The Road to Development of Preventive and Therapeutic Treatments for Human Herpesvirus 6B (HHV-6B)

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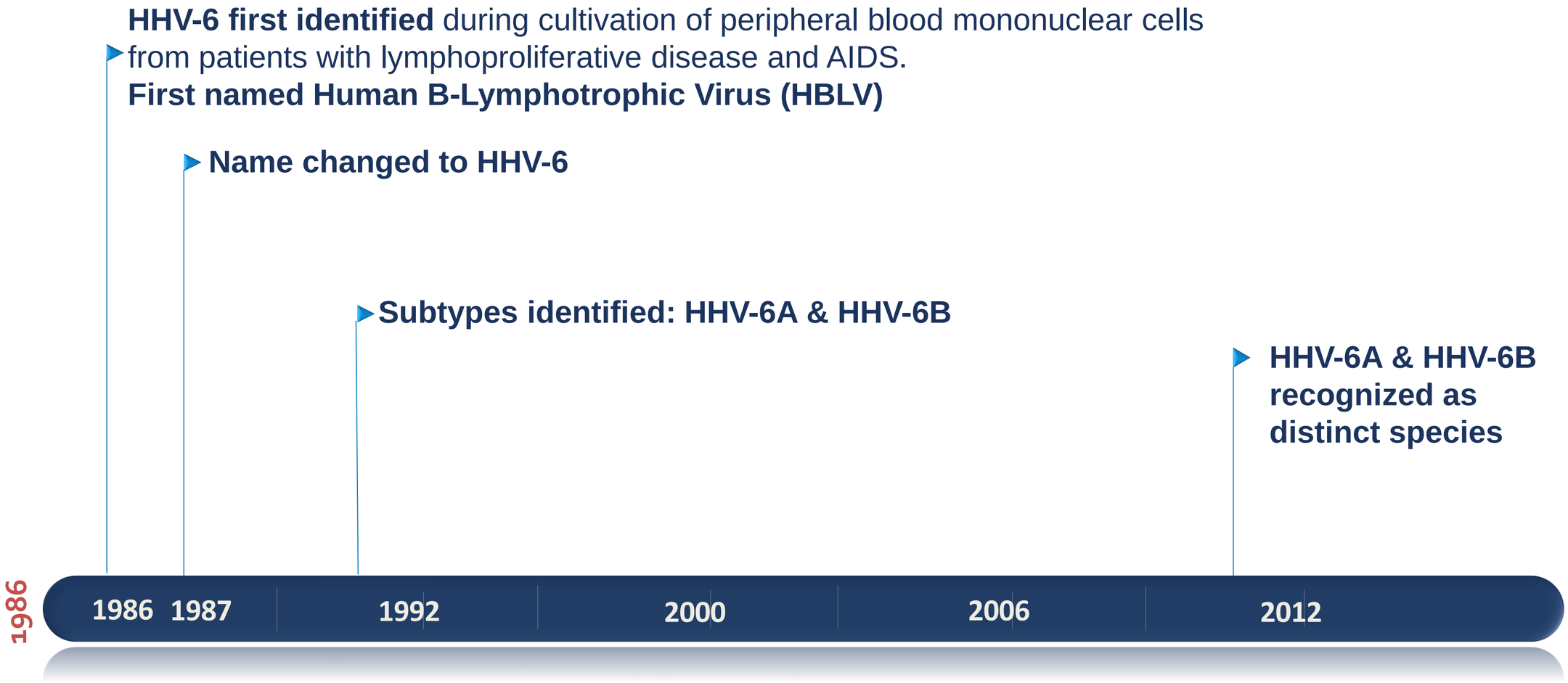
Epidemiology and Disease Associations

History of discovery and naming



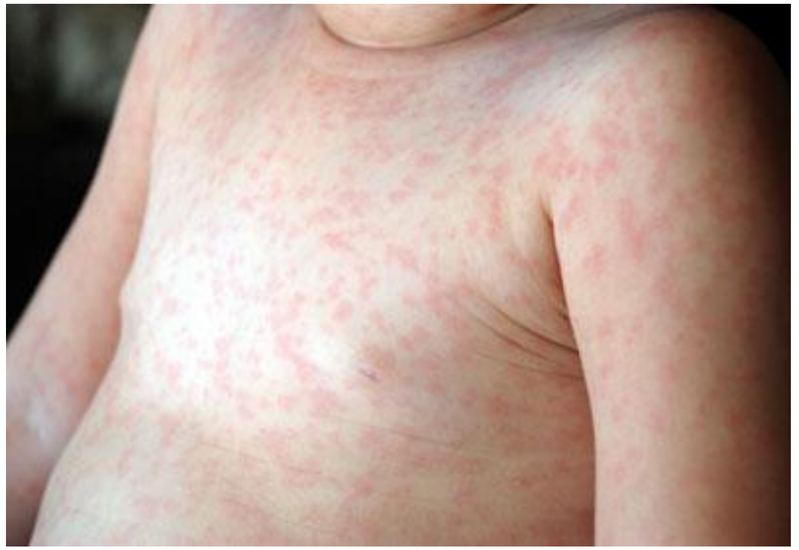
Courtesy of Danielle Zerr

Human Herpesvirus 6B

Identified as the cause of roseola infantum in 1988

Primary infection typically occurs during infancy

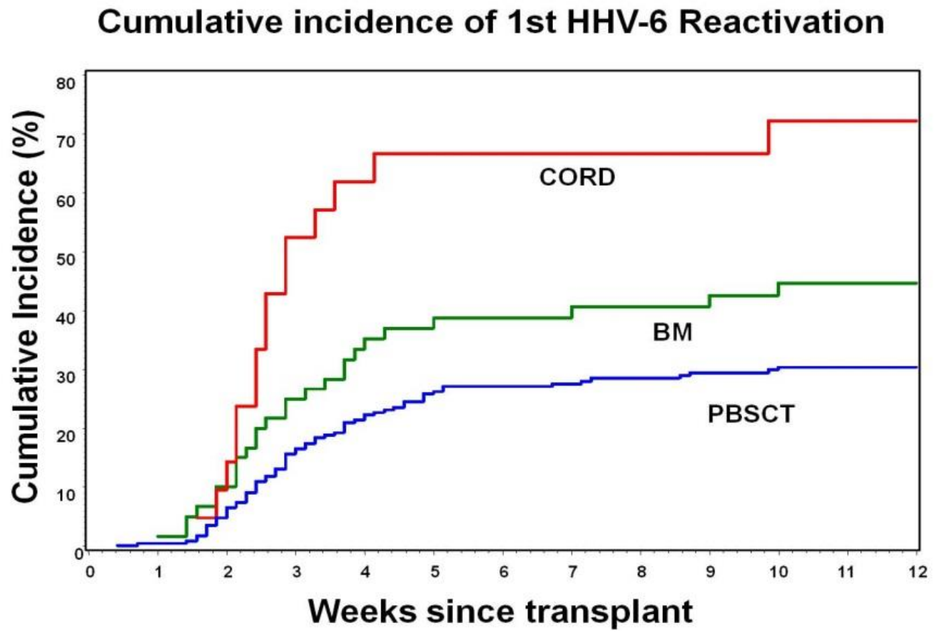
- Adult seropositivity is >95%
- Latency in a wide variety of host cells
- Reactivation may occur during immunosuppression

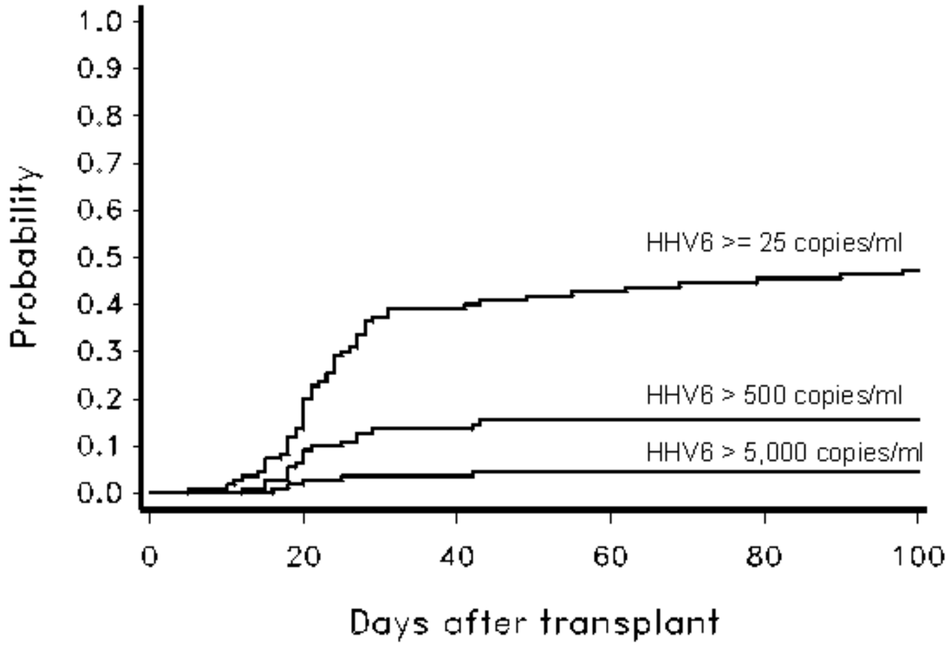


Ablashi et al, Arch Virol 2014
Zerr et al, NEJM 2005
De Bolle et al, Clin Microbiol Rev 2005

HHV-6B after allogeneic hematopoietic cell transplant (HCT)

HHV-6B viremia is common 2-6 weeks after HCT





Risk factors

- Cord blood HCT, HLA mismatch, GVHD, steroids

Hill et al, Curr Opin Virol 2014
Zerr et al, BBMT 2012
Yamane et al, BBMT 2007

haematologica
Open access journal of the Ferrata-Storti Foundation, a non-profit organization

Vol. 104 No. 11 (2019): November, 2019 > Guidelines from the 2017 European Conference on Infections...

