Transplantation and Cellular Therapy 32 (2026) 615.e1–615.e14

Transplantation and Cellular Therapy

journal homepage: www.astctjournal.org

ASTCT American Society for Transplantation and Cellular Therapy

Full Length Article
Infectious Disease

Clinical Impact of Human Herpesvirus 6B Reactivation on Engraftment and Outcomes Following Allogeneic Hematopoietic Stem Cell Transplantation

Seyed M. Hosseini-Moghaddam[1,5,*], Rochelle B. Johnstone[1,5], Tony Mazzulli[3,4], Mats Remberger[6], Ivan Pasic[2,5], Jonas Mattsson[2,5], Ferdous Parveen[1], Carol Chen[2], Shahid Husain[1,5], Florence Runyo[1,5], Fotios V. Michelis[2,5]

[1] *Transplant Infectious Diseases and Ajmera Transplant Centre, University Health Network, Toronto, Ontario, Canada*
[2] *Hans Messner Allogeneic Transplant Program, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario, Canada*
[3] *Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada*
[4] *Department of Microbiology, University Health Network/Sinai Health System, Toronto, Ontario, Canada*
[5] *Department of Medicine, University of Toronto, Toronto, Ontario, Canada*
[6] *Department of Medical Sciences, Uppsala University and KFUE, Uppsala University Hospital, Uppsala, Sweden*

Article history:
Received 11 November 2025
Accepted 7 January 2026

Key Words:
Herpesvirus 6
Human
Hematopoietic stem cell transplantation
Relapse

A B S T R A C T

Human herpesvirus 6B (HHV-6B) reactivation is a recognized event following allogeneic hematopoietic stem cell transplantation (HSCT). However, its impact on engraftment kinetics and post-transplant outcomes remains incompletely defined, particularly in the era of letermovir prophylaxis, when the use of antivirals with anti-HHV-6B activity, such as ganciclovir and valganciclovir, has declined. To determine the incidence of HHV-6B reactivation and assess its impact on post-transplant outcomes, including time to platelet and neutrophil engraftment, lymphocyte recovery, and transplant-related complications. We conducted a prospective cohort study of adults who underwent allogeneic HSCT between March 1 and December 1, 2022. Plasma HHV-6B DNAemia was monitored serially during the first 100 days post-transplant, with clinical follow-up for 6 mo and extended follow-up to 2 yr for mortality and relapse outcomes. In this cohort of 102 patients (49 females [48%]; median age, 58 yr [IQR, 48 to 66]), HHV-6B reactivation occurred in 50 patients (49%), with a median onset of 28 days post-transplant (IQR, 22 to 31) and a median peak viral load of 684 IU/mL (IQR, 72.7 to 3500). Compared with patients without DNAemia, those with HHV-6B reactivation had delayed platelet engraftment (26 days [IQR 18 to 34] versus

Abbreviations: AA, aplastic anemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BMI, body mass index; CLL, chronic lymphocytic leukemia; CMML, chronic myelomonocytic leukemia; CML, chronic myelogenous leukemia; CMV, cytomegalovirus; DRI, Disease Risk Index; ET, essential thrombocythemia; GVHD, graft-versus-host disease; MDS, myelodysplastic syndrome; MPAL, mixed-phenotype acute leukemia; MF, myelofibrosis; NRM, non-relapse mortality; PTCy, post-transplant cyclophosphamide; rATG, rabbit antithymocyte globulin; SE, standard error; SOS, sinusoidal obstruction syndrome; VOD, veno-occlusive disease.

Financial disclosure: See Acknowledgments on page 615.e12.

*Correspondence and reprint requests: Seyed M. Hosseini-Moghaddam, MD, MPH, MSc, Department of Medicine Toronto General Hospital, University Health Network, University of Toronto, 200 Elizabeth St., Toronto, ON M5G 2C4, Canada.
E-mail address: sasan.hosseini@uhn.ca (S.M. Hosseini-Moghaddam).

https://doi.org/10.1016/j.jtct.2026.01.008

19 days [IQR 17 to 26]; $P = .025$) and longer time to achieve an absolute lymphocyte count (ALC) $>300 \times 10^6$/L (29 days [IQR 25 to 40] versus 26 days [IQR 22 to 32]; $P = .04$). Persistent HHV-6B DNAemia ($n = 21$, 20.6%), defined as >1000 IU/mL for two consecutive weeks, was associated with further delays in platelet (30 days [IQR 19 to 39] versus 19 days [IQR 17 to 26]; $P = .01$), ALC (33 days [IQR 24 to 42] versus 26 days [IQR 22 to 32]; $P < .05$), and neutrophil engraftment (22 days [IQR 19 to 24] versus 20 days [IQR 17 to 22]; $P = .05$). In adjusted analysis, HHV-6B DNAemia remained an independent predictor of relapse (aHR, 2.21; 95% CI, 1.00 to 4.85; $P = .04$). In competing risk analysis, persistent HHV-6B DNAemia was significantly associated with relapse (8/21 [39.5%; 95% CI, 18.0 to 60.0] versus 9/52 [17.0%; 95% CI, 8.0 to 28.0]; $P = .04$). HHV-6B reactivation was frequent after allogeneic HSCT and was associated with delayed hematopoietic recovery and an increased risk of disease relapse, particularly among patients with persistent DNAemia. These findings highlight the clinical significance of HHV-6B in post-transplant outcomes and underscore the need for prospective studies to refine monitoring and management strategies.

INTRODUCTION

Human herpesvirus 6 (HHV-6), a member of the *Roseolovirus* genus within the *β-herpesvirus* subfamily, comprises two distinct species: HHV-6A and HHV-6B. While our knowledge of HHV-6A is still limited, HHV-6B is highly prevalent, with almost universal seropositivity observed by early childhood [1]. After initial infection, HHV-6B establishes latency in host cells, particularly in mononuclear cells, and can reactivate under immunosuppressive conditions, especially following allogeneic hematopoietic stem cell transplantation (HSCT) [1–4]. Reactivation often occurs within the first few weeks after transplantation and is associated with various clinical complications, such as encephalitis [5]. Despite its frequent detection, the clinical significance of HHV-6B DNAemia remains debated, partly due to a lack of mechanistic insight into its immunopathogenesis and challenges in distinguishing pathogenic reactivation from bystander replication.

Recent studies suggest that HHV-6B reactivation may contribute to impaired immune recovery by modulating host cytokine responses, disrupting antigen presentation, and impairing the function of hematopoietic progenitor cells [6]. These effects could influence important post-transplant outcomes such as disease relapse; however, HHV-6B is not routinely included in prophylactic or preemptive strategies. In this prospective cohort study of allogeneic HSCT recipients, we investigated the relationship between HHV-6B DNAemia and clinically relevant outcomes.

METHODS

This single-center cohort study was conducted at the Hans Messner Allogeneic Transplant Program at the Princess Margaret Cancer Centre in Toronto, Canada, with approval from the University Health Network Research Ethics Board. Written informed consent was obtained from all participants. All patients enrolled were adults (≥18 yr) who underwent allogeneic HSCT between March 1 and December 1, 2022, with follow-up for 2 yr post-transplant.

In this cohort, patients received one of the following regimens for graft-versus-host disease (GVHD) prophylaxis [1]: rabbit antithymocyte globulin (rATG) in combination with post-transplant cyclophosphamide (PTCy) and cyclosporine (CsA), with tacrolimus substituted for CsA in one patient [2]; PTCy, CsA, and mycophenolate mofetil (MMF); or [3] a methotrexate (MTX)-based regimen consisting of rATG, CsA, and MTX. The rATG dose varied among regimens, ranging from 2 to 4.5 mg/kg.

