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Шановні колеги!

Щиро вітаємо колектив Інституту мікробіології та імунології ім. І. І. Мечникова НАМН України зі знаменним ювілеєм — 140-річчям від дня заснування установи.

За роки своєї діяльності інститут пройшов славний шлях становлення та розвитку, утвердившись як один із провідних наукових центрів України у галузях мікробіології, вірусології та імунології. Заснований на міцних традиціях фундаментальної науки, сьогодні він залишається потужним осередком наукової думки, інноваційних досліджень і підготовки висококваліфікованих фахівців.

Вагомий внесок учених інституту у розвиток вітчизняної та світової науки, впровадження новітніх технологій, удосконалення методів профілактики, діагностики та лікування захворювань здобув заслужене визнання наукової спільноти та практичної медицини.

У цей урочистий день висловлюємо щиру вдячність усім поколінням науковців, дослідників і працівників інституту за відданість обраній справі, високий професіоналізм, наполегливість і самовіддану працю. Ваші знання, досвід і відданість науці є запорукою подальшого розвитку медичної науки та зміцнення системи охорони здоров'я України.

Бажаємо колективу Інституту міцного здоров'я, невичерпного натхнення, нових наукових звершень, плідної праці, добробуту та миру, а установі — подальшого процвітання, реалізації амбітних проєктів і нових вагомих досягнень.

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CLINICAL FEATURES OF HUMAN HERPESVIRUS 6 INFECTION IN IMMUNOCOMPETENT AND IMMUNOCOMPROMISED PATIENTS: A COMPARATIVE REVIEW

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Abstract. ***Introduction.*** Human herpesvirus 6 (HHV-6) is a ubiquitous beta-herpesvirus that infects nearly the entire human population during early childhood. Following primary infection, the virus establishes lifelong latency within host immune cells. While HHV-6 infection in immunocompetent individuals is typically benign and self-limiting, viral reactivation in immunocompromised patients may result in severe multisystem and potentially fatal complications.
Objective. To provide a comprehensive comparative analysis of the clinical manifestations, pathogenesis, diagnostic challenges, and therapeutic approaches to HHV-6 infection in immunocompetent and immunocompromised patients.
Materials and methods. A review of the medical literature indexed in PubMed, Scopus, and Web of Science from 2000 to 2025 was conducted. Particular emphasis was placed on clinical studies, systematic reviews, cohort analyses, and expert consensus documents addressing HHV-6 infection in patients with different immune statuses.
Results. In immunocompetent hosts, HHV-6 infection predominantly manifests as exanthema subitum in early childhood and is usually associated with a favourable prognosis. In contrast, immunocompromised patients, particularly hematopoietic stem cell and solid organ transplant recipients, frequently experience HHV-6 reactivation associated with encephalitis, pneumonitis, hepatitis, bone marrow suppression, and increased mortality. Diagnostic interpretation is complicated by chromosomally integrated HHV-6 (ciHHV-6), which may mimic active viral infection.
Conclusions. HHV-6 demonstrates dual clinical behaviour determined primarily by the host immune status. Accurate interpretation of molecular diagnostic findings and early recognition of clinically significant viral reactivation are essential for optimizing outcomes in high-risk patient populations.
Key words: human herpesvirus 6, immunocompromised host, chromosomally integrated HHV-6, viral reactivation, molecular diagnostics, antiviral therapy.

КЛІНІЧНІ ОСОБЛИВОСТІ ІНФЕКЦІЇ, СПРИЧИНЕНОЇ ВІРУСОМ ГЕРПЕСУ ЛЮДИНИ 6 ТИПУ, В ІМУНОКОМПЕТЕНТНИХ ТА ІМУНОКОМПРОМЕТОВАНИХ ПАЦІЄНТІВ: ПОРІВНЯЛЬНИЙ ОГЛЯД

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Резюме. ***Вступ.*** Вірус герпесу людини 6 типу (HHV-6) — це повсюдно поширений бета-герпесвірус, який інфікує майже всю людську популяцію в ранньому дитинстві. Після первинного інфікування вірус встановлює довічну латентність в імунних клітинах хазяїна. Хоча інфекція HHV-6 в імунокомпетентних осіб зазвичай має доброякісний та самообмежувальний перебіг, реактивація вірусу в імунокомпрометованих пацієнтів може призводити до тяжких, полісистемних та потенційно фатальних ускладнень.
Мета. Провести комплексний порівняльний аналіз клінічних проявів, патогенезу, діагностичних труднощів і терапевтичних підходів до HHV-6-інфекції в імунокомпетентних та імунокомпрометованих осіб.