GUIDELINES

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

Katherine N Ward, Joshua A Hill, Petr Hubacek, Rafael de la Camara, Roberto Crocchiolo, Hermann Einsele, David Navarro, Christine Robin, Catherine Cordonnier, Per Ljungman

HHV-6B disease associations

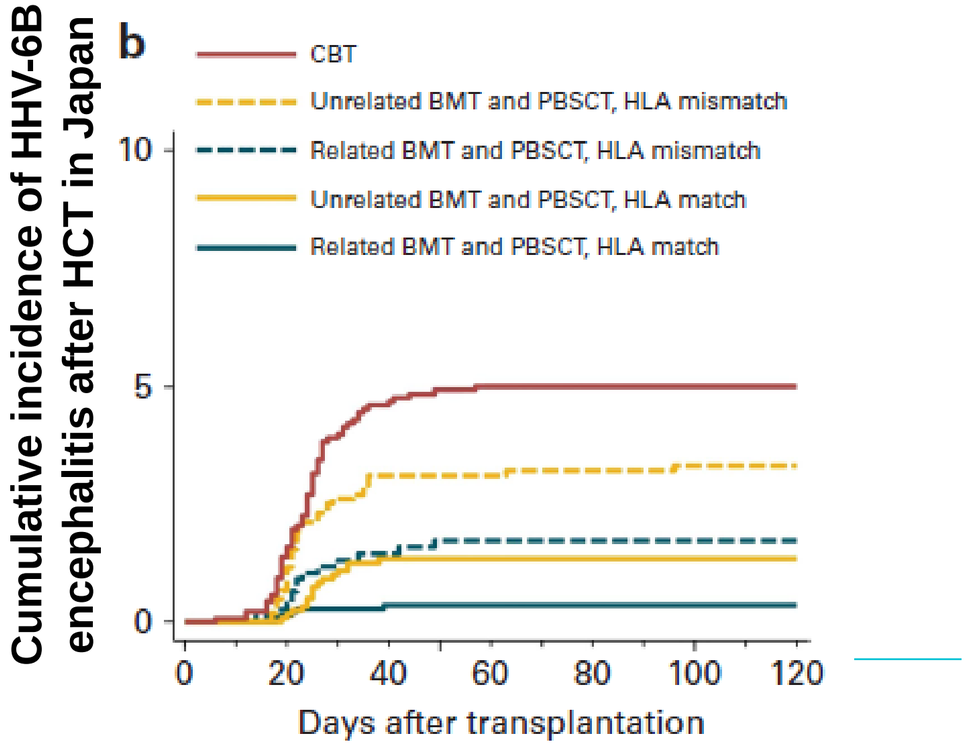
	Epidemiological associations	Level of in vitro or in vivo support for causation
HHV-6B end-organ disease	Encephalitis (predominantly limbic)	Strong
	Non-encephalitic CNS dysfunction e.g. delirium, myelitis	Moderate
	Myelosuppression, allograft failure	Moderate
	Pneumonitis	Weak
	Hepatitis	Weak
Other	Fever & rash	Strong
	Acute GVHD	Moderate
	CMV reactivation	Moderate
	Increased all-cause mortality	Weak

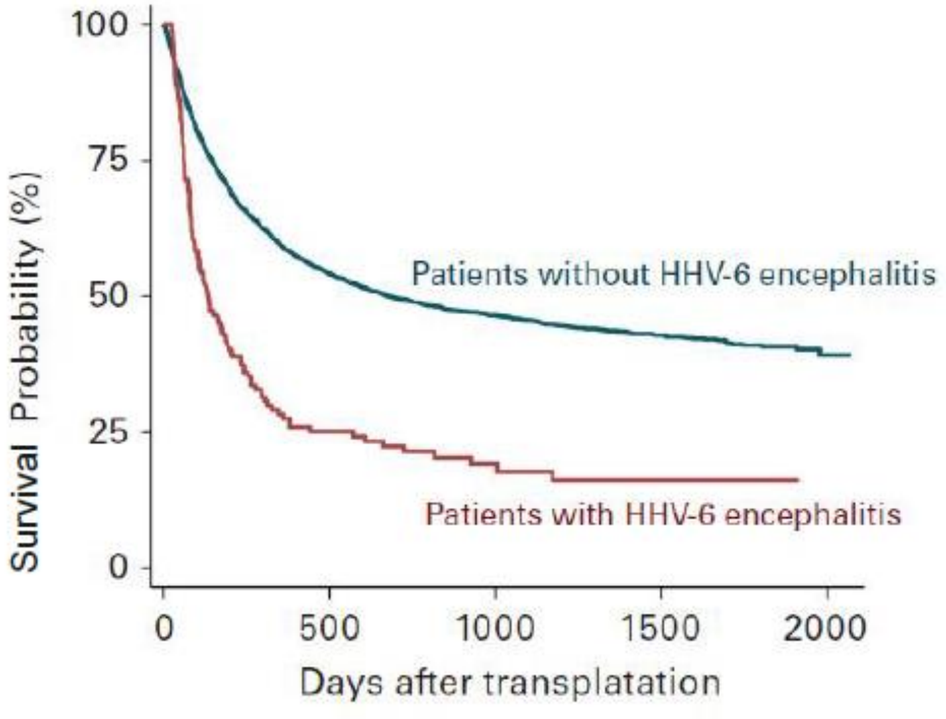
Adapted from Table 29.2 JA Hill & DM Zerr, Transplant Infections, 4th edition (2016)

HHV-6B encephalitis

Most common infectious cause of encephalitis post-HCT

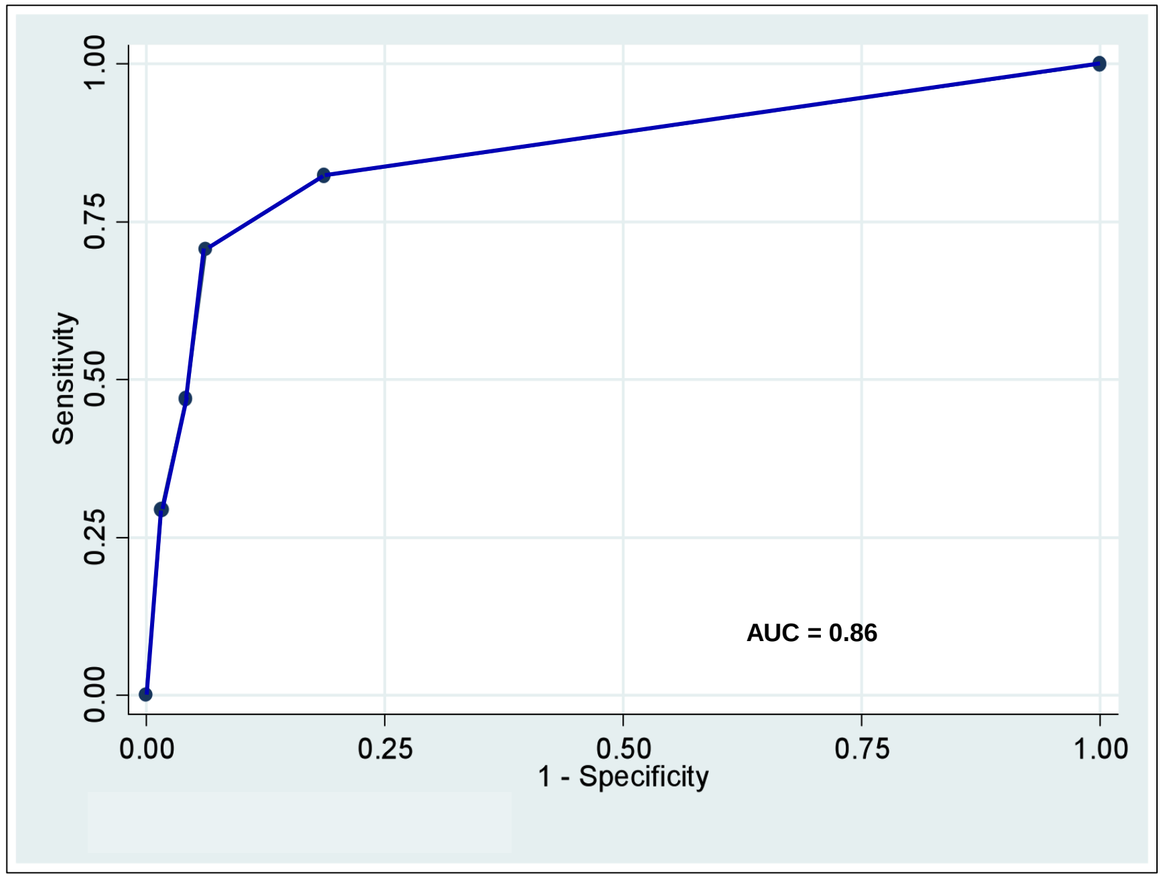
- Affects 1-10% allogeneic HCT recipients
- Cord blood stem cell recipients particularly high risk
- Occurs early after HCT: median 21 days





