

# Assessment of HHV-6 and HHV-7 in Patients after Renal Transplantation: Impact on Clinical and Immune Parameters.

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EIROPAS SAVIENĪBA

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# Background

- Immune suppression after RT renders the transplant recipient susceptible to a broad array of viral pathogens
- Epidemiologically -
  - some are the result of community exposures,
  - some are transmitted with the allograft,
  - others are the result of reactivation in the setting of immune suppression...

*Jay A. Fishman and Robert H. Rubin. N Engl J Med 1998; 338:1741-1751*



## The main viral pathogens involved in infectious complications in RT

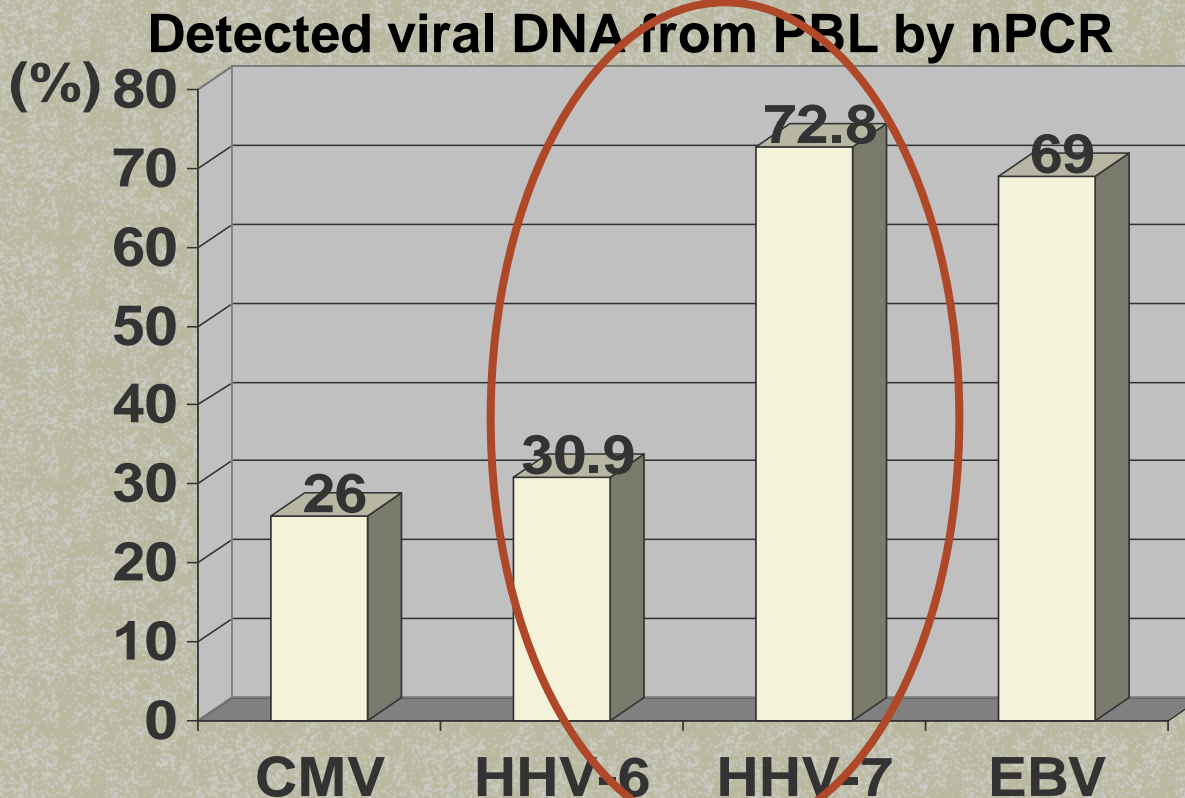
- HERPES SIMPLEX
- VARICELLA ZOSTER
- EPSTEIN-BARR VIRUS
- CYTOMEGALOVIRUS
- HHV6 (& role with CMV)
- HHV7 (role?)
- HHV8/KSHV
- HIV
- WEST NILE VIRUS
- RABIES
- HEPATITIS B and C
- PAPILOMAVIRUS
- POLYOMAVIRUS BK/JC
- ADENOVIRUS, RSV
- INFLUENZA, PARAINFLUENZA
- PARVOVIRUS B19
- SARS coronavirus