Universal antiviral prophylaxis with acyclovir or valacyclovir was provided for at least 1 yr post-HSCT, or until immunosuppression was discontinued and T-cell reconstitution was determined to be adequate. Patients at high risk for cytomegalovirus (CMV) reactivation—including CMV-seropositive recipients, patients that received rATG during conditioning, those receiving haploidentical grafts, individuals with prior CMV disease, and patients treated with ≥1 mg/kg/day of prednisone or other immunosuppressive agents for acute GVHD, received letermovir prophylaxis starting from day +21 to day +121 post-transplant [7].

Detection of HHV-6B DNAemia

HHV-6B DNAemia was measured using the RealStar HHV-6B PCR Kit 1.0 (Altona Diagnostics, Canada), a quantitative real-time PCR assay. Testing was performed on plasma samples using a validated in-house workflow, with results expressed

in international units per milliliter (IU/mL). HHV-6B viral load was measured at intervals of 1 to 3 wk during the first 100 days post-transplant. Quantification is standardized to WHO reference material, enabling consistent inter-laboratory comparison [8,9]. We considered persistent HHV-6B DNAemia defined as >1000 IU/mL (>3 logs) for 2 consecutive weeks [10]. All HHV-6B testing was performed for research purposes only, and results were not available to the clinical care teams.

Study Outcomes

The primary outcome was the time interval between transplantation and platelet engraftment, defined as the first of three consecutive days with a platelet count $>20 \times 10^9$/L (20,000/μL) without transfusion support [11]. Secondary outcomes included the time to neutrophil, lymphocyte, and monocyte recovery. Neutrophil engraftment was defined as the first of three consecutive days with an absolute neutrophil count >500 cells/μL without growth factor support [11]. We also assessed the time from transplantation to achieving an absolute lymphocyte count (ALC) $>300 \times 10^6$/L and an absolute monocyte count $>300 \times 10^6$/L in peripheral blood—thresholds associated with improved overall survival (OS) in previous studies [12–15].

Within the first 6 mo post-transplant, we evaluated clinical complications—including pneumonia of undetermined microbiologic etiology (a new pulmonary infiltrate with compatible symptoms and no identified pathogen, despite standard diagnostic evaluation such as bronchoscopy when clinically indicated), as well as diarrhea of unclear etiology and encephalitis—in relation to HHV-6B DNAemia. We also compared HHV-6B DNAemia in patients with and without a composite central nervous system (CNS) outcome, defined as delirium, seizure, or encephalitis. Encephalitis was defined as altered mental status lasting ≥24 h accompanied by cerebrospinal fluid pleocytosis, and compatible neuroimaging findings, and delirium as an acute, fluctuating disturbance in attention and cognition documented by the clinical team using standard bedside assessments.

Mortality and relapse outcomes were assessed over a 2-yr follow-up period, comparing relapse and non-relapse mortality (NRM) between patients with and without HHV-6B DNAemia.

STATISTICS

Baseline characteristics were analyzed using the Mann–Whitney *U* and Chi-square tests. OS was estimated with the Kaplan–Meier method and compared using the log-rank test. NRM, relapse, and engraftment were evaluated with competing risk analysis based on the Fine and Gray model. Cox proportional hazards regression was used for univariate and multivariate analyses; variables with $P \leq .10$ in univariate testing were entered into a backward elimination multivariable model. Since relapse risk is strongly influenced by disease type and status, we included the Disease Risk Index (DRI) as a covariate in the limited multivariable analysis for relapse; this CIBMTR (Center for International Blood and Marrow Transplant Research)–derived index stratifies patients into low, intermediate, high, or very high risk groups based on their underlying hematologic malignancy and disease status at the time of transplantation [16,17]. For engraftment outcomes, we used a parsimonious multivariable Cox proportional hazards model to reduce overfitting, given the cohort size. The model included covariates associated with engraftment based on prior evidence or univariable analyses, while interaction terms were excluded to limit complexity and preserve model stability. All tests were two-sided. Statistical analyses were performed with Statistica 14.1 (TIBCO, Palo Alto, USA) and EZR 1.61 (Kanda) [18].

RESULTS

A total of 102 patients were included in this cohort (49 female [48%]; median age 58 yr [IQR 48 to 66] yr). Table 1 presents the characteristics of the cohort. Overall, 50 patients (49%) developed HHV-6B reactivation, with a median peak viral load of 684 IU/mL (IQR, 72.7 to 3500). The maximum recorded viral load was 223,000 IU/mL. The median time from transplant to peak DNAemia was 28 days (IQR 23 to 36; range 11 to 100). One haploidentical HSCT recipient was identified with findings suggestive of chromosomally integrated HHV-6B (ciHHV-6B), including persistently elevated viral loads in blood and detection of HHV-6B DNA in both bone marrow and buccal mucosa. The patient's sibling donor also exhibited consistently high HHV-6B DNA levels, further supporting a pattern consistent with inherited chromosomal integration.

HHV-6B DNAemia was observed more frequently among patients receiving GVHD prophylaxis with rATG + PTCy + CsA (56.1%) or PTCy + MMF + CsA (44.0%) compared with those treated with MTX-based regimens (18.2%); however, this difference did not reach statistical significance (P = .06). The median age was significantly higher among patients with HHV-6B

Table 1
Patients in the Cohort, with and without HHV-6B DNAemia

Variable	Patients in the Cohort *N* = 102 (%)	HHV-6B DNAemia		*P* Value
		No, *n* = 52 (50.5)	Yes, *n* = 50 (49.5)	
Age, median, IQR	58 (49-66)	56 (37-63)	61 (53-68)	.014
Female	49 (48)	26 (50)	23 (46)	.69
BMI median, IQR	26.2 (22.5-29.6)	26.4 (22.7-29.9)	25.9 (22.5-29.4)	.63
Comorbidities				
Diabetes mellitus	11 (10.8)	7 (13.5)	4 (8.0)	.53
Chronic kidney disease	3 (2.9)	1 (1.9)	2 (4.0)	.61
Chronic lung disease	7 (6.9)	3 (5.8)	4 (8.0)	.71
Hypertension	33 (32.4)	14 (26.9)	19 (38.0)	.29
Coronary arterial disease	8 (7.8)	5 (9.6)	3 (6.0)	72
Autoimmune disease	7 (6.9)	3 (5.8)	3 (6.0)	1.0
Donor				.03
Related	25 (24.5)	16 (30.8)	9 (18.0)	.17
MUD	55 (53.9)	29 (55.8)	26 (52.0)	.84
MM URD	7 (6.9)	3 (5.8)	4 (8.0)	.71
Haploidentical	15 (14.7)	4 (7.7)	11 (22.0)	.05
Underlying disease				.47
AML	49 (48.0)	25 (48.1)	24 (48)	
ALL	12 (11.8)	4 (7.7)	8 (16)	
AA	2 (2.0)	2 (3.8)	0	
CML	3 (2.9)	2 (3.8)	1 (2)	
CLL	1 (1.0)	1 (1.9)	0	
CMML	7 (6.9)	4 (7.7)	3 (6)	
ET	1 (1)	0	1 (2)	
MDS	22 (21.6)	10 (19.2)	12 (24)	
MF	4 (3.9)	3 (5.8)	1 (2)	
MPAL	1 (1)	1 (1.9)	0	
Myeloablative conditioning	41 (40.2)	28 (53.8)	13 (26.0)	.005
GVHD prophylaxis	66 (64.7)	29 (55.8)	37 (74)	.11
rATG + PTCy + CsA	11 (10.7)	9 (17.3)	2 (4)	
MTX-based regimen	25 (24.5)	14 (26.9)	11 (22)	
PTCy + MMF + CsA				
Post-transplant events				
Acute GVHD	53 (52.0)	28 (53.8)	25 (50.0)	.84
GVHD, grade ≥2	37 (36.3)	18 (34.6)	19 (38.0)	.84
Chronic GVHD	23 (22.5)	10 (19.2)	13 (26.0)	.63
Moderate-severe cGVHD	14 (13.7)	6 (11.5)	8 (16.0)	.77
Requiring systemic steroid	24 (23.5)	10 (19.2)	14 (28.0)	.48
Requiring ruxolitinib	3 (2.9)	0	3 (6.0)	.24
SOS/VOD	3 (2.9)	2 (3.8)	1 (2.0)	.97
Primary graft failure	1 (1)	0	1 (2.0)	.49
Antiviral therapy				
Acyclovir/valacyclovir	102 (100%)	46 (88.5)	46 (92.0)	.74
Ganciclovir/valganciclovir	15 (14.7)	8 (15.4)	7 (14.0)	.93
Foscarnet	4 (3.9)	1 (1.9)	3 (6.0)	.36