Schmidt-Hieber M, *Haematologica* 2011
Ogata et al, BMT 2017

Plasma HHV-6 viral load correlation with HHV-6 encephalitis

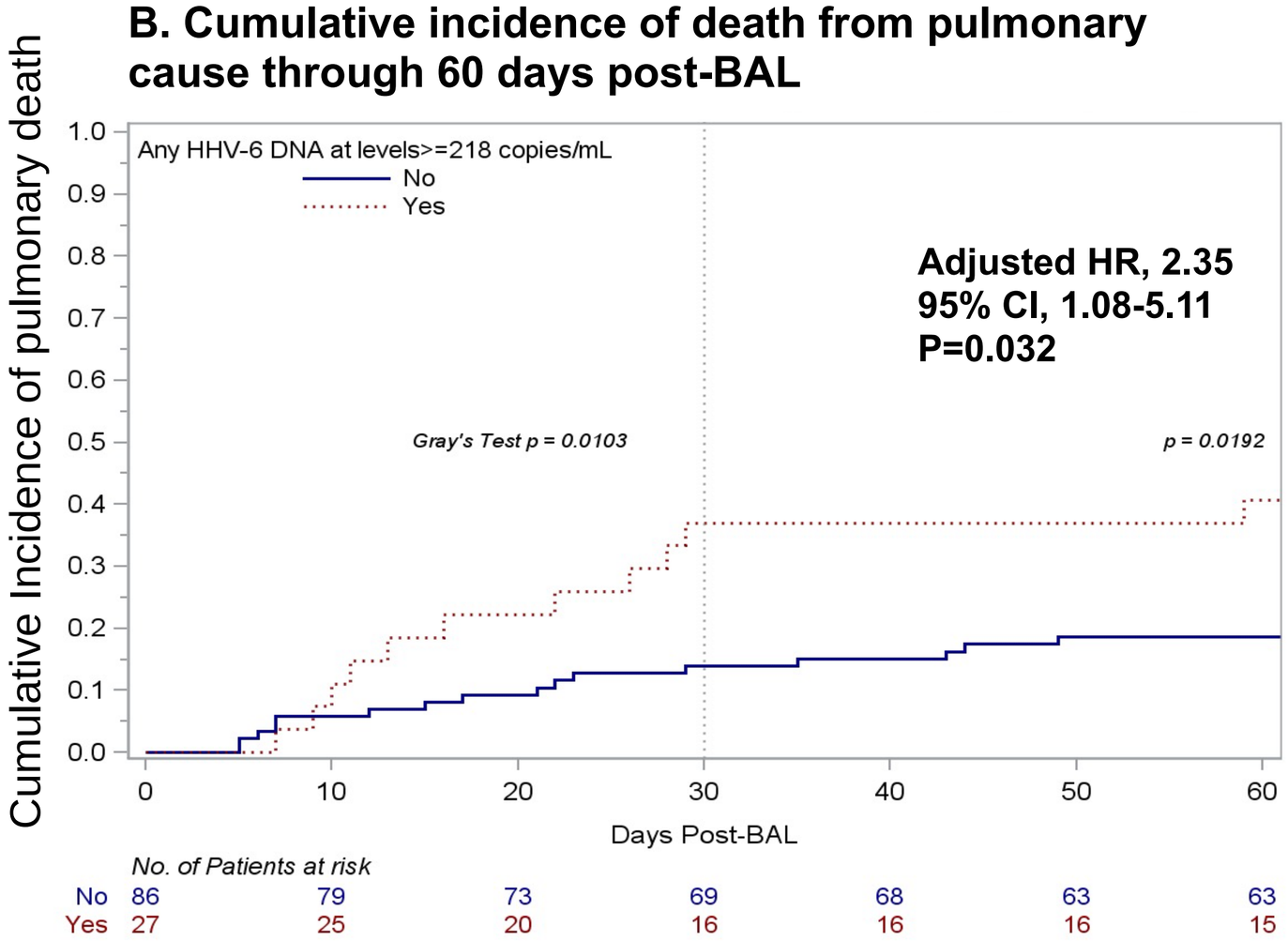


Cutpoint*	Sensitivity	Specificity
≥ 10,000	100%	81%
≥ 100,000	71%	94%
≥ 250,000	47%	96%
≥ 999,000	29%	98%

*HHV-6 plasma viral load (copies/mL)

Hill et al, BBMT 2012

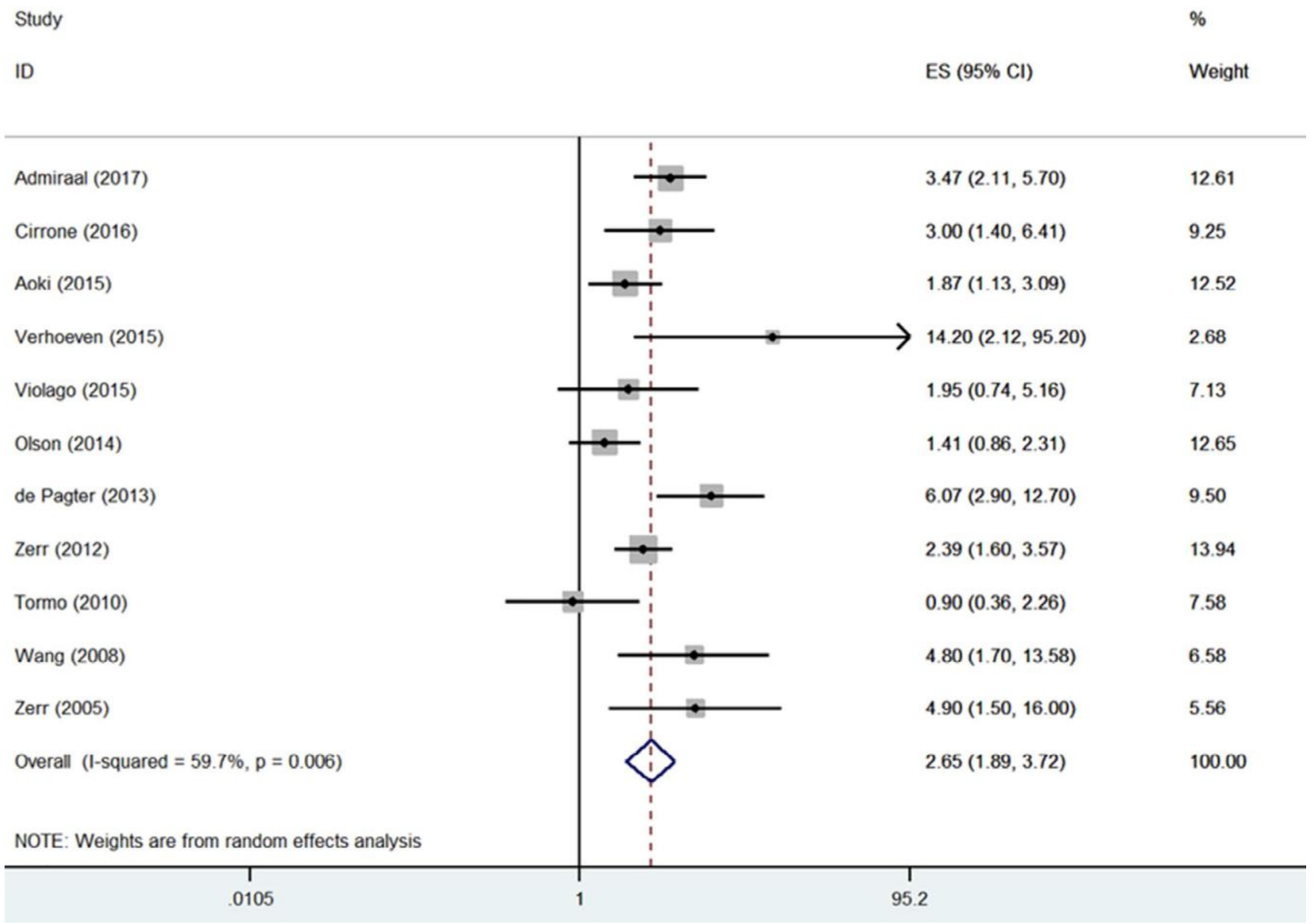
HHV-6B in BAL fluid is associated with increased mortality after allogeneic HCT



Hazard ratios (HR) are from multivariable Cox models adjusted for age, oxygen use (>2 liters by nasal cannula), and steroid use at the time of the BAL.

