII**).

Patterns of HHV-6 detection after allogeneic HCT may vary depending on iciHHV-6 source:

- In iciHHV-6 negative recipients of iciHHV-6 positive grafts, HHV-6 viral loads typically rise with engraftment³⁵.
- In iciHHV-6-positive recipients of iciHHV-6-negative grafts, HHV-6 viral loads typically decline with engraftment; increased HHV-6 viral load in these cases may accompany relapse of the underlying malignancy³⁶.
- Importantly, cell lysis that occurs after blood draw and during sample processing, means that HHV-6 will be persistently detected in serum and plasma from patients with iciHHV-6 (or receiving allografts with iciHHV-6). However, levels are approximately 100-fold lower in serum^{11,12} compared to whole blood and up to 10–100-fold lower in plasma compared to serum depending on the time elapsed from sample collection and degree of cell lysis^{11,12,37,38}.

Diagnosis of iciHHV-6:

- A ratio of one copy of the HHV-6 genome per cellular genome is diagnostic of iciHHV-6. Droplet digital PCR (ddPCR) in whole blood is recommended to test for suspected iciHHV-6, because it is the most accurate method for providing precise estimates of HHV-6 DNA per cellular genome (**BII**)³⁸. Tests are commercially available for this purpose (e.g., available at University of Washington Virology Laboratory [Seattle, Washington, USA] and Coppe Laboratories [Waukesha, Wisconsin, USA]).
- ddPCR in stored or fresh plasma or serum samples can be used when whole blood is not available (**BII**)^{38–40}.
- A single viral load result and differences in viral loads by sample type are not useful in diagnosing iciHHV-6.

Alternatives when ddPCR is not available or not accessible:

- a. Comparison of quantitative PCR results of HHV-6 DNA to a human gene present in all nucleated cells is a possible although less accurate alternative (**BIII**)^{12,41}.
- b. Fluorescent in situ hybridization (FISH) can be used to confirm iciHHV-6 in cellular samples (peripheral blood mononuclear cells or tissue) but is not commercially available (**BIII**)⁴².
- c. Quantitative PCR in nail or hair follicles can be considered to confirm iciHHV-6, as only individuals with iciHHV-6 would have HHV-6 detection in these tissues (**BIII**)^{12,43}.
- d. Testing pre-HCT recipient samples or donor samples at any time could be considered to establish recipient or donor iciHHV-6 status (if negative, iciHHV-6 is unlikely) (**BIII**).

II. Epidemiology and diagnosis of end-organ disease

a. Allogeneic HCT

FAQ5: How common is HHV-6B reactivation, when does it occur, and what are the risk factors?: Reactivation incidence varies from 30% to 80% by day 100 after allogeneic HCT^{3,44–51} and occurs at a median of 3–5 weeks^{3,49,51,52} post-HCT. HHV-6B detection commonly lasts ≤ 1 week, while less than a quarter have HHV-6B detection for >4 weeks⁵². The incidence of reactivation is up to 90% or higher after umbilical cord blood transplantation (CBT) or T-cell depleted transplants^{2,51,53–55}. Other risk factors include human leukocyte antigen-mismatched or unrelated donors, acute GVHD and glucocorticoid therapy^{2,46,47,49,53,56} and post-transplant cyclophosphamide (PTCy)^{57–59}.

FAQ6: How common is HHV-6B encephalitis, when does it occur, and what are the risk factors?: HHV-6B is the leading cause of viral encephalitis after allogeneic HCT¹⁵ and typically occurs within the first 100 days. The incidence varies from 0.3% to 10.0%, depending on donor type and conditioning regimen^{2,4,48,54,55}, and is highest in recipients of a CBT^{2,48,54}. Risk factors for HHV-6B reactivation and encephalitis largely overlap, including systemic corticosteroid therapy for acute GVHD⁶⁰ and CBT, where HHV-6B accounts for $>95\%$ of reported cases of viral encephalitis⁶¹.

The median time from HHV-6B detection to onset of encephalitis is only 4–5 days^{48,52,62}, which is an important limitation for serial monitoring and preemptive intervention (**FAQ16**)⁶². Higher levels of HHV-6B DNAemia have been associated with an increased risk for HHV-6B encephalitis^{2,48,63}. However, the specificity is low^{48,64}, and HHV-6B encephalitis has been reported in the absence of blood detection. These challenges preclude establishing thresholds for preemptive intervention. Testing of blood samples for HHV-6B in the absence of clinical manifestations is not recommended, as there is insufficient evidence to support preemptive treatment in asymptomatic patients (**DII**).