Матеріали та методи. Проведено огляд медичної літератури, проіндексованої в PubMed, Scopus та Web of Science упродовж 2000–2025 років. Основну увагу приділено клінічним дослідженням, систематичним оглядам, когортним аналізам та експертним консенсусним документам, присвяченим HHV-6-інфекції при різних станах імунної системи.
Результати. В імунокомпетентних осіб HHV-6-інфекція переважно проявляється раптовою екзантемою в ранньому дитячому віці та зазвичай асоціюється зі сприятливим прогнозом. Натомість в імунокомпрометованих пацієнтів, особливо у реципієнтів трансплантатів гемопоетичних стовбурових клітин і солідних органів, часто спостерігається реактивація HHV-6, асоційована з енцефалітом, пневмонітом, гепатитом, пригніченням кісткового мозку та підвищеною смертністю. Діагностична інтерпретація ускладнюється наявністю хромосомно інтегрованого HHV-6 (ciHHV-6), який може імітувати активну вірусну інфекцію.
Висновки. HHV-6 демонструє подвійний характер клінічного перебігу, що визначається насамперед імунним статусом хазяїна. Точна інтерпретація результатів молекулярної діагностики та раннє виявлення клінічно значущої реактивації вірусу є важливими для оптимізації результатів лікування у групах пацієнтів високого ризику.
Ключові слова: вірус герпесу людини 6 типу, імунокомпрометований хазяїн, хромосомно інтегрований HHV-6, реактивація вірусу, молекулярна діагностика, противірусна терапія.

Introduction. Human herpesvirus 6 (HHV-6) occupies a unique position among human herpesviruses due to its near-universal prevalence, pronounced neurotropism, and exceptional biological ability to integrate into the human genome. First isolated in 1986 from patients with lymphoproliferative disorders, HHV-6 was later classified into two closely related species — HHV-6A and HHV-6B — based on genetic, biological, and epidemiological differences [1, 2]. The key biological and clinical distinctions between these two species are summarized in Table 1. HHV-6B is responsible for the vast majority of primary infections in early childhood, whereas HHV-6A is more frequently detected in immunocompromised individuals, and its precise clinical significance remains insufficiently defined.

Table 1

Key differences between human herpesvirus 6 variants A and B

Parameter	HHV-6A	HHV-6B
Taxonomic status	Distinct species	Distinct species
Global prevalence	Lower, geographically variable	Nearly universal
Primary infection	Less well defined	Early childhood (6–24 months)
Typical clinical manifestation	Often asymptomatic; unclear	Exanthema subitum (roseola)
Predominant host	Adults, immunocompromised	Infants and young children
Neurotropism	Pronounced	Moderate
Association with CNS disease	Encephalitis, possible chronic neurological disorders	Febrile seizures, post-transplant encephalitis
Cell tropism	CD4 , CD8 T cells, glial cells	Primarily $CD4^+$ T cells
Reactivation in immunosuppression	Frequent	Very frequent
Role in transplantation	Possible contributor to CNS disease	Major cause of post-HSCT encephalitis
Chromosomal integration (ciHHV-6)	Yes	Yes
Diagnostic detection	Less frequently differentiated	Most commonly detected
Antiviral susceptibility	Ganciclovir, foscarnet, cidofovir	Ganciclovir, foscarnet, cidofovir

From an epidemiological perspective, HHV-6 is among the most widespread human pathogens. By the age of two years, more than 90% of children worldwide demonstrate serological evidence of previous infection [1]. Primary infection usually occurs through close contact and exposure to saliva. Following the initial infection, the virus establishes lifelong latency within monocytes, macrophages, and $CD4^+$ T lymphocytes. In immunocompetent hosts, effective cellular immune surveillance — particularly virus-specific T-cell responses — suppresses viral replication and prevents clinically significant reactivation.