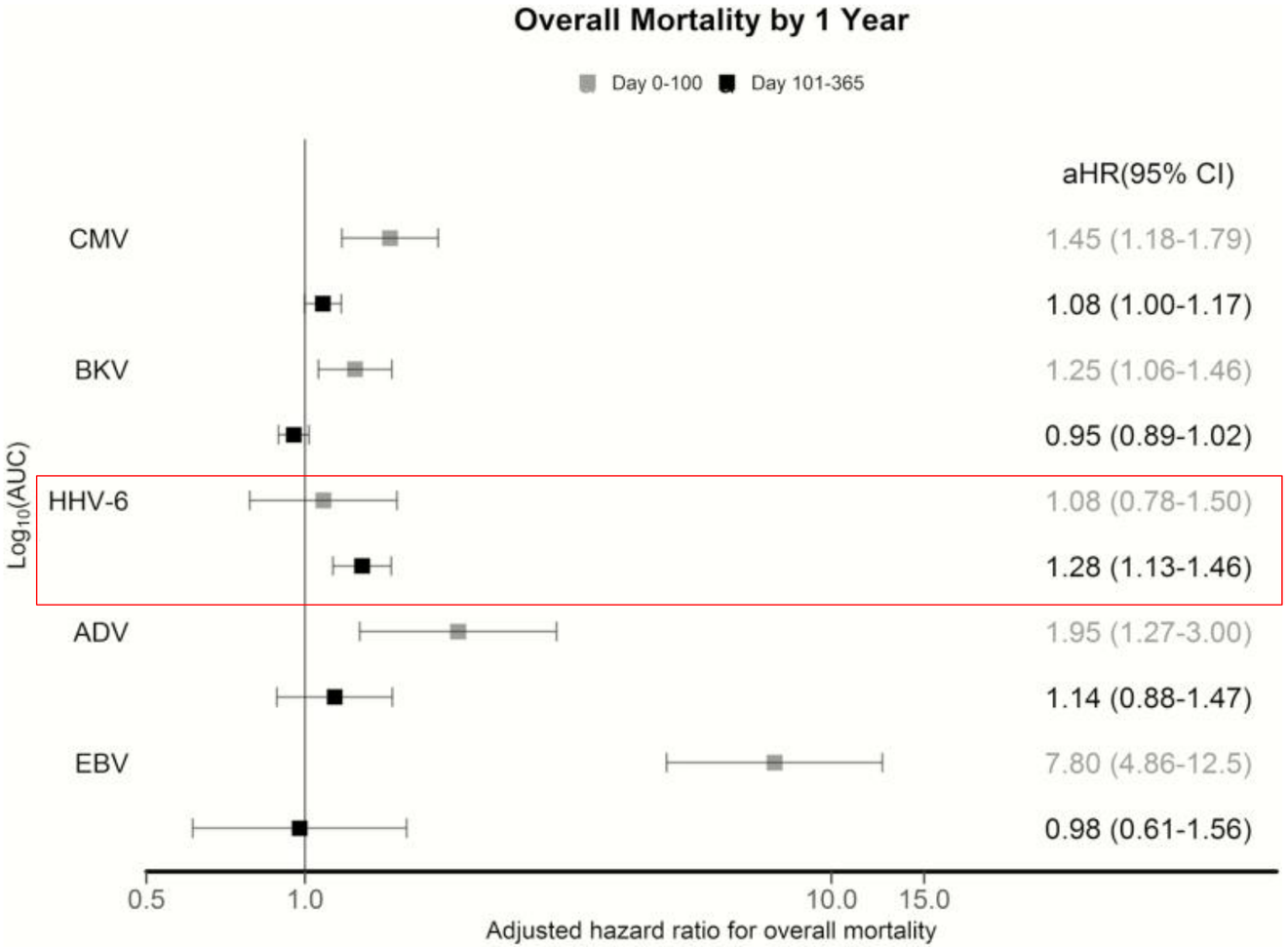
Hill et al, IDWeek 2022
Hill et al, JCO 2019
Zhou et al, Am J Respir Crit Care Med 2019

HHV-6B & subsequent acute graft-versus-host disease



Phan et al, BBMT 2018

HHV-6B and overall mortality after HCT



Hill et al, Clin Infect Dis 2018

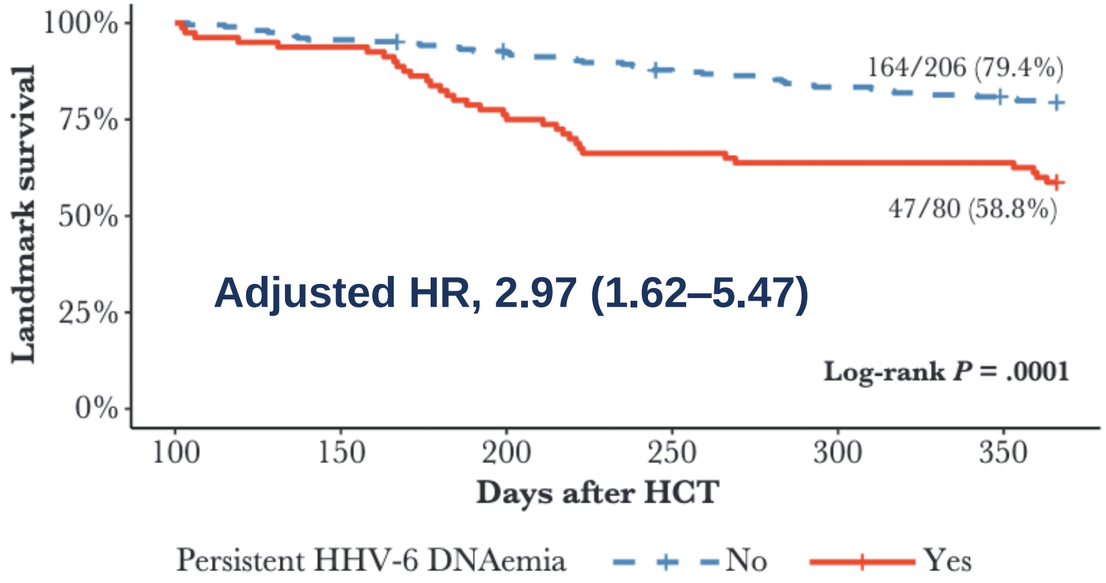
The Journal of Infectious Diseases

MAJOR ARTICLE

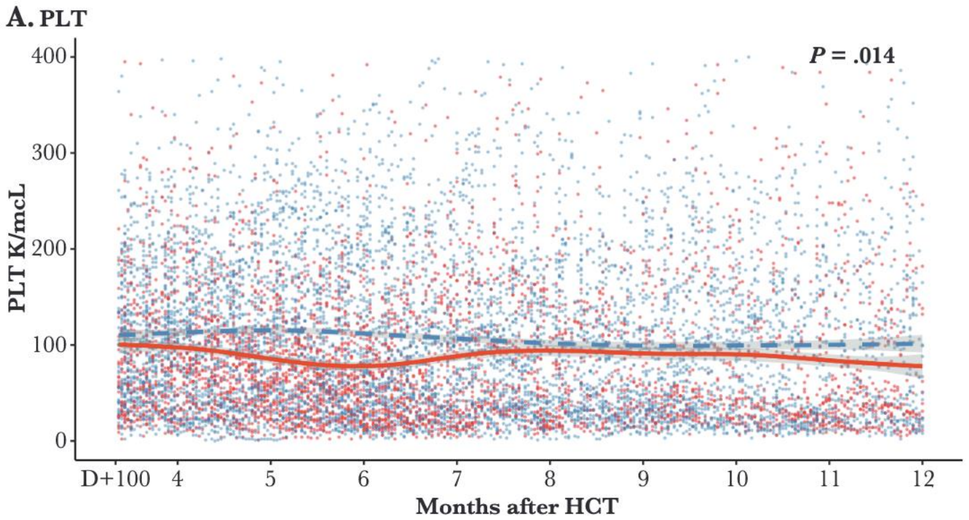
Human Herpesvirus 6 DNAemia Is Associated With Worse Survival After Ex Vivo T-Cell–Depleted Hematopoietic Cell Transplant

