Antiretroviral central nervous system toxicity

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Background
Pre-clinical and clinical data suggest central nervous system (CNS) toxicity for many antiretrovirals, particularly the non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz. We hypothesised that greater antiretroviral exposure would be associated with CNS toxicity:

- Poorer cognitive function
- Neuroimaging abnormalities

Aims
To determine the relationships between plasma and CSF antiretroviral drug exposure with objective markers of:

- Cognitive function
- Brain volumetrics and cortical thickness
- Diffusion MRI metrics

Methods
Participants
For the present analysis, we identified HIV-positive participants in the COBRA study who were receiving a non-nucleoside antiretroviral that was used by at least 30 participants (n=91). This ensured that we would have sufficient numbers on each drug to permit adjusted analyses. Participants receiving regimens including other ‘third-agents’ were excluded from analyses.

Antiretroviral pharmacokinetics
Plasma and cerebrospinal fluid antiretroviral concentrations were assessed using ultra high-performance liquid chromatography (UPLC) at the Department of Clinical Pharmacy of Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands on plasma stored at -80°C.

Due to the variable timing of sampling extrapolated trough concentrations were calculated assuming consistent plasma and CSF kinetics:

\[ C_{\text{min}} = C_{\text{measured}} \times e^{-0.693/T_{1/2}} \]

In which \( T_{1/2} \) was 15, 47.5 and 30 hours for darunavir, efavirenz and nevirapine respectively and \( T_{1/2} \) is time between trough and time of sampling.

Cognitive function testing
Subjects completed a comprehensive battery of neuropsychological tests assessing the domains of attention, executive function, language, memory, speed of information processing and motor function as previously described. Raw scores were converted to demographically adjusted T-scores (mean of 50 and standard deviation of 10) accounting for age and level of education, with higher T-scores representing better cognitive function and the global score representing the mean domain T-score.

Neuroimaging
High-resolution 3D T1-weighted structural images and diffusion-weighted images along 64 non-collinear directions were acquired in London and Amsterdam using a harmonised neuroimaging protocol.

Imaging processing:

Results
Statistics
- Associations between drug exposure (independent variable), cognitive T-scores and neuroimaging measures (dependent variables) were determined using regression of ranks (non-parametric).
- Associations with cognitive T-scores were adjusted for education and ethnicity (+/− weight, BMI, eGFR, age, and gender).
- Associations with neuroimaging measures were adjusted for age, intracranial volume and scanner (+/− height, weight, BMI, eGFR, ethnicity and gender).

Results cont...
Greater plasma nevirapine exposure was associated with reduced grey matter volume (\( r_{\text{adj}} = -0.44, \ p < 0.02, \) Figure 3). Yoxselle analysis demonstrated that plasma nevirapine concentration was negatively correlated with grey matter volume principally in the intracalcarine cortex (Figure 4).

Plasma efavirenz exposure was associated with reduced mean cortical thickness (left: \( r_{\text{adj}} = 0.46, \ p = 0.03; \) right: \( r_{\text{adj}} = 0.45, \ p = 0.01, \) Figure 5). Plasma and CSF efavirenz exposure were associated with white matter microstructural abnormalities (axial diffusivity: plasma \( r_{\text{adj}} = -0.33, \ p = 0.05, \) CSF \( r_{\text{adj}} = -0.44, \ p < 0.01, \) Figures 6 & 7).

Plasma and CSF concentrations of efavirenz and nevirapine were both negatively associated with cognitive T-scores, particularly in the domain of attention (plasma nevirapine \( r_{\text{adj}} = 0.54, p < 0.01, \) Figures 1 & 2), whereas there was no association between darunavir exposure and cognitive function (p>0.1 for all).

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Figure 1. Global cognitive function by drug concentration

Plasma

CSF

Dashed lines indicate unadjusted data. Solid lines adjusted for age, intracranial volume and scanner.

Figure 2. Selected cognitive domains by plasma exposure

Figure 3. Brain volumetrics by plasma exposure

Figure 4. Grey matter volume by plasma nevirapine exposure

Figure 5. Cortical thickness by plasma exposure

Figure 6. Diffusion imaging - CSF exposure

Plasma

CSF

Dashed lines indicate unadjusted data. Solid lines adjusted for age, intracranial volume and scanner.

Figure 7. White matter fractional anisotropy by efavirenz exposure

Limitations
- Small, cross-sectional study
- n too small to adjust for treatment heterogeneity
- Too few on raltegravir to permit adjusted analyses and none on dolutegravir
- Assumptions about CSF dynamics (and CNS dynamics)

Conclusions
- We observed consistent evidence of CNS toxicities associated with both efavirenz and nevirapine but not with darunavir's exposure.
- Poorer cognitive function associated with greater exposure to efavirenz and nevirapine may be secondary to intoxicating effects and/or structural neuroimaging abnormalities.
- Future work assessing the clinical implications of these findings with longitudinal data are justified as well as assessing associations with newer third agents, including integrase strand transfer inhibitors.

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References