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A systematic review of HHV-6 infections in recipients of organ and tissue transplantation and chimeric antigen receptor T-cell infusions

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Background: We systematically reviewed the published literature to describe the epidemiology and outcomes of human herpes virus 6 (HHV-6) syndromes and diseases after solid organ transplantation (SOT), hematopoietic transplantation (HCT), and chimeric antigen receptor T-cell (CAR-T) therapy.

Methods: PubMed, Scopus, Embase, and Ovid/Medline were reviewed from inception through May 31, 2024, using the keywords HHV-6 and transplantation or CAR-T. Abstracts, case reports, and cohort and case–control studies among adults that were published or translated into English were included.

Results: A total of 136 case reports or series contributed 268 unique cases—225 HCT, 37 SOT, and 6 CAR-T—while 39 cohort studies on HCT (28), SOT (9), CAR-T (1), and mixed SOT/HCT (1) recipients were included. The HHV-6 incidence varied widely from 1% to 95% among cohort studies on HCT and SOT but was low in CAR-T recipients (5.6%). Among the case reports, the median age was 46 years (range, 18–73 years), and most were men (159/236, 67.4%). HHV-6 subtyping was performed only in 66 cases, and 46 were variant B. There were 10 cases that were chromosomally integrated (ciHHV-6). Among the 268 cases with detailed clinical information, fever was reported only in 89 patients (33.2%). The most common clinical syndrome was neurological (204/268, 76.1%), followed by viral syndrome (28/268, 10.4%) and disseminated disease (14/268, 5.2%). The initial therapy was ganciclovir (87/234, 37.2%) or foscarnet (82/234, 35%). At least a third of patients developed neurological sequelae (45/151, 29.8%). HHV-6-attributable mortality was 20.6% (22/107).

Conclusions: Neurological disease is the most frequent clinical syndrome of HHV-6 infection. Early recognition of limbic involvement either through the triad of confusion, amnesia, and seizures or through compatible MRI findings may help

with early identification. Diagnosis is secured through molecular methods, although an extremely high viral load needs to be interpreted in the context of ciHHV-6. The neurological sequelae of HHV-6 can be disabling and cause significant morbidity.

KEYWORDS

HHV 6, HHV6-induced post-transplantation acute limbic encephalitis (PALE), solid organ transplant (SOT), hematopoietic (stem cell) transplant (HSCT), viral infection, transplant infections, review - systematic

1 Introduction

Human herpes virus-6 (HHV-6) is a β-herpes virus that was first described in children in 1988 as the causative agent of exanthem subitum (1). HHV-6 infects nearly all children by 3 years of age (2) and is now classified into two closely related but distinct species: HHV-6A and HHV-6B (3). This recognition as separate viruses was made by the International Committee on Taxonomy of Viruses in 2012, primarily due to their different epidemiological, biological, and immunological distinctions. Primary HHV-6B infection may be asymptomatic and present with nonspecific symptoms such as fever, fussiness, rash, diarrhea, and seizures in children (1). The epidemiology of HHV-6A, on the other hand, is still largely uncertain, although it is thought to be acquired later in life and may be more commonly associated with severe neurological disease compared with HHV-6B (4). In adults, the virus has been associated with a broad range of clinical syndromes, ranging from mild undifferentiated rashes, temporal lobe epilepsy (5) to multiple sclerosis and encephalitis (6, 7). Unique to HHV-6 is its ability to integrate into chromosomes (8, 9). As a consequence of the presence of the viral genome in every nucleated human cell, patients with chromosomally integrated HHV-6 (ciHHV-6) are characterized by very high levels of HHV-6 DNA in the blood and tissues (10). ciHHV-6 has been misinterpreted as "active" infection, leading to unnecessary antiviral treatment.

The pathogenicity of HHV-6A, HHV-6B, and ciHHV-6 in immunocompromised hosts, such as recipients of hematopoietic cell transplantation (HCT), solid organ transplantation (SOT), and chimeric antigen receptor T-cell (CAR-T) therapy, has been reported. It is assumed that HHV-6B is the more prevalent species, while HHV-6A is suspected as the etiology of most cases of HHV-6 encephalitis with some outliers (11). However, there are also sporadic reports of other clinical syndromes including myelitis, myocarditis, hepatitis, and hemophagocytic syndromes. ciHHV-6, on the other hand, has been associated with an increased risk of acute graft-*versus*-host disease (aGvHD) in allogeneic hematopoietic transplants, and it has been most often mistaken for active infection (10).

Earlier reviews have focused only on specific hosts (12), virus types (13), or an aspect of HHV-6 (14). Hence, we aimed to perform a more encompassing systematic review to comprehensively examine the epidemiology of HHV-6 in all these populations by describing its different syndromes and patient outcomes.

2 Methods

With the help of a professional librarian, we searched multiple databases (i.e., PubMed, Embase, Scopus, and Medline/Ovid) and identified all cases of HHV-6 after SOT, HCT, and CAR-T from inception to May 31, 2024. Search terms included the keywords "human herpes virus 6 or HHV-6" and "solid organ or hematopoietic transplant" or "encephalitis." The complete search strategy is shown in *Appendix 1*. The article references were reviewed for additional cases. Our search was limited to publications in English or those with an English translation. All reports of adult SOT, HCT, and CAR-T recipients who developed HHV-6 after transplantation within the study period were eligible for study inclusion and were screened by two authors (CLA and RRR). Only those cases where the symptoms were attributed to HHV-6 were included. HHV-6 infection was defined as evidence of viremia or DNAemia, while disease was confirmed in the presence of a compatible clinical syndrome [e.g., fever and rash, post-transplant acute limbic encephalitis (PALE), myelitis, myocarditis, and hepatitis, among others] and/or isolation of HHV-6 from culture, shell vial assay, or via molecular methods (e.g., polymerase chain reaction or metagenomic sequencing). The abstracts of case reports were included if sufficient clinical information was provided. Recipients with ciHHV-6 were included only if there was clinical disease. All case reports or series included symptomatic HHV-6, but incidences of asymptomatic (e.g., viremic) or symptomatic HHV-6 as reported by cohort studies were captured and recorded. We excluded pediatric cases and cases diagnosed prior to transplantation or upon removal of the transplant allograft. Reports on HHV-6 where clinical information was inadequate or lacking, could not be extracted in detail, or had mixed populations (e.g., predominantly pediatric or non-transplant) were excluded. Data were extracted (CLA) and coded into an Excel spreadsheet. Informed consent was not required as these cases have already been previously reported.

The PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) was used to help generate the four-phase flow diagram.

2.1 Statistical analysis

Detailed case reports, case series, and cohorts of SOT, HCT, and CAR-T recipients were described and analyzed separately or in combination, as appropriate. Frequency statistics (e.g., median, range, and percent) were used to describe categorical and continuous variables.

3 Results

Our search identified a total of 1,239 studies across multiple databases (PubMed, *n* = 122; Embase, *n* = 987; Medline, *n* = 85; and Scopus, *n* = 45). After the reference review (*n* = 25) and the exclusion of duplicates (*n* = 24), a total of 164 studies were included in the final review (Figure 1). There were 136 (32 SOT, 100 HCT, 3 CAR-T, and 1 both SOT/HCT) case reports or series (11, 15–149) that contributed a total of 268 unique cases: 225 HCT, 37 SOT, and 6 CAR-T recipients.

A total of 39 cohort studies (34, 42, 45, 51, 58, 94, 126, 131, 138, 143, 146, 147, 149–175) on HCT (28), SOT (9), CAR-T (1), and mixed SOT/HCT (1) recipients were also included. Of these, 13 studies provided detailed clinical cases that were included in our systematic review of case reports or series (34, 42, 45, 51, 58, 94, 126, 131, 138, 143, 146, 147, 149).