(*continued*)

Table 1 (*Continued*)

Variable	Patients in the Cohort *N* = 102 (%)	HHV-6B DNAemia		*P* Value
		No, *n* = 52 (50.5)	Yes, *n* = 50 (49.5)	
DRI:				.93
Low	3 (3.0)	3 (5.8)	0	
Intermediate	73 (73.0)	34 (65.4)	39 (78.0)	
High	20 (20.0)	11 (21.2)	9 (18.0)	
Very High	4 (4.0)	2 (3.8)	2 (4.0)	

AA indicates aplastic anemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BMI, body mass index; CLL, chronic lymphocytic leukemia; CMML, chronic myelomonocytic leukemia; CML, chronic myelogenous leukemia; CsA, cyclosporine A; DRI, Disease Risk Index; ET, Essential thrombocythemia; GVHD, graft-versus-host disease; MDS, myelodysplastic syndrome; MPAL, mixed-phenotype acute leukemia; MF, myelofibrosis; MMF, mycophenolate mofetil; MTX, methotrexate; PTCy, post-transplant cyclophosphamide; rATG, rabbit antithymocyte globulin; SE, standard error; SOS, sinusoidal obstruction syndrome; Tac, tacrolimus; VOD, veno-occlusive disease.

DNAemia compared with those without (61 yr [IQR, 53 to 68] versus 56 yr [IQR, 37 to 63]; P = .014). HHV-6B DNAemia was also more frequent among recipients of haploidentical grafts (22.0% versus 7.7%; P = .05). In a multivariable model adjusting for age and transplant type, both age ≥60 yr (aHR, 2.77; 95% CI, 1.54 to 4.96; P < .001) and haploidentical transplantation (aHR, 2.69; 95% CI, 1.34 to 5.38; P = .005) remained independently associated with HHV-6B DNAemia.

Table 2 compares study outcomes between patients with and without HHV-6B DNAemia. The interval between transplantation and platelet engraftment was significantly different between patients with and without DNAemia, median 26 days (IQR 18 to 34) for those with DNAemia and 19 days (IQR 17 to 26) for those without (P = .025). In contrast, the interval between transplantation and neutrophil engraftment showed no difference between the two groups, with 21 days (IQR 18 to 23) for patients with DNAemia and 20 days (IQR 18 to 22) for those without (P = .29). Additionally, the time taken to achieve an ALC >300 × 10^6/L was significantly different: 29 days (IQR 25 to 40) for patients with DNAemia compared to 26 days (IQR 22 to 32) for those without (P = .04). In contrast, the time to reach an absolute monocyte count >300 × 10^6/L did not differ significantly (20 days [IQR 17 to 24] versus 19 days [IQR 16 to 21]; P = .10). Table 1 compares patient characteristics, transplant-related variables, complications, and study outcomes between patients with and without HHV-6B DNAemia.

In Cox proportional hazards analyses, HHV-6B DNAemia was not significantly associated with neutrophil engraftment (HR, 0.80; 95% CI, 0.52 to 1.21; P = .28) or monocyte recovery (HR, 0.68; 95% CI, 0.45 to 1.03; P = .07). However, HHV-6B DNAemia was significantly negatively associated with time to platelet engraftment (HR, 0.56; 95% CI, 0.35 to 0.90; P = .02) and lymphocyte recovery (HR, 0.43; 95% CI, 0.24 to 0.76; P = .004).

Overall, relapse of the underlying disease occurred in 13 patients (12.7%) within 6 mo, 22 patients (21.5%) within 1 yr, and 27 patients (26.4%) within 2 yr post-transplant. Patients with HHV-6B DNAemia had higher relapse rates than those without DNAemia at 6 mo (16.0% versus 9.6%; P = .32) and 1 yr (28.0% versus 15.4%; P = .13), with the difference reaching statistical significance at 2 yr post-transplant (36.3% versus 17.4%; P = .03; Figure 1). In univariate analysis, both HHV-6B DNAemia (HR, 2.30; 95% CI, 1.03 to 5.10; P = .04) and a high DRI (HR, 2.61; 95% CI, 1.22 to 5.60; P = .01) were significantly associated with an increased risk of relapse within 2 yr post-transplant. In the multivariable model incorporating both DRI and HHV-6B DNAemia, a high DRI (adjusted hazard ratio [aHR], 2.62; 95% CI, 1.21 to 5.68; P = .01) and the presence of HHV-6B DNAemia (aHR, 2.21; 95% CI, 1.00 to 4.85; P < .05) each remained independent predictors of relapse.

OS at 1 yr (39/50 [78.0%] versus 39/52 [75.0%]; P = .32) and 2 yr (31/50 [62.0%] versus 37/52 [71.2%]; P = .40) did not differ significantly between patients with and without HHV-6B DNAemia. In competing risk analysis, NRM did not differ significantly between patients with and without HHV-6B DNAemia at 1 yr (3/50 [6.0%; 95% CI, 1.5 to 15.0] versus 7/52 [13.5%; 95% CI, 5.9 to 24.2]; P = .19) or at 2 yr (6/50 [12.2%; 95% CI, 4.9 to 23.0] versus 7/52 [13.5%; 95% CI, 5.9 to 24.2]; P = .79; Figure 2). In Cox proportional hazards analysis, HHV-6B DNAemia was not associated with increased NRM risk (HR, 0.49; 95% CI, 0.12 to 1.97; P = .32).

Two patients developed encephalitis: one had laboratory-confirmed HHV-6B encephalitis, while

