HIV Persistence and Viral Reservoirs

Akademisk avhandling

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av

Arvid Edén

Fakultetsopponent:

Professor Birgitta Åsjö

Gades institutt, Infektsjon

Bergen, Norge

The thesis is based on the following papers:

I. Arvid Edén, Lars-Magnus Andersson, Örjan Andersson, Leo Flamholc, Filip Josephson, Staffan Nilsson, Vidar Ormaasen, Veronica Svedhem, Christer Säll, Anders Sönnerborg, Petra Tunbäck, Magnus Gisslén
Differential Effects of Efavirenz, Lopinavir/r and Atazanavir/r on the Initial Viral Decay Rate in Treatment Naïve HIV-1 Infected Patients
AIDS Research and Human Retroviruses, in press

II. Annica Lindkvist*, Arvid Edén*, Melissa M Norström, Veronica D Gonzalez, Staffan Nilsson, Bo Svennerholm, Annika C Karlsson, Johan K Sandberg, Anders Sönnerborg and Magnus Gisslén
Reduction of the HIV-1 reservoir in resting CD4+ T-lymphocytes by high dosage intravenous immunoglobulin treatment: a proof-of-concept study
AIDS Research and Therapy 2009, 6:15
*equal contributors

III. Arvid Edén, Richard W. Price, Serena Spudich, Dietmar Fuchs, Lars Hagberg, and Magnus Gisslén
Immune Activation of the Central Nervous System Is Still Present after >4 Years of Effective Highly Active Antiretroviral Therapy
Journal of Infectious Diseases 2007; 196:1779–83

IV. Arvid Edén, Dietmar Fuchs, Lars Hagberg, Staffan Nilsson, Serena Spudich, Bo Svennerholm, Richard W Price, Magnus Gisslén
HIV-1 viral escape in cerebrospinal fluid of subjects on suppressive antiretroviral treatment
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Arvid Edén

Department of Infectious Diseases, Institute of Biomedicine
Sahlgrenska Academy at University of Gothenburg
Göteborg, Sweden

ABSTRACT

Although antiretroviral therapy (ART) can effectively inhibit replication of human immunodeficiency virus type 1 (HIV-1), the virus is able to persist in cellular and anatomical viral reservoirs. Latently infected resting memory $CD4^+$ T-cells are an important cellular reservoir, and the central nervous system (CNS) an important anatomical reservoir for HIV-1 infection. The overall aim of this thesis was to gain greater understanding of HIV-1 persistence, in regards to latent infection as well as the central nervous system.

The initial viral decay rate after initiation of ART has been proposed as a measure of relative regimen potency. We compared initial viral decay in subjects treated with three ART regimens, and found that efavirenz-based therapy gave a faster initial viral decay than protease inhibitor (PI) treated subjects. In turn, lopinavir/ritonavir-based therapy gave a faster initial viral decay than atazanavir/ritonavir-based therapy. This may reflect different inherent antiretroviral potency between the treatment regimens.

Latently infected $CD4^+$ T-cells constitute a major barrier for the eradication of HIV-1 infection. We investigated if a high dose of intravenous immunoglobulin (IVIG) given in addition to effective ART could reduce the size of the pool of latently infected resting cells, and found a reduction in the pool size in five of seven individuals where the latent reservoir was quantifiable. Our findings suggest that the reservoir became accessible through IVIG treatment, and indicate that novel modes of intervention can have an effect on the latent reservoir.

Increased levels of intrathecal immune activation are often found in cerebrospinal fluid (CSF) of treated patients despite effective systemic suppression of HIV-1. We investigated intrathecal immune activation, measured as neopterin and IgG-index, in patients with several years of successful therapy, and found that although ART has a substantial effect on lowering viral replication and immune activation in the CSF, a majority of patients still have ongoing intrathecal immune activation despite effective suppression of the virus for extended periods of time.

Occasional cases of CSF viral escape have been reported. We investigated the occurrence of CSF viral escape in neuroasymptomatic patients effectively treated with commonly used ART regimens. We found that 7 (10%) of 69 patients had evidence of CSF viral escape, which is more common than previously recognized and may have important implications for future treatment strategies and the use of new drug combinations.

Keywords: HIV-1; antiretroviral therapy; latency; cerebrospinal fluid; central nervous system; efavirenz; lopinavir; atazanavir; neopterin; viral decay.

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