3.1 Case reports/series

3.1.1 Hematopoietic transplantation

3.1.1.1 Epidemiology and patient characteristics

A total of 101 reports (11, 15, 17, 19, 22, 24–26, 28–36, 41–49, 51, 53–59, 61–66, 70–76, 78–81, 83–85, 87–95, 97, 98, 102, 103, 106, 110–113, 115, 117, 118, 121–127, 129–131, 135–149, 165) described 225 cases of HHV-6 among 223 HCT recipients (e.g., two recipients were retransplanted and developed another episode of HHV-6 after the second transplant) (64, 84). Of these reports, the majority were from the Asia-Pacific region (*n* = 41, 40.6%) (15, 24, 29, 45, 51, 54, 55, 57–59, 62, 63, 65, 75, 79, 80, 83–85, 88–90, 92–94, 118, 121, 122, 124–127, 135–138, 141, 145–147, 165) and the USA or Canada (*n* = 33, 32.7%) (11, 17, 26, 28, 31–33, 41, 42, 46–49, 53, 64, 70–72, 78, 81, 95, 97, 106, 110, 112, 113, 130, 139, 140, 142, 144, 148, 149). Information on sex was provided in some case reports, and the majority of the patients were men (125/188, 66.5%). The median age was 46 years (range, 18–73 years) (Table 1). Of 225 transplant cases, the vast majority occurred after allogeneic stem cell transplantation [including 139 (61.8%) allogeneic bone marrow or stem cell recipients (11, 15, 19, 24, 28, 29, 31–33, 35, 36, 41, 42, 44, 46, 49, 51, 53, 54, 56–59, 62, 64–66, 70–74, 81, 83, 85, 87–89, 91, 97,

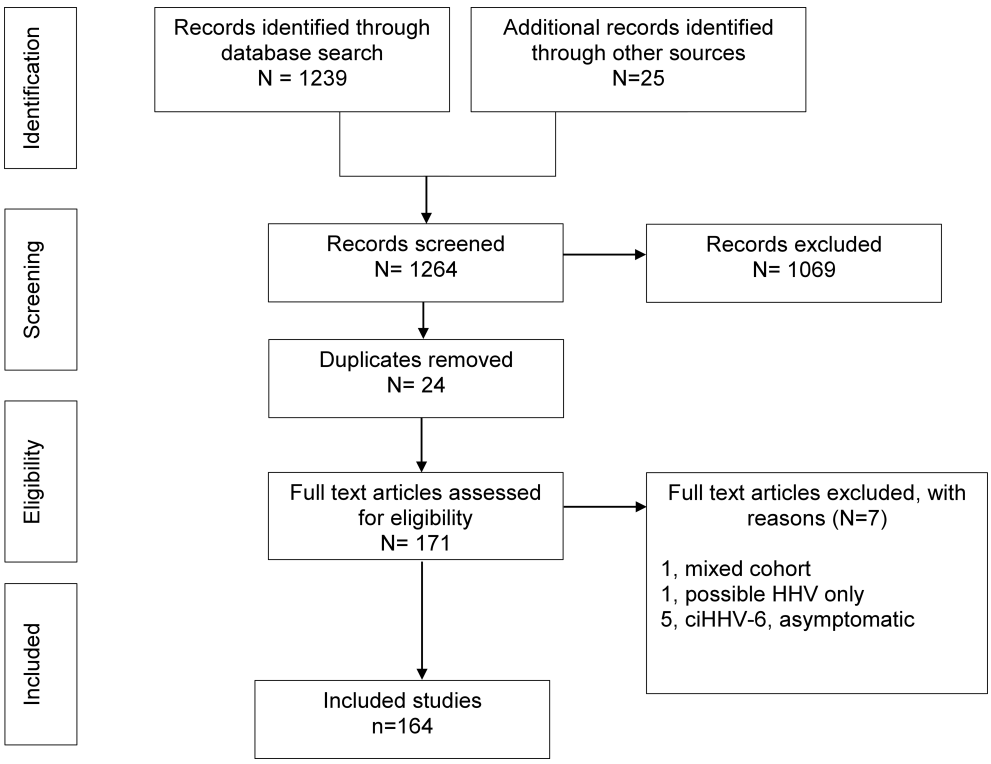

FIGURE 1
Flow diagram of the included studies.

TABLE 1 Clinical and demographic characteristics of patients with human herpes virus 6 (HHV-6) infection after CAR-T infusion and transplantation.

Characteristic	Overall, *N* (%)	SOT, *n* (%)	HCT, *n* (%)	CAR-T, *n* (%)
No. of studies by region	136[b] (100)	33 (100)	101 (100)	3 (100)
Asia-Pacific	45 (33.1)	3 (9.1)	41 (40.6)	1 (33.3)
Europe	43[b] (31.6)	18 (54.5)	26 (25.7)	0
South America	2 (1.5)	1 (3)	1 (1)	0
USA and Canada	46 (33.8)	11 (33.3)	33 (32.7)	2 (66.7)
Transplanted cases, *n*	268	37	225	6
Age (years), median (range)	46 (18–73)	49 (19–71)	46 (18–73)	48.5 (31-69)
Sex, M/F	156/75	28/9	125/63	3/3
History of ACR, GvHD, or CRS	99(100)	8 (100)	85 (100)	6 (100)
Yes	95 (96)	7 (87.5)	82 (96.5)	6 (100)
No	4 (4)	1 (12.5)	3 (3.5)	0 (0)
Time to clinical presentation from transplant or CAR-T infusion (days), median (range)	–	23 (10–2,190)	23 (2–2,130)	6 (5–29)
Syndrome, *n* (%)	268 (100)	37 (100)	225 (100)	6 (100)
Cardiac	2 (0.7)	1 (2.7)	1 (0.4)	0
Disseminated	14 (5.2)	7 (18.9)	7 (3.1)	0
Gastrointestinal	11 (4.1)	5 (13.5)	6 (2.7)	0
Neurological	204 (76.1)	15 (40.5)	183 (81.3)	6 (100)
Pulmonary	9 (3.4)	3 (8.1)	6 (2.7)	0
Viral	28 (10.4)	6 (16.2)	22 (9.8)	0
HHV-6 type	66 (100)	15 (100)	48 (100)	3 (100)
A	9 (13.6)	6 (40)	3 (6.2)	0 (0)
B	46 (69.7)	7 (46.7)	36 (75)	3 (100)
Both	1 (1.5)	0 (0)	1 (2.1)	0 (0)
ciHHV	10 (15.2)	2 (13.3)	8 (16.7)	0 (0)
Fever, Y	89/268 (33.2)	15/37 (40.5)	69/225 (30.7)	5/6 (83.3)
Site of HHV-6	239 (100)	37 (100)	196 (100)	6 (100)
CSF	94 (39.3)	4 (10.8)	86 (43.9)	4 (75)
Blood (serum/plasma)	41 (17.2)	9 (24.3)	32 (16.3)	0 (0)
Other sites	10 (4.2)	5 (13.5)	5 (2.6)	0 (0)
Multiple sites	94 (39.3)	19 (51.4)	73 (37.2)	2 (25)
Cranial imaging (MRI), initial	152 (100)	16 (100)	133 (100)	3 (100)
Normal	46 (30.3)	6 (37.5)	39 (29.3)	1 (33.3)
Abnormal	106 (69.7)	10 (62.5)	94 (70.7)	2 (66.7)
Treatment, initial	234 (100)	33 (100)	196 (100)	5 (100)
Foscarnet	82 (35)	7 (21.2)	74 (37.8)	1 (25)
Ganciclovir	87 (37.2)	18 (54.5)	67 (34.2)	2 (50)
Other monotherapy[a]	25 (10.7)	3 (9.1)	22 (11.2)	0 (0)
Combination therapy	38 (16.2)	5 (15.2)	31 (15.8)	2 (25)

(Continued)

TABLE 1 Continued

Characteristic	Overall, *N* (%)	SOT, *n* (%)	HCT, *n* (%)	CAR-T, *n* (%)
Drug not specified	2 (0.9)	0 (0)	2 (1)	0 (0)
Length of treatment (weeks), median (range)	–	4 (2–104)	3.1 (0.7–27)	16 (8–24)[c]
Neurological outcome	151 (100)	16 (100)	133 (100)	2 (100)
Recovery	68 (45)	4 (25)	63 (47.4)	1 (50)
Neurological sequelae	45 (29.8)	4 (25)	41 (30.8)	0 (0)
Not specified	38 (25.2)	8 (50)	29 (21.8)	1 (50)
Outcome, *n* (%)	265 (100)	36 (100)	223 (100)	6 (100)
Alive	160/265 (60.4)	24/36 (66.7)	133/223 (59.6)	3/6 (50)
Attributable mortality	22/107 (20.6)	1/12 (8.3)	20/89 (22.5)	1/6 (16.7)

Other: one pancreas, one small bowel. Combined: kidney–heart, kidney–liver, and kidney–pancreas.
ACR, acute cellular rejection; *CAR-T*, chimeric antigen receptor T cell; *ciHHV*, chromosomally integrated human herpes virus 6; *CRS*, catecholamine release syndrome; *GvHD*, graft-*versus*-host disease; *HCT*, hematopoietic cell transplant; *SOT*, solid organ transplant.
[a]includes valganciclovir, acyclovir, valacyclovir and gamma globulin.
[b]One study with both SOT and HCT.
[c]Two patients only.