## **Routine virological screening in transplant candidates (D/R)**

- Cytomegalovirus
- Epstein-Barr virus
- Hepatitis C virus
- Hepatitis B surface and core Ab
- Hepatitis B surface Ag
- HIV Ag/Ab Combo-Ab

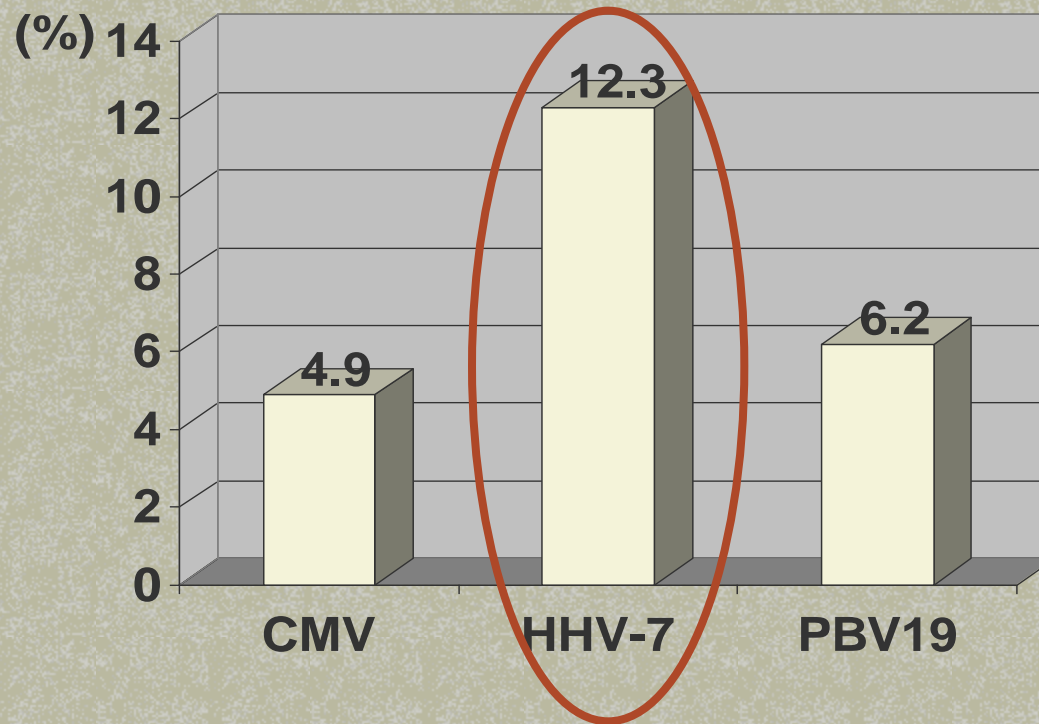
# Latent/persistent blood-borne viral infection in RT donors (N=81) in Latvia



Concurrent infection was diagnosed in 46/81 donors

## Active viral infection in RT donors

According to IgM Ab and viral DNA in plasma by nPCR



**Concurrent active viral infection was diagnosed in 4/46 donors**



## The role of HHV-6 and HHV-7 in RT

- Is incompletely defined
- Reactivation of endogenous latent viruses rates of 30 – 50%
- The effects of viruses are classified as “direct” and “indirect”
- A growing body of evidence suggests that the major impact of HHV-6 and HHV-7 reactivation in RT is related to indirect immunomodulatory effects...