Table 2
Study Outcomes and Complications

Study Outcomes	Patients in the Cohort *N* (%)	HHV-6 DNAemia		*P* Value	Persistent HHV-6B DNAemia		*P* Value
		No, *n* = 52 (50.5)	Yes, *n* = 50 (49.5)		No *n* = 52 (79.4%)	Yes *n* = 21 (20.6%)	
HHV-6B DNAemia, median, IQR	684 (72.7-3550)	-	684 (72.7-3550)	-	-	4880 (2690-23,300)	.05
Neutrophil engraftment, days, median (IQR)	20 (18-23)	20 (18-22)	21 (18-23)	.29	20 (18-22)	22 (19-24)	.01
Platelet engraftment, days, median (IQR)	23 (17-32)	19 (17-26)	26 (18-34)	.025	19 (17-26)	30 (19-39)	<.05
Days to ALC >300 × 10^6/L, median, IQR	28 (23-37)	26 (22-32)	29 (25-40)	.04	26 (22-32)	33 (24-42)	.07
Days to AMC >300 × 10^6/L, median, IQR	20 (17-22)	19 (16-21)	20 (17-24)	.10	19 (16-21)	20 (18-23)	.77
Death—at 1 yr	24 (23.5)	13 (25.0)	11 (22.0)	.82	13 (25.0)	6 (28.6)	.87
NRM-1 yr	9 (8.8)	6 (11.5)	3 (6.0)	.49	6 (11.5)	2 (9.5)	.69
Death-at 100 days	4 (3.9)	3 (5.8)	1 (2.0)	.62	3 (5.8)	1 (4.8)	.91
NRM-100 days	2 (2.0)	2 (3.8)	0	.50	2 (3.8)	0	
Infectious diseases							
CMV reactivation	30 (29.4)	12 (23.1)	18 (36.0)	.19	12 (23.1)	9 (42.9)	.15
Maximum viral load (IU/mL), median, IQR	1395 (407-3830)	1260 (556-3580)	1510 (369-13,400)	.72	1260 (556-3580)	3200 (1490-3830)	.42
Interval since transplantation, median, IQR	40 (21-133)	28 (20-43)	49 (31-148)	.09	28 (20-43)	33 (21-49)	.70
EBV DNAemia	51 (50.0)	26 (50.0)	25 (50.0)	1.0	26 (50.0)	10 (47.6)	1.0
Fungal pneumonia	7 (6.9)	3 (5.8)	4 (8.0)	.71	3 (5.8)	2 (9.5)	.62
Viral pneumonitis[*,†]	3 (2.9)	1 (1.9)	2 (4.0)	.61	1 (1.9)	1 (4.8)	.50
Pneumonia with undetermined etiology	24 (23.5)	8 (15.4)	16 (32.0)	.06	8 (15.4)	7 (33.3)	.11
Febrile neutropenia	90 (88.2)	46 (88.5)	44 (88.0)	1.0	46 (88.5)	19 (90.5)	1.0
Bloodstream infection	54 (52.9)	30 (57.7)	24 (48.0)	.43	30 (57.7)	13 (61.9)	.80
Diarrhea	45 (44.1)	18 (34.6)	27 (54.0)	.07	18 (34.6)	13 (61.9)	.04
Other complications							
Rash	51 (50)	27 (51.9)	24 (48.0)	.84	27 (51.9)	11 (52.4)	1.0
Rash without GVHD or engraftment syndrome	18 (17.6)	10 (19.2)	8 (16.0)	.80	10 (19.2)	4 (19.0)	1.0

(*continued*)

Table 2 (*Continued*)

Study Outcomes	Patients in the Cohort *N* (%)	HHV-6 DNAemia		*P* Value	Persistent HHV-6B DNAemia		*P* Value
		No, *n* = 52 (50.5)	Yes, *n* = 50 (49.5)		No *n* = 52 (79.4%)	Yes *n* = 21 (20.6%)	
Delirium	14 (13.7)	6 (11.5)	8 (16.0)	.57	6 (11.5)	5 (23.8)	.28
Encephalitis	2 (2)	1 (1.9)	1 (2.0)	1.0	1 (1.9)	1 (4.8)	.50
Seizure	1 (1)	1 (1.9)	0	.98	1 (1.9)	0	.64
Neurologic deficit	1 (1)	1 (1.9)	0	.98	1 (1.9)	0	.64
Composite CNS outcome	14 (13.7)	6 (11.5)	8 (16.0)	.57	6 (11.5)	5 (23.8)	.28
Relapse							
180 days	13 (12.7)	5 (9.6)	8 (16.0)	.32	5 (9.6)	5 (23.8)	.14
1 yr	22 (21.5)	8 (15.4)	14 (28.0)	.13	8 (15.4)	6 (28.6)	.160
2 yr	27 (26.4)	9 (17.4)	18 (36.3)	.03	9 (17.4)	8 (39.5)	.045

CMV indicates cytomegalovirus; GVHD, graft-versus-host disease; NRM, non-relapse mortality.

* Peak viral load.

† 2 cases of viral pneumonitis with SARS-CoV-2 in HHV-6B group and 1 patient with viral pneumonitis with non-COVID coronavirus infection.

the other showed no detectable HHV-6B in cerebrospinal fluid or blood. Patients with HHV-6B DNAemia demonstrated a trend toward higher incidences of pneumonia of undetermined etiology (32.0% versus 15.4%; P = .06) and diarrhea without an identified microbiologic cause (54.0% versus 34.6%; P = .07) compared with those without DNAemia.

Persistent HHV-6B DNAemia

A total of 21 patients (20.6%) developed persistent HHV-6B DNAemia, including one patient with findings suggestive of ciHHV6 (Table 3). Persistent HHV-6B DNAemia was associated with delayed engraftment, including platelets (median: 30 days [IQR 19 to 39] versus 19 [17–26]; P = .01), ALC (33 days [24–42] versus 26 [22–32]; $P < .05$), and neutrophils (22 days [19–24] versus 20 [17–22]; P = .05) (Table 2). In multivariable Cox proportional hazards analyses, HHV-6B DNAemia was not significantly associated with platelet engraftment, whereas persistent HHV-6B DNAemia showed a significant negative association with time to platelet engraftment. Both HHV-6B DNAemia and persistent HHV-6B DNAemia were significantly negatively associated with time to lymphocyte recovery, whereas no such associations were observed for neutrophil engraftment (Table 4). The incidence of diarrhea without an identified microbiologic cause was significantly higher in patients with persistent HHV-6B DNAemia than in those without (61.9% versus 34.6%; P = .04).

Compared to patients without HHV-6B DNAemia, those with persistent DNAemia had higher relapse rates at 6 mo (5/21 [23.8%] versus 5/52 [9.6%], P = .14) and 1 yr (6/21 [28.6%] versus 8/52 [15.4%], P = .16), with the difference reaching statistical significance at 2 yr (8/21 [39.5%] versus 9/52 [17.4%], P = .04). In competing risk analysis, persistent HHV-6B DNAemia was significantly associated with relapse (8/21 [39.5%; 95% CI, 18.0 to 60.0] versus 9/52 [17.0%; 95% CI, 8.0 to 28.0]; P = .04, Figure 3).

DISCUSSION

In the preemptive therapy era, antivirals with dual activity against CMV and HHV-6B (eg, ganciclovir, valganciclovir, foscarnet) were frequently used [5,19]. With the advent of letermovir prophylaxis, CMV incidence—and consequently exposure to these agents—has declined, necessitating re-evaluation of HHV-6B reactivation. In this prospective cohort from the letermovir era, HHV-6B DNAemia occurred in 49% of patients, with

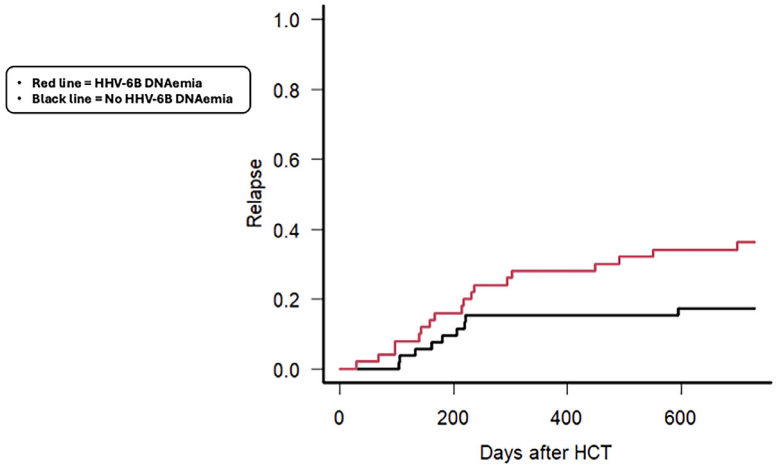

Figure 1. Two-year relapse rates in patients with HHV-6B DNAemia compared to those without HHV-6B DNAemia. Black color: patients without HHV-6B DNAemia; red color: patients with persistent HHV-6B DNAemia.

persistent DNAemia in 20.6%, comparable to rates reported before letermovir use [20,21]. HHV-6B DNAemia was associated with delayed platelet engraftment and prolonged time to achieve an ALC $\geq 300 \times 10^6$/L, while persistent DNAemia was associated with significantly further delays in platelet, ALC, and neutrophil recovery.