98, 102, 103, 106, 110–113, 118, 121, 123–125, 129, 131, 135–143, 146–149, 165), and 64 (28.4%) umbilical cord blood (UCB) recipients (25, 30, 43, 45, 47, 48, 55, 63, 75, 79, 80, 84, 90, 92–95, 122, 126, 130, 145)], while 21 (9.3%) were autologous stem cell recipients (17, 22, 26, 34, 76, 78, 115, 117, 127, 144) and 1 (0.44%) was not specified (61). The donor characteristics were described as fully matched related or unrelated in half of the cohort (54/107, 50.5%), mismatched or unmatched related or unrelated in 19 (17.8%), haploidentical in 7 (6.5%), unrelated in 24 (22.4%), and related in 3 (2.8%). The underlying hematological disorder requiring transplantation was highly varied, with acute myelogenous leukemia (AML) being the most frequent (37/181, 20.4%) (25, 36, 43, 58, 59, 64, 66, 72, 75, 79, 84, 97, 111, 122, 139, 142, 149, 165), followed by acute lymphocytic leukemia (ALL) or mantle cell lymphoma (30/181,16.6%) (15, 19, 33, 44, 47, 48, 62, 83, 85, 88, 89, 102, 115, 135, 136) and myelodysplastic syndrome (MDS) (19/181, 10.5%) (26, 32, 45, 54, 55, 63, 73, 80, 81, 118, 143, 145, 148). The conditioning regimens were diverse and dependent on the underlying disease and the institutional protocol. Information regarding the aGvHD prophylaxis regimens were provided in less than half (95/225, 42.2%) of the recipients (15, 17, 19, 24, 25, 30, 32, 36, 45–47, 51, 55, 57–59, 62, 63, 65, 66, 75, 79, 80, 83, 84, 87–89, 91, 93, 97, 102, 103, 111, 113, 121, 122, 125, 126, 129, 135–137, 140–142, 145, 148, 149, 165). Of these, tacrolimus was the most frequent drug for prophylaxis (n = 54, 56.8%), followed by cyclosporine (n = 42, 44.2%), methotrexate (n = 36, 37.9%), mycophenolate mofetil (n = 24, 25.3%), and corticosteroids (n = 12, 12.6%).

3.1.1.2 Clinical presentation and syndromes

The overall time to presentation had a median of 23 days (range, 2–2,130 days) after transplantation. Fever was reported only in 69/225 (30.7%) transplant cases (17, 19, 26, 29–34, 36, 44, 46, 48, 55, 63, 64, 71, 72, 74, 79, 87, 102, 111, 115, 117, 123–125, 127, 136, 144, 145, 147, 165). Subtyping of HHV-6 was performed in only 48 cases (11, 19, 22, 31, 33, 36, 44, 46, 53, 59, 62, 63, 66, 70, 76, 79, 83, 87, 89, 91, 93, 94, 98, 102, 110–113, 118, 141, 143, 145, 165), and the majority (36/48, 75%) were classified as HHV-6 variant B. There were eight identified cases of symptomatic ciHHV-6 (31, 70, 76, 91, 98, 102, 143) (Table 1) who presented at a median time of 148 days (range, 11–750 days) after transplantation. Of those with ciHHV-6, six were men, and the median age was 48.5 years (range, 18–66 years).

The most common clinical syndrome was neurological (183/225, 81.3%) (11, 15, 17, 19, 25, 28–33, 35, 36, 41–45, 47, 49, 51, 54–59, 61–63, 70–73, 75, 78–80, 83, 89, 90, 92–94, 97, 98, 102, 103, 110–112, 118, 121–127, 129–131, 136–142, 146–149, 165), described as encephalitis (137/183, 74.9%), mixed encephalomyelitis (10/183, 5.5%) (89), or myelitis (18/183, 9.8%) (15, 126). Subsets of those with encephalitis were categorized as PALE (15/183, 8.2%), Guillain–Barré syndrome (GBS) (2/183, 1.1%), or posterior reversible encephalopathy syndrome (PRES) (1/183, 0.5%). The initial symptoms were confusion (n = 58), disorientation (n = 26), mental status impairment (n = 11), hallucination (n = 4), amnesia (n = 27), memory impairment or loss (n = 48), seizures (n = 36), headache (n = 9), or loss of consciousness (n = 4). Those with myelitis presented with pain around the affected nerves (n = 12), pruritus (n = 9), dysesthesia/paresthesia (n = 6), bladder disturbance (n = 4), or epigastralgia (n = 3).

Magnetic resonance imaging (MRI) of the brain was the initial imaging modality (n = 133) (11, 15, 17, 19, 22, 25, 29, 32, 33, 35, 36, 41–43, 47, 49, 51, 54–59, 61–63, 65, 70, 71, 73, 75, 76, 80, 83, 85, 89, 90, 92, 93, 95, 98, 102, 103, 106, 111, 112, 118, 121–125, 127, 129, 130, 136–138, 140–142, 147–149, 165) and had abnormal findings in 70.7% (94/133), with signal abnormalities typically involving either the hippocampus (41/94, 45.6%) and/or the temporal lobe (22/94 24.4%). In some instances (n = 30), the initial CT imaging was normal (32, 34, 43, 49, 51, 56, 62, 63, 71, 73, 121, 123, 125, 127, 129, 142, 148), but on MRI imaging (n = 12) (17, 32, 43, 49, 51, 56, 71, 121, 142) or repeat imaging days later (n = 18) (49, 57, 58, 62, 121, 122, 127, 129, 148) eventually showed abnormal radiographic

findings. Electroencephalogram (EEG) was performed in only a few cases (n = 35) (17, 25, 28, 32, 36, 41, 63, 71, 73, 111, 112, 122, 125, 130, 131, 136, 139, 142, 146, 148), but the majority (32/35, 91.4%) showed abnormal activity often described as increases or spikes in theta activity (n = 10) or bursts of sharp waves with diffuse or bitemporal slowing (n = 9). Other descriptions included mild or severe diffuse abnormalities (n = 3), periodic lateralized epileptiform discharge (n = 2), pronounced pathologic episodes (n = 1), left temporal spikes (n = 1), flat waves (n = 1), low frequencies of background activity (n = 3), metabolic encephalopathy (n = 1), or epileptiform activity (n = 1).

A viral-like syndrome with fever, rashes, and cytopenias was the next most common clinical syndrome, occurring in 22/225 (9.8%) transplant cases (29, 34, 64, 66, 76, 84, 106, 113, 115, 117, 135, 143–145). The time to presentation of this viral syndrome was a median of 21 days (range, 2–629 days) after transplantation. Other clinical syndromes occurred much less frequently and are summarized in Table 2.

3.1.1.3 Diagnosis

Laboratory diagnosis of HHV-6 was primarily through quantitative (n = 125) or qualitative (n = 63) polymerase chain reaction (PCR) DNA-based tests. Other less common tests included immunohistochemical (IHC) staining (n = 4) (11, 24, 26, 91), shell vial assay (n = 1) (33), metagenomic sequencing (n = 1) (141), and fluorescent *in situ* hybridization (n = 1) (91). The sites of HHV-6 DNA positivity included the cerebrospinal fluid (CSF) (n = 86), blood/serum (n = 32), lung (n = 1), and bone marrow (n = 1) alone or a combination of sites (n = 73).

For those with neurological disease, CSF cytologic analysis was reported in approximately half (83/183, 45.4%) of the cases (11, 15, 17, 19, 25, 28–33, 35, 36, 41–43, 47, 49, 51, 56–59, 62, 63, 70, 71, 73, 75, 79, 83, 89, 97, 98, 102, 103, 111, 112, 122–125, 129, 131, 136, 137, 140–142, 149). The CSF white blood cell (WBC) count (67/83, 80.7%) had a median of 6 cells/mm^3 (range, 0–81 cells/mm^3). CSF protein and glucose were carried out in 71/91 (78%) and 46/91 (50.5%) cases, respectively. The median CSF protein was 59.5 mg/dl (range, 71–384 mg/dl), while the median CSF glucose was 67 mg/dl (range, 46–133 mg/dl).

3.1.1.4 Treatment and outcomes

Treatment was described for 196/225 (87.1%) HCT recipients (11, 15, 17, 19, 22, 24–26, 28–36, 41–43, 45–49, 51, 53–59, 62, 63, 65, 66, 70–76, 78–81, 83–85, 87–89, 91–95, 97, 98, 102, 103, 110–113, 115, 117, 121–127, 129, 131, 135–143, 146–148, 165), including eight cases of symptomatic ciHHV-6. The initial drug of choice was either foscarnet (74/196, 37.8%) or ganciclovir (67/196, 34.2%). A smaller proportion of patients were started on combination therapy (31/196, 15.8%), which was commonly ganciclovir with foscarnet (n = 25). Other combinations included one each of ganciclovir with intravenous immunoglobulin (IVIg); ganciclovir, foscarnet, and IVIg; ganciclovir and acyclovir; foscarnet, plasmapheresis, and IVIg; foscarnet and IVIg; and foscarnet with valganciclovir. Other monotherapies (22/196, 11.2%) included acyclovir (n = 13, 58.6%), valganciclovir (n = 4, 18.2%), cidofovir (n = 3, 13.6%), valacyclovir (n = 1, 4.5%), and gamma globulin (n = 1, 4.5%). Treatment was not specified in two recipients (73, 139), while nine recipients were not treated (26, 144, 145). Overall, the median length of treatment was 3 weeks (range, 0.7–27 weeks). Of the 223 patients with reported outcomes, 133 (59.6%) were alive at the last follow-up, but 41/133 (30.8%) had persistent neurological deficits. HHV-6-attributed mortality was reported in 20/89 (22.5%) cases.