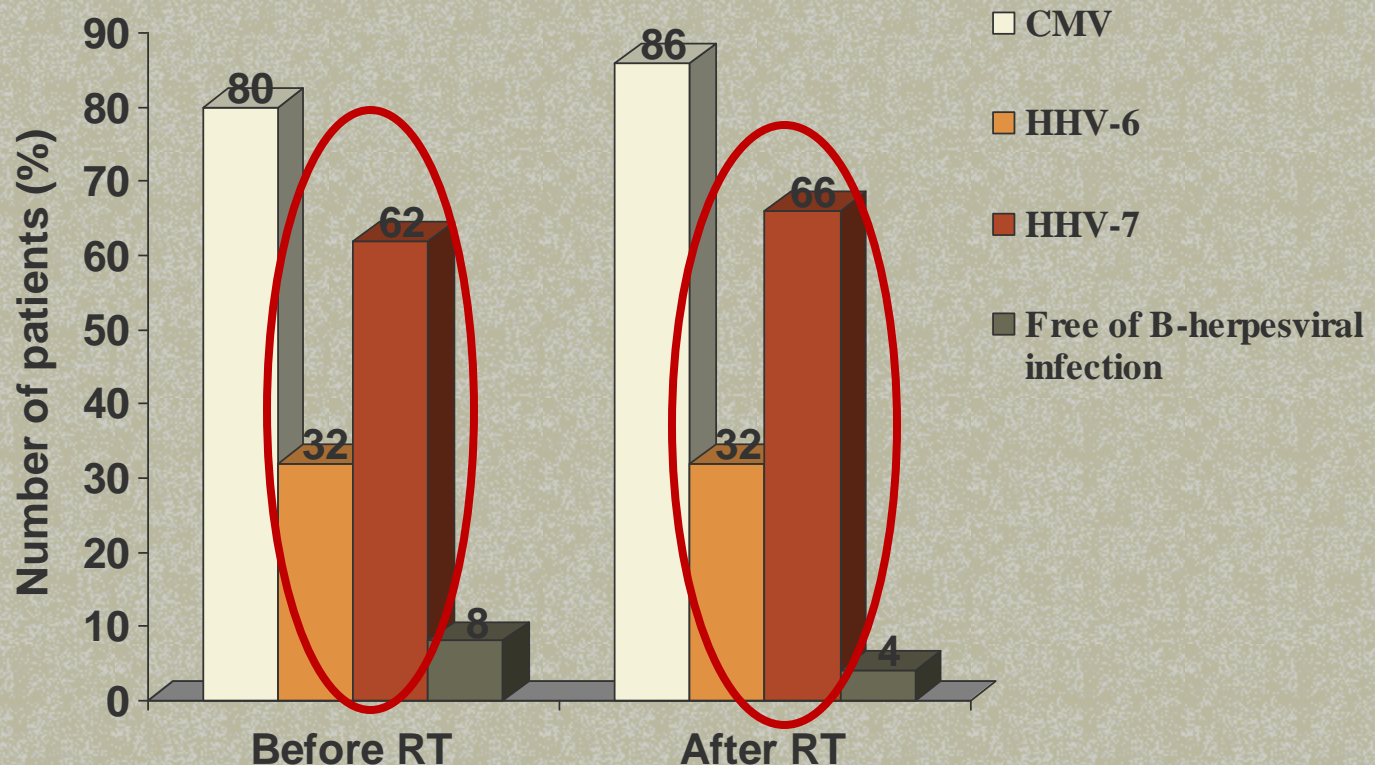


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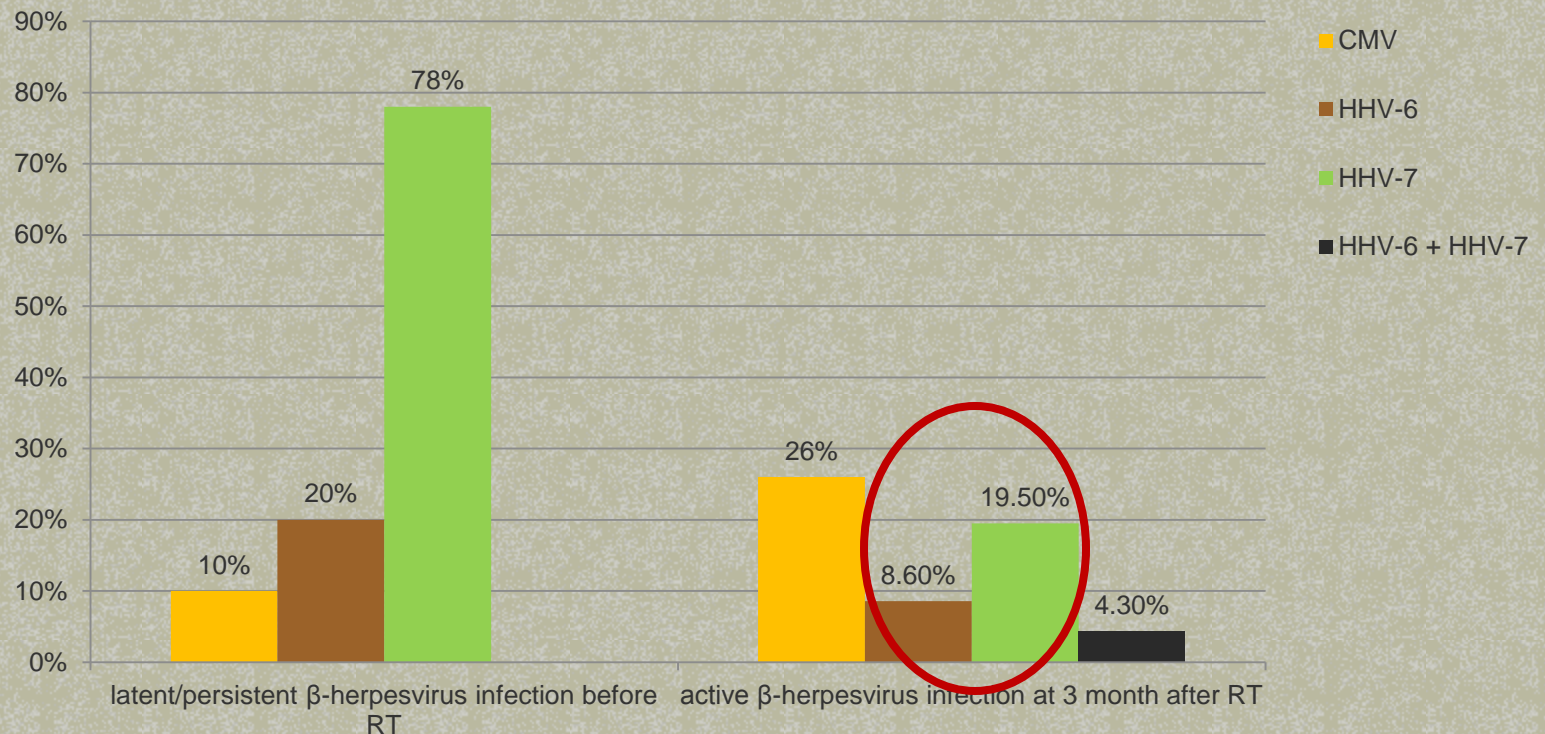


# Prevalence of latent/persistent $\beta$ -herpesvirus infection in 50 recipients before and after RT



Chapenko S, Folkmane I, et al. *Transplantation Proceedings*, Vol 33, No 4, 2001, p. 2463-2464