We observed a significant association between HHV-6B DNAemia and a higher relapse risk, with a graded increase over time, and the strongest divergence occurring at 2 yr. Recent studies have focused mainly on the association between HHV-6 and NRM, whereas, to our knowledge, no study has specifically evaluated relapse as an outcome; our findings, therefore, extend the literature by suggesting a potential link between HHV-6B reactivation and attenuated graft-versus-leukemia (GVL) effects [4]. Two non-mutually exclusive mechanisms may underlie this association. First, an indirect effect, whereby delayed lymphocyte recovery in patients with HHV-6B reactivation may increase relapse risk. Second, a direct viro-immunologic effect, as HHV-6B–induced CD4/CD8 lymphopenia, NK-cell dysfunction, and cytokine dysregulation could impair alloreactive and tumor-specific responses, thereby weakening GVL [22–25]. HHV-6B DNAemia could also be a surrogate marker of more profound immune dysfunction. This is supported by data showing that HHV-6B reactivation is more frequent in patients with intense immunosuppression (eg, PTCy) and that HHV-6B replication can impair dendritic-cell maturation, lymphocyte proliferation, monocyte function, and critical cytokine pathways—features consistent with a host environment already predisposed to poor immune surveillance [26–28]. Therefore, HHV-6B DNAemia appears to represent both a biologic mediator and a marker of

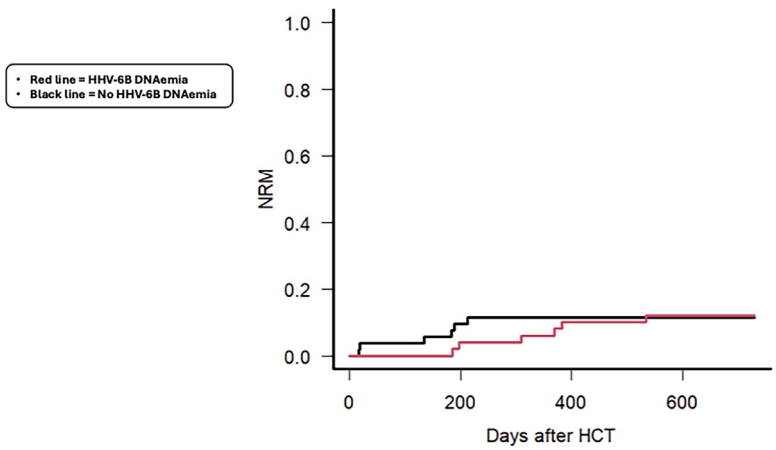

Figure 2. Two-year non-relapse mortality (NRM) in patients with HHV-6B DNAemia compared to those without HHV-6B DNAemia. Black color: patients without HHV-6B DNAemia; red color: patients with persistent HHV-6B DNAemia.

Table 3
Patients with and without Persistent HHV-6 DNAemia

Variable	Persistent HHV-6B DNAemia		*P* Value
	No *n* = 52 (79.4%)	Yes *n* = 21 (20.6%)	
Age, median, IQR	56 (37-63)	60 (53-65)	.16
Female	26 (50)	10 (47.6)	.94
BMI, median, IQR	26.4 (22.7-29.9)	24.0 (21.6-26.6)	.18
Comorbidities			
Diabetes mellitus	7 (13.5)	2 (9.5)	.94
Chronic kidney disease	1 (1.9)	2 (9.5)	.20
Chronic lung disease	3 (5.8)	1 (4.8)	.69
Hypertension	14 (26.9)	7 (33.3)	.58
Coronary arterial disease	5 (9.6)	0	.31
Autoimmune disease	3 (5.8)	2 (9.5)	.62
Donor			
Related	16 (30.8)	3 (14.3)	.24
MUD	29 (55.8)	12 (57.1)	.88
MM URD	3 (5.8)	2 (9.5)	.62
Haploidentical	4 (7.7)	4 (19.0)	.22
Underlying disease			.67
ALL	4 (7.7)	5 (23.8)	
AML	25 (48.1)	10 (47.6)	
AA	2 (3.8)	0	
CML	2 (3.8)	0	
CLL	1 (1.9)	0	
CMML	4 (7.7)	1 (4.8)	
ET	0	0	
MDS	10 (19.2)	5 (23.8)	
MF	3 (5.8)	0	
MPAL	1 (1.9)	0	
Myeloablative conditioning	28 (53.8)	5 (23.8)	.02
GVHD prophylaxis			.09
rATG + PTCy + CsA	29 (55.8)	17 (81)	
MTX-based regimen	9 (17.3)	0	
PTCy + MMF + CsA	14 (26.9)	4 (19)	
Antiviral therapy			
Acyclovir/valacyclovir	46 (88.5)	18 (85.7)	.71
Ganciclovir/valganciclovir	8 (15.4)	6 (28.6)	.21
Foscarnet	1 (1.9)	3 (14.3)	.07
DRI			.58
Low	3 (5.8)	0	
Intermediate	34 (65.4)	15 (71.4)	
High	11 (21.2)	5 (23.8)	
Very High	2 (3.8)	1 (4.8)	

AA indicates aplastic anemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BMI, body mass index; CLL, chronic lymphocytic leukemia; CMML, chronic myelomonocytic leukemia; CML, chronic myelogenous leukemia; CsA, cyclosporine A; DRI, Disease Risk Index; ET, essential thrombocythemia; GVHD, graft-versus-host disease; MDS, myelodysplastic syndrome; MPAL, mixed-phenotype acute leukemia; MF, myelofibrosis; MMF, mycophenolate mofetil; MTX, methotrexate; PTCy, post-transplant cyclophosphamide; rATG, rabbit antithymocyte globulin; SE, standard error; SOS, sinusoidal obstruction syndrome; Tac, tacrolimus; VOD, veno-occlusive disease.

Table 4
Multivariable Cox Proportional Hazards Models Including HHV-6B DNAemia and Persistent HHV-6B DNAemia

Multivariable Model Including HHV-6B DNAemia						
Variable	Platelet Engraftment		Lymphocyte Engraftment		Neutrophil Engraftment	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age, yr	0.98 (0.96-1.00)	.046	0.99 (0.97-1.00)	.303	0.98 (0.97-1.00)	.071
Sex, female	1.34 (0.89-2.02)	.148	1.65 (1.08-2.53)	.021	1.12 (0.75-1.68)	.560
rATG	1.05 (0.65-1.68)	.832	1.15 (0.72-1.85)	.542	0.92 (0.57-1.46)	.726
HHV-6 DNAemia	0.64 (0.41-1.00)	.055	0.57 (0.37-0.88)	.012	0.84 (0.55-1.28)	.434
Multivariable Model Including Persistent HHV-6B DNAemia						
Variable	Platelet Engraftment		Lymphocyte Engraftment		Neutrophil Engraftment	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age, yr	0.98 (0.97-1.00)	.170	0.98 (0.97-1.00)	.193	0.98 (0.97-1.00)	.114
Sex, female	1.62 (0.99-2.66)	.053	1.78 (1.05-3.03)	.032	1.16 (0.72-1.87)	.540
rATG	1.11 (0.62-1.96)	.718	1.18 (0.68-2.05)	.543	0.92 (0.52-1.62)	.776
Persistent HHV-6 DNAemia	0.70 (0.52-0.94)	.019	0.75 (0.56-0.99)	.043	0.85 (0.64-1.12)	.253

maladaptive immune recovery, and distinguishing these possibilities requires prospective studies integrating immune profiling, time-dependent modeling, and mediation analyses. Although analyses were adjusted for DRI and no difference in DRI categories was observed between patients with and without HHV-6B DNAemia, residual confounding related to cumulative immunosuppression, or disease biology cannot be excluded [16,25]. The stronger association seen with persistent DNAemia is biologically plausible as a dose–duration effect. Future investigations should incorporate time-dependent and mediation analyses to delineate direct and indirect mechanisms and integrate comprehensive immune response assessments. Although causality cannot be confirmed, our findings warrant validation in larger cohorts and support prospective studies integrating HHV-6B monitoring with immunologic and biochemical markers relevant to GVL activity.