3.1.2 Solid organ transplantation

3.1.2.1 Epidemiology and patient characteristics

There were 33 reports (16, 18, 20, 21, 23, 27, 37–40, 50, 60, 67, 69, 77, 86, 96, 99–101, 104, 105, 108, 109, 114, 116, 119, 120, 128, 132–134, 143) that described 37 SOT recipients with HHV-6 infection. The majority of the reports originated from Europe (n = 17, 51.5%) (18, 21, 23, 27, 37, 39, 60, 67, 77, 96, 100, 108, 109, 114, 116, 133, 143) or the USA (n = 11, 33.3%) (16, 38, 40, 69, 86, 99, 104, 105, 119, 120, 128). Most of the SOT recipients were men (28/37, 75.7%), and the median age was 49 years (range, 19–71 years) (Table 1). The majority were recipients of liver (n = 17, 45.9%) (16, 23, 38, 40, 50, 77, 99, 104, 109, 119, 120, 128, 132, 133) or kidney (n = 10, 27%) (20, 37, 60, 69, 96, 100, 101, 108, 114, 116) transplants. Heart (n = 3, 8.1%) (27, 86, 105), lung (n = 2, 5.4%) (21, 67), small bowel (n = 1, 2.7%) (143), pancreas (n = 1, 2.7%) (134), and combined transplants (n = 3, 8.1%) (18, 39, 67) were less common. Maintenance immunosuppression was detailed in 25 recipients, of whom 18 (72%) were on tacrolimus, 5 (20%) on cyclosporine, and 2 (8%) on azathioprine.

3.1.2.2 Clinical presentation and syndromes

Less than half of the SOT recipients (15/37, 40.5%) with HHV-6 infection developed fever (18, 21, 39, 60, 69, 86, 96, 99, 104, 108, 109, 114, 120, 128, 133). The median time to presentation was 23 days (range, 10–2,190 days) after transplantation. Acute cellular rejection (ACR) prior to infection was reported in 7/8 (87.5%) recipients; for four patients, ACR occurred 0–83 days prior to symptom onset. The HHV-6 subtype was described in 15 patients (23, 40, 50, 67, 100, 101, 104, 105, 109, 114, 120, 132, 134, 143) and, of these, 7 (46.7%) were variant B, 6 (40%) were variant A, and 2 (13.3%) were symptomatic ciHHV-6A (23, 100). The most common clinical syndrome was neurological (15/37, 40.5%) (16, 18, 21, 38–40, 50, 77, 86, 99, 120, 128, 132–134), followed by disseminated disease (7/37, 18.9%) (23, 100, 101, 105, 109, 114, 116) (Table 1).

Those who developed encephalitis had a median age of 49 years (range, 19–71 years) and were mostly men (10/15, 66.7%). Two-thirds (10/15, 66.7%) presented with neurological symptoms at the onset, including headache (n = 4), confusion (n = 3), unresponsiveness (n = 4), or seizures (n = 3). The remaining five patients (33.3%) initially presented with fever and rash before subsequently developing neurological symptoms. Fever occurred in approximately half (8/15, 53.3%) of the patients. The median time to presentation was 23 days (range, 12–90 days) after transplantation. Brain MRI was the initial diagnostic imaging in 11 patients, with the majority (9/11, 81.8%) showing abnormalities including non-enhancing lesions in the temporal lobe or the hippocampus (n = 5) (16, 18, 21, 77, 128), cortical and subcortical hyperintensity (n = 1) (40), ischemic changes

TABLE 2 Clinical syndromes of human herpes virus 6 (HHV-6) among hematopoietic cell transplant (HCT) and solid organ transplant (SOT) recipients.

Hematopoietic transplant recipients						
Characteristic	Neurological (183)	Cardiac (1)	GI/hepatic (6)	Pulmonary (6)	Viral syndrome (22)	Disseminated (7)
Age (years), median (range)	46 (18–73)	62	48 (23–64)	42 (29–63)	56 (22–66)	31 (18–53)
Sex, M/F	98/49	1/0	2/4	3/3	17/5	4/3
Time to presentation (days), median (range)	23 (4–979)	16	58.5 (19–98)	365 (14–2,130)	21 (2–629)	171.5 (12–570)
HCT type	Au (3), Allo (116), CBT (60), NS (4)	Allo (1)	Au (4), Allo (2)	Au (1), Allo (5)	Au (13), Allo (7), CBT (2)	Au (1), Allo (5), CBT (1)
Fever, Y (%)	43/183 (23.5)	0/1 (0)	5/6 (83.3)	2/6 (33.3)	15/22 (68.2)	4/7 (57.1)
Common symptoms or presentation	Confusion (58), disorientation (26), amnesia (37), memory loss (48), seizure (28), convulsion (5), headache (9), hallucination(4), loss of consciousness (4), mental status impairment (11)	Pancytopenia	Diarrhea (5), abdominal pain (1)	Dyspnea (2), pleural pain (1), effusion (1), infiltrates (2)	Rash (12), cytopenia (6), diarrhea (4)	Cough (2), dyspnea (3), mental status change (2), loss of consciousness (2), diarrhea/ vomiting (3)
GvHD, Y (%)	76/183 (41.5)	NS	1/6 (16.7)	1/6 (16.7)	NS	4/7 (57.1)
Site/s involved	CSF only (77), serum only (13), CSF and other sites (41)	Cardiac, serum (1)	Serum (5/6); liver (1/6), colon/ esophagus (1/6)	Serum, BAL, pleural effusion	Blood/serum (20), skin (2), bone marrow (2)	Multiple sites
Initial treatment (*n*)	FOS (61), GAN (56), Other (19), Comb (28), None (1), NS (2)	None	GAN (5), FOS (1)	GAN (1), FOS (3), none (2)	GAN (4), FOS (7), other (2), none (6), NS (3)	GAN (1), FOS (2) Comb (3), CID (1)
Treatment duration (weeks), median (range)	3.1 (0.9–27)	NA	3.6 (2–8)	2.1[a]	3 (0.7–10.5)	8.5 (2.1–16)
Outcome Alive, *n*/*N* (%)	100/177 (56.5)	0/1 (0)	6/6 (100)	2/5 (40)	18/21 (85.7)	4/7 (57.1)
SOT recipients						
Characteristic	Neurological (15)	Cardiac (1)	GI/ hepatic (5)	Pulmonary (3)	Viral syn- drome (6)	Disseminated (7)
Age (years), median (range)	49 (19–71)	33	51 (43–66)	43 (39–49)	47 (27–66)	53 (35–69)
Sex, M/F	10/5	1/0	5/0	3/0	6/0	3/4
Time to presentation (days), median (range)	23 (12–90)	17	19 (10–196)	25[a]	90.5 (17–2,190)	21 (16–120)
SOT type	1H, 10L, 1 Lu, 1KP 1KL, 1P	KH	2K, 1L, 1Lu, 1H	1K, 1L, 1SB	3K, 3L	1H, 4K, 2L
Fever, Y (%)	8/15 (53.3)	0/1 (0)	2/5 (40)	0/3 (0)	3/6 (50)	2/5 (40)
Initial symptoms or presentation	Headache (4), seizure (3), confusion (3), unresponsive (3)	Abdominal pain, constipation, pancytopenia	Abdominal pain (3), nausea, vomiting (1), diarrhea (3), cytopenia (1)	Pneumonitis (1), cytopenia (1), respiratory failure (1)	Fatigue (1), cytopenia (3), cough (1), sore throat (1)	Facial swelling (1), rash (1), diarrhea (4), disorientation (2), buttock pain (1), abdominal pain (1)
ACR, Y	2	–	2	–	1	–
Site/s involved	CSF alone (4), blood (4), multiple sites (7)	Blood and heart	Blood (1), blood and liver (1), blood and	Lung (2), lung/ blood (1)	Blood (4), BM (1), blood and BM (1)	Multiple sites (7)

(Continued)

TABLE 2 Continued

SOT recipients						
Characteristic	Neurological (15)	Cardiac (1)	GI/ hepatic (5)	Pulmonary (3)	Viral syn-drome (6)	Disseminated (7)
			colon (1), ileum (1)			
Initial treatment (*n*)	FOS (2), GAN (9), Comb (2)	VGCV	GAN (4), VGCV (1)	FOS (1)[a]	FOS (1), GAN (4), Comb (1)	FOS (3), GAN (1), ACV (1), GAN + IgG (1), GAN + FOS + IVIg (1)
Treatment duration (weeks), median (range)	4 (2–7)	2	104[a]	4.4[a]	3 (3–8)	16.8 (5.6–28)
Outcome, Alive	13/15 (86.7)	1/1 (100)	4/5 (80)	NS[a]	4/6 (66.7)	2/7 (28.6)

ACR, acute cellular rejection; ACV, acyclovir; *Allo*, allogeneic transplant; *Au*, autologous transplant; *BM*, bone marrow; *CBT*, cord blood transplant; *CID*, cidofovir; *Comb*, combined; *CSF*, cerebrospinal fluid; *FOS*, foscarnet; *GAN*, ganciclovir; GvHD, graft versus host disease; *H*, heart; *IVIg* intravenous immunoglobulin, *L*, liver; *Lu*, lung; *K*, kidney; *NS*, not specified; *P*, pancreas; *SB*, small bowel; *VGCV*, valganciclovir.
[a]Only for one patient.