# Prevalence of active $\beta$ -herpesvirus infection in recipients after RT (n=46)



*I. Folkmane, S. Chapenko et al. 2011, not publicated data*



## The role of HHV-6 and HHV-7 in RT

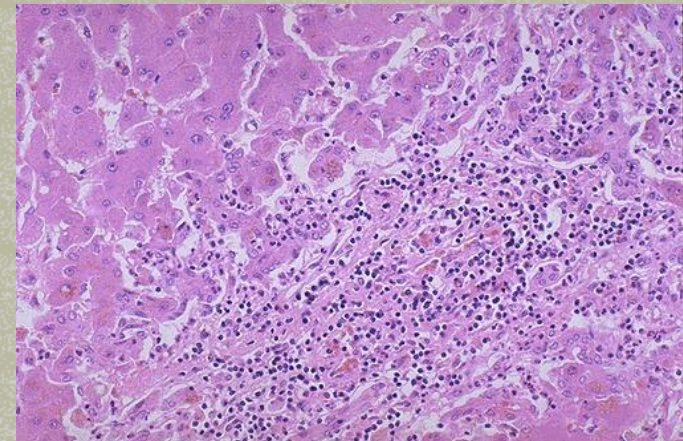
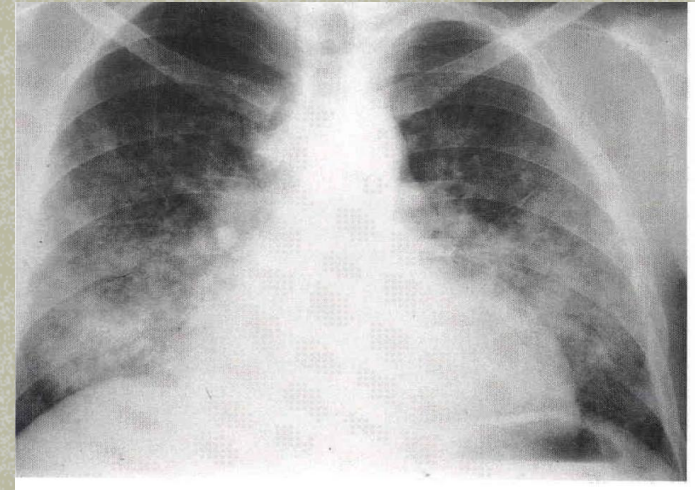
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## Studies of HHV-6 and HHV-7 following renal transplantation

