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 assayed using **ultra high-performance liquid chromatography** (HPLC) 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:

$$C_{min} = C_{measured} * e^{-(0.693/T_{1/2})*(\Delta T)}$$

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

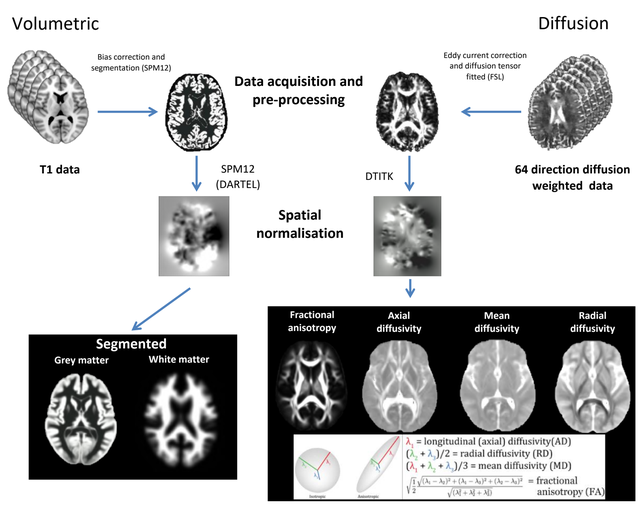
Cognitive function testing

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:



Methods cont...

Statistics

- Relationships 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 +/- height, 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.

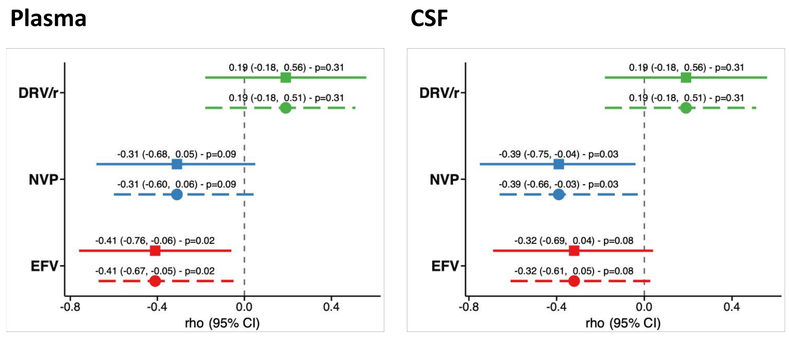
Results

Table 1. Baseline demographics

	Efavirenz (n=30)	Nevirapine (n=30)	Darunavir/r (n=31)
Gender			
Male	30 (100%)	28 (93.3%)	29 (93.5%)
Female	0 (0%)	2 (6.7%)	2 (6.5%)
Age (years)	59 (53, 63)	55 (50, 61)	55 (50, 63)
Ethnicity			
Black-African	3 (10.0%)	5 (17.2%)	1 (3.2%)
White	27 (90.0%)	24 (82.8%)	30 (96.8%)
HIV duration (years)	12.9 (10.2, 17.8)	16.3 (13.8, 20.3)	18.4 (9.5, 23.1)
ART duration (years)	11.8 (8.3, 15.5)	15.0 (10.1, 16.8)	15.0 (7.2, 18.3)
Third agent duration (years)	9.2 (5.2-11.4)	11.5 (8.3-14.3)	3.5 (1.5-5.2)
Nadir CD4 (cells/μL)	150 (70, 200)	215 (80, 270)	150 (50, 230)
BMI (kg/m²)	24.2 (22.7, 27.3)	24.8 (22.8, 27.4)	24.7 (21.7, 27.2)

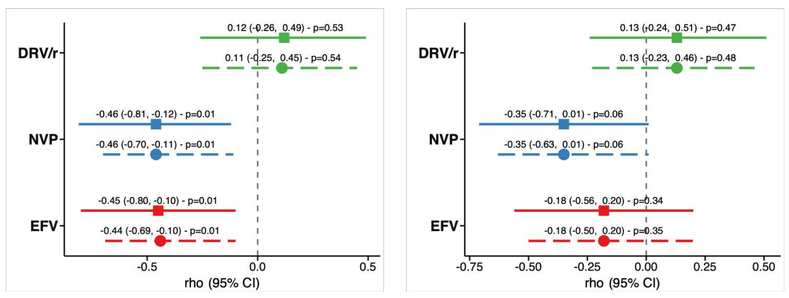
Plasma and CSF concentrations of efavirenz and nevirapine were both negatively associated with cognitive T-scores, particularly in the domain of attention (plasma nevirapine rho_{adj} = -0.54, p<0.01, Figures 1 & 2), whereas there was **no association between darunavir exposure and cognitive function**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

Figure 1. Global cognitive function by drug concentration



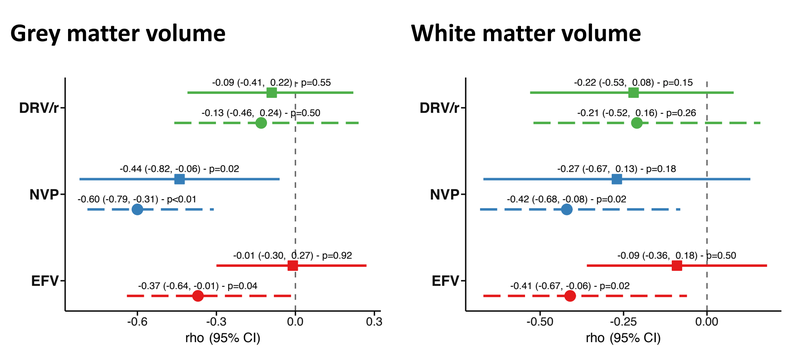
Dashed lines indicate unadjusted data. Solid lines adjusted for age, level of education and ethnicity.