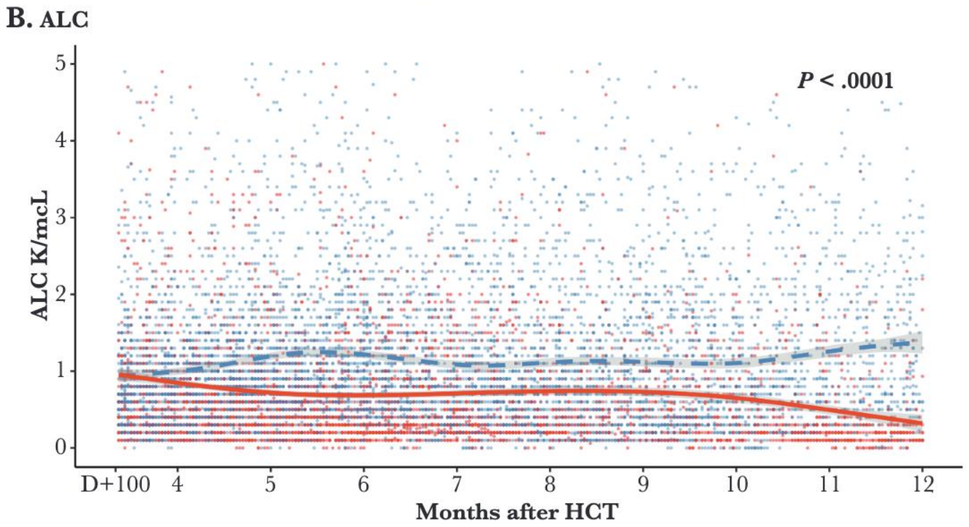
Yeon Joo Lee,[1,2] Yiqi Su,[1] Christina Cho,[2,3] Roni Tamari,[2,3] Miguel-Angel Perales,[2,3] Ann A. Jakubowski,[2,3,a] and Genovefa A. Papanicolaou[1,2]

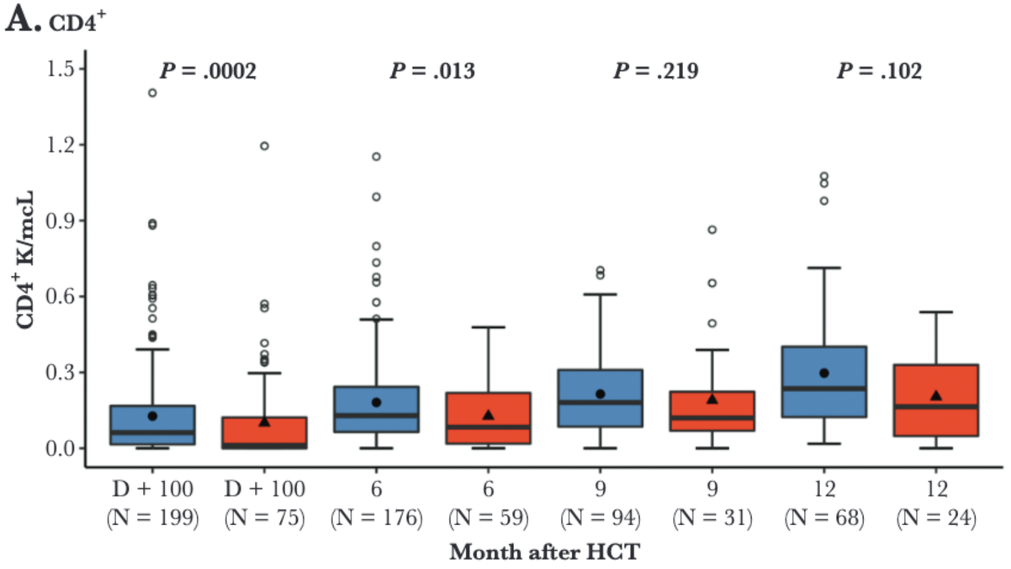
[1]Infectious Diseases Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York, USA, [2]Weill Cornell Medical College, New York, New York, USA, and [3]Adult Bone Marrow Transplant Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York, USA