(*n* = 2) (50, 132), or nonspecific subcortical white matter areas of abnormal intensity, most prominent in the right parietal region (*n* = 1) (86). In three patients, CT was reported as normal (18, 21, 77), but abnormal findings were observed on MRI performed on the same day.

Those who had disseminated disease (7/37, 18.9%) had a median age of 53 years (range, 35–69 years). The presenting symptoms were varied, and HHV-6 was isolated from multiple sites including the CSF (5), the visceral (e.g., duodenal, colonic, and cardiac) tissues (6), and the blood (5). Other less common syndromes are summarized in Table 2.

3.1.2.3 Diagnosis

HHV-6 was diagnosed using different methods, including qualitative (*n* = 13) or quantitative (*n* = 16) PCR, IHC staining (*n* = 6), shell vial assay or culture (*n* = 7), and next-generation sequencing (*n* = 2). In some recipients, HHV-6 was positive from a single site, including the CSF (4/37, 10.8%), the blood/serum (9/37, 24.3%), the lung (2/37, 5.4%), the bone marrow (1/37, 2.7%), and the gastrointestinal (GI) tract (2/37, 5.4%). In others, HHV-6 was identified from multiple sites (19/37, 51.3%), including the CSF (*n* = 11), the blood/serum (*n* = 11), and in body tissues such as the colon (*n* = 4), the duodenum (*n* = 2), the bone marrow (*n* = 3), and the liver (*n* = 2).

CSF analysis was performed in a few studies (15/33, 45.4%) (16, 18, 21, 23, 50, 77, 86, 99, 100, 109, 114, 116, 128, 132, 134). The median CSF WBC, protein, and glucose were 11 cells/mm^3 (range, 0–90 cells/mm^3), 28 mg/dl (range, 87–101 mg/dl), and 75 mg/dl (64–78 mg/dl), respectively.

3.1.2.4 Treatment and outcomes

Antiviral treatment was provided to 33/37 (89.2%) SOT recipients (16, 18, 21, 23, 27, 37, 38, 40, 50, 60, 67, 69, 77, 86, 96, 99–101, 104, 105, 108, 109, 114, 116, 119, 120, 128, 132–134, 143). Initial monotherapy with ganciclovir (18/33, 54.5%) was the most common antiviral therapy, followed by foscarnet (7/33, 21.2%). Combination therapy with both drugs was started in 5/33 (15.2%) patients. The median length of treatment was 4 weeks (range, 2–104 weeks). Many were alive on the last follow-up (24/36, 66.7%), but at least 4/16 (25%) had neurological sequelae. The outcome was unknown for one patient (20). HHV-6-attributable mortality was reported only in one patient (1/12, 8.3%).

3.1.3 CAR-T

3.1.3.1 Epidemiology and patient characteristics

There were six cases (52, 68, 107) of HHV-6 reported after CAR-T therapy for underlying diffuse large B-cell lymphoma (DLBCL). Half of the CAR-T recipients were men. The median age was 48.5 years (range, 31–69 years) (Table 1). All patients experienced cytokine release syndrome (CRS), of whom two were given tocilizumab and one dexamethasone. Four developed immune effector cell-associated neurotoxicity syndrome (ICANS).

3.1.3.2 Clinical presentation and syndromes

The time to presentation after CAR-T was described only in three patients, with a median time of 6 days (range, 5–29 days). The majority presented with fever (5/6, 83.3%); for 3/6 (50%) patients, delirium and memory loss occurred later. All were reported to have neurological involvement, with 2/6 (33.3%) developing myelitis.

3.1.3.3 Diagnosis

HHV-6 subtyping was performed in 3/6 (50%) patients, all with sub-type B. HHV-6 was detected in the CSF in all cases, either by quantitative DNA PCR (*n* = 2), qualitative PCR (*n* = 1), or next-generation sequencing (*n* = 3). HHV-6 in the blood or plasma was elevated in two patients. MRI was performed in 3/6 (50%), which showed T2 increased activity in the limbic system (2/3, 66.7%) or hyperintensity in the white matter and brainstem (1/3, 33.3%). Two other patients had CT imaging, the results of which were normal. EEG was reported in only one patient and showed diffuse generalized slowing.

3.1.3.4 Treatment and outcomes

Treatment with ganciclovir was initiated in 2/6 (33.3%) patients, who both survived. One patient who was given foscarnet

and IVIg died on day 24, while another, who was on foscarnet prophylaxis at the time of illness, survived. This patient (69) completed a course of 24-day ganciclovir and foscarnet with additional IVIg for 1 week. The remaining two patients who were not on prophylaxis at the time of HHV-6 disease died before antiviral treatment could be initiated.

3.2 Cohorts

3.2.1 Hematopoietic transplant

There were 25 cohort (34, 42, 45, 51, 58, 126, 138, 146, 147, 149, 151, 154, 157, 158, 161, 162, 164–166, 168–170, 173–175) and three case–control studies (94, 131, 153) that reported on HHV-6. Of these, the majority (22/28, 78.6%) were single-center studies from Japan (n = 9) (51, 58, 126, 138, 146, 164, 169, 173, 175), the USA (n = 7) (42, 149, 153, 154, 157, 170, 174), Sweden (n = 3) (131, 161, 162), France (n = 2) (34, 158), or Egypt (168). The remaining papers were multicenter studies from Japan (45, 94, 147, 165, 166) and France (151). Almost all included only allogeneic HCT recipients, but three studies (153, 158, 168) included autologous HCT recipients. Most of the studies (n = 24) (34, 45, 51, 58, 94, 126, 131, 138, 146, 147, 149, 151, 153, 154, 157, 158, 161, 162, 166, 169, 170, 173–175) reported on the incidence of asymptomatic HHV-6 reactivation or clinical disease, which ranged from 1% to 95%. The median time to HHV-6 diagnosis also varied, with most occurring within the first 30 days of transplantation, except in three studies where the median values were 40 (153), 60 (149), and 70 days (161), respectively. Most of the studies described encephalitis or encephalomyelitis (15/18) (45, 58, 94, 126, 131, 147, 149, 157, 162, 164–166, 169, 173, 175) or possible central nervous system (CNS) dysfunction (174), while a few reported cases of pneumonitis (153), bone marrow suppression (154), hepatitis (162), and rashes (151) among their cohorts of patients (Table 3). Concomitant cytomegalovirus (CMV) reactivation was reported in 10 studies (138, 146, 151, 153, 154, 158, 161, 162, 170, 175), of whom eight had confirmed disease (one pneumonitis and seven not specified) and 91 were viremic.

The occurrence of GvHD was reported only in 14 studies (42, 58, 94, 126, 146, 149, 157, 161, 165, 166, 168–170, 173) and ranged from none (grade 0) to severe (grade IV). Treatment choices were described in 22 studies (34, 42, 51, 58, 94, 126, 131, 138, 146, 147, 149, 151, 154, 157, 161, 162, 164, 165, 169, 170, 173, 175), with ganciclovir or foscarnet being the most often used. The duration of therapy was specified in only eight studies (34, 42, 58, 131, 147, 151, 157, 173), and the median length of treatment was as short as 6 days (157) to as long as 41 days (147). The survival outcomes were reported in 21/28 (75%) studies (34, 42, 45, 51, 58, 94, 126, 131, 138, 146, 147, 149, 154, 157, 161, 162, 164, 165, 169, 170, 175) (Table 3).

3.2.2 Solid organ transplant

There were eight single-center cohorts [four prospective (160, 167, 171, 172) and four retrospective (152, 155, 156, 163)] and one case–control study (150) on SOT recipients. Many studies included liver transplant recipients only (152, 163, 167, 171, 172), while the remainder included kidney (150, 155), kidney–pancreas (155), or lung and heart–lung (160) allografts (Table 4).