HHV-6B may also infect bone marrow stromal cells or monocytes, disrupting the bone marrow microenvironment essential for effective engraftment [2,29,30]. Importantly, HHV-6B DNAemia occurs more commonly in patients undergoing intensive immunosuppressive regimens, such as PTCy, and may further contribute to delayed hematopoietic engraftment [30,31]. Our study demonstrated that patients with HHV-6B DNAemia experienced a significant delay in achieving an ALC $\geq 300 \times 10^6$/L compared with those without DNAemia, suggesting a more prolonged state of immunosuppression. Wang et al. [32] reported that HHV-6B reactivation suppresses specific lymphocyte proliferative responses and is associated with post-transplant lymphocytopenia in allogeneic HSCT recipients. HHV-6B replication may impair monocyte differentiation into dendritic cells—key initiators of adaptive immunity—and disrupt Toll-like receptor–mediated signaling, contributing to immunomodulation [33,34]. HHV-6B replication can also trigger apoptosis in infected lymphocytes and monocytes and suppress interleukin-12 production, collectively impairing T-cell activation, NK-cell function, and antigen presentation after HSCT [6,22,24,34–38]. These combined effects compromise immune surveillance and may increase the risk of disease relapse [39,40].

We observed a significant negative association between HHV-6B DNAemia—particularly persistent DNAemia—and time to platelet engraftment. Several mechanisms may underlie this association. HHV-6B is known to target $CD34^+$

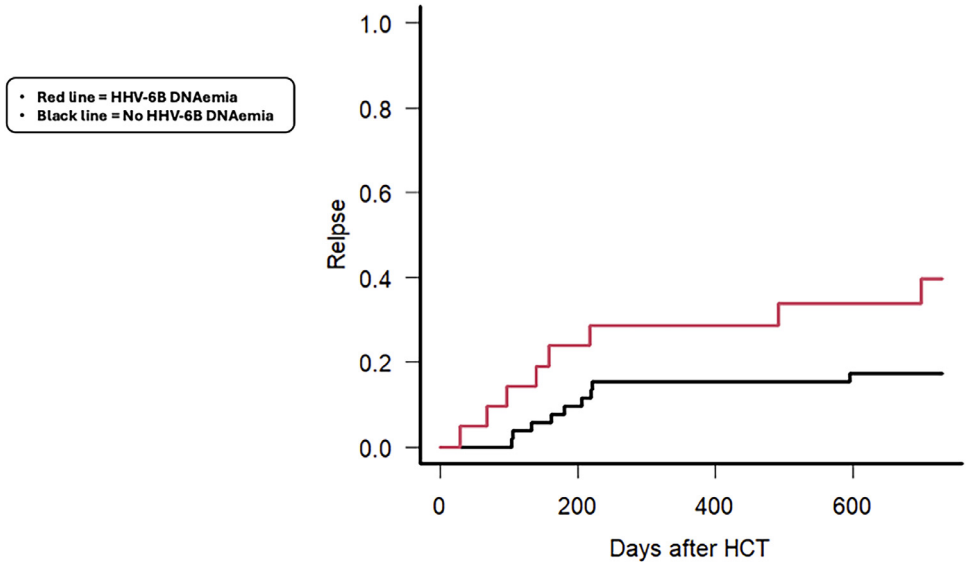

Figure 3. Relapse in patients with persistent HHV-6B. Black color: patients without HHV-6B DNAemia; red color: patients with persistent HHV-6B DNAemia.

hematopoietic progenitor cells, including megakaryocytic precursors, and it may directly impair their proliferation and differentiation, as demonstrated in in vitro studies [41–43].

Furthermore, HHV-6B reactivation triggers a proinflammatory cytokine response, including interleukin-6, tumor necrosis factor-alpha, and interferon-gamma, which can suppress megakaryopoiesis and contribute to bone marrow dysfunction [44]. Therefore, individuals with HHV-6B reactivation appear to be at increased risk of bleeding complications, higher transfusion requirements, and potentially elevated NRM [4].

In our study, myeloablative conditioning (MAC) was significantly less frequent among patients with HHV-6B DNAemia. This association likely reflects a confounding effect of age, as MAC is typically reserved for younger, healthier patients with minimal comorbidities. In contrast, two prior studies reported an association between HHV-6B reactivation and MAC. De Pagter et al. found that HHV-6B reactivation in MAC recipients was linked to a higher risk of grade 2 to 4 acute GVHD, while Aoki et al. reported that the association between HHV-6B infection and acute GVHD was more pronounced in MAC-treated patients [30,45]. These studies, however, differ from ours in several important respects: GVHD prophylaxis was limited to CsA and MMF without rATG in the first study, and was not described in the second; both included younger populations (median ages 40 and 46 yr versus 58 yr in our cohort); and both were conducted in the CMV preemptive era, when antiviral agents with anti–HHV-6B activity were more commonly used.

Prior research by Ogata et al. [46] showed that pre-emptive monitoring and antiviral therapy for HHV-6 did not prevent HHV-6B encephalitis, indicating the limited effectiveness of current antiviral treatments for HHV-6-related diseases. Thus, even if HHV-6B is linked to indirect post-transplant complications, antiviral therapy alone may not reduce this risk, highlighting the necessity for further mechanistic and interventional studies beyond antiviral approaches.

HHV-6B reactivation was associated with several adverse outcomes. Two patients developed encephalitis, including one with virologically confirmed HHV-6B CNS infection. The composite CNS outcome was also more common among viremic patients, though the association did not reach statistical significance, likely due to limited sample size. In our cohort, acute GVHD and rash were not associated to HHV-6B DNAemia. Although a prior study suggested a connection between HHV-6B DNAemia and early-onset rash, the significance vanished when follow-up extended to 50 or 100 days [20]. Furthermore, a systematic review indicated no significant relationship between HHV-6B DNAemia and GVHD in 29% of studies with defined temporality and 56% without [47]. Diarrhea and pneumonia of undetermined microbiologic etiology occurred more frequently among patients with HHV-6B DNAemia than among those without, and persistent HHV-6B DNAemia was significantly associated with diarrhea, which

in some cases may have been attributable to gastrointestinal GVHD. We included diarrhea without an identified microbiologic cause as an exploratory outcome because HHV-6B has been linked to gastrointestinal manifestations, and unexplained diarrhea often prompts viral testing in HSCT recipients. Given the many potential causes of diarrhea after HSCT—infectious, toxic, GVHD-related, or medication-related—this endpoint was not intended to imply causality but to capture a possible association, whether reflecting increased GVHD risk or a direct enteric effect of HHV-6B [48]. In a multicenter study of HSCT recipients undergoing bronchoalveolar lavage for pneumonia, HHV-6B DNA was detected in 37% of samples and was associated with increased mortality. Patients with HHV-6B also exhibited interferon-enriched gene expression signatures, supporting a potential pathogenic role in post-transplant lung disease [49].

This study has several limitations. First, the study was conducted at a single transplant center in Toronto, which may limit the generalizability of the findings to other settings with different patient populations, transplant practices, or viral monitoring protocols. Second, HHV-6B PCR testing was performed at variable intervals (every 1 to 3 wk) during the first 100 days post-transplant. This variation may have missed transient episodes of low-level DNAemia, leading to an underestimation of its true incidence and the persistence of DNAemia. In most studies, monitoring for HHV-6B DNAemia has been limited to the first 100 days post-transplant, reflecting the period of highest risk for viral reactivation [27,50]. Third, the observational design of the study prevents causal inferences, and residual confounding factors may have influenced the outcomes. Fourth, some determinants of hematopoietic recovery were not collected, limiting the reliability of multivariable modelling. Accordingly, exploratory Cox analyses of engraftment should be viewed cautiously. HHV-6B PCR testing (every 1 to 3 wk) was far less frequent than daily hematologic monitoring, making the true timing of DNAemia onset uncertain; therefore, no causal or temporal conclusions can be drawn from these analyses. Ultimately, a larger sample size is necessary to comprehensively evaluate the long-term clinical implications of HHV-6B reactivation on immune recovery, relapse, and NRM.