A distinctive biological feature that differentiates HHV-6 from other human herpesviruses is its ability to integrate its genome into the telomeric regions of

host chromosomes. This phenomenon, referred to as chromosomally integrated HHV-6 (ciHHV-6), occurs in approximately 1% of the general population and is inherited in a Mendelian manner through the germline [3]. Individuals with ciHHV-6 exhibit persistently high HHV-6 DNA levels in whole blood and various tissues independent of active viral replication. This unique property represents a major diagnostic challenge, as it may be misinterpreted as evidence of active or disseminated infection.

The clinical significance of HHV-6 infection therefore depends critically on the host immune status. In immunocompetent individuals, HHV-6 infection is usually benign and self-limiting. In contrast, in immunocompromised hosts — including hematopoietic stem cell transplant recipients, solid organ transplant recipients, patients receiving intensive immunosuppressive therapy, and critically ill individuals — HHV-6 reactivation may lead to severe neurological, pulmonary, hepatic, and haematological complications associated with substantial morbidity and mortality [4].

Objective. To provide a comprehensive comparative analysis of the clinical manifestations, pathogenesis, diagnostic challenges, and therapeutic approaches to HHV-6 infection in immunocompetent and immunocompromised patients.

Materials And Methods. This narrative review was conducted through a structured search of the PubMed (MEDLINE), Scopus, and Web of Science databases for publications published between January 2000 and January 2025. The search strategy included combinations of the following terms: “human herpesvirus 6”, “HHV-6A”, “HHV-6B”, “HHV-6 encephalitis”, “chromosomally integrated HHV-6”, “immunocompromised host”, “hematopoietic stem cell transplantation”, and “solid organ transplantation”.

Priority was given to systematic reviews, meta-analyses, prospective cohort studies, and multicentre clinical investigations. Case reports were included selectively when they illustrated rare but clinically significant manifestations or diagnostic challenges. Only peer-reviewed publications were considered. Unpublished data and non-peer-reviewed sources were excluded.

Results.

CLINICAL MANIFESTATIONS IN IMMUNOCOMPETENT HOSTS

Primary HHV-6 infection in childhood. In the vast majority of individuals, primary HHV-6 infection occurs during early childhood, most commonly between 6 and 24 months of age. The classic clinical presentation is exanthema subitum (roseola infantum), also known as sixth disease. The illness typically begins abruptly with a high fever, frequently exceeding 39–40 °C, which persists for three to five days. A characteristic feature of this febrile phase is the discrepancy between the degree of fever and the relatively preserved general condition of the child, who often remains alert, active, and hemodynamically stable.

Following defervescence, a macular or maculopapular rash appears, initially involving the trunk and subsequently spreading to the neck, face, and extremities. The rash is usually non-pruritic, pale pink in colour, and resolves spontaneously within one to three days without desquamation. Additional clinical signs may include periorbital oedema (Berliner sign), mild cervical or occipital lymphadenopathy, and erythematous papules on the soft palate (Nagayama spots). Although non-specific, these findings may support the clinical diagnosis of HHV-6 infection [1, 5].

Neurological manifestations represent the most clinically significant complications of primary HHV-6 infection in children. HHV-6 is recognized as one of the leading infectious causes of febrile seizures, accounting for up to 30% of first-time febrile seizure episodes in children aged 6–36 months [5]. Most seizures are simple, generalized, and self-limiting. However, complex febrile seizures and status epilepticus have also been reported, underscoring the neurotropic potential of the virus.

Despite these complications, the overall prognosis of primary HHV-6 infection in immunocompetent children is favourable. Long-term neurological sequelae are uncommon, and antiviral therapy is not indicated in uncomplicated cases.

