

“Promotion of International Cooperation  
Activities of Riga Stradiņš University in Science and Technologies”, agreement  
No. 2010/0200/2DP/2.1.1.2.0/10/APIA/VIAA/006

# Frequency of HHV-6 and HHV-7 Infection Markers in Rheumatoid Arthritis and Osteoarthritis Patients and Changes in Cytokine Expression Levels

Anda Kadisa, Zaiga Nora-Krukle, Svetlana Kozireva,  
Peteris Studers, Aivars Lejnieks, Modra Murovska

# HHV-6 and HHV-7

- *Roseolovirus* genus in Betaherpesvirinae subfamily
- Up to 90% of adults being seropositive
- Primary infection commonly occurs in early childhood



latency



reactivation under conditions of stress and  
immunocompromised state



contribution of further immunosuppression

# Rheumatoid arthritis



through direct joint tropism

through ability to activate immune response directed at joint tissue

- The primary target for HHV-6 and HHV-7 replication is CD4+ T lymphocytes, pivotal cells in generation of humoral and cell-mediated adaptive immune response
- Both viruses have been shown to up-regulate TNF-alpha secretion by PBMC
- HHV-7 could also act as a trigger factor for HHV-6 activation

Lusso HHV-6 and the immune system: mechanisms of immunomodulation and viral escape. *J Clin Virol* 2006; Suppl 1:S4-10.

Wang F-Z, Pellet PE. HHV-6A, 6B and 7: immunobiology and host response. *Human Herpesviruses Biology*. Arvin A, Campadelli-Fiume G, Mocarski E ed. Cambridge: Cambridge University Press, 2007.

Prober CG. Human herpesvirus 6. *Adv Exp Med Biol* 2011; 697:87-90.

## **The aim**

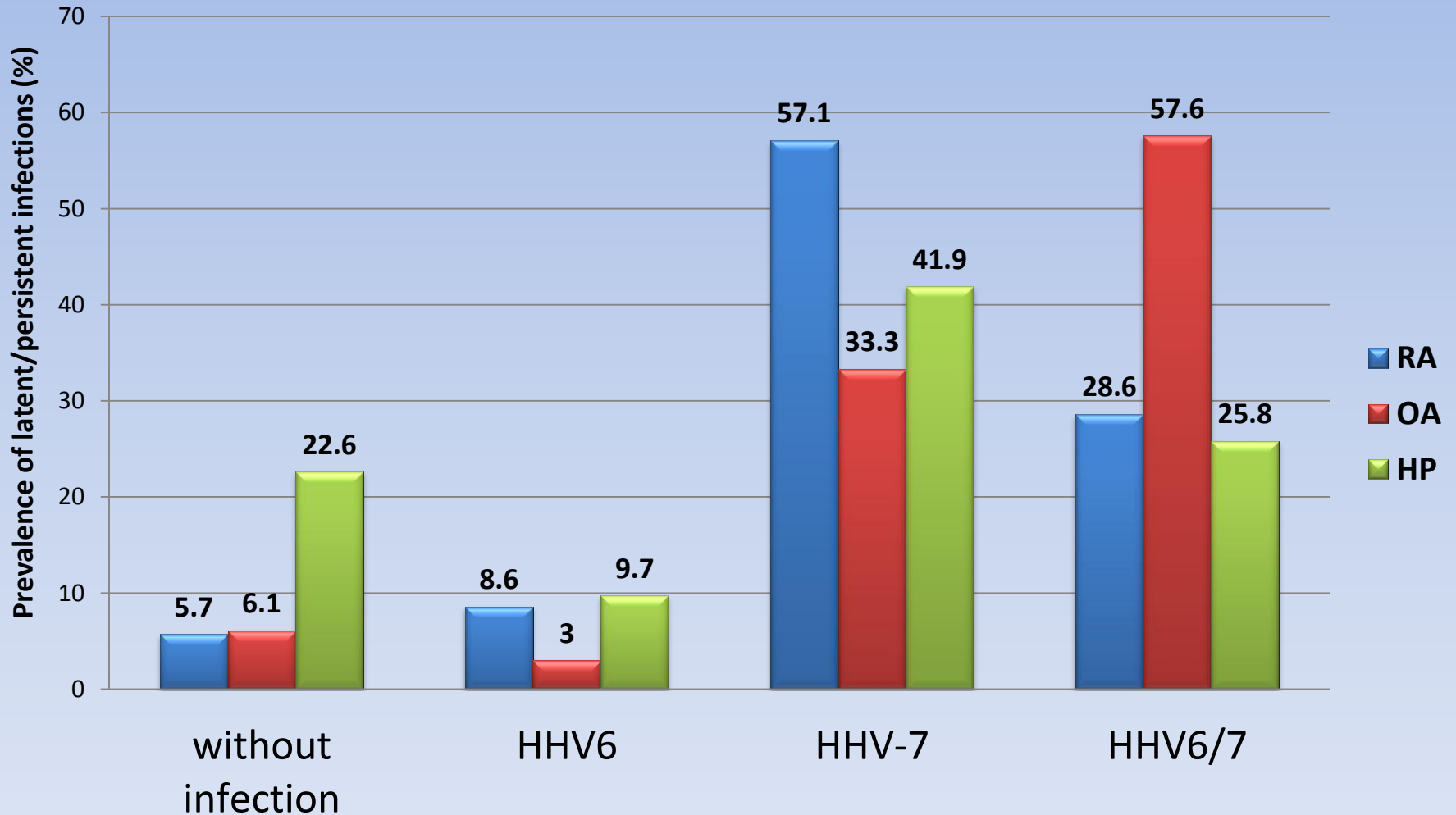
To assess the relevance of viral infection in RA  
we evaluated the frequency of HHV-6 and  
HHV-7 reactivation in RA and OA patients and  
changes in cytokine expression levels