CONCLUSION

In this prospective cohort of allogeneic HSCT recipients, HHV-6B reactivation was common and was associated with delayed platelet engraftment, prolonged lymphocyte recovery, and an increased risk of disease relapse. Although delays in platelet and lymphocyte recovery were modest, they may still be clinically meaningful—especially in patients with persistent DNAemia—but these findings require confirmation in larger cohorts. HHV-6B reactivation correlated with a higher incidence of clinical complications, particularly diarrhea without an identifiable microbiologic etiology and pneumonia of undetermined cause, while persistent DNAemia was independently associated with an increased risk of early-onset CNS manifestations. Although NRM did not differ significantly, these findings highlight the potential impact of HHV-6B reactivation on post-transplant recovery and outcomes and underscore the need for further investigation into its pathophysiologic role and clinical management in the post-HSCT setting.

ACKNOWLEDGMENTS

Financial Disclosure: This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors confirm that all organizations contributing to this work, if any, have been acknowledged, and no external financial support was provided.

Conflict of Interest Statement: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

REFERENCES

1. Hall CB, Long CE, Schnabel KC, et al. Human herpesvirus-6 infection in children – a prospective study of complications and reactivation. *N Engl J Med*. 1994;331(7):432–438. Available from; https://pubmed.ncbi.nlm.nih.gov/8035839/.
2. Zerr DM, Boeckh M, Delaney C, et al. HHV-6 reactivation and associated sequelae after hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2012;18(11):1700.. Available from; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3439599/.
3. Zerr DM, Meier AS, Selke SS, et al. A population-based study of primary human herpesvirus 6 infection. *N Engl J Med*. 2005;352(8):768–776.
4. Stathis CJ, Zhu H, Carlin K, et al. A systematic review and meta-analysis of HHV-6 and mortality after hematopoietic cell transplant. *Bone Marrow Transplant*. 2024;59(12):1683–1693. Available from; https://www.nature.com/articles/s41409-024-02398-w.
5. Ward KN, Hill JA, Hubacek P, et al. Guidelines from the 2017 European Conference on Infections in Leukaemia for management of HHV-6 infection in patients with hematologic malignancies and after hematopoietic stem cell transplantation. *Haematologica*. 2019;104(11):2155–2163. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31467131.

6. Lusso P. HHV-6 and the immune system: mechanisms of immunomodulation and viral escape. *J Clin Virol*. 2006;37(suppl 1):S4–S10.
7. Pang I, Chen P, Trinh G V, et al. Letermovir prophylaxis for cytomegalovirus reactivation in allogeneic hematopoietic cell transplant recipients: single center Canadian data. *Eur J Haematol*. 2024;112(2):301–309. Available from: /doi/pdf/10.1111/ejh.14117 .
8. altona DIAGNOSTICS RealStar ® Instructions for Use RealStar ® HHV-6 PCR Kit 1.0 [cited 2020 Jul 12]. Available from: https://altonadiagnostics.com/files/public/ContentHomepage/02RealStar/MANCEEN/RealStarHHV6PCRKit1.0_WEB_CE_ENS04.pdf.
9. Kim TY, Park M-S, Yun SA, et al. Performance evaluation of the SMG HHV-6 Q real-time PCR kit for quantitative detection and differentiation of human herpesvirus 6A and 6B. *Microbiol Spectr*. 2024;12(4):1–11. Available from; https://pubmed.ncbi.nlm.nih.gov/38451228/.
10. Winestone LE, Punn R, Tamaresis JS, et al. High human herpesvirus 6 viral load in pediatric allogeneic hematopoietic stem cell transplant patients is associated with detection in end organs and high mortality. *Pediatr Transplant*. 2017;22(2):1–18. https://doi.org/10.1111/petr.13084. Available from; https://pmc.ncbi.nlm.nih.gov/articles/PMC5820136/.
11. Hutt D. Engraftment, graft failure, and rejection. *The European Blood and Marrow Transplantation Textbook for Nurses: Under the Auspices of EBMT*. 2017:259–270. Available from; https://www.ncbi.nlm.nih.gov/books/NBK543659/.
12. Gul Z, Bailey SD, Van Meter E, et al. Lymphocyte count above 300 X 106/Ml 90 days post transplant predicts better overall survival after alemtuzumab for unrelated donor stem cell transplant. *Biol Blood Marrow Transplant*. 2013;19(2):S199–S200. Available from; https://www.astctjournal.org/action/showFullText?pii=S1083879112007264.
13. Dhakal B, Brazauskas R, Lara CA, et al. Monocyte recovery at day 100 is associated with improved survival in multiple myeloma patients who undergo allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant*. 2015;51(2):297.. Available from; https://pmc.ncbi.nlm.nih.gov/articles/PMC4956087/.
14. Thoma MD, Huneke TJ, DeCook LJ, et al. Peripheral blood lymphocyte and monocyte recovery and survival in acute leukemia postmyeloablative allogeneic hematopoietic stem cell transplant. *Biol Blood Marrow Transplant*. 2012;18(4):600–607. Available from; https://pubmed.ncbi.nlm.nih.gov/21843495/.
15. Decook LJ, Thoma M, Huneke T, et al. Impact of lymphocyte and monocyte recovery on the outcomes of allogeneic hematopoietic SCT with fludarabine and melphalan conditioning. *Bone Marrow Transplant*. 2013;48(5):708–714. Available from; https://pubmed.ncbi.nlm.nih.gov/23103674/.
16. Armand P, Kim HT, Logan BR, et al. Validation and refinement of the disease risk index for allogeneic stem cell transplantation. *Blood*. 2014;123(23):3664.. Available from; https://pmc.ncbi.nlm.nih.gov/articles/PMC4047501/.
17. Armand P, Gibson CJ, Cutler C, et al. A disease risk index for patients undergoing allogeneic stem cell transplantation. *Blood*. 2012;120(4):905.. Available from; https://pmc.ncbi.nlm.nih.gov/articles/PMC3412351/.
18. Kanda Y. Investigation of the freely available easy-to-use software "EZR" for medical statistics. *Bone Marrow Transplant*. 2013;48(3):452–458. Available from; https://pubmed.ncbi.nlm.nih.gov/23208313/.
19. Agut H, Bonnafous P, Gautheret-Dejean A. Laboratory and clinical aspects of human herpesvirus 6 infections. *Clin Microbiol Rev*. 2015;28(2):313–335. Available from; http://www.ncbi.nlm.nih.gov/pubmed/25762531.
20. Wang LR, Dong LJ, Zhang MJ, et al. The impact of human herpesvirus 6B reactivation on early complications following allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2006;12(10):1031–1037. Available from; https://www.astctjournal.org/action/showFullText?pii=S1083879106004095.
21. Wang L-R, Dong L-J, Lu D-P. Surveillance of active human herpesvirus 6 infection in Chinese patients after hematopoietic stem cell transplantation with 3 different methods. *Int J Hematol*. 2006;84(3):262–267. Available from; http://www.ncbi.nlm.nih.gov/pubmed/17050202.
22. Rizzo R, Di Luca D. Human herpesvirus 6A and 6B and NK cells. *Acta Microbiol Immunol Hung*. 2018;65(2):119–125.
23. Grivel J-C, Santoro F, Chen S, et al. Pathogenic effects of human herpesvirus 6 in human lymphoid tissue ex vivo. *J Virol*. 2003;77(15):8280–8289.
24. Eliassen E, Di Luca D, Rizzo R, et al. The interplay between natural killer cells and human herpesvirus-6. *Viruses*. 2017;9(12):367. Available from; https://pubmed.ncbi.nlm.nih.gov/29194419/.
25. Damlaj M, Ghazi S, Mashaqbeh W, et al. Lymphocyte recovery is an independent predictor of relapse in allogeneic hematopoietic cell transplantation recipients for acute leukemia. *World J Transplant*. 2017;7(4):235.. Available from; https://pmc.ncbi.nlm.nih.gov/articles/PMC5573899/.
26. Singh A, Dandoy CE, Chen M, et al. Post-transplantation cyclophosphamide is associated with an increase in non-cytomegalovirus herpesvirus infections in patients with acute leukemia and myelodysplastic syndrome. *Transplant Cell Ther*. 2022;28(1):48.e1–48.e10. Available from; https://www.astctjournal.org/action/showFullText?pii=S2666636721012574.
27. Handley G, Yepes A, Eliassen E, et al. Outcomes of haploidentical stem cell transplant recipients with HHV-6B reactivation. *Open Forum Infect Dis*. 2024;11(10):ofae564.. Available from; https://pmc.ncbi.nlm.nih.gov/articles/PMC11475747/.
28. Kachur, PharmD, BCOP E, N. Patel, et al. Post-transplant cyclophosphamide for the prevention of graft-vs.-host disease in allogeneic hematopoietic cell transplantation: a guide to management for the advanced practitioner. J Adv Pract Oncol. 2023;14(6):520. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10558021/.
29. Dulery R, Salleron J, Dewilde A, et al. Early human herpesvirus type 6 reactivation after allogeneic stem cell transplantation: a large-scale clinical study. *Biol Blood Marrow Transplant*. 2012;18(7):1080–1089. Available from; http://www.ncbi.nlm.nih.gov/pubmed/22212513.
30. Aoki J, Numata A, Yamamoto E, et al. Impact of human herpesvirus-6 reactivation on outcomes of allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2015;21(11):2017–2202.
31. Noviello M, Lorentino F, Xue E, et al. Human herpesvirus 6–specific T-cell immunity in allogeneic hematopoietic stem cell transplant recipients. *Blood Adv*. 2023;7(18):5446–5457. Available from; https://pubmed.ncbi.nlm.nih.gov/37067947/.