FAQ7: What is the clinical presentation of HHV-6B encephalitis and how to diagnose it?: The clinical presentation is variable but may include disorientation, loss of consciousness, anterograde amnesia, and seizures^{15,48,65}. Hyponatremia due to syndrome of inappropriate antidiuretic hormone secretion (SIADH) frequently precedes HHV-6B encephalitis⁶⁶. Cerebrospinal fluid (CSF) analysis is typically normal but may reveal low-level pleocytosis and protein elevation^{2,37}.

Diagnosis of HHV-6B encephalitis is based on detection of HHV-6B DNA in CSF, coinciding with acute-onset compatible neurological manifestations, after exclusion of other infectious and non-infectious causes and icHHV-6. Quantitative PCR testing for HHV-6B DNA in the plasma and CSF is recommended in patients with a clinical syndrome compatible with HHV-6B encephalitis (**AII**)^{35,67,68}. Targeted quantitative HHV-6B PCR in CSF is recommended to confirm a positive result if qualitative multiplex PCR testing is performed initially, as well as in cases of a negative multiplex PCR result but high clinical suspicion.

Brain imaging with magnetic resonance imaging (MRI) is preferred to CT due to its greater sensitivity in identifying findings of encephalitis⁶⁹ **(BII)**. MRI abnormalities are detected in up to 60% of affected patients but imaging can be normal, especially early in the disease course^{4,70}. Hallmark findings include limbic system abnormalities, particularly the mesial temporal lobes and hippocampus^{48,71,72}. Typical findings include hyperintense lesions on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences while DWI/ADC (diffusion-weighted imaging/apparent diffusion coefficient) sequences may show restricted diffusion in the affected areas^{73,74}. Electroencephalogram (EEG) may be considered to evaluate for clinical or subclinical seizures **(CII)** and often shows focal seizures originating from temporal lobes, generalized or focal periodic discharges, and focal or diffuse slowing⁷².

Cognitive sequelae frequently include memory deficits^{2,4,15,75}. Up to 60% of patients with HHV-6B encephalitis may have neuropsychological sequelae, and in one study, only 20% were able to return to work, school, or household activities⁴. Attributable mortality from HHV-6B encephalitis ranges from 11% to 50% despite therapy^{2,4,15,75}.

FAQ8: What is known about the role of HHV-6B in pulmonary infection and how to diagnose it?: The pathogenic role of HHV-6B in post-HCT pneumonia has long been suspected, with supportive data from autopsy series, epidemiologic studies, and animal models.^{63,76,77} A prospective multicenter study in allogeneic HCT recipients undergoing bronchoalveolar lavage (BAL) for evaluation of pneumonia within the first four months after HCT demonstrate that patients with HHV-6B detection at $\geq 2.8 \log_{10}$ (578) copies/mL in BAL fluid had increased risk for overall mortality and death due to respiratory failure in adjusted analyses, independent of other possible causes of pneumonia, implicating HHV-6B as a possible pulmonary pathogen¹⁷. However, it remains uncertain whether antiviral treatment improves outcomes. Some experts recommend testing for HHV-6B in BAL fluid from allogeneic HCT recipients being evaluated for lower respiratory tract infection within 120 days after HCT **(CII)**.

FAQ9: What are other clinical manifestations and outcomes associated with HHV-6B reactivation beyond encephalitis and pneumonia?: HHV-6B has been associated with delirium in the absence of encephalitis, neurocognitive decline, myelitis^{78–81} and hepatitis^{82,83}. Myocarditis^{84,85} has rarely been reported. Testing in tissue biopsy (e.g., liver) can be considered in select cases in which there is no other apparent cause or if the suspicion is higher for other reasons (e.g., concomitant viremia) **(CII)**.

HHV-6B viremia has also been associated with fever and rash, acute GVHD, thrombocytopenia, delayed T-cell recovery and allograft failure^{3,46,47,55,86–88}. In cases of myelosuppression and allograft failure, testing for HHV-6B of blood and bone marrow samples can be considered along with evaluation for other infectious and non-infectious causes^{47,86,89–92}. However, direct causality is challenging to establish, and the benefit of antiviral therapy is not known **(FAQ12)**. An association with subsequent CMV reactivation has also been observed^{3,93,94}. Finally, a recent meta-analysis found HHV-6B reactivation to be associated with higher non-relapse mortality and overall mortality, but the role of treatment or prevention of HHV-6B to improve outcomes is unclear⁹⁵.