Extra-cutaneous and systemic manifestations in immunocompetent hosts. Although exanthema subitum represents the prototypical manifestation of HHV-6 infection, the clinical spectrum in immunocompetent individuals extends beyond cutaneous involvement. Gastrointestinal symptoms such as diarrhoea, vomiting, and abdominal discomfort may accompany the febrile phase, particularly in infants and young children. Mild respiratory symptoms, including rhinorrhoea and cough, have also been described.

Transient hepatic involvement is not uncommon. Mild to moderate elevation of serum aminotransferase levels may be detected during acute infection, reflecting subclinical hepatitis. In most cases, liver enzyme abnormalities resolve spontaneously without clinical consequences. Haematological abnormalities, including transient leukopenia or thrombocytopenia, have also been reported and are believed to result from temporary bone marrow suppression during viremia.

Rare but severe manifestations have been documented in immunocompetent hosts, including myocarditis, pneumonitis, hemophagocytic lymphohistiocytosis, and acute encephalitis. Although such cases are exceptional, they highlight the intrinsic pathogenic potential of HHV-6 even in the absence of overt immunodeficiency.

Primary infection and reactivation in adults. Primary HHV-6 infection in adulthood is uncommon because of the widespread exposure to the virus during childhood. When it does occur, it often presents as a mononucleosis-like syndrome characterized by prolonged fever, lymphadenopathy, pharyngitis, and hepatosplenomegaly. Differentiation from Epstein–Barr virus or cytomegalovirus infection requires specific serological or molecular testing.

HHV-6 reactivation has been increasingly recognized in critically ill immunocompetent adults, particularly in intensive care unit settings. Studies have demonstrated HHV-6 DNA detection in up to 20–25% of mechanically ventilated patients, frequently in association with reactivation of other herpesviruses, such as cytomegalovirus [6]. In this context, HHV-6 reactivation is generally considered a marker of severe physiological stress and immune dysregulation rather than a primary cause of organ dysfunction. Nevertheless, its presence has been associated with prolonged intensive care unit stays and poorer clinical outcomes.

CLINICAL MANIFESTATIONS IN IMMUNOCOMPROMISED PATIENTS

Hematopoietic stem cell transplantation. Recipients of allogeneic haematopoietic stem cell transplantation (HSCT) represent the population at highest risk for clinically significant HHV-6 reactivation. The incidence of HHV-6 reactivation in this group ranges from 40% to 50%, with viral replication typically occurring between two- and four-weeks following transplantation, often preceding cytomegalovirus reactivation [7].

The most severe and clinically significant complication is HHV-6–associated limbic encephalitis. Patients typically present with acute onset of confusion, disorientation, impaired short-term memory, behavioural changes, and seizures. Anterograde amnesia is a particularly characteristic feature. Magnetic resonance imaging frequently reveals bilateral hyperintense lesions in the medial temporal lobes, including the hippocampus and amygdala [8]. Without prompt antiviral therapy, HHV-6 encephalitis is associated with high mortality and substantial long-term neurocognitive impairment among survivors.

HHV-6 also exerts detrimental effects on haematopoiesis. The virus demonstrates tropism for $CD34^+$ hematopoietic progenitor cells, and viral replication within the bone marrow may result in delayed neutrophil and platelet engraftment. Clinically, this manifests as persistent cytopenias, increased transfusion requirements, and prolonged hospitalization [9].

An additional area of concern is the interaction between HHV-6 reactivation and graft-versus-host disease (GVHD). HHV-6–induced immune activation may exacerbate GVHD, while intensified immunosuppressive therapy used to treat GVHD increases the risk of viral reactivation, creating a complex bidirectional relationship.

Solid organ transplantation. HHV-6 reactivation is also common among solid organ transplant recipients, with reported incidence rates ranging from 30% to 55%, depending on the transplanted organ and the intensity of immunosuppressive therapy [10]. In contrast to HSCT recipients, HHV-6–associated disease in this population is often organ-specific.