All except one study (163) provided information on the incidence of HHV-6 infection (which were mostly asymptomatic reactivation), which ranged from 26.7% to 91%. The median time to HHV-6 infection for the majority (156, 160, 163, 171, 172) was within the first month of transplantation, except in two studies where the median times were 2.7 (152) and 6.4 months (150). ACR that occurred in close proximity to the HHV-6 infection was described in five studies (150, 156, 167, 171, 172), as was CMV co-infection (155, 156, 160, 171, 172).

Specific HHV-6 treatment was reported in only four studies (150, 152, 160, 171), and the duration was mentioned only in one (160). Overall survival was described in three studies (156, 167, 171) and appeared high, ranging from 42% (11/26) (167) to 100% (156).

3.2.3 Other cohorts

Two other cohorts described HHV-6 infections in mixed SOT and allogeneic HCT recipients (143) and among CAR-T recipients (159).

The study by Potenza et al. (143) was the only single-center prospective study that evaluated the prevalence of ciHHV-6 among 343 mixed SOT (303 liver, 15 kidney–liver, 1 heart–liver, 3 liver–small bowel, and 21 small bowel) and 78 HCT recipients. Prevalence was reported in 7/52 (13.4%) SOT and 3/16 (18%) HCT recipients. In addition, CMV co-infection occurred in 19/52 (36.5%) SOT and 4/16 (25%) HCT recipients.

The only study that evaluated HHV-6 among CAR-T recipients (159) included both a prospective and a retrospective cohort, which comprised 89 and 626 recipients, respectively. Of the prospective cohort, 5/89 (5.6%) developed HHV-6 variant B within a median of 21 days (range, 14–42 days) of CAR-T. All five patients with HHV-6 developed CRS, and three of the five experienced ICANS. In the retrospective cohort, CSF testing was carried out in 34 patients due to suspicion of neurological disease. Of these, there was only one positive HHV-6 PCR test with a viral load of 1,100 copies/ml, giving an overall prevalence of 0.16%. The patient was given steroids and responded well; he was not treated with an antiviral due to the lack of typical features of HHV-6 encephalitis.

4 Discussion

Through this systematic review of HHV-6 in SOT, HCT, and CAR-T recipients, we synthesized information from more than 200 cases and 38 cohort studies and draw attention to the following observations: 1) the rates of clinical and asymptomatic reactivation are highly variable; 2) encephalitis is the most common but not the only clinical syndrome; 3) fever occurrence is highly variable, ranging from 30% to 80%; 4) diagnosis is most often secured using molecular methods in addition to compatible clinical disease; 5) MRI is the imaging modality of choice for neurological disease; 6) antiviral drug preference differs between HCT and SOT; and 7) there is a high rate of long-term neurological sequelae.

Based on our review, the incidence of HHV-6 reactivation is variable and can be as high as 95% in either the SOT or the HCT

TABLE 3 Characteristics of cohort studies of human herpes virus 6 (HHV-6) among hematopoietic transplant recipients.

Year, first author, (country)	Type of study (SC/MC) Study period	Sex M/F	Age (years), (range)	*n/N* with HHV incidence (%)	Time to HHV6 (days), median (range)	Disease (%)	Treatment	Survival (neurological sequelae)
1993, Cone (153) (USA)	RC (SC) 7/1983–4/1988	7/8	30 (3–45)	6/15 (40)	40 (16–259)	Pneumonitis 6/15 (40)		NR
1993, Drobyski (USA) (154)	PC (SC) NR	NR	NR	6/16 (38)	33 (27–85) For 4 patients[b]	BM suppression 4/6 (66.7)	FOS 3, GAN 1	3/4
1999, Wang (SWE) (131)	RCC (SC) 1/1990–4/1997	13/9	17 (1–53)	5/22 (23)		Encephalitis 5/22 (23)	FOS 4, GAN 1	4/5
2000, Imbert (158) (FRA)	PC (SC) 1/1997–1/1998	54/38	Allo 38.5 (3–52); Au 53 (18–65)	39/92 (42)	17 (16–117)			
2000, Ljungman (162) (SWE)	PC (SC) NS		38.3 (3.6–55.3)	4/74 (5.4)		Hepatitis 1, encephalitis 3	FOS 1, GAN 1	
2005, Zerr (174) (USA)	RC (SC) 1998	66/44 35/17	42 (15–67) 39 (16–63)	52/110 (47)	23 (19–28)	CNS dysfunction 3/4		2/4
2006, Fujimaki (45) (JPN)	RC (MC) 1/1999–12/2003	4/7	40 (11–68) 45 (28–58)	11/1148 (1)	23 (15–33)	Encephalitis 11/1148 (0.96)		3/10
2006, Ogata (146) (JPN)	RC (SC) 1/1995–12/2004	30/20	40.5 (12–59) 42.5 (21–56)	24/50 (48)	18 (0–48)	Encephalitis 4	GAN 3	3/4 (short-term memory deficit)
2007, Vu (149) (USA)	RC (SC) 1/2004–9/2006	2/3[a]	46 (39–58)[a]	5/43 (12)	60 (41–103)	Encephalitis 5	FOS 5	3/5 (4/5 complete recovery)
2007, Yamane (175) (JPN)	RC (SC) 7/2003–5/2005	21/25	47 (20–63)	22/46 (48)	21 (14–35)	Encephalitis 3	GAN 3	1/3
2009, Muta (165) (JPN)	RC (MC) 1/1999–12/2003	15/8	38 (18–63)	NA	22 (12–614)	Encephalitis 23	GAN 13, FOS 4, GAN > FOS 5, GAN + FOS 2	16/23 (10/21 with short-term memory impairment)
2011, Betts (170) (USA)	PC (SC) 12/2005–9/2006	45/12 35/11	26 (1–66) 24 (1–67)	46/82 (56)	23 (10–168)	Hepatitis 18, Pneumonitis 16, Fever/rash 11, CNS 8, BM suppression 4	20/46: GAN 11, FOS 8, CID 1	HHV6+ and HHV6– 3 (85% *vs.* 78%, $p = 0.46$), 6 (70% *vs.* 72%, $p = 0.89$), 12 (63% *vs.* 56%, $p = 0.52$), and 24 months (52% *vs.* 53%, $p = 0.93$)
2011, Sakai (147) (JPN)	RC (MC) 1/2004–3/2008	5/3	40.5 (22–57)	8/197 (4)	18 (8–27)	Encephalitis 8	GAN 3, FOS 5	1 year and 3 years survival after HHV-6 encephalitis 62.5 ± 17.1
2012, Hill (157) (USA)	RC (SC) 3/2003–3/2010	NS	NS(18–74)	19/1344 (1)	32 (16–67) UCB; 20 (7–37) Allo	PALE, 19	FOS (18/19)	HCT 9/9 CB 5/10

(Continued)

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TABLE 3 Continued

Year, first author, (country)	Type of study (SC/MC) Study period	Sex M/F	Age (years), (range)	*n/N* with HHV incidence (%)	Time to HHV6 (days), median (range)	Disease (%)	Treatment	Survival (neurological sequelae)
2013, Lindahl (161) (SWE)	RC (SC) 1/1997–12/2001	53/46	40 (17–63)	15/54 (27.8)	76 (24–387)		9/15 treated, 11 treatment episodes: 5/11 FOS, 4/11 GAN,1 FOS > GAN, 1 GAN+FOS	75% at 1 year; 55% at 5 years *vs.* 73% at 1 year; 67% at 5 years
2013, Shimazu (169) (JPN)	RC (SC) 1/2005–9/2009	69/71	46 (17–66); 50 (23–64)[b]	22/140 (16)	With encephalitis 20 (14–54) Without encephalitis 16 (8–24)	Encephalitis 11/140 (7.9)	FOS ± GAN	9/11 (2 with persistent memory loss)
2017, Colombier (34) (FRA)	RC (SC) 1/2008–1/2014	17/10	55 (18–66)[b]	27/316 (4)	13 (9–25)		FOS 4, FAN 4, VGCV 1 25 days	13/13
2017, Hanajiri (51) (JPN)	RC (SC) 1/2005–12/2011	210/143	49.5 (34–64)[b]	6/353 (2)	26 (19–49)		GAN > FOS 4, FOS 2	1/6
2017, Murakami (164) (JPN)	RC (SC) 1/2000–3/2016	9/7	52 (17–68)	NA	20 (16–31)	Encephalitis and myelitis 5, myelitis, 11	All responded to therapy	16/16
2018, Ogata (94) (JPN)	PCC (MC) 4/2010–3/2014 HC; 11/2014–2/2016 cases	38/25 31/26	53 (17–71) 56 (24–71)	63 *vs.* 57 57.3% *vs.* 18.3%	NS	Encephalitis 7 (4.9% controls *vs.* 12.4% cases)	FOS	4/7 (loss of consciousness, 1; mild memory disturbance 3; dysesthesia 1)
2018, Ueki (126) (JPN)	RC (SC) 1/1998–2/2015	69/52	51 (17–68)	5/121 (4)	23 (16–39)	Myelitis 5	GAN 4, FOS 1	2/5
2018, Yoshimoto (138) (JPN)	RC (SC) 2002–2014	245/190 20/5	48 (16–69) 49 (22–67)	24/435 (6)			GAN+FOS 11, FOS 12, GAN 1	23/24 (3 with short-term memory loss)
2019, Balsat (151) (FRA)	PC (MC) 7/2012–2/2015	113/61 14/8	59.5 (53.6–64.8) 58.2 (48.6–61.8)	22/196 (11)	13 (12–15.8)	2 with skin rash with positive skin biopsy; 1 fever	GAN 2	
2019, Fida (42) (USA)	RC (SC) 2011–2017	5/4	52.5 (39.3–58.3)	NA	23 (20.5–29.5)		GAN 10 FOS 2	8/8 (5 with residual neurological deficits)
2019, Inui (58) (JPN)	RC (SC) 3/2010–9/2017	CB 21/12 Non-CB 31/19	CB 52 (19–65) NCB 52 (21–66) HHV 52 (30–61)	7/73 (10)	23 (17–98)	Encephalitis 7 (4 CB and 3 BM)	GAN 1, FOS 5, GAN+FOS 1	6/7 CB, 2/7 NCB (with neurological sequelae)
2020, Shiroshita (173) (JPN)	RC (SC) 5/2003–5/2018	10/9	50 (17–61)[b]	19/460 (4)	20 (13–31)	Myelitis19, encephalitis 3	FOS 10, GAN 7, FOS + GAN 2; IVIG 9	