32. Wang FZ, Linde A, Dahl H, et al. Human herpesvirus 6 infection inhibits specific lymphocyte proliferation responses and is related to lymphocytopenia after allogeneic stem cell transplantation. *Bone Marrow Transplant*. 1999;24(11):1201–1206. Available from; https://pubmed.ncbi.nlm.nih.gov/10642809/.
33. Niiya H, Lei J, Guo Y, et al. Human herpesvirus 6 impairs differentiation of monocytes to dendritic cells. *Exp Hematol*. 2006;34(5):642–653.
34. Murakami Y, Tanimoto K, Fujiwara H, et al. Human herpesvirus 6 infection impairs Toll-like receptor signaling. *Virol J*. 2010;7:91.. Available from; https://pmc.ncbi.nlm.nih.gov/articles/PMC2874541/.
35. Li L, Gu B, Zhou F, et al. Human herpesvirus 6 suppresses T cell proliferation through induction of cell cycle arrest in infected cells in the G2/M phase. *J Virol*. 2011;85(13):6774.. Available from; https://pmc.ncbi.nlm.nih.gov/articles/PMC3126536/.
36. P L. HHV-6 and the immune system: mechanisms of immunomodulation and viral escape. *J Clin Virol*. 2006;37(suppl 1):S4–10. Available from; https://pubmed.ncbi.nlm.nih.gov/17276368/.
37. Smith AP, Paolucci C, Di Lullo G, et al. Viral replication-independent blockade of dendritic cell maturation and interleukin-12 production by human herpesvirus 6. *J Virol*. 2005;79(5):2807–2813. Available from; http://www.ncbi.nlm.nih.gov/pubmed/15708999.
38. Bortolotti D, Gentili V, Caselli E, et al. DNA sensors' signaling in NK cells during HHV-6A, HHV-6B and HHV-7 infection. *Front Microbiol*. 2020;11:226.. Available from; http://www.ncbi.nlm.nih.gov/pubmed/32140147.
39. Savani BN, Mielke S, Rezvani K, et al. Absolute lymphocyte count on day 30 is a surrogate for robust hematopoietic recovery and strongly predicts outcome after T cell-depleted allogeneic stem cell transplantation. *Biol Blood Marrow Transplant*. 2007;13(10):1216–1223. Available from; https://www.sciencedirect.com/science/article/pii/S1083879107003357.
40. Barrett AJ, Battiwalla M. Relapse after allogeneic stem cell transplantation. *Expert Rev Hematol*. 2010;3(4):429.. Available from; https://pmc.ncbi.nlm.nih.gov/articles/PMC3426446/.
41. Zerr DM, Corey L, Kim HW, et al. Clinical outcomes of human herpesvirus 6 reactivation after hematopoietic stem cell transplantation. *Clin Infect Dis*. 2005;40(7):932–940. Available from; http://www.ncbi.nlm.nih.gov/pubmed/15824982.
42. Isomura H, Yoshida M, Namba H, et al. Suppressive effects of human herpesvirus-6 on thrombopoietin-inducible megakaryocytic colony formation in vitro. *J Gen Virol*. 2000;81(3):663–673. Available from; https://pubmed.ncbi.nlm.nih.gov/10675403/.
43. Assinger A. Platelets and infection—an emerging role of platelets in viral infection. *Front Immunol*. 2014;5:649.
44. Arena A, Liberto MC, Capozza AB, Focà A. Productive HHV-6 infection in differentiated U937 cells: role of TNF alpha in regulation of HHV-6. *New Microbiol*. 1997;20(1):13–20.
45. De Pagter PJA, Schuurman R, Keukens L, et al. Human herpes virus 6 reactivation: important predictor for poor outcome after myeloablative, but not non-myeloablative allo-SCT. *Bone Marrow Transplant*. 2013;48(11):1460–1464. Available from; https://pubmed.ncbi.nlm.nih.gov/23771003/.
46. Ogata M, Satou T, Kawano R, et al. Plasma HHV-6 viral load-guided preemptive therapy against HHV-6 encephalopathy after allogeneic stem cell transplantation: a prospective evaluation. *Bone Marrow Transplant*. 2008;41(3):279–285. Available from; https://www.nature.com/articles/1705907.
47. Phan TL, Carlin K, Ljungman P, et al. Human herpesvirus-6B reactivation is a risk factor for grades II to IV acute graft-versus-host disease after hematopoietic stem cell transplantation: a systematic review and meta-analysis. *Biol Blood Marrow Transplant*. 2018;24(11):2324–2336. Available from; https://www.astctjournal.org/action/showFullText?pii=S1083879118302246.
48. Chorão P, Pardal AA, de Cossio S, et al. Infectious enterocolitis in hematopoietic cell transplant with post-transplant cyclophosphamide. *Transplant Cell Ther*. 2025;31(6):392.e1–392.e11. Available from; https://pubmed.ncbi.nlm.nih.gov/40068801/.
49. Hill JA, Lee YJ, Vande Vusse LK, et al. HHV-6B detection and host gene expression implicate HHV-6B as pulmonary pathogen after hematopoietic cell transplant. *Nat Commun*. 2024;15(1):1–12. Available from; https://www.nature.com/articles/s41467-024-44828-9.
50. Olson AL, Dahi PB, Zheng J, et al. Frequent human herpesvirus-6 viremia but low incidence of encephalitis in double-unit cord blood recipients transplanted without anti-thymocyte globulin. *Biol Blood Marrow Transplant*. 2014;20(6):787.. Available from; https://pmc.ncbi.nlm.nih.gov/articles/PMC4097025/.