Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs universitet kommer att offentligen försvaras i *Aulan Järneken*, KK-huset, Sahlgrenska Universitetssjukhuset/Östra, Göteborg den 28 maj 2015 kl 9.00

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Avhandlingen baseras på följande arbeten:

I. Tomas Mellberg, Veronica D Gonzalez, Annica Lindkvist, Arvid Edén, Anders Sönnerborg, Johan K Sandberg, Bo Svennerholm and Magnus Gisslén. **Rebound of residual plasma viremia after initial decrease following addition of intravenous immunoglobulin to effective antiretroviral treatment of HIV**
AIDS Research and Therapy 2011, 8:21

II. Tomas Mellberg, Jon Krabbe, Maria J Buzon, Ulrika Noborg, Magnus Lindh, Magnus Gisslén and Bo Svennerholm. **Sensitive, subtype independent HIV-1 PCR assays for assessment of residual viremia and total HIV-1 DNA**
In submission

III. Tomas Mellberg, Jon Krabbe, Bo Svennerholm and Magnus Gisslén. **Subtype independent sequencing of low level viremia in HIV-1 infected patients, a pilot study**
In submission

IV. Jan Jessen Krut*, Tomas Mellberg*, Richard W Price, Lars Hagberg, Dietmar Fuchs, Lars Rosengren, Staffan Nilsson, Henrik Zetterberg, and Magnus Gisslén. **Biomarker evidence of axonal injury in neuroasymptomatic HIV-1 patients**
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On HIV-1 Latency and Viral Reservoirs

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ABSTRACT

HIV-1 establishes a latent infection that is inaccessible to treatment in cellular and anatomical reservoirs. This thesis concerns several problematic issues of HIV-1 persistence, including ways to measure and monitor both the virus at low viral concentrations and the depletion of the reservoir. Since the central nervous system (CNS) is a potentially important anatomical reservoir, we also explore the extent of neurological injury in HIV-1 disease.

Results from a previous study indicate that the reservoir in resting memory $CD4^+$ T-cells and levels of residual viremia was reduced through intravenous immunoglobulin (IVIG) treatment given to patients on combination antiretroviral therapy (cART). We analyzed T-cell activation markers and potential long-term effects of IVIG on residual viremia. We found no lasting effect on residual viremia, indicating that the effect of IVIG was transient. Activation markers and interleukins were not correlated to levels of residual viremia.

Correct measurements of residual viremia and of the reservoir size are crucial in HIV-1 eradication trials and may have other clinical utility. The methods employed need to be sensitive and subtype independent. We evaluated a modification of the COBAS TaqMan HIV-1 test, version 2.0 and a polymerase chain reaction (PCR) assay for total HIV-1 DNA. We achieved a sensitive quantification of plasma HIV-1 RNA that could be used to assess residual viremia. Sensitive quantification of total HIV-1 DNA in peripheral blood mononuclear cells was demonstrated and both assays were subtype independent.

Low level viremia in patients on cART, defined as a residual viral load of 20–1000 copies/ml is associated with increased risk of virologic failure. We evaluated a method used for sequencing in the case of low level viremia. The method was sensitive and also subtype independent, a feature making it useful in clinical settings where a diversity of subtypes is present.

HIV-1 establishes a chronic infection that also infiltrates the CNS and carries the risk of developing neurological symptoms. By measuring neurofilament light protein (NFL) and markers of inflammation in cerebrospinal fluid (CSF), we wished to determine the extent of neurological injury and neuropathogenesis in HIV-1 disease. We found increased CSF NFL both in patients with neurological symptoms and in neuroasymptomatic patients. Treatment decreased these levels, but treated patients still retained higher levels than controls, indicating either continued virus-related injury or an aging-like effect of HIV-1 infection.

Keywords: HIV-1, latency, intravenous immunoglobulin, residual viremia, low level viremia, ultrasensitive PCR methods, central nervous system
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