# Materials and methods

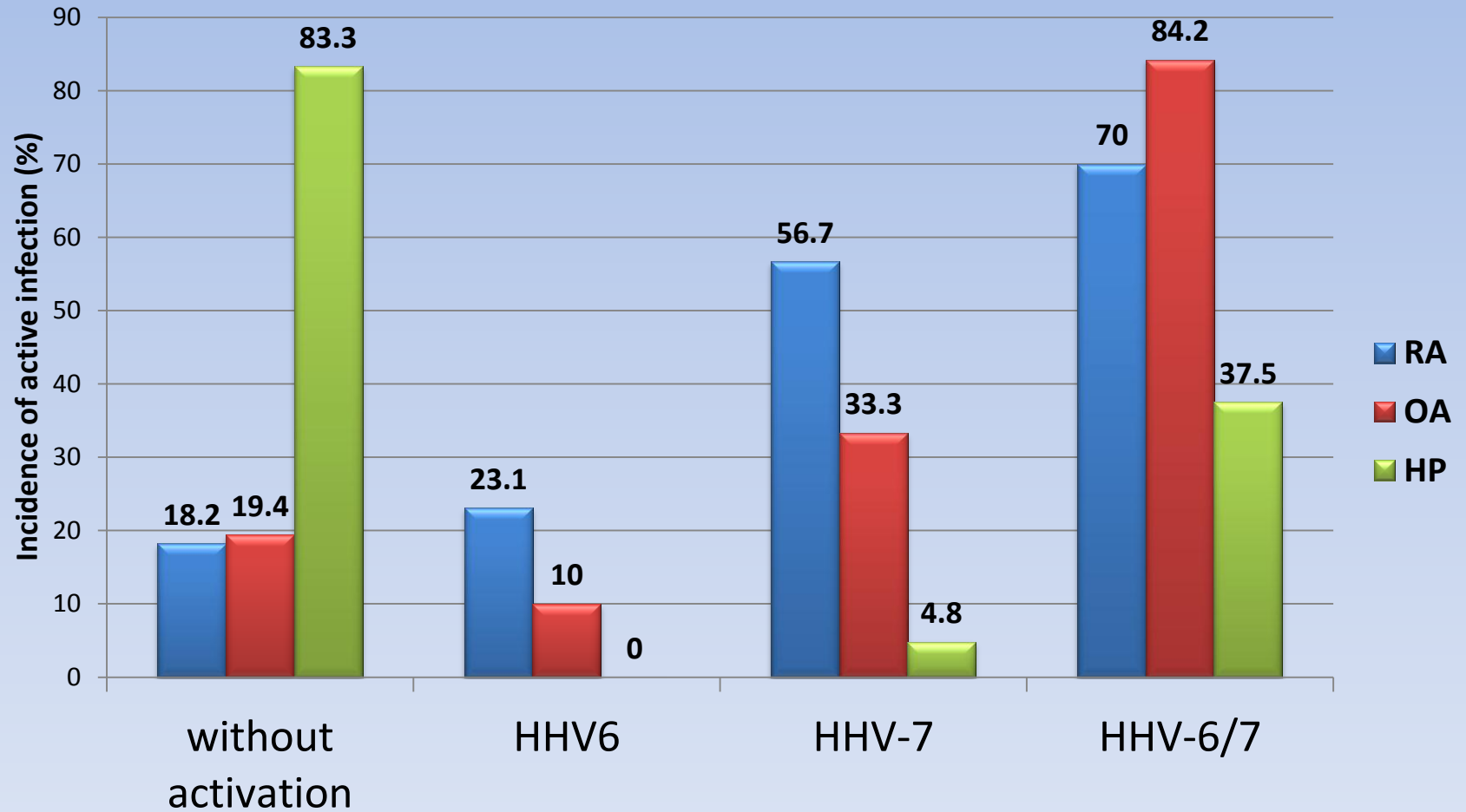
- ***Patients and controls.***
  - 35 patients with RA (27 females and 8 males) with mean age 56.1 years (range 38-76),
  - 33 patients with OA (25 females and 8 males) with mean age 66.1 years (range 46-83)
  - 31 apparently healthy persons (mean age 53.6 years, range 38-72).
- The clinical features and laboratory parameters (hemoglobin, C reactive protein, rheumatoid factor and anti-cyclic citrullinated peptide) and disease activity score *DAS28* (only for RA patients) were examined for their potential relationship with HHV-6 and HHV-7 infections.