(Continued)

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TABLE 3 Continued

Year, first author, (country)	Type of study (SC/MC) Study period	Sex M/F	Age (years), (range)	*n/N* with HHV incidence (%)	Time to HHV6 (days), median (range)	Disease (%)	Treatment	Survival (neurological sequelae)
2023, Raouff (168) (EGY)	PC (SC) 1/2020–6/2022	25/15	39.5 (19–72)	15/40 (37.5)		Symptomatic, 13	None treated	
2024, Ogata (166) (JPN)	PC (MC) 12/2018–12/2020	19/9	57(20–70)	36/38 (94..7) viremia	15–28 days viremia	Encephalitis 5		

Symbol > denotes shift to.
BM, bone marrow; *CB*, cord blood; *C*, cohort; *CC*, case–control; *CNS*, central nervous system; *EGY*, Egypt; *FOS*, foscarnet; *FRA*, France; *GAN*, ganciclovir; *JPN*, Japan; *IVIg*, intravenous immunoglobulin; *MC*, multicenter; *NA*, not applicable; *NCB*, non-cord blood; *NS*, not specified; *PALE*, post-transplant acute limbic encephalitis; *P*, prospective; *R*, retrospective; *SC*, singe center; *SWE*, Sweden.
[a]HHV disease only.
[b]Mean.

populations. This is not surprising as HHV-6, similarly to other human herpes viruses, exhibits lifelong latency and tends to reactivate with immunosuppression. The high rate of HHV-6 reactivation is documented in studies from centers that have systematically performed HHV-6 PCR testing, either prospectively or retrospectively in stored clinical samples (146, 174, 175). The vast majority of HHV-6 reactivation that was detected through surveillance is asymptomatic and transient. Hence, the monitoring of HHV-6 is controversial, as asymptomatic or subclinical reactivation happens very often, occurring only transiently, with no impact on the clinical outcomes, and leading to unnecessary treatment with antivirals. As shown in Tables 3 and 4, clinical HHV-6 disease did not occur (138) or occurred in a much smaller proportion of patients, despite the high overall incidence of HHV-6 reactivation in both HCT (94, 140, 146, 151) and SOT recipients (155, 160, 171, 172). Thus, the clinical utility of routine HHV-6 surveillance is debated. More research is needed to identify patients at high risk of clinical disease and to define the optimal timing and frequency of monitoring for HHV-6 infections in these high-risk patients.

This review confirms that the majority of clinical HHV-6 disease (204/268, 76.1%) in transplant and CAR-T populations manifests as a neurological syndrome, primarily encephalitis. These patients presented within the first month of transplantation with varied neurological symptoms, including confusion, amnesia, and seizures, and the majority had abnormal findings on initial imaging. We propose that HHV-6 viremia in the presence of confusion, amnesia, and seizures plus limbic involvement seen on MRI in a post-transplant or CAR-T recipient is defined as probable HHV-6, until proven otherwise. Notably, many of those who developed a neurological syndrome were HHV-6B. While this could be due to reporting bias and the overall higher prevalence of HHV-6B, it highlights that it has a similar neurotrophic property to that of HHV-6A (176). Indeed, in one study, it was proposed that both viruses are equally neurotrophic but that HHV-6A may potentially be more virulent (177). Whether these *in vitro* data translate into worse outcomes for those infected with HHV-6A remains to be seen. Interestingly, only a small subset of patients (15 HCT and 1 SOT) was specifically reported as HHV-6 PALE. HHV-6 PALE was first described in HCT recipients (11) and has not been formally defined but is the primary involvement of the limbic system driven by HHV-6 infection. One study (148) proposed characterizing it as a distinct entity with acute alterations in mental status, prominent amnesia, and unexplained seizures. Based on this definition, and compatible with the MRI findings, at least 14 other cases fit the criteria for HHV-6 PALE; however, these cases were simply described as "encephalitis." This is worth mentioning as it highlights the under-recognition of this entity, as well as the need to more clearly define this category of patients. Early recognition of this specific syndrome may have clinical implications for treating clinicians—such as the association with HHV-6, the prevention of progressive disease, and the potential avoidance of neurological sequelae with early antiviral therapy. Among the HCT recipients, the majority with encephalitis were either allogeneic or cord blood recipients, which may be due to their greater level of immunosuppression compared with autologous transplants. The risk factors for HHV-6 reactivation and disease included the use of a mismatched donor and steroids (146,

TABLE 4 Characteristics of cohort studies of human herpes virus 6 (HHV-6) among solid organ transplant recipients.

Year, first author, (country)	Type of study Study period	Type of allograft	Sex, M/F Age (years), (range)	*n*/*N* with HHV Incidence (%)	Time to HHV-6 (days), median (range)	Disease	Treatment	Survival
1991, Gudnason (155) (USA)	RC 6/1989–1/1990	8 KP 17 K	13/12 35 (2–68)	9/25 (36)		7/9 with clinical illness		NR
2002, Humar (171) (CAN)	PC 1/1997–3/2000	L	127/73 53 (18–70)	56/200 (28)	27 (0–177)	2	GAN 1, decrease IS 1	50/56
2006, Harma (156) (FIN)	RC 5/1996–9/2002	L		18/32 (56.3)	19 (6–38)		GAN for CMV w/loss of HHV6 antigenemia in liver	6 months, 100%; 1 year, 100%
2007, Lehto (160) (FIN)	PC 12/2000–10/2004	4 SL, 15 DL, 3 HL	13/9 48 (22–65)	20/22 (90.9)	16 (9–232)	1	GAN (3 weeks)	NR
2008, Ohashi (167) (JPN)	PC 11/2001–1/2006	LR, L	34/33 46 ± 14	26/67 (38.8)		26/67 (38.8) with reactivation		11/26 with HHV *vs.* 6/41 without HHV (p = 0.0118)
2012, Sampaio (172) (BRA)	PC 2007–2009	L		12/45 (26.7)	32	Encephalitis 1		NR
2013, Buyse (152) (FRA)	RC 1986–2006	L	6/4 HHV+; 5/11 HHV– 44[a] (16–63); 50.5[a] (35–62)	10/26 (38.5)	2.7 months[b] (0.3–180)	4/10	GAN > VGCV	NR
2013, Magalhaes (163) (BRA)	RC 9/2008–3/2010	L	13/7 48 (18–67)	NA	10 (5–21)	7/20 (symptomatic)		NR
2018, Al Obaidi (150) (IRN)	PCC 1/2015–6/2015	LU K 18, LR K 31	36/13 33.49[a] ± 11	8/49 (16.3)	6.4 ± 3.5 months		GAN 1	NR

Symbol > denotes shift to.

BRA, Brazil; *CAN*, Canada; *DL-* double lung; *FIN*, Finland; *GAN*, ganciclovir; *IRN*, Iran; *IS*, immunosuppression; *JPN*, Japan; *HL*, heart–lung; *L*, liver; *Lu*, lung; *LU*, living unrelated; *LR*, living related; *K*, kidney; *NR*, not reported; *P*, pancreas; *SL*, single lung; *PCC*, prospective case–control; *PC*, prospective cohort; *RC*, retrospective cohort; *VGCV*, valganciclovir.