Study	Virus	Observed disease
<i>Osman et al, 1996</i>	HHV-6, HHV-7	None (HHV-6); ↑ CMV disease (HHV-7)
<i>Ratnamohan et al, 1998</i>	HHV-6	Fever
<i>Kidd et al, 2000</i>	HHV-6, HHV-7	None (HHV-6); ↑ CMV disease, rejection (HHV-7)
<i>Tong et al, 2000</i>	HHV-6, HHV-7	None (HHV-6); ↑ CMV disease (HHV-7)
<i>Chapenko et al, 2009</i>	HHV-6, HHV-7	Association with CAN
<i>Pilmore et al, 2009</i>	HHV-6	Colitis, hepatitis, cytopenia

## Direct effects of HHV- 6 infection

- Are effects of invasive viral infection and associates with cellular and tissue injury:
  - Fever
  - Rash
  - Encephalitis
  - Hepatitis
  - GI tract ulcerations
  - Myelosuppression
  - Interstitial pneumonitis





## Indirect effects of HHV- 6 and HHV-7 infection

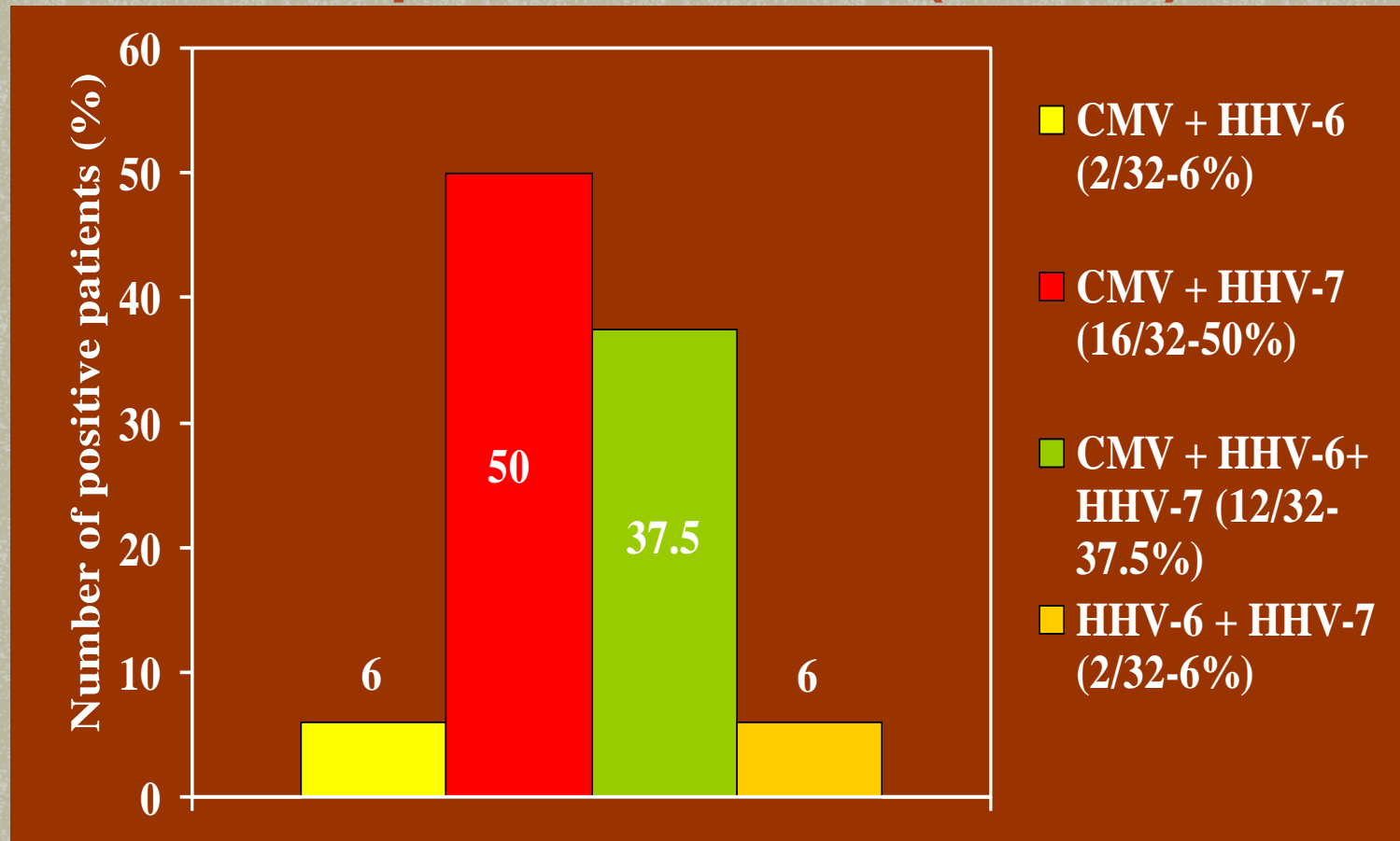
- Are mediated by inflammatory responses (cytokines) or by alterations in host immune and inflammatory responses,
- resulting in further immune suppression and increasing the risk of other opportunistic infections.
- Viruses may alter expression of MHC antigens, provoking graft rejection and/or causing dysregulated cellular proliferation (↑ oncogenesis)