Figure 2. Selected cognitive domains by plasma exposure



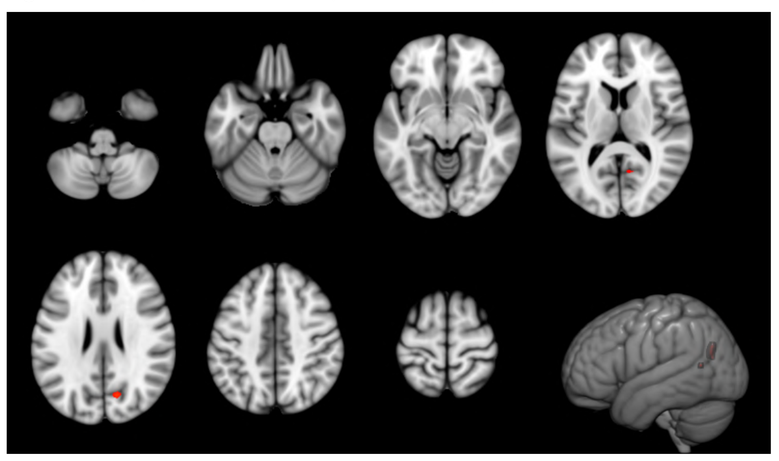
Dashed lines indicate unadjusted data. Solid lines adjusted for age, level of education and ethnicity.

Figure 3. Brain volumetrics by plasma exposure



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

Figure 4. Grey matter volume by plasma nevirapine exposure



Red-yellow areas depict regions of grey matter volume negatively correlated with plasma nevirapine concentration coloured by the t-statistic - corrected for multiple comparisons (TFCE). Adjusted for age, intracranial volume and scanner. Overlaid on MNI 152 T1 brain image (greyscale).

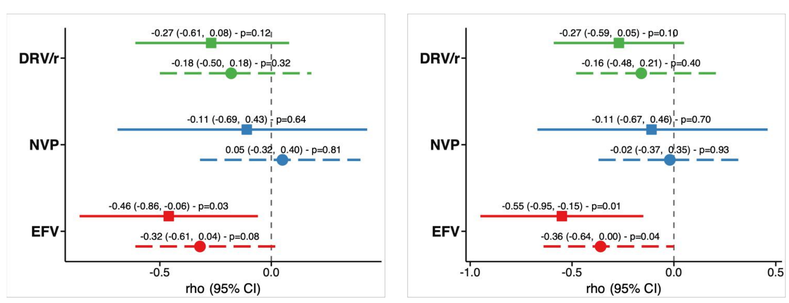
Results cont…

Greater plasma nevirapine exposure was associated with reduced grey matter volume (rho_{adj} = -0.44, p=0.02, Figure 3). Voxelwise 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: rho_{adj}= -0.46, p=0.03; right: rho_{adj}= -0.55, p=0.01, Figure 5). Plasma and CSF efavirenz exposure were associated with white matter microstructural abnormalities (axial diffusivity: plasma rho_{adj} = -0.33, p=0.05, CSF rho_{adj} = -0.44, p=0.01, Figures 6 & 7).

Darunavir exposure was not associated with any neuroimaging abnormalities (p>0.1 for all).

Figure 5. Cortical thickness by plasma exposure

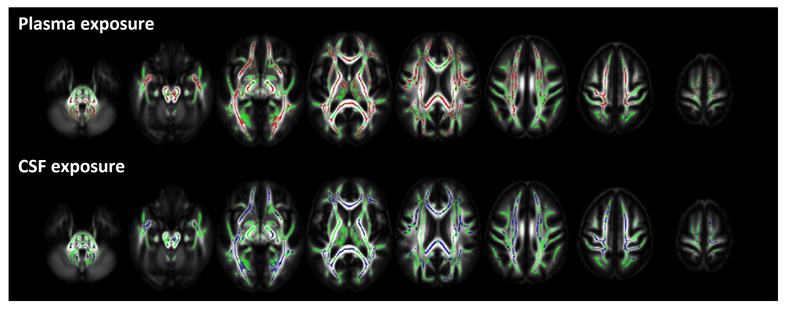


Dashed lines indicate unadjusted data. Solid lines adjusted for age, intracranial volume and scanner.

Figure 6. Diffusion imaging - CSF exposure

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

Figure 7. White matter fractional anisotropy by efavirenz exposure



White matter tract-based spatial statistics of patients receiving efavirenz. Red-yellow areas depict regions of white matter fractional anisotropy positively correlated with plasma and CSF efavirenz concentrations - corrected for multiple comparisons and adjusted for age, intracranial volume and scanner. Significant differences overlaid on the white matter skeleton (green) and the mean fractional anisotropy image (greyscale).

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/r exposure.
- Poorer cognitive function associated with greater exposure to efavirenz and nevirapine may be secondary to intoxicant 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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