- ***The presence of HHV-6 and HHV-7 DNA in clinical samples was detected by nested PCR.***
- Detection of viral DNA in cell-associated material – leucocytes and synovial tissues, has been used as a marker of latent/persistent infection while detection of viral DNA in cell-free plasma and synovial fluid as a marker of active infection (virus reactivation).
- ***Secretion level of IL-6, TNF-alpha, IL-1beta and IFN-gamma in peripheral blood was determined by quantitative ELISA (Immunotool, Germany).***
- ***Statistical analysis.*** Data were analyzed by Fisher's exact test. Values of  $p < 0.05$  were considered to be significant.

# Prevalence of latent/persistent HHV-6 and HHV-7 infections among RA and OA patients

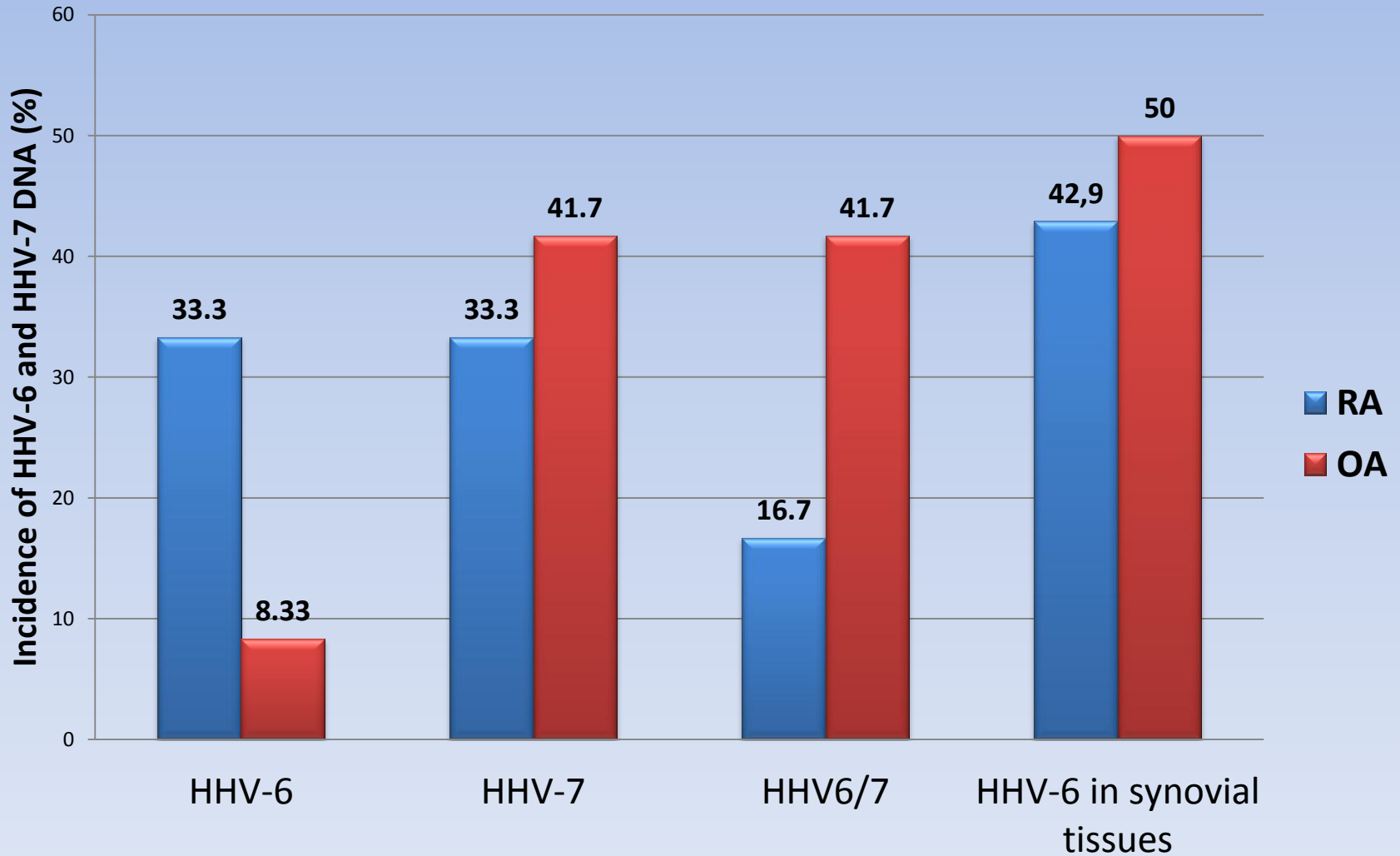