## Indirect effects of HHV- 6 and HHV-7 infection (cont...)

- Infection with one virus may cause immune suppression or otherwise stimulate replication of other viruses (e.g., CMV and hepatitis C) in a form of viral "cross-talk."
- Multiple observational studies implicate infection with HHV-6 and/or HHV-7 as risk factors for CMV disease and CMV infection may trigger HHV-6 and HHV-7 reactivation.
- Increased viral replication and persistence may contribute to allograft injury (fibrosis) or CAN.

## Composition of concurrent $\beta$ herpesvirus infection in patient after RT ( n= 32 )



Chapenko S, Folkmane I, et al. *Transplantation Proceedings*, Vol 33, No 4, 2001, p. 2463-2464





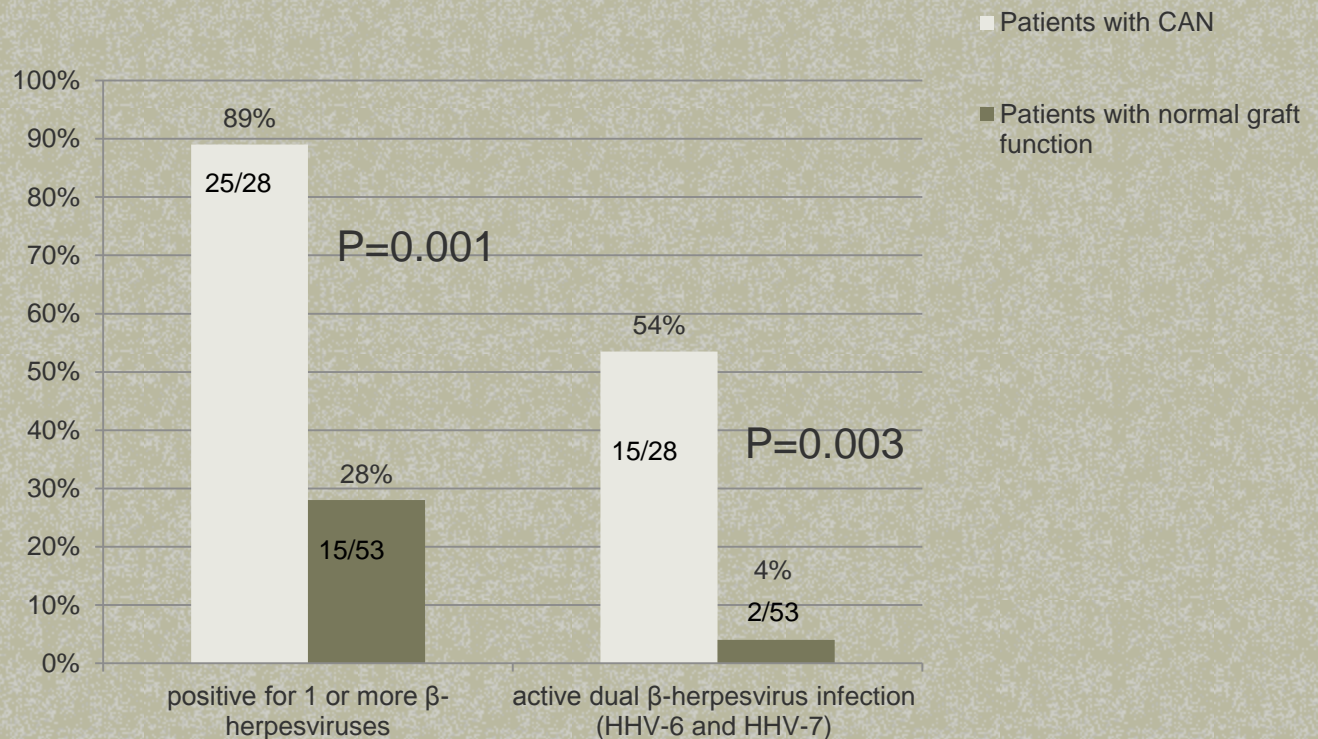
## Risk of the development of viral disease in recipients with either viral infection alone or concurrent $\beta$ -herpesviruses infection