[a]Mean.

[b]Time to histological diagnosis.

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174). For the patients in this review, approximately half were mismatches or unrelated donors (50/92, 54.3%) or were given steroids for GvHD (76/183, 41.5%). There may be other host factors related to the complex immunological CD8 T-cell responses, which are dampened by transplant-related immunosuppression that may have significantly influenced the HHV-6 reactivation (178); however, these were not explored in this review.

When there is suspicion of encephalitis, we advocate MRI as the preferred imaging of choice. MRI was able to capture findings not initially seen on the CT scan, even when done on the same day. Imaging evidence involving one or both hippocampi and adjacent medial temporal lobe structures of the limbic system, including the amygdalae and parahippocampal gyri, is suggestive of "limbic encephalitis" and should help narrow the differential diagnosis (148). Although other causes such as paraneoplastic malignancies, neurosyphilis, herpes simplex, and varicella zoster have been implicated in limbic encephalitis, HHV-6 should be a leading impression given the right clinical context.

Other syndromes of HHV-6 occurred but were much less common. Disseminated disease was infrequently seen among both SOT and HCT recipients. For HCT recipients, the median time to presentation of disseminated disease was beyond the period of engraftment (e.g., 171 days). Of the reported cases, 5/8 (62.5%) developed aGvHD and were treated with steroids. We propose that this increased level of immunosuppression contributed to the risk of disseminated disease. However, given the limited number, more definite conclusions cannot be made. In contrast, disseminated disease among SOT recipients occurred within the first month of transplantation. Although it is unclear what drove early disseminated disease in these patients, we hypothesize that the choice of induction immunosuppression played a role.

Fever was more frequent among CAR-T recipients and occurred in a third of other patients. As such, for individuals without a fever, other concomitant symptoms of HHV-6-related disease should be sought. Rashes, diarrhea, and cytopenias were commonly reported with other HHV-6 syndromes. Rashes from a viral exanthem such as HHV-6 are difficult to distinguish from aGvHD based on clinical appearance. In most cases, a biopsy is necessary to determine the etiology of the rashes as the approach to treatment differs.

The diagnosis of HHV-6 was secured primarily using molecular methods (e.g., DNA PCR) in the majority of patients. Confirmation via tissue diagnosis was rarely done, even among SOT recipients. Although the isolation of HHV-6 in cell cultures is the reference method and unambiguously demonstrates the presence of infectious viral particles, it is poorly sensitive, time-consuming, expensive, and unavailable in most centers and thus cannot be used for routine diagnosis (179). However, HHV-6 DNAemia by itself can be exceptionally tricky to interpret in the context of ciHHV-6. ciHHV-6 diagnosis previously required hair follicle or molecular cytogenetic analysis, which is impractical in the clinical setting. Experts propose that ciHHV-6 can be assumed in the presence of >1 million genomic copies of HHV-6 per milliliter of whole blood (10). In our review, the 10 ciHHV-6 cases were treated because all had symptoms consistent with clinical disease. However, the literature is replete with reports of asymptomatic high-level HHV-6 viremia (10, 180–182), with delayed realization of the possibility of ciHHV-6 and the need for treatment (10). As such, careful consideration for ciHHV-6 should be made when there is high-level viremia in an asymptomatic patient.

Interestingly, ganciclovir was the primary therapy used in 54.5% (18/33) of SOT recipients, while foscarnet (74/196, 37.8%) and ganciclovir (67/196, 34.2%) were almost equally used in HCT recipients. Ganciclovir, a nucleoside analogue, is likely preferred in SOT as it has fewer nephrotoxic effects than foscarnet. Foscarnet also causes multiple electrolyte imbalances and QTc prolongation, which poses increased difficulty in terms of monitoring, particularly among kidney allografts. In contrast, ganciclovir and valganciclovir are generally avoided in HCT recipients due to their myelosuppressive effects, which can delay marrow recovery. Unfortunately, the optimal drug of choice and the duration of therapy against HHV-6 are unknown and need to be defined. To highlight the key features of HHV-6, a summary is provided (Table 5).

Although the attributable mortality from HHV-6 was modest (22/107, 20.6%), at least a third of patients (45/151, 29.8%) had some neurological deficits at the last follow-up, long after resolution of the clinical disease. The incidence may even be higher, as the neurological outcome was unspecified in a fourth of cases (38/151, 25.2%). Morbidity from HHV-6 disease can be debilitating; as such, HHV-6 neurological involvement should be recognized early and treated aggressively.

TABLE 5 Summary of the key characteristics of human herpes virus 6 (HHV-6).

Characteristic	Comment
Clinical features	• More frequently reported in HCT (allogeneic > autologous) compared with SOT recipients • Encephalitis syndrome with confusion, anemia, and/or seizures is most common. However, myelitis can occur as well. • Other non-neurological presentations can occur, including viral syndrome, disseminated disease, or cardiac syndrome. • Symptoms occur within the first month after SOT/HCT and within days of CAR-T. • Fever occurs only in 1/3 of patients. • HHV-B more commonly reported than HHV-A • CI-HHV6 should be suspected when HHV viremia is in the millions. • Neurological sequelae can be long-lasting.
Diagnostics	• Quantitative HHV-6 PCR in the CSF or plasma is preferred. • CSF analysis compatible with viral etiology with mild pleocytosis and normal or slightly elevated glucose and protein • Detection of HHV-6 in blood should be interpreted in the context of the clinical syndrome.
Radiology	• MRI is the imaging modality of choice. • Imaging should be repeated in a few days if initially normal or non-diagnostic • Frequently involves the temporal and limbic areas (e.g., amygdala, thalamus, and parahippocampus)
Treatment	• Ganciclovir and foscarnet are preferred. • Treatment duration usually 4 weeks

CAR-T, chimeric antigen receptor T cell; *CI*, chromosomally integrated; *CSF*, cerebrospinal fluid; *HCT*, hematopoietic cell transplant; *SOT*, solid organ transplant.

Other unique observations from this systematic review deserve mention. Firstly, the higher proportion of men could suggest that they are disproportionately affected by HHV-6. Although this may be a reflection of the overall gender disparity of the transplant population, which is predominantly male, this merits further exploration. Secondly, CMV co-infection was more frequently reported in hematopoietic than in SOT recipients, which mirrors the expectations in the larger transplant population. This review also encompasses a period where CMV surveillance and preemptive therapy comprise a more common CMV prevention strategy in hematopoietic stem cell transplants compared with universal prophylaxis among SOT recipients. However, most case reports did not explicitly state whether CMV was evaluated, and the risk of CMV reactivation may have been underreported overall. Finally, HHV-6A appears to be as prevalent as HHV-6B among SOT recipients, which challenges the notion that HHV-6B is more common in the transplant population. However, as the numbers are limited, no definitive conclusions can be made, and this must be interpreted with caution.

Our study has several limitations. Firstly, there are duplications across studies (e.g., case reports and cohorts) as some cases from larger cohorts were described in detail. Secondly, we excluded asymptomatic HHV-6 and ciHHV-6, but these could have been inadvertently misclassified as asymptomatic when true disease was present. Alternatively, other viral infections (e.g., CMV and EBV) or syndromes (e.g., ICANS) can present similarly, and symptoms attributable to HHV-6 could have been from these other causes. Important publications in non-English journals may have been missed as the language was limited to English. Reports lacking patient-level data, pediatric transplants, and abstracts of cohort studies were also excluded; thus, our numbers likely underestimated the true magnitude of HHV-6. Finally, due to the heterogeneity of cohort and case–control studies, we were unable to perform a meta-analysis. A formal assessment of risk factors predictive of HHV-6 disease, for example, may be helpful for transplant clinicians, and a future analysis needs to be performed. Despite these, our study is the first to provide cumulative data on HHV-6 for transplant and CAR-T recipients.

5 Conclusions

Our review highlights that HHV-6 subclinical reactivation frequently occurs. HHV-6 clinical disease is more commonly reported among HCT compared with SOT or CAR-T recipients. However, only six CAR-T cases and one cohort study were included, prohibiting conclusions for this group. Neurological disease in the form of encephalitis is the most frequent clinical syndrome. Early recognition of limbic involvement either through the triad of confusion, amnesia, and seizures or through compatible MRI findings may help with the early identification of HHV-6. Diagnosis is secured through molecular methods, although HHV-6 detection per se may not necessarily indicate disease. Extremely high viremia needs to be interpreted with caution in the context of ciHHV-6, which may not warrant treatment. HHV-6-associated mortality is modest; however, the neurological sequelae can be disabling and cause significant morbidity.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

CA: Data curation, Writing – review & editing, Conceptualization, Writing – original draft. RR: Writing – original draft, Supervision, Writing – review & editing, Validation.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fviro.2025.1641157/full#supplementary-material

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