HIV suppression and changes in markers in CSF from patients randomly switched to DTG + 3TC

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Background

A major concern of dual therapy is the potential lower efficacy in viral reservoirs, especially in the central nervous system (CNS). The aim of this study was to evaluate the maintenance of HIV viral suppression as well as changes in neuronal injury and inflammatory markers in cerebrospinal fluid (CSF) in a group of patients receiving 3 drug regimen and after switching to Dolutegravir plus Lamivudine dual therapy.

Objectives

-To assess changes in HIV RNA in CSF after treatment switch from 3 drug-regimen to 2 drug therapy.

-To assess changes in inflammatory and neuronal damage markers in CSF.

-To assess Dolutegravir (total and unbound) concentrations in CSF.

Methods

Prospective, single arm study. HIV+ virologically suppressed patients on triple therapy were randomly selected to switch to Dolutegravir 50 mg + Lamivudine 300 mg once daily within the DOLAM Study (EUDRACT 2015-000274-35). A group of pts enrolled in two centers consented to participate in the Neuro-Substudy. CSF and blood samples were taken at BL and week 48. HIV-1 RNA in plasma and CSF were determined by real-time PCR. Neurofilament light chain (NFL) as well as inflammatory markers (sTREM-2, and YKL-40) were measured in CSF by ELISA.

NFL *is a major structural component of myelinated axons is essential to maintain axonal caliber and to facilitate effective nerve conduction. CSF concentrations of NFL provide a sensitive marker of CNS injury in a number of neurological diseases, including HIV-related neuronal injury.*

TREM2 *is a receptor glycoprotein that belongs to the immunoglobulinsuperfamily. In the brain, TREM2 is expressed exclusively by myeloid cells, including microglia and macrophages. It is more specific for activation of microglia and macrophages than neopterin, since the secreted form of the receptor is exclusively expressed on myeloid cells such as macrophages and microglia, but not on astrocytes.*

YKL40*, represents the activation of different cell types, especially astrocytes.*

DOLAM Neuro Substudy

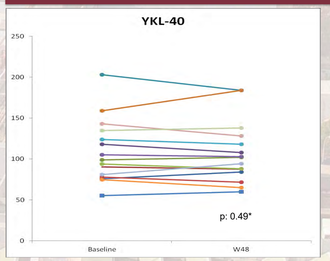


RESULTS

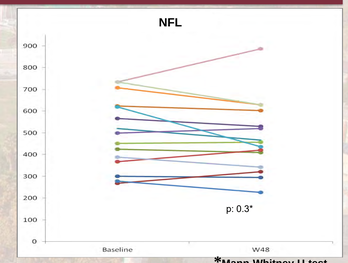
- 15 patients had baseline and week 48 plasma and CSF samples.
- 80% male.
- Median age was 46 years
- Current CD4 count 746 (356) cells/µl, and nadir CD4 was 302 (165) cells/µl.
- Baseline HIV viral load (Median IQR): 114000 (64248) copies/ml
- Most patients switched from a NNRTI based regimen (60%) followed by INSTI (26.7%).

Variable	Baseline (Median)	Week 48(Median)
Plasma HIV RNA (copies/ml)	undetectable	undetectable
CSF HIV RNA (copies/ml)	undetectable	undetectable
CSF proteins (g/L)	0,35 (0,2-0,6)	0,4 (0,2-0,6)
CSF cells	<0.001 × 109/L	<0.001 × 109/L
CSF (mg/L)/serum albumin (g/L) index	-	6,54 (Normal < 9)

CSF Inflammation markers | **Neuronal damage marker**

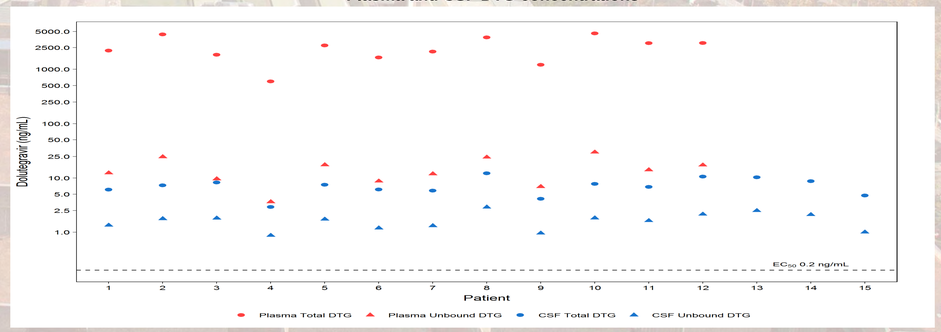






*Mann-Whitney U-test

Plasma and CSF DTG concentrations



Patients 13, 14 and 15 had no available plasma samples for DTG concentrations. DTG concentration values are adapted to a logarithmic (Log10) scale.

DOLAM Neuro Study Group
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CONCLUSIONS

Treatment simplification from triple therapy to Dolutegravir+Lamivudine resulted in no changes in viral suppression in plasma and CSF. No evidence of neuronal damage or changes in inflammatory markers were found in CSF after 48 weeks of dual therapy. Unbound CSF DTG concentrations were only 23% of total CSF concentrations, however unbound DTG CSF exceeded the EC50 (0.2 ng/mL) by 8 fold.

Our data suggests that dual therapy with Dolutegravir+Lamivudine maintains viral control within the CNS reservoir.