<b>Viral infection</b>	<b>Relative risk of disease (95% CI)</b>	<b>P</b>
CMV	0.45 (1.16 - 1.27)	
CMV+HHV-6	2.17 (0.39 - 11.92)	p=0.43
CMV+HHV-7	2.71 (0.94 - 7.84)	p=0.03
CMV+HHV-6+HHV-7	2.17 (0.69 - 6.79)	p=0.16
$\beta$ -herpesviral infection	4.46 (0.87 - 6.95)	p=0.04

*S. Chapenko, I. Folkmane, et al. Transplantation Proceedings, Vol 33, No 4, 2001, p. 2463-2464*

# Association of HHV-6 and HHV-7 reactivation with the development of CAN


Number of patients



Chapenko S, Folkmane I, et al. *J Clin Virol* 2009; 46 (1): 29-32.

## HHV-6 and HHV-7: clinical and immune consequences (44 recipients, Tx in 1997)

Parameters	HHV-6 (n=4)	HHV-7 (n=9)	Control (n=31)
• Recipient age (years)	41.7±8.1	43.8±13.9	45.7±14.5
• Donor age (years)	46.4±12.1	47.2±8.3	46.2±10.2
• ATG induction therapy	0	0	3 (9.6%)
• Prophylaxis with valganciclovir	3 (75%)	6 (66.6%)	18 (58.0%)
• Active CMV infection	0	1 (11.1%)	9 (29%)
• Acute rejection incidence	2 (50%)	3 (33.3%)	10 (32.2%)
• Graft function (S-Cr, mmol/L)			
At 3 months	0.13±0.04	0.11±0.02	0.12±0.03
At 12 months	0.14±0.04	0.11±0.02	0.13±0.05



## Lymphocyte subsets number in recipients at the 3 months after RT

Cell subset (in 1 mm <sup>3</sup> )	Control	HHV-6	<i>P</i> controls vs HHV-6	HHV-7	<i>P</i> controls vs HHV-7
CD3+	0.73±0.68	0.84±0.50	0.30	1.14±0.73	0.13
CD4+	0.37±0.40	0.48±0.29	0.33	0.59±0.37	0.15
CD8+	0.32±0.32	0.37±0.22	0.25	0.54±0.43	0.10
CD4+/CD8+	1.33±0.81	1.32±0.41	0.95	1.24±0.66	0.76
CD19+	0.06±0.05	0.07±0.06	0.13	0.11±0.07	0.04
CD25+	0.01±0.01	0.01±0.01	0.06	0.03±0.03	0.03

Increase in expression of CD19+ and CD25+ cells in HHV-7 group could be caused by down rgulation of cellular and humoral immune response due to HHV-7 immunomodulatory effects...

*I. Folkmane, S. Chapenko et al. 2011, not publicated data*



# Conclusions

- The impact of  $\beta$ -herpesviruses after solid organ transplantation can be ranked:  
CMV > HHV-6 = HHV-7
- The main HHV-6 and HHV-7 effects on RT outcomes are associated with viral “indirect” effects.
- Relatively low rate of clinical and immunological complications were disclosed in our recent studies.
- We can speculate, that extensive prophylactic therapy is effective against  $\beta$ -herpesviruses and
- The current IS therapy with CsA, MMF and P does not create overimmunosuppression...



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# Thank you !

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