# Incidence of active HHV-6 and HHV-7 infection in RA and OA patients



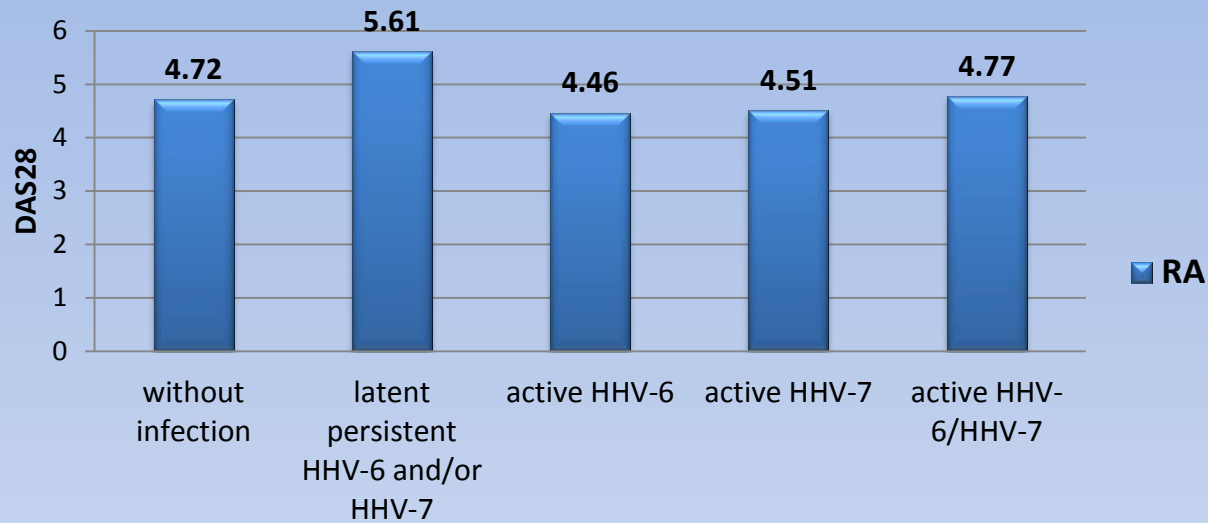


# Incidence of HHV-6 and HHV-7 DNA in synovial fluid and sinovial tissues

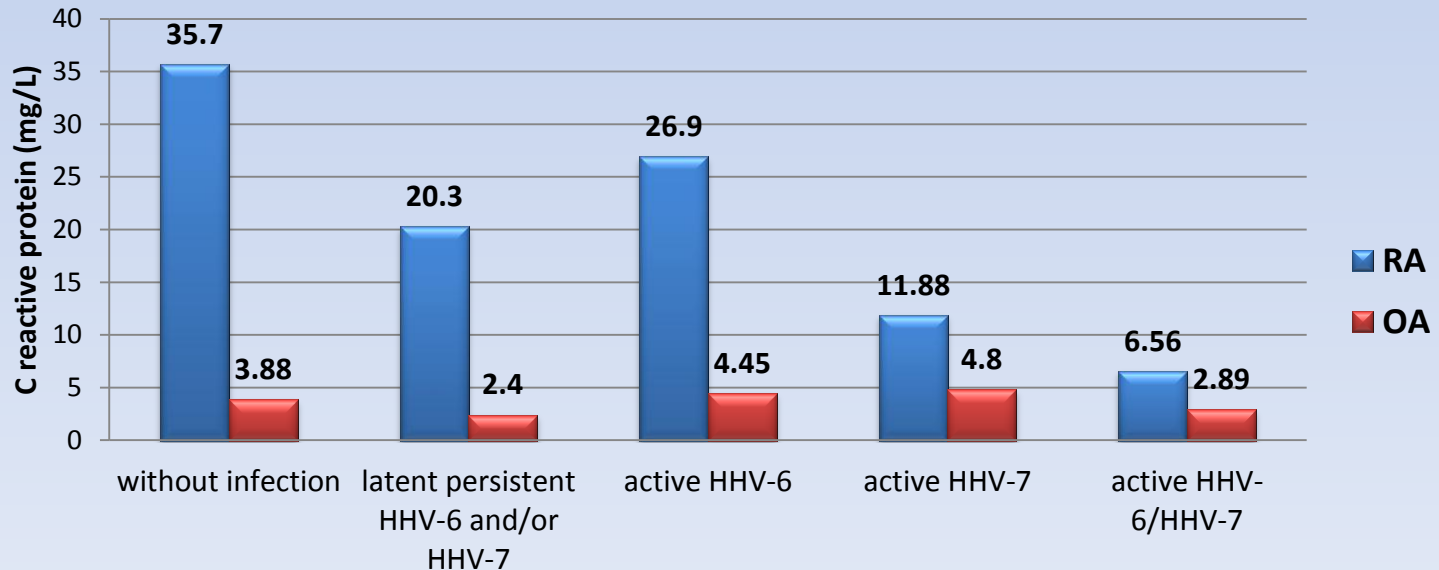


# Medium results of laboratory parameters

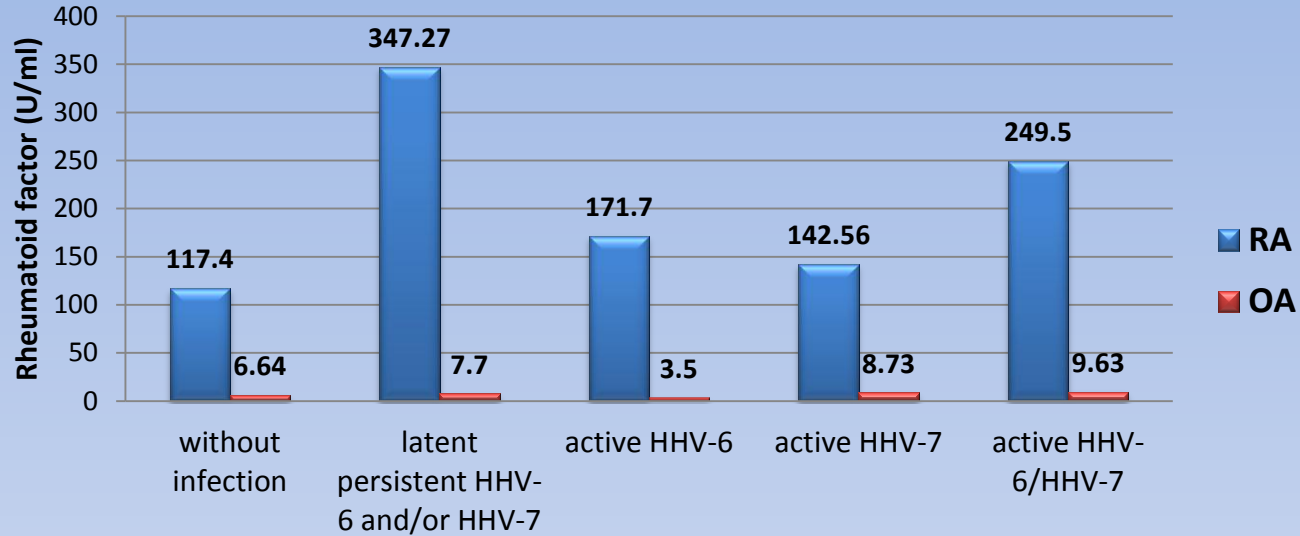