In liver transplant recipients, HHV-6 reactivation may manifest as hepatitis with elevated liver enzyme levels, which can mimic acute graft rejection or cytomegalovirus infection. In lung transplant recipients, HHV-6 has been associated with pneumonitis and has been implicated as a potential contributor to chronic lung allograft dysfunction. In kidney transplant recipients, HHV-6 infection is less frequently associated with direct graft injury but often occurs in conjunction with cytomegalovirus infection, complicating clinical management.

Key clinical differences between immunocompetent and immunocompromised hosts are summarized in Table 2.

Table 2

Clinical characteristics of HHV-6 infection in immunocompetent and immunocompromised hosts

Parameter	Immunocompetent hosts	Immunocompromised hosts
Typical population	Infants, young children; rarely adults	HSCT recipients, solid organ transplant recipients, critically ill patients
Type of infection	Primary infection	Reactivation
Frequency	Nearly universal by age 2 years	30–55% depending on risk group
Clinical course	Self-limiting	Severe, progressive
Common manifestations	Fever, rash, febrile seizures	Encephalitis, pneumonitis, hepatitis, myelosuppression
Neurological involvement	Febrile seizures (usually benign)	Limbic encephalitis, seizures, cognitive impairment

Continuation of Table 2

Parameter	Immunocompetent hosts	Immunocompromised hosts
Haematological effects	Rare, transient	Cytopenia, delayed engraftment
Mortality	Negligible	Up to 50% in untreated encephalitis
Treatment approach	Supportive care	Antiviral therapy required
Prognosis	Excellent	Depends on early diagnosis and treatment

PATHOGENESIS AND IMMUNOLOGICAL ASPECTS

The pathogenic mechanisms of HHV-6 infection are complex and involve both direct viral cytopathic effects and indirect immune-mediated processes. Following primary infection, HHV-6B establishes latency primarily in $CD4^+$ T lymphocytes, monocytes, and macrophages. Viral persistence is maintained through multiple immune evasion strategies, including downregulation of major histocompatibility complex (MHC) class I molecules and modulation of cytokine signalling pathways [1, 4].

HHV-6A demonstrates pronounced neurotropism. The virus is capable of infecting glial cells and neurons, which explains its association with seizures and encephalitis. Experimental studies suggest that HHV-6 can induce apoptosis of infected neural cells and disrupt synaptic signalling, contributing to neurological manifestations. Additionally, HHV-6 infection has been shown to alter the expression of pro-inflammatory cytokines, including interleukin-6 and tumour necrosis factor-α, further amplifying neuroinflammation.

A unique aspect of HHV-6 biology is its ability to integrate into the telomeric regions of human chromosomes. Chromosomal integration allows the virus to persist in a latent form that is transcriptionally silent but genetically stable. Reactivation from ciHHV-6 may occur under conditions of profound immunosuppression, although the clinical relevance of such events remains incompletely understood [3].

Secondary immunodeficiency plays a central role in HHV-6 reactivation. Impaired cellular immunity — whether due to underlying disease, intensive immunosuppressive therapy, or severe infectious stress — leads to diminished virus-specific T-cell responses, allowing viral replication to resume. Studies examining immune status in patients with secondary immunodeficiency have demonstrated dysregulation of T-cell subsets and cytokine imbalance, creating a permissive environment for herpesvirus reactivation [11].

Critical illness represents an additional immunological stressor. Patients in intensive care units frequently develop a state of immune exhaustion characterized by lymphopenia, impaired antigen presentation, and altered cytokine profiles. Under these conditions, latent herpesviruses, including HHV-6, may reactivate. Such reactivation is increasingly recognized as a marker of immune dysfunction and disease severity rather than a purely incidental finding [12].

DIAGNOSTIC CHALLENGES

Accurate diagnosis of HHV-6 infection relies on careful integration of clinical findings and laboratory data. Quantitative polymerase chain reaction (PCR) testing for HHV-6 DNA in blood or plasma remains the cornerstone of diagnosis. In immunocompromised patients, serial viral load measurements are particularly useful, as rising HHV-6 DNA levels often precede the onset of clinical symptoms.