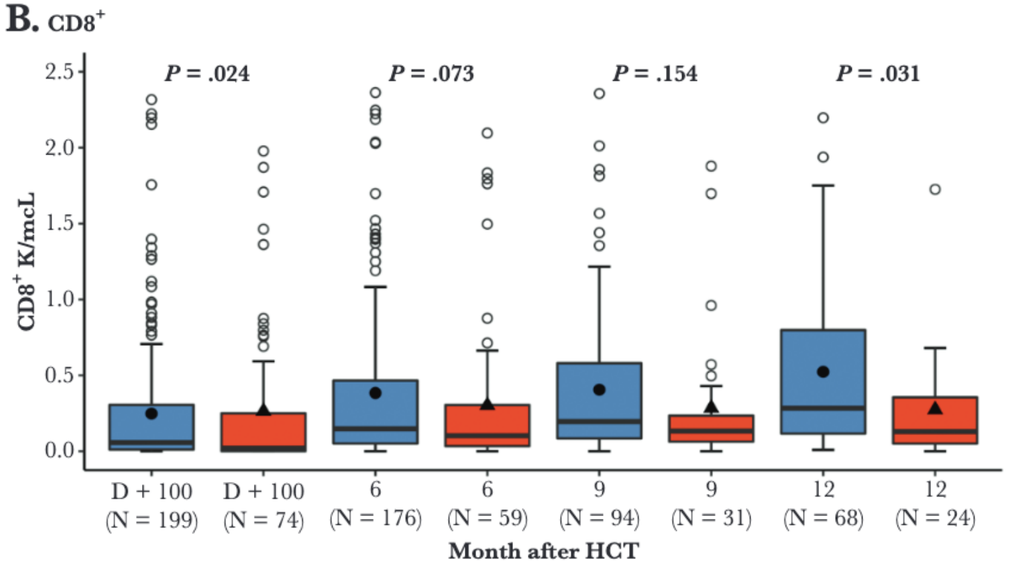


HHV-6B reactivation and myelosuppression







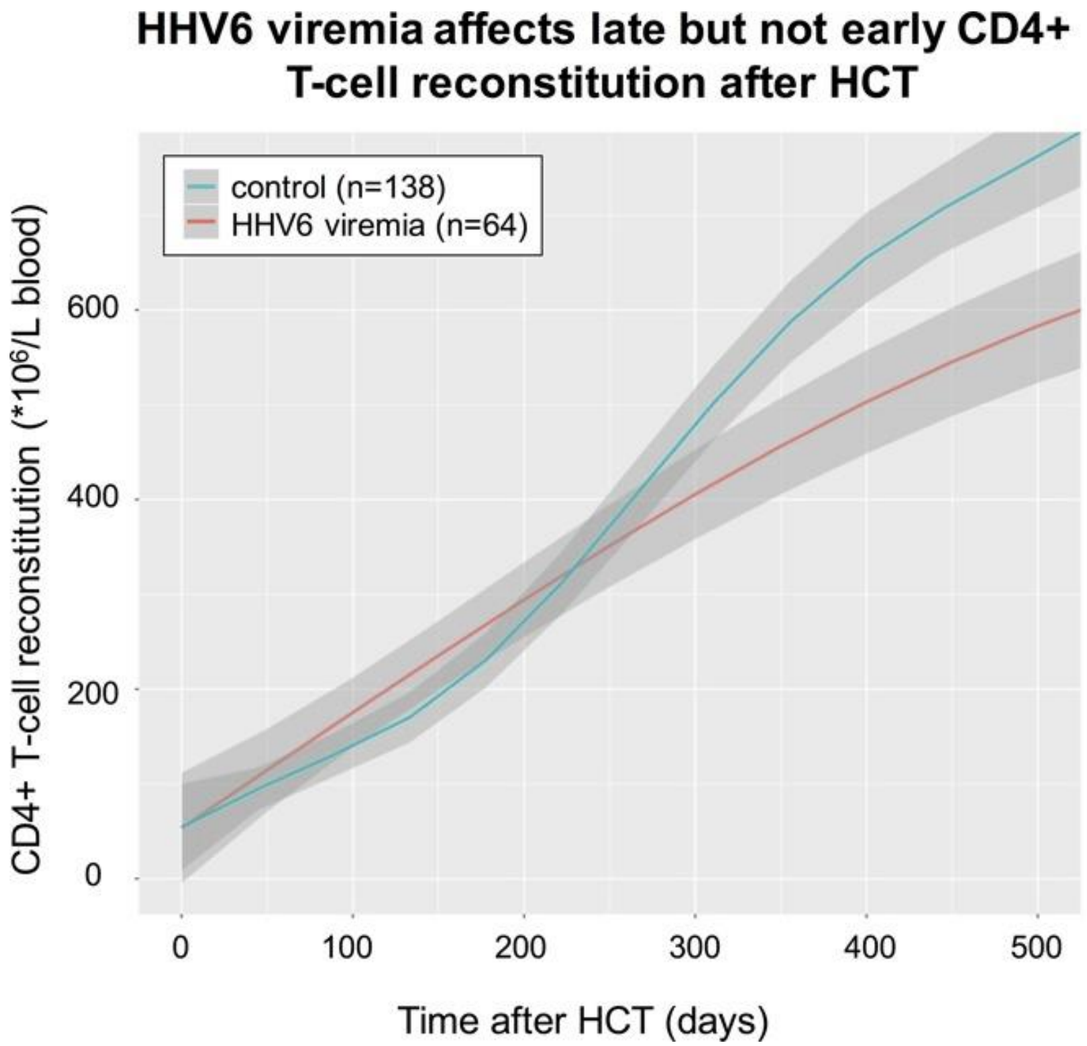


Persistent HHV-6 DNAemia — No — Yes

Persistent HHV-6 DNAemia — No — Yes

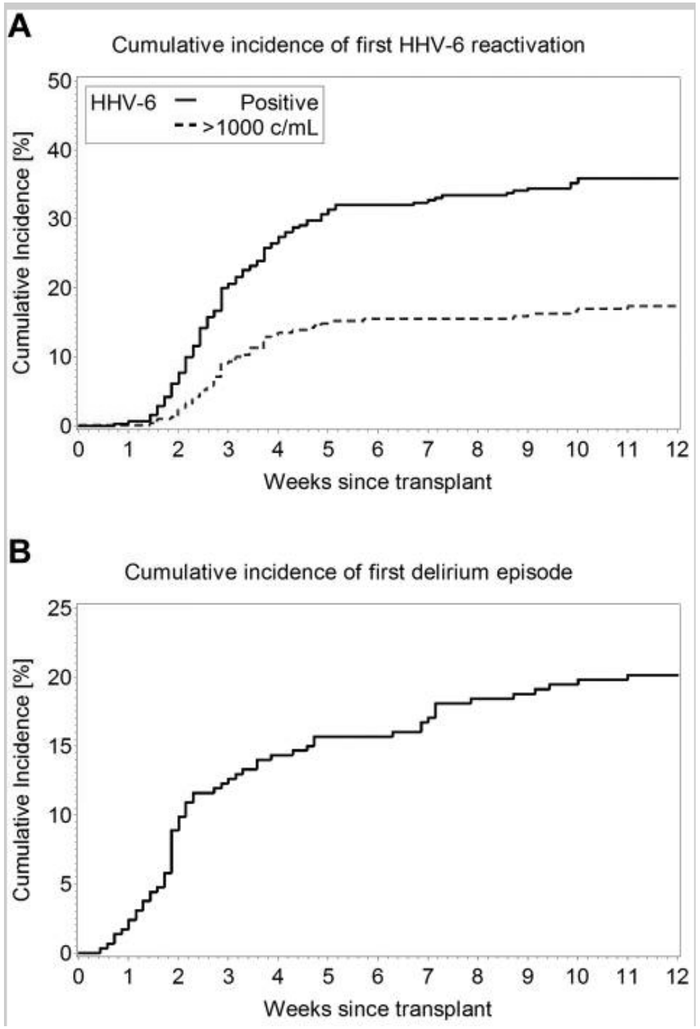
Fred Hutchins

HHV-6B reactivation and myelosuppression



de Konig et al, Blood Adv 2018

HHV-6B, Delirium, and Cognitive Decline

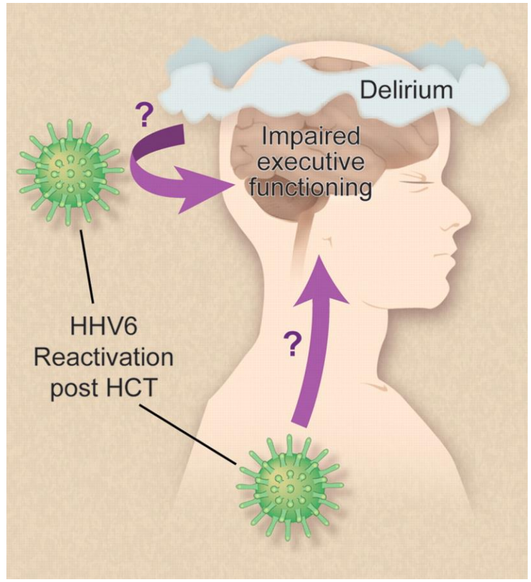


HHV-6B increased risk of delirium

- aOR 2.5 (95% CI: 1.2-5.3)

HHV-6B increased risk of neurocognitive decline

- aOR 2.6 (95% CI: 1.1-6.2)



Zerr et al, Blood 2011
Caserta et al, Blood 2011

Diagnostics

Diagnostic strategies

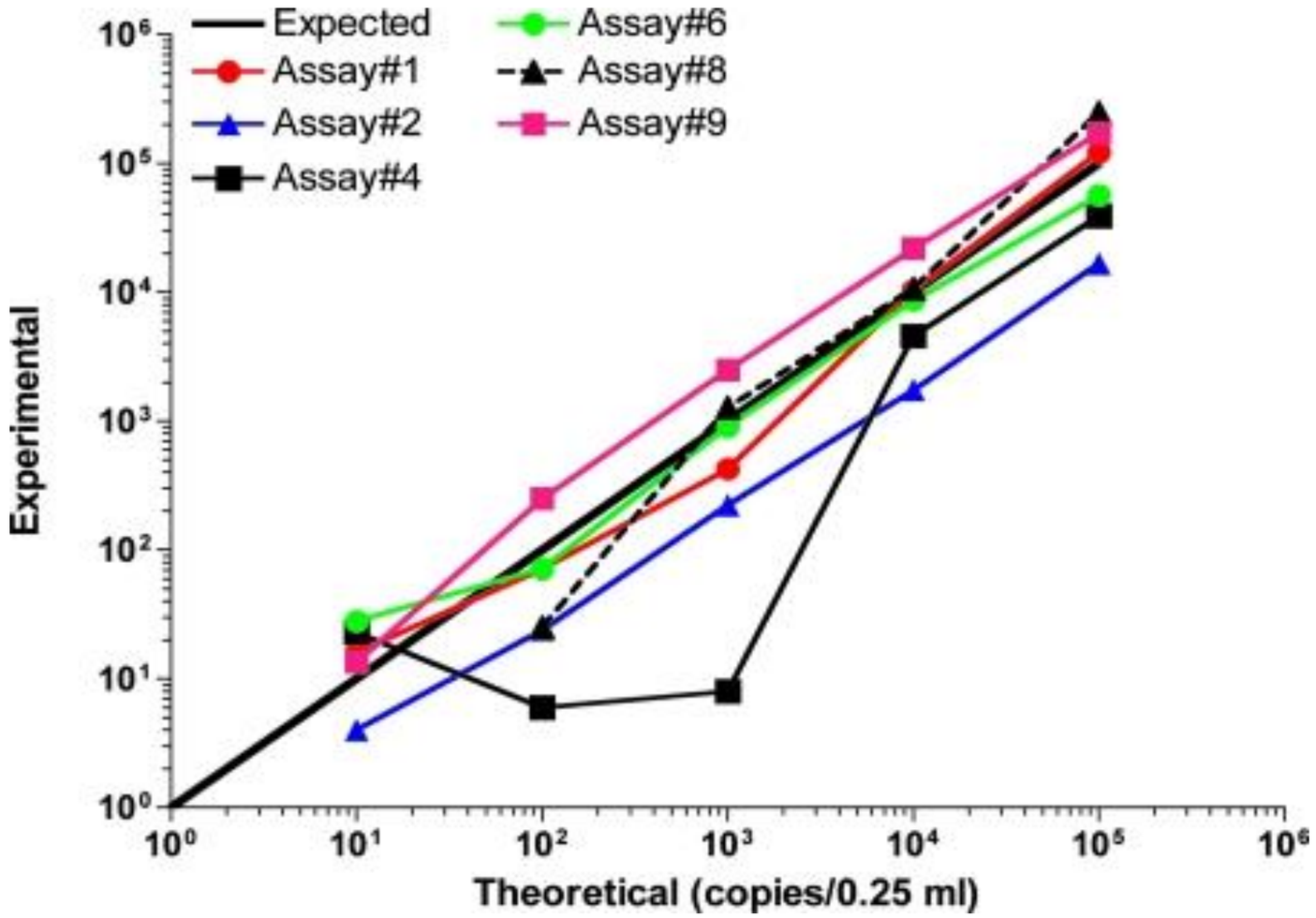
Serology not helpful
Culture not practical
Direct detection of virus using PCR

- DNA vs RNA PCR
- Quantitative vs qualitative PCR
- Serum or plasma vs whole blood or lymphocytes

WHO International Standard is available (since 2017):

https://www.nibsc.org/products/brm_product_catalogue/detail_page.aspx?catid=15/266

PCR standardization is required



Flamand et al, J Clin Micro 2008

Not all HHV-6 DNA Detection is Associated With Disease: *Navigating Koch's Postulates in the Molecular Era*