b. Cellular therapies beyond allogeneic HCT

FAQ10: What is the incidence and clinical significance of HHV-6B reactivation after autologous HCT?:

While the risk for HHV-6B reactivation after autologous HCT is lower compared to allogeneic HCT, the epidemiology of HHV-6B reactivation and disease after autologous HCT is less well-characterized⁹⁶. Systematic weekly testing has shown reactivation rates of 25%–46% at a median of 2 weeks post-HCT^{97–101}. HHV-6B has been associated with a spectrum of complications similar to those observed after allogeneic HCT, with peri-engraftment fever being the most frequently reported symptom, followed by rash, lung infiltrates and delayed platelet and neutrophil engraftment, while encephalitis is rare^{100–104}. Diagnostic testing for HHV-6B, along with other latent viral infections, should be considered when compatible clinical manifestations exist without an alternative cause (CIII).

FAQ11: What is the epidemiology of HHV-6B reactivation after CAR-T-cell therapy?:

Despite increasing reports of HHV-6B encephalitis following CAR-T-cell therapies, the overall impact of HHV-6B in this population remains largely unexplored¹⁰⁵. In a study of CAR-T-cell therapy recipients with prospectively weekly HHV-6B testing, the cumulative incidence of reactivation was 6% within 2 to 6 weeks post-infusion and was self-limiting without any cases of HHV-6B encephalitis¹⁰⁶. HHV-6B reactivation was only identified in patients who had prior treatment for cytokine release syndrome (CRS). In a retrospective cohort of >600 CAR-T cell therapy recipients with symptom-driven testing, only one case of possible HHV-6B encephalitis was identified for an incidence of 0.17% (95% confidence interval, 0.02–0.94%), although the low rate of combined plasma and cerebrospinal fluid testing was a limitation¹⁰⁶. HHV-6B encephalitis may be infrequent after CAR-T cell therapy but it may be clinically indistinguishable from immune effector-cell associated neurotoxicity syndrome (ICANS)^{107,108} and HHV-6B should be considered in patients with neurological symptoms not resolving with ICANS management or other compatible manifestations (BII).

III. Treatment

FAQ12: When and how should HHV-6B be treated?

a. Encephalitis: Given the high morbidity and mortality associated with HHV-6B encephalitis^{2,4,48,75,109}, diagnostic CSF testing should be performed without delay, and empiric treatment should be strongly considered when there is high suspicion for HHV-6B encephalitis while additional workup is ongoing (BIII). Early Infectious Diseases consultation is recommended to guide treatment. If CSF is negative for HHV-6B and brain MRI does not show signs of encephalitis, the likelihood of HHV-6B encephalitis is low. HHV-6B DNA detection in the plasma is typical in patients with HHV-6B encephalitis, but diagnosis and treatment decisions should be based on CSF testing when possible¹⁵. If workup is suggestive of HHV-6B encephalitis, treatment should be continued for at least 3 weeks and discontinued with clearance (or decrease below limit of quantification) of HHV-6B DNA from plasma and CSF, whichever is longer (AII)^{35,110,111}.

b. End-organ disease outside of encephalitis: There is insufficient evidence to support clinical benefit, and therefore to provide recommendations for initiation or duration of therapy, in patients with possible HHV-6B associated end-organ disease outside of encephalitis. Consideration to treat should balance medication toxicities and should involve consultation with an infectious diseases physician (CII). In the setting of HHV-6B viremia and allograft failure, treatment and evidence of improving viremia can be considered prior to subsequent hematopoietic cell or donor lymphocyte infusions. Treatment recommendations are summarized in Table 1.

c. Asymptomatic viremia: There is no conclusive evidence for treatment of asymptomatic viremia, and there are no established thresholds. Some experts would consider empiric treatment in a high-risk setting (CIII).

FAQ13: What are the recommended antiviral therapies for HHV-6B?