However, interpretation of PCR results is complicated by the phenomenon of chromosomally integrated HHV-6 (ciHHV-6). Individuals with ciHHV-6 typically exhibit persistently high HHV-6 DNA levels in whole blood, often exceeding 10^5–10^6 copies/mL, regardless of clinical status [3, 13]. In such cases, plasma viral load may be low or undetectable, reflecting the absence of active viral replication.

Confirmation of ciHHV-6 requires detection of viral DNA in non-replicating tissues such as hair follicles or fingernails. Failure to recognize ciHHV-6 may result in misdiagnosis and unnecessary exposure to potentially toxic antiviral therapy.

Key diagnostic features distinguishing active HHV-6 infection from ciHHV-6 are summarized in Table 3.

In patients with suspected central nervous system involvement, cerebrospinal fluid (CSF) analysis is essential. Detection of HHV-6 DNA in CSF supports the diagnosis of HHV-6 encephalitis, particularly when accompanied by compatible clinical features and neuroimaging findings. A CSF-to-blood viral load ratio $\geq$1:1 suggests intrathecal viral replication and strengthens the diagnosis of active central nervous system infection.

Table 3

Diagnostic differentiation between active HHV-6 infection and chromosomally integrated HHV-6 (ciHHV-6)

Parameter	Active HHV-6 infection	Chromosomally integrated HHV-6 (ciHHV-6)
Clinical symptoms	Present, progressive	Usually, absent
Whole blood HHV-6 DNA	Moderate to high, dynamic	Persistently very high ($>10^5$–10^6 copies/mL)
Plasma HHV-6 DNA	Detectable	Often low or undetectable
CSF HHV-6 DNA	Elevated in CNS disease	Usually, negative
CSF-to-blood ratio	≥1:1	<1:1
Hair/nail PCR	Negative	Positive
Response to antiviral therapy	Clinical and virological improvement	No response
Main diagnostic risk	Delayed treatment	Overtreatment and drug-related toxicity

DIFFERENTIAL DIAGNOSIS

The clinical manifestations of HHV-6 infection overlap with a broad range of infectious and non-infectious conditions, necessitating a thorough differential diagnostic approach.

In immunocompetent children, exanthema subitum must be differentiated from measles, rubella, enteroviral exanthems, adenoviral infection, parvovirus B19 infection, and drug-induced hypersensitivity reactions. The characteristic temporal pattern of high fever followed by rash after defervescence serves as an important clinical clue supporting HHV-6 infection [1, 5].

In immunocompromised adults presenting with neurological symptoms, HHV-6 encephalitis should be distinguished from herpes simplex virus encephalitis, varicella-zoster virus infection, cytomegalovirus encephalitis, autoimmune limbic encephalitis, metabolic encephalopathy, and medication-related neurotoxicity. Magnetic resonance imaging findings, particularly involvement of the medial temporal lobes, in combination with CSF PCR results, are critical for establishing the diagnosis [8, 13].

Another important differential consideration is the distinction between clinically significant HHV-6 reactivation and incidental viral detection. Low-level HHV-6 DNAemia in the absence of symptoms may not require treatment, whereas progressive increases in viral load accompanied by compatible clinical features warrant prompt intervention. The risk of misinterpretation is particularly high in patients with ciHHV-6, emphasizing the need for careful diagnostic evaluation.

TREATMENT STRATEGIES

Management of HHV-6 infection is fundamentally determined by host immune status and the presence or absence of clinically significant disease.

In immunocompetent individuals, HHV-6 infection is typically self-limiting and does not require specific antiviral therapy. Supportive care, including antipyretics, adequate hydration, and monitoring for complications, is sufficient in the vast majority of cases.

In contrast, antiviral therapy is indicated in immunocompromised patients with symptomatic HHV-6 infection, particularly in cases involving central nervous system disease, pneumonitis, hepatitis, or severe bone marrow suppression. Currently, no antiviral agents are specifically licensed for HHV-6; therefore, treatment recommendations are based on clinical experience and extrapolation from cytomegalovirus management.