Ubiquitous infection

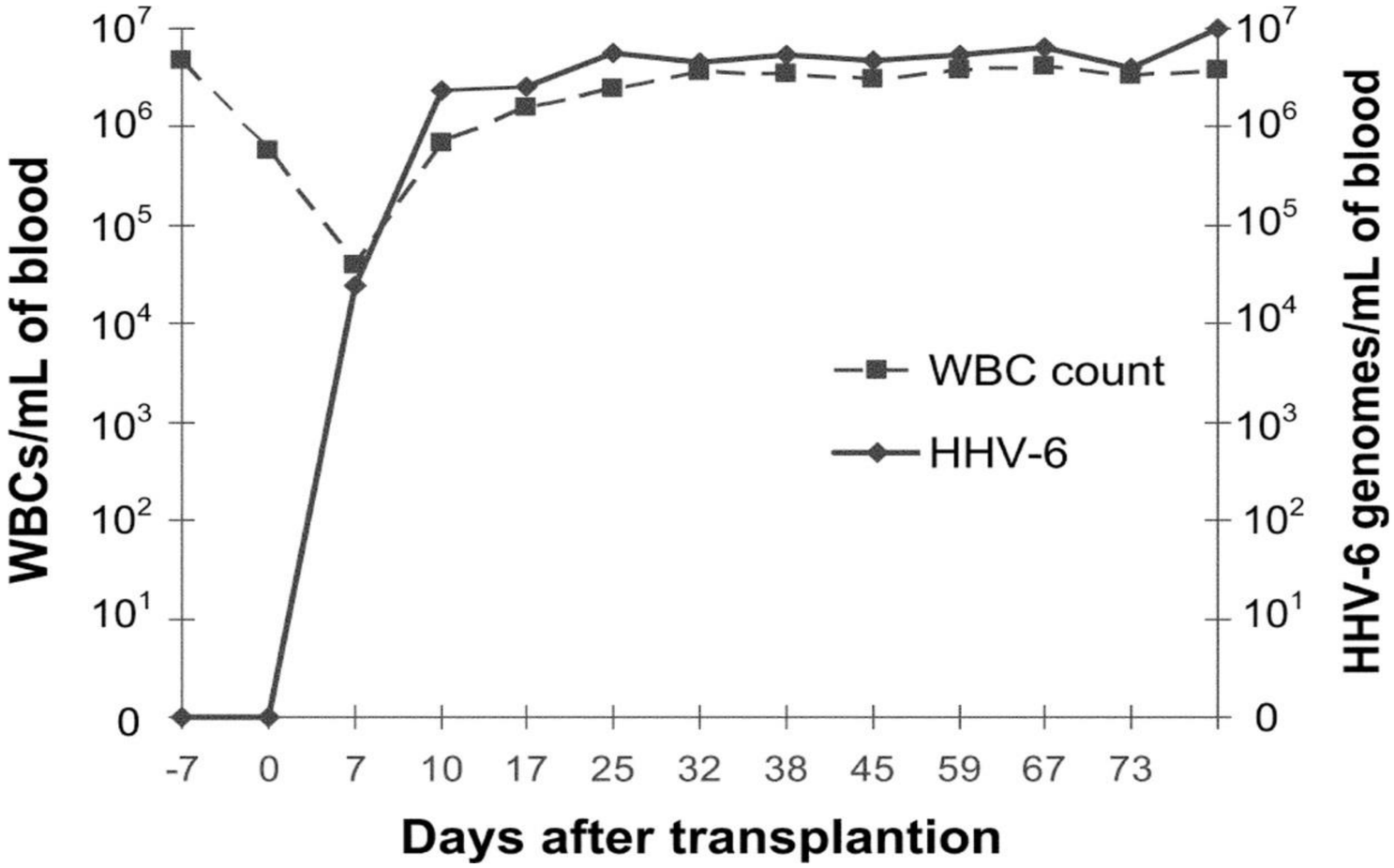
Latency in many cell types

No standardized test

Results affected by sample type

Poor correlation of DNA detection with end-organ disease

Another challenge: Inherited chromosomally integrated HHV-6

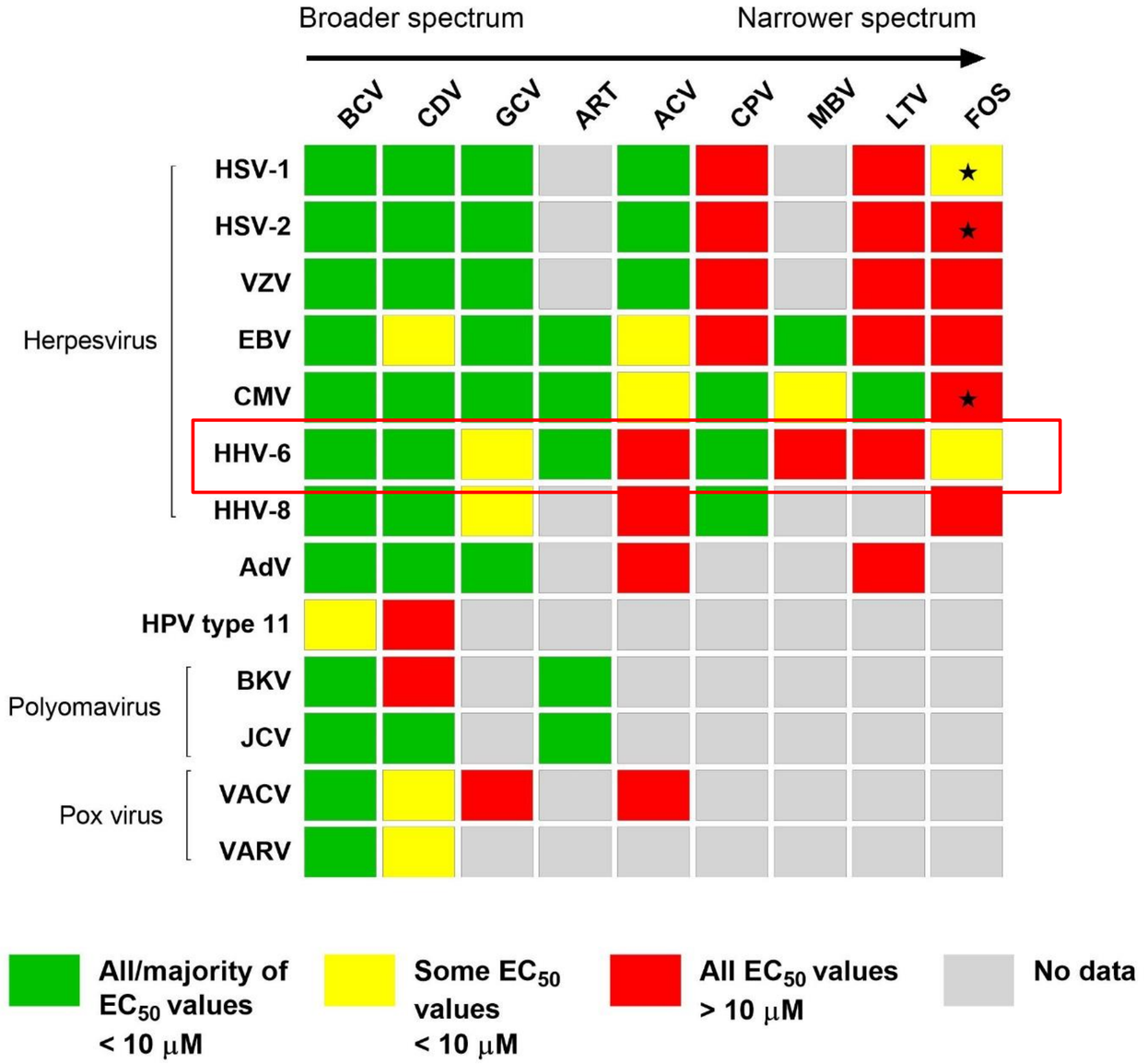


Clark et al, JID 2006

Treatment

Treatment of HHV-6B

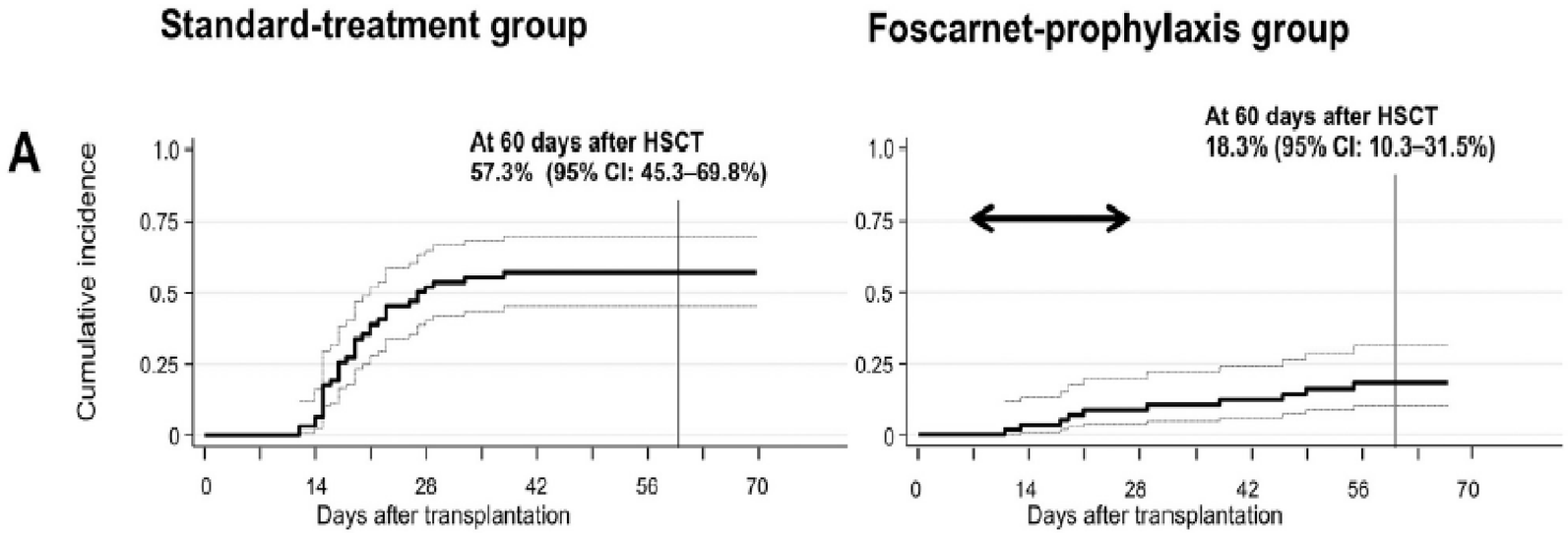
- No FDA approved agent
- Ganciclovir and foscarnet are 1st line