a. Encephalitis: In the absence of randomized controlled data showing superiority of any agent, treatment of HHV-6B encephalitis may be with either foscarnet at 90 mg/kg q12h or 60 mg/kg q8h (total daily dose of 180 mg/kg) or ganciclovir 5 mg/kg q12h^{4,35,70,111,112} (AII). Dose adjustments for impaired renal function are required and consultation with Clinical Pharmacy is recommended where available. Foscarnet, ganciclovir, and cidofovir have demonstrated *in vitro* and *in vivo* activity against HHV-6^{7,113–116}. However, while *in vitro* data suggest that foscarnet has increased antiviral activity with consistent inhibition, a favorable selectivity index (SI), and better CNS penetration compared to ganciclovir; clinical data demonstrating superiority are lacking^{115–121}. Cidofovir has limited CNS penetration and has largely been used as second- or third-line therapy or in combination therapy^{122–124} (CIII). The choice of agent should be based on the risk for myelosuppression with ganciclovir or nephrotoxicity with foscarnet. Every 12-hour foscarnet dosing may be preferred over q8h-dosing to minimize volume overload associated with the required fluid boluses for nephroprotection. Valganciclovir has not been studied but could be considered as an oral step-down agent due to its excellent oral bioavailability in the absence of gastrointestinal GVHD (CIII).

b. End-organ disease outside of encephalitis: There is insufficient evidence to provide recommendations for optimal dosing of antiviral agents for HHV-6B end-organ disease outside of encephalitis; however, standard dosing of similar agents may be considered (CIII).

FAQ14: Is there a role for combination therapies in HHV-6B encephalitis?:

Combination therapy may be considered in severe or refractory cases of HHV-6B encephalitis, but in the absence of sufficient data showing clear superiority versus monotherapy it is not routinely recommended (CIII). In allogeneic HCT, retrospective studies have suggested possible improved long-term neurologic sequelae with combination therapy with ganciclovir and foscarnet (standard dosing)^{4,75}. Decision to use combination therapy must be balanced with treatment-related toxicities^{4,75,122,125}.

FAQ15: What other therapeutic approaches for HHV-6B are in development?:

A lipid formulation of cidofovir (brincidofovir) has high *in vitro* activity against HHV6. In an exploratory analysis of the phase 3 trial of oral brincidofovir study for CMV prevention, HHV-6B DNAemia was significantly reduced in the brincidofovir arm compared to placebo¹²⁶. Studies establishing efficacy for treatment of end-organ disease have not been conducted¹²⁶. The intravenous formulation of brincidofovir appears to be well tolerated (with less gastrointestinal toxicity than the oral formulation) in initial studies in HCT recipients and is under development for adenovirus and other double stranded DNA viruses¹²⁷.

Adoptive cellular therapies with virus-specific immune effector cells (e.g., T cells or natural killer cells) including HHV-6B specific T-cells have been used in a few patients with HHV-6B infection after HCT, but the data using these therapies for HHV-6B treatment and prevention are inconclusive^{128–132}.

IV. Prevention**FAQ16: Is there a role for monitoring and preemptive therapy of HHV-6B reactivation?:**

Serial testing of blood samples for HHV-6B and routine preemptive therapy is not recommended after HCT or CAR-T-cell therapy, as there is insufficient evidence to support the efficacy of preemptive intervention with currently available therapies and no established thresholds (**DII**); however, some experts would consider empiric treatment in high-risk settings (**CIII**). A few small studies showed that preemptive foscarnet or ganciclovir for HHV-6 viremia did not reduce the incidence of encephalitis, but the data are limited^{44,62,133}.

FAQ17: Is there a role for HHV-6B prophylaxis?: Antiviral prophylaxis with currently available therapies is not recommended due to insufficient evidence for efficacy in preventing HHV-6B encephalitis or other HHV-6B associated complications (**DII**). Published studies are limited by lack of appropriate controls, small sample sizes, and heterogeneous approaches^{134–138}. Effective prophylaxis may become feasible with the development of safer antivirals and well-designed clinical trials.