Ganciclovir and its oral prodrug valganciclovir are considered first-line agents for the treatment of HHV-6 infection. These drugs inhibit viral DNA polymerase and have demonstrated clinical efficacy in HHV-6–associated encephalitis and systemic disease. However, their use is limited by significant myelotoxicity, including neutropenia and thrombocytopenia, which may be particularly problematic in hematopoietic stem cell transplant recipients who already experience delayed engraftment [14].

Foscarnet represents an important alternative, especially in patients with pre-existing cytopenias or intolerance to ganciclovir. While foscarnet is not myelotoxic, its use is associated with nephrotoxicity and electrolyte disturbances, necessitating careful monitoring of renal function and electrolytes.

Cidofovir is generally reserved as a third-line agent for refractory cases due to its marked nephrotoxicity.

Routine antiviral prophylaxis against HHV-6 is not currently recommended, primarily due to the toxicity of available agents and the lack of evidence demonstrating clear benefit. Instead, many transplant centres adopt a pre-emptive strategy, initiating antiviral therapy when viral load exceeds pre-

defined thresholds or when early clinical symptoms emerge.

CLINICAL IMPLICATIONS

From a clinical perspective, HHV-6 infection should not be regarded as a benign incidental finding in immunocompromised patients. Routine monitoring of HHV-6 viral load in high-risk populations, particularly during the early post-transplant period, may facilitate early detection of clinically significant reactivation.

As summarized in Table 2, immunocompromised hosts exhibit a markedly different disease course and risk profile compared to immunocompetent individuals. Clinicians should maintain a high index of suspicion for HHV-6–associated disease in transplant recipients presenting with unexplained encephalopathy, seizures, or delayed haematopoietic recovery (Table 2).

Early recognition and prompt initiation of antiviral therapy in symptomatic patients may significantly reduce morbidity and improve neurological outcomes. Equally important is the avoidance of unnecessary antiviral therapy.

Misinterpretation of persistently high HHV-6 DNA levels in patients with chromosomally integrated HHV-6 (ciHHV-6) may lead to overtreatment and drug-related toxicity. Awareness of this diagnostic pitfall, together with appropriate confirmatory testing, is therefore essential for clinical decision-making, as outlined in Table 3.

Discussion. ***Limitations and future directions***

This review has several limitations. First, much of the available evidence regarding HHV-6 infection in immunocompromised patients is derived from observational studies, retrospective analyses, and single-centre cohorts. Randomized controlled trials evaluating antiviral treatment strategies are limited, and standardized viral load thresholds for treatment initiation remain undefined.

Second, the clinical significance of HHV-6 reactivation in certain contexts, such as critically ill immunocompetent patients, is not yet fully understood.

Conclusions. HHV-6 infection represents a striking example of how host immune status determines viral pathogenicity. While primary infection in immunocompetent individuals is usually benign and self-limiting, HHV-6 reactivation in immunocompromised patients is associated with severe complications, including encephalitis, bone marrow suppression, and increased mortality.

Accurate diagnosis — particularly differentiation between active infection and chromosomally integrated HHV-6 (ciHHV-6) — and timely initiation of antiviral therapy remain central to optimal patient management.

Improved diagnostic strategies and safer antiviral therapies are essential to reduce HHV-6–associated morbidity and mortality in high-risk populations.

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Perspectives for further research. It is necessary to clarify whether HHV-6 plays a direct pathogenic role or primarily serves as a marker of immune dysfunction.

Future research should focus on the development of less toxic antiviral agents, the identification of reliable biomarkers of clinically relevant reactivation, and the establishment of evidence-based diagnostic and therapeutic algorithms.

Long-term neurocognitive outcomes following HHV-6–associated encephalitis also warrant systematic investigation.

Compliance with ethical requirements

This article does not contain any studies involving human participants performed by any of the authors. The study was conducted in accordance with the Declaration of Helsinki and the regulatory requirements of Ukraine.

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