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**Institutionen för mikrobiologi, tumör- och cellbiologi**

# The EBV-HIV interrelationship and the value of EBV-DNA analysis

**AKADEMISK AVHANDLING**

som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Hillarpsalen, Retzenius väg 8

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av

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## Abstract

Epstein-Barr virus (EBV) infects the vast majority of humans and resides latently in B-cells. This virus carries genes that can induce and sustain mature B cell growth. EBV is associated with a wide range of B-cell lymphomas including Burkitt lymphoma and non Hodgkin lymphoma (NHL) in human immunodeficiency virus 1 (HIV-1) infected patients. Latent EBV infection in B lymphocytes is a risk factor for B-cell lymphomas in conditions of combined antigen stimulation and immunosuppression as with Burkitts lymphoma in malaria endemic African regions and non Hodgkin lymphoma in HIV-1 infected patients. In the era of modern combination antiretroviral therapy (cART) there has been an impressive reduction of Acquired Immunodeficiency syndrome (AIDS)-related opportunistic infections and lymphomas, although patients still suffer an increased risk for NHL. This work is based on EBV-DNA load measurement in blood as a tool to analyse EBV-host relationship in HIV-1 infection.

In general HIV-1 infected individuals have a higher EBV-DNA load and symptomatic HIV-1 infected even higher. Individual variables, immunological factors and treatments as cART affect this pattern. In one of our studies we identified one group and one risk factor that influenced EBV-DNA load. HIV-1 infected individuals with a history of a symptomatic primary infection in combination with induced immune stimulation by therapeutic vaccination/adjuvant showed an increased load. Without the vaccination/adjuvant stimuli this group did not show the same increase. HIV-1 infected patients with a history of a symptomatic primary infection might therefore be at risk for developing NHL. Therapeutic vaccination/adjuvant increases the EBV-DNA load and we regard this immunomodulation as a risk factor. Different pattern of EBV-host restoration by cART was seen in a long term follow of patients with increased EBV-DNA load after vaccination. The EBV-host relation seems to be reconditioned by successful cART treatment, measured by the CD4+ cell count returning to normal levels, with some reservation for the functional restoration, together with remaining undetectable HIV-1 RNA. For individuals with unsuccessful cART treatment the distinct decrease of EBV-DNA could not be seen. In a patient treated for EBV positive plasmablastic lymphoma we observed a sharp increase of EBV-DNA load before clinical signs of recurrence.

Measurement of EBV-DNA load is valuable in monitoring disease progression in HIV-1 infected patients. After cART treatment the dynamics of EBV-DNA load reveal if the antiviral treatment is suboptimal, even if breakthroughs detected as HIV RNA peaks are missed. When an EBV positive tumour is treated successfully EBV-DNA monitoring can be of importance to observe early signs of relapse. Monitoring EBV-DNA load during therapeutic vaccination studies seems highly motivated. In conclusion EBV-DNA load analysis is a useful additional instrument to monitor different groups of HIV-1 patients with increased risk for lymphoma development.