

On HIV in the elderly and vitamin B metabolism in HIV infection

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinargatan 3, torsdagen den 10 februari, klockan 09.00

av Erika Tyrberg

Fakultetsopponent:

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Avhandlingen baseras på följande delarbeten

- I. Tyrberg E, Edén A, Eriksen J, Nilsson S, Treutiger CJ, Thalme A, Mellgren Å, Gisslén M, Andersson LM. **Higher plasma drug levels in elderly people living with HIV treated with darunavir.** PLoS ONE 2021; 16(2): e0246171.
- II. Tyrberg E, Skovbjerg S, Samuelsson E, Nilsson S, Edén A, Treutiger CJ, Thalme A, Mellgren Å, Gisslén M, Andersson LM. **Markers of inflammation and immune activation in elderly HIV-1 infected individuals on stable ART treatment with efavirenz, darunavir, or atazanavir.** *In manuscript.*
- III. Ahlgren E, Hagberg L, Fuchs D, Andersson LM, Nilsson S, Zetterberg H, Gisslén M. **Association between Plasma Homocysteine Levels and Neuronal Injury in HIV infection.** PLoS ONE 2016; 11(7): e0158973.
- IV. Tyrberg E, Hagberg L, Andersson LM, Nilsson S, Yilmaz A, Mellgren Å, Blennow K, Zetterberg H, Gisslén M. **The effect of vitamin B supplementation on neuronal injury in PLHIV – a randomised controlled trial.** *Submitted manuscript.*

**SAHLGRENKA AKADEMIN
INSTITUTIONEN FÖR BIOMEDICIN**



Abstract

The evolution of the human deficiency virus (HIV) field is unparalleled in the history of infectious diseases. From the first cases in the beginning of the 1980s, when an HIV diagnosis was a death sentence, through the discovery of the first effective medicines, up till today when people living with HIV (PLHIV) with access to antiretroviral therapy (ART) can lead a near normal life. The aim of this thesis was to investigate further into two areas where knowledge is still lacking, and important questions remain. We investigated HIV in the elderly and the role of vitamin B metabolism in HIV-associated central nervous system (CNS) disease.

In paper I and II we studied HIV infection in the elderly (≥ 65 years of age) compared to a control group (≤ 49 years of age). In a study of cross-sectional design 100 elderly PLHIV and 99 controls, on ART regimens containing atazanavir, darunavir, or efavirenz were included. In paper I we showed that elderly had a higher number of concomitant medications, comorbidities, and potential drug-drug interactions, than the younger controls. In the darunavir arm, the elderly had higher steady-state concentrations. This was also found in the atazanavir arm, although not statistically different, but suggesting a possible class effect of protease inhibitors. Paper II investigated the role of ART regimen on markers of inflammation and immune activation in elderly PLHIV. The regimens had different inflammatory profiles with lower interleukin-6 levels in the atazanavir arm, and lower ICAM-1 in the efavirenz arm. The darunavir arm had higher CXCL10 levels compared to the efavirenz arm.

Paper III and IV studied the role of homocysteine and vitamin B metabolism in CNS injury in HIV infection. Paper III describes an association between plasma homocysteine, a marker of vitamin B₁₂ and folate deficiency, and cerebrospinal fluid neurofilament light protein (NfL), a sensitive marker of neuroaxonal damage in HIV infection. In paper IV this association was further studied in a randomised controlled clinical trial. Sixty-one virally suppressed PLHIV were randomised either to the active treatment arm (treatment with vitamin B₁₂, B₆, and folate) or control arm. After 12 months the levels of homocysteine had decreased, and the plasma B₁₂ and folate levels had increased in individuals in the treatment arm. However, no difference in plasma levels of NfL was found compared to the control arm at 12 months. Furthermore, in the treatment arm, no difference in NfL was found after 24 months, compared to baseline plasma NfL levels.

In conclusion, we found that elderly PLHIV are at risk of adverse drug events through a high prevalence of concomitant medications, potential drug-drug interactions, and higher drug concentrations of protease inhibitors. In addition, we found different inflammatory profiles of efavirenz, atazanavir, and darunavir, a finding that needs to be confirmed in future studies. Furthermore, a novel finding of an association between homocysteine and NfL was made. However, supplementation with B vitamins did not decrease NfL, suggesting a non-vitamin B dependent cause of the association.

Keywords: HIV-1, elderly, drug levels, potential drug-drug interactions, inflammation, immune activation, antiretroviral therapy, homocysteine, neurofilament light protein.