Chemaly et al, Antiviral Res 2019

Current interventions for HHV-6B are inadequate for prophylaxis

- Preemptive GCV or FOS does NOT prevent encephalitis due to short time between plasma reactivation and CNS disease.
- Foscarnet prophylaxis from day 7-27 after HCT with unrelated cord blood reduced HHV-6B viremia but not encephalitis.

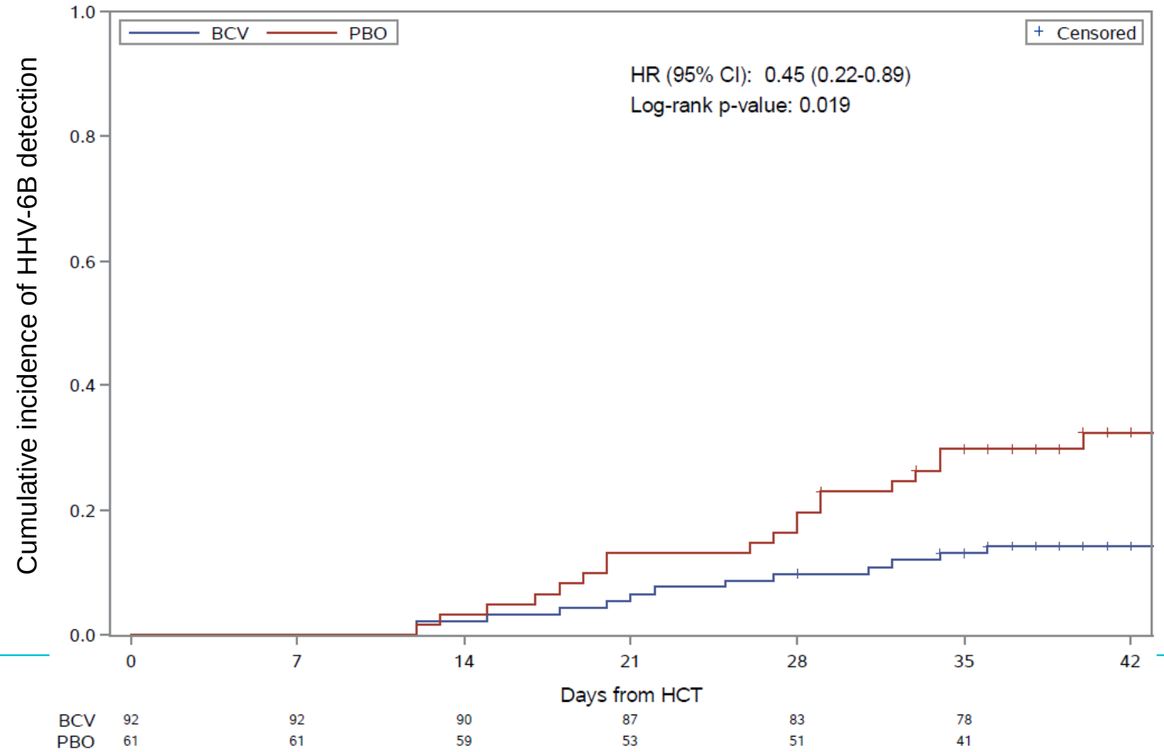


- New antiviral agents with better CNS penetration needed.
- ***Insufficient data to recommend prophylactic or preemptive treatment.***

Ogata et al, BMT 2008; Ogata et al, BMT 2013; Ishiyama et al, BMT 2011;Ogata et al, BBMT 2018

Brincidofovir (BCV) for HHV-6B?

- The SUPPRESS trial was a randomized, double-blind, placebo (PBO)-controlled trial of oral BCV for cytomegalovirus (CMV) prophylaxis after allo-HCT
- 452 adult CMV-seropositive HCT recipients without CMV viremia at screening were randomized 2:1 to receive BCV or PBO twice-weekly until week 14 post-HCT
- Efficacy of BCV against HHV-6B evaluated using banked plasma samples



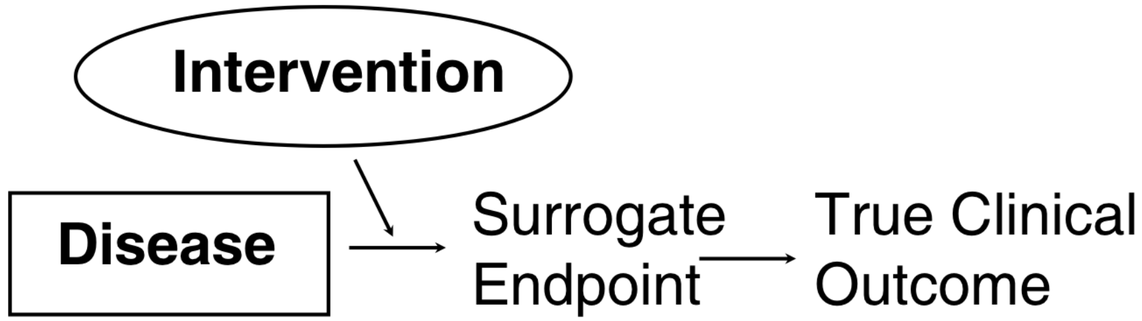
Hill et al, Blood 2020

Next steps

The ‘Prentice Criteria’ for establishing a surrogate endpoint

Statistics in Medicine, Ross L Prentice, Vol 8, 1989.

1) Randomized controlled trial(s) in which the treatment impacts the biomarker.
2) The biomarker must be associated with clinical outcomes in the interventional and placebo groups.
3) The biomarker “captures” the full extent of the intervention’s effect.



- **All mechanisms of action of the intervention on the true endpoint are mediated through the surrogate.**

Ref: Fleming, DeMets. Ann Intern Med. 1996

Duke et al, JCI 2021

HHV-6B viral load as a surrogate endpoint

- The surrogate endpoint has to be in the direct pathway of the disease pathogenesis (Fleming et al. 1996)
  - Viremia ⇒ HHV-6 disease
  - Absence of viremia ⇒ Absence of disease
- Evidence
  - Observational studies — Need more
  - Meta-analyses — Only one so far
  - Randomized placebo controlled trials — Difficult but feasible, secondary observations possible from prior and/or ongoing trials

Slide courtesy of Michael Boeckh

Road map

- **CNS disease**
  - Meta-analysis (viremia association)
- **LRTD**
  - Additional studies
  - Meta-analysis (incidence, viremia association)
- **GvHD**
  - Effect size
  - Role of HHV-6 in tissue
- **Myelosuppression**
  - Engraftment, platelet requirement
  - Cohort studies
  - Meta-analysis (viremia association)

- **Neurocognitive dysfunction**
  - Additional studies
  - Meta-analysis (incidence, viremia association)
- **Rash**
  - Clinical significance?
  - Additional tissue studies (viremia association, drug effects)
  - Meta-analysis
- **Overall mortality**
  - Additional studies (viremia association)
  - Meta-analysis

Slide courtesy of Michael Boeckh

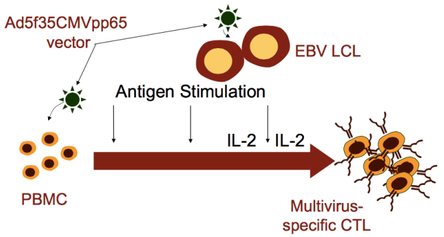
Road map

- Goal: establish an endpoint of “**clinically-significant HHV-6 infection**”
  - End-organ disease
    - CNS disease (PCR confirmed)
    - Lung disease (PCR confirmed)
    - Other? Composite endpoints (GVHD-free survival)?
  - Viremia
    - Requires international standard
    - Requires studies and meta-analyses to demonstrate that viremia is a surrogate, or at least a correlate
    - Establish viral load thresholds
    - Avoid confounding by inherited ciHHV-6
- Efficacious AND safe antivirals (RCTs)

Small molecules

Vaccines

Virus-specific T cells



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