## DAS28 in RA patients



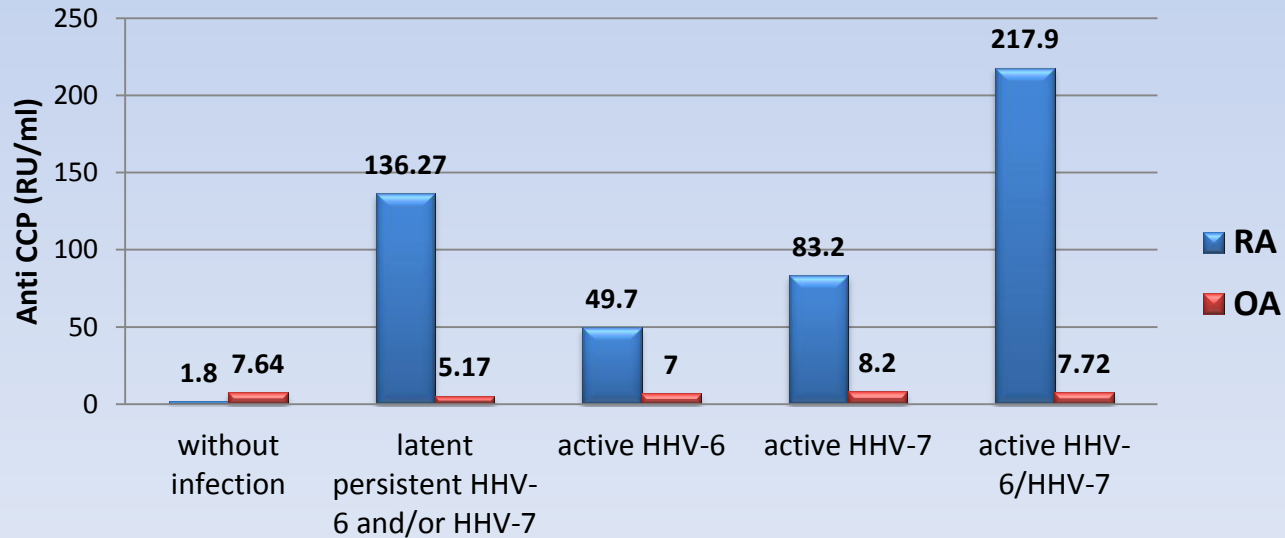
## C reactive protein



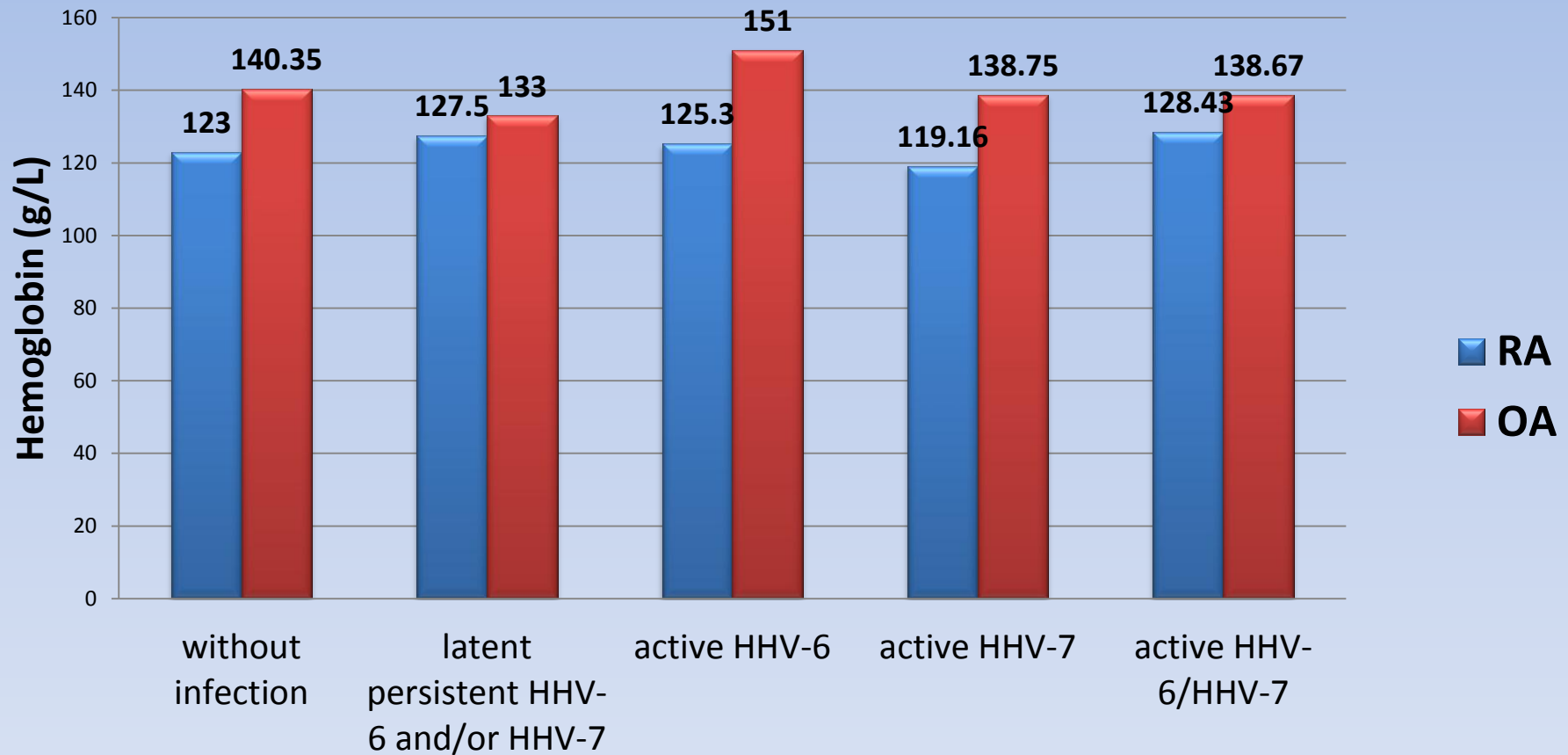
## Rheumatoid factor



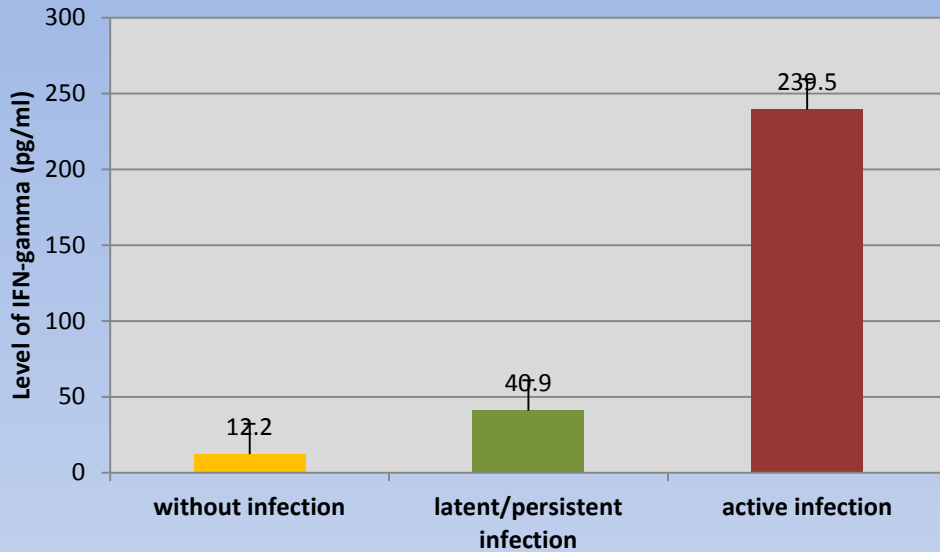
## Anti CCP



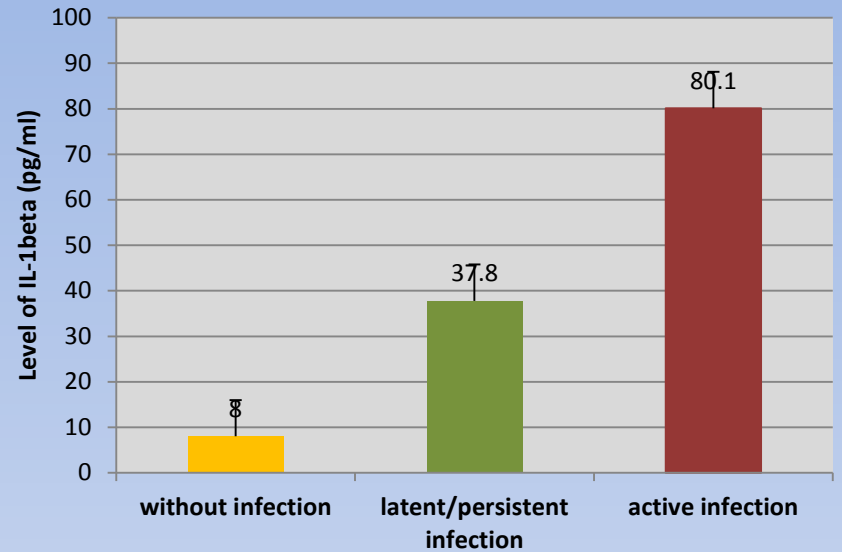
# Hemoglobin



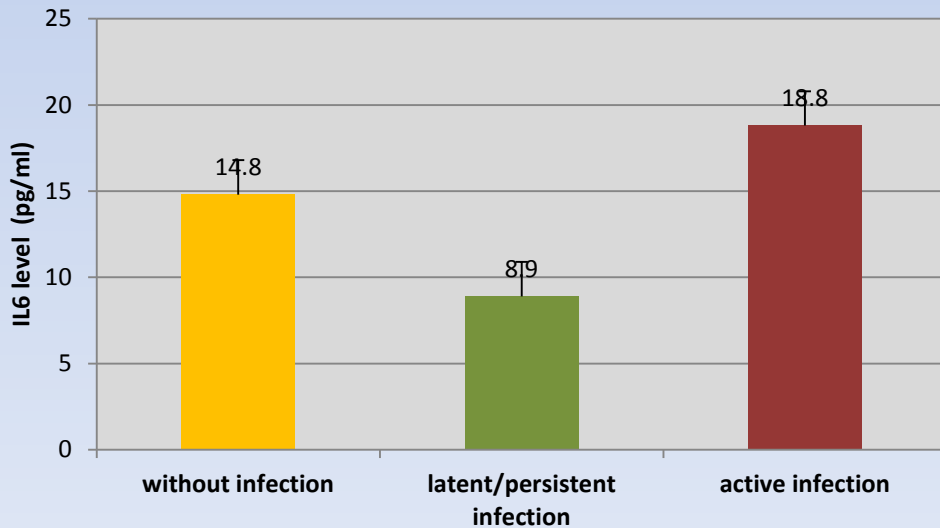
### Serum IFN-gamma level in RA patients



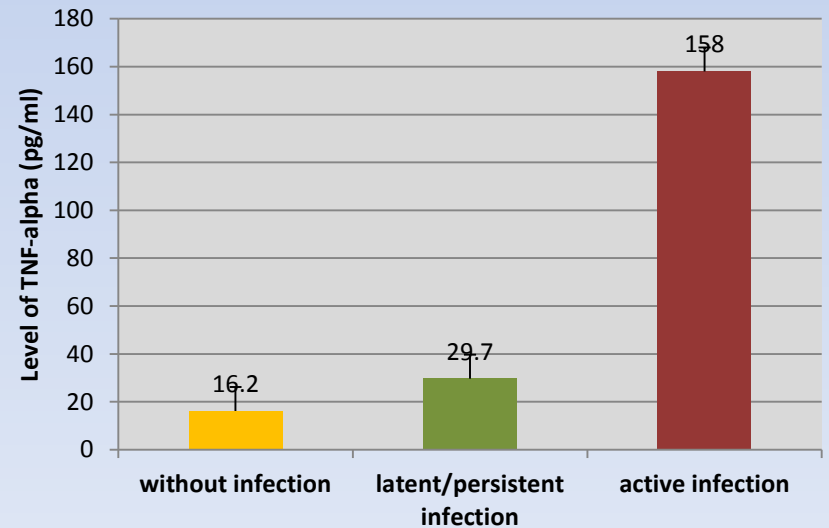
### Serum IL-1beta level in RA patients



### Serum IL-6 level in RA patients

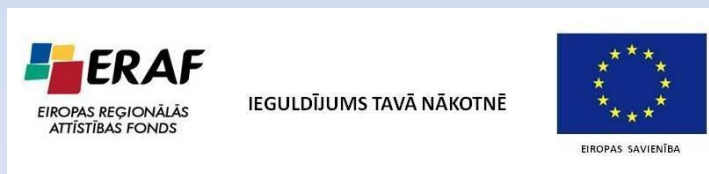


### Serum TNF-alpha level in RA patients



# Conclusion

- Concurrent HHV-6 and HHV-7 reactivation may cause more aggressive progress of RA.
- Concurrent HHV-6 and HHV-7 reactivation in RA patients leads to significant increase of tumor necrosis factor alpha and interferon-gamma secretion.
- The role of HHV-6 and HHV-7 infection in the RA pathogenesis through immune dysregulation could not be excluded.



"Promotion of International Cooperation  
Activities of Riga Stradiņš University in Science and Technologies", agreement  
No. 2010/0200/2DP/2.1.1.2.0/10/APIA/VIAA/006