

# HHV-6 Reactivations and Outcomes Following Hematopoietic Stem Cell Transplant

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Human herpesvirus 6 (HHV-6) infects 90% to 100% of individuals during childhood and then establishes a latent infection in hematopoietic reservoirs. In cases of severe immunosuppression, such as during hematopoietic cell transplant (HCT), this latent infection can reactivate. Previous studies have shown that HHV-6 reactivates in approximately 40% of HCT patients, and reactivation has variably been associated with cytomegalovirus (CMV) reactivation, acute graft-versus-host-disease (aGVHD), and increased mortality. Previous studies were small and most were retrospective, so lead author Dr. Danielle Zerr, Dr. Wendy Leisenring, and collaborators at Fred Hutchinson Cancer Research Center performed a prospective study of HHV-6 in HCT patients to investigate the nature of the relationship between HHV-6 reactivation and outcomes in HCT patients.

A total of 315 patients were included in the analysis, with baseline (pre-HCT) and twice-weekly plasma specimens collected over 12 weeks post-HCT for HHV-6 testing. The patients were also followed through day 200 for mortality. Cox proportional hazards models were used to investigate the associations between HHV-6 reactivation and CMV reactivation, aGVHD, and mortality.

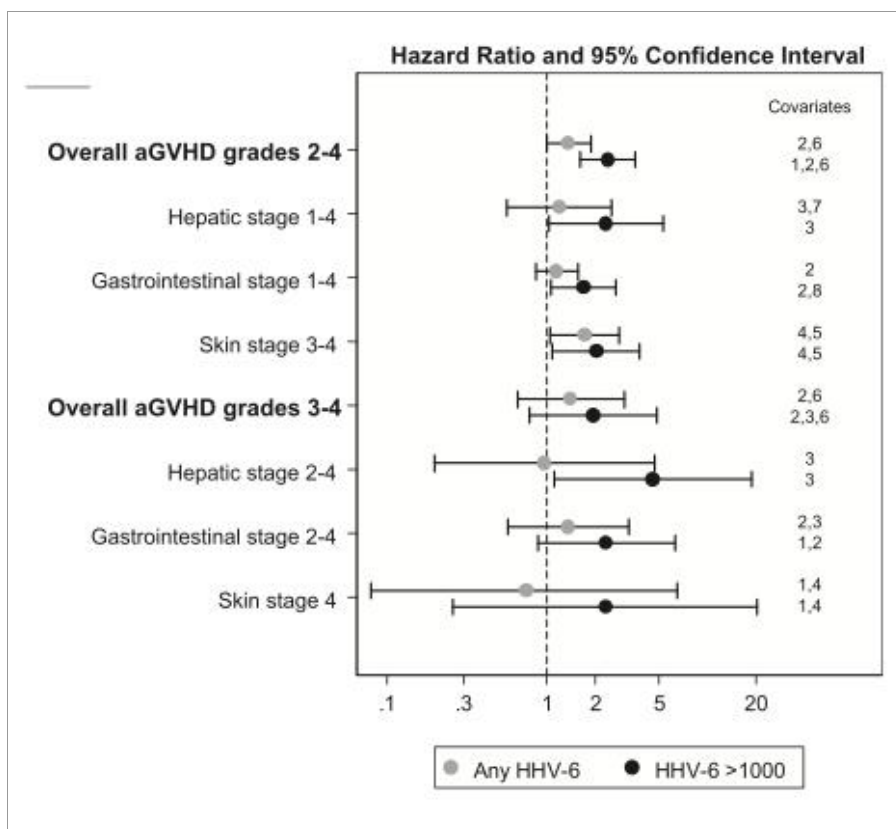
HHV-6 reactivation was detected in 111 (35%) of the patients through 12 weeks post-HCT, with a median time to reactivation of 20 days post-HCT. This reactivation was associated with subsequent CMV reactivation (adjusted hazard ratio [aHR], 1.9, 95% confidence interval [CI], 1.3-2.8,  $p=0.002$ ). Additionally, high-level HHV-6 (defined as  $>1000$  HHV-6 DNA copies/mL) was associated with subsequent grades II to IV aGVHD (aHR, 2.4; 95% CI, 1.60-3.6,  $p<0.001$ ). High level HHV-6 reactivation was also associated with nonrelapse mortality (aHR, 2.7; 95% CI, 1.2-6.3;  $p=0.02$ ).

The results of this study suggests that the association between HHV-6 and mortality in HCT may be partially mediated by aGVHD. Previous clinical data suggest that HHV-6 reactivation may also cause a pro-inflammatory response that may be important in the development of aGVHD; however, Zerr and colleagues note that many complex pathways could link HHV-6 reactivation with increased complications following HCT.

In summary, HHV-6 reactivation was independently and quantitatively associated with increased risk of subsequent CMV reactivation, aGVHD, and mortality post-HCT. Given the results of this study, the authors suggest that a randomized controlled antiviral trial, which could definitively establish causality, is warranted to determine if reducing HHV-6 reactivation will reduce the incidence of these outcomes after HCT.

[Zerr DM, Boeckh M, Delaney C, Martin PJ, Xie H, Adler AL, Huang ML, Corey L, Leisenring WM.](#)

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Results from multivariable models evaluating HHV-6 reactivation as a risk factor for subsequent aGVHD by day 100. Covariates included in the final multivariable models: 1:age, 2:conditioning regimen, 3:stem cell source, 4:sex, 5:underlying disease, 6:HLA match, 7:CMV serostatus, 8:CD34 dose