V. Unmet needs and future directions**FAQ18: What are future directions for HHV-6 management and prevention?:**

Large studies are needed to redefine the epidemiology of HHV-6B reactivation, particularly as HCT practices evolve and novel populations, such as allogeneic CAR-T cell recipients, emerge. Standardized and widely accessible diagnostic tools, including robust testing for *ici*HHV-6, are essential to distinguish true viral reactivation from latent integration. Additionally, further research is required to determine the pathogenic role of *ici*HHV-6 and its potential for reactivation. Beyond encephalitis, the role of antiviral therapy in treating other HHV-6B-associated end-organ diseases remains unclear and warrants investigation. Finally, novel antiviral agents like brincidofovir to prevent HHV-6B reactivation present promising opportunities to mitigate direct effects, such as HHV-6B encephalitis, and indirect effects, including reducing GVHD, enhancing graft success, and potentially lowering mortality in HCT recipients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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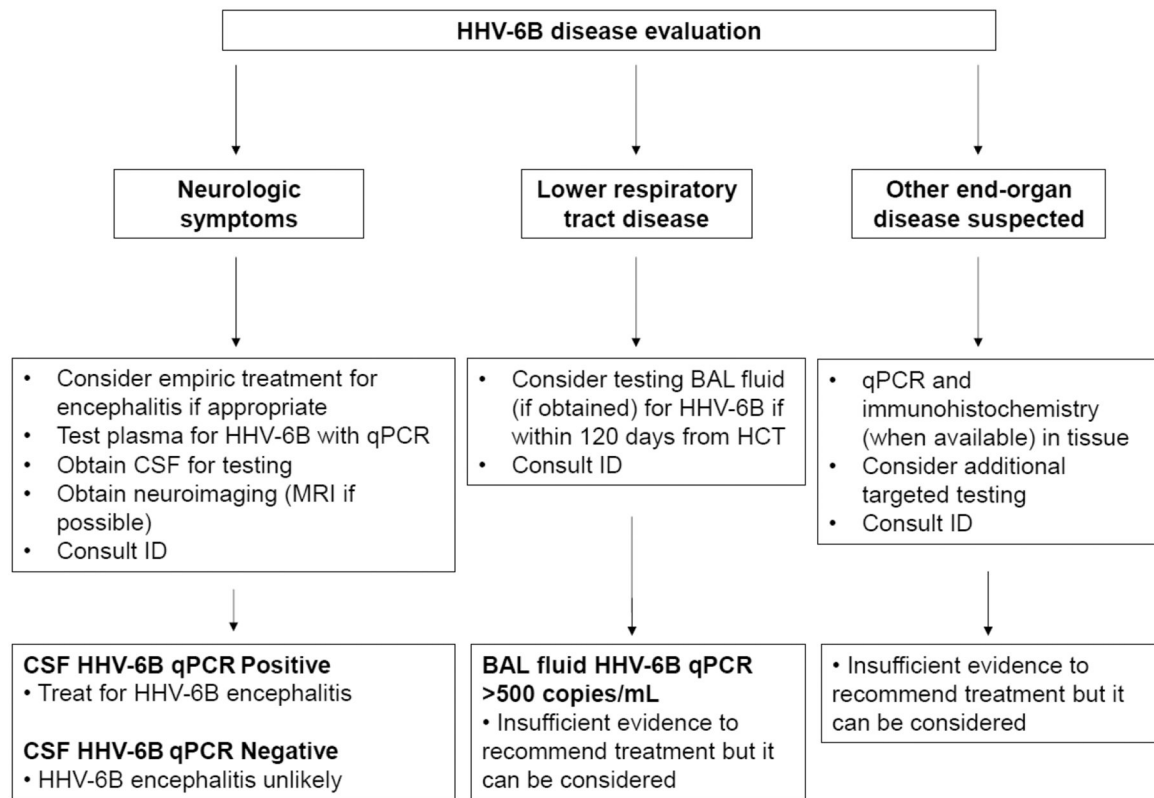


Figure 1: Algorithm for HHV-6B disease evaluation and management

Testing and management by clinical manifestation of HHV-6B reactivation.

BAL: bronchoalveolar lavage; CSF: cerebrospinal fluid; ID: infectious diseases;

MRI: Magnetic resonance imaging; qPCR: quantitative polymerase chain reaction.

Immunohistochemistry testing is available at Coppe Laboratories (Waukesha, Wisconsin, USA).

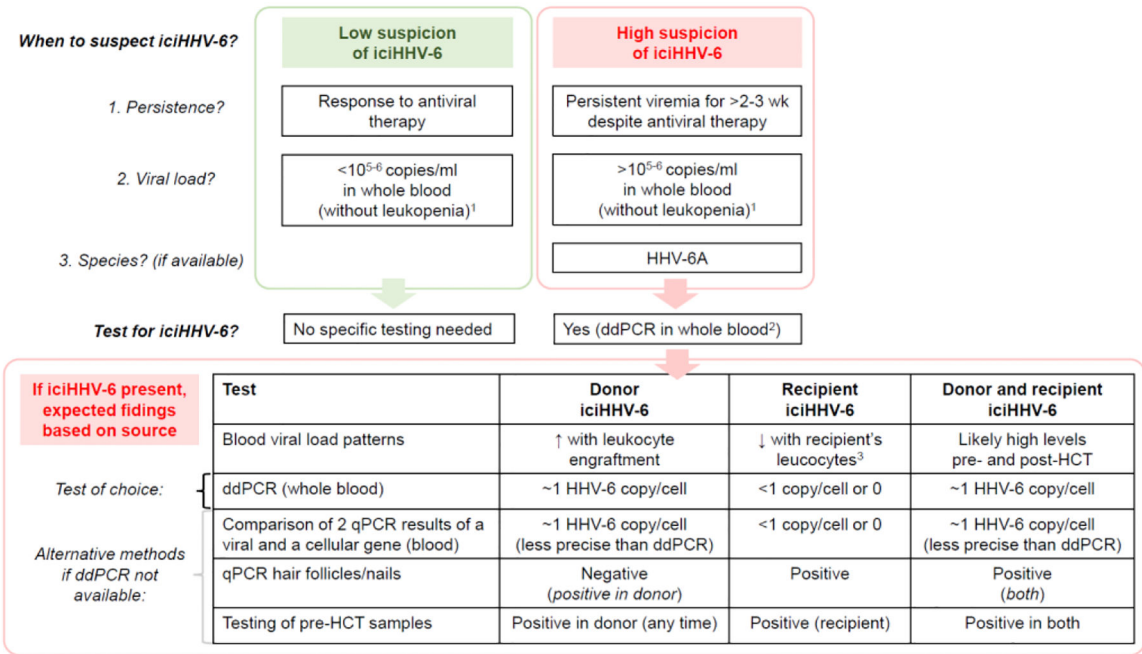


Figure 2: Algorithm for testing for inherited chromosomally integrated HHV-6 (*iciHHV-6*)

Algorithm summarizing when to suspect and how to test for *iciHHV-6*. Testing for *iciHHV-6* is indicated in case of high clinical suspicion including persistent HHV-6B viremia despite antiviral therapy, viral loads above 10⁵–10⁶ copies/mL in cellular samples such as whole blood, or detection of HHV-6A (when species is available). Blood viral load patterns according to the state of *iciHHV-6* (donor, recipient, both) refers to allogeneic HCT.

¹Levels are approximately 100-fold lower in serum compared to whole blood and up to 10–100-fold lower in plasma compared to serum depending on the time elapsed from sample collection and degree of cell lysis^{11,12,37,38}.

² Testing of whole blood for *iciHHV6* with ddPCR is available at University of Washington Virology Laboratory, (Seattle, Washington, USA) and Coppe Laboratories (Waukesha, Wisconsin, USA).

³Detection at high-levels pre-HCT; HHV-6 will continue to be detected in non-hematopoietic tissues while a rise in blood may accompany relapse of underlying malignancies.

ddPCR: droplet digital PCR; *iciHHV-6*: inherited chromosomally integrated HHV-6 (*iciHHV-6*); qPCR: quantitative PCR; wk: weeks. Figure adapted from Kampouri et al⁹⁶.

Table 1:

Antiviral treatment for HHV-6B

Disease Manifestation	Agent	Grade	When to chose	Disadvantage	Duration
	Recommended as first line (AII)				
Encephalitis	Foscarnet 90 mg/kg bid IV	AII	Pre-engraftment/ cytopenias	Nephrotoxicity	≥3 weeks and clearance of HHV-6B DNA from blood and CSF
	Ganciclovir 5 mg/kg bid IV	AII	Post-engraftment/risk of kidney injury	Myelotoxicity	
	May be considered as salvage therapy (CIII)				
	Cidofovir 5 mg/kg/week for 2 doses then biweekly	CIII	Salvage therapy	Nephrotoxicity/poor CNS penetration	
	Combination: Ganciclovir + Foscarnet	CIII	Salvage therapy severe or refractory encephalitis	Toxicities	
	May be considered (limited evidence to support) (CII)				
Other end-organ disease (e.g., pneumonia, hepatitis)	Ganciclovir 5 mg/kg bid IV ^I Foscarnet 90 mg/kg bid IV ^I	CII		Benefit not established	2–3 weeks and clearance from blood and/or tissue site
	Not recommended (DII)				
Asymptomatic viremia ²	Prophylaxis	DII		Efficacy not established/ toxicities	Unknown
	Preemptive therapy	DII			

¹There is insufficient evidence to provide recommendations for optimal dosing of antiviral agents for HHV-6B end-organ disease outside of encephalitis; however, standard dosing of similar agents may be considered (CIII).

²Some experts would consider empiric treatment of asymptomatic HHV-6B viremia in a high-risk setting (CIII).

CNS: central nervous system; CSF: cerebrospinal fluid; ID: infectious diseases. Grade of evidence according to ASTCT guidelines⁶.