

Efavirenz and Emtricitabine Concentrations Consistently Exceed Wild-type IC_{50} in Cerebrospinal Fluid: CHARTER Findings

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OBJECTIVE

This study's objective was to determine concentrations of efavirenz and emtricitabine in cerebrospinal fluid (CSF).

BACKGROUND AND SIGNIFICANCE

Persistent HIV replication with subtherapeutic concentrations of antiretrovirals (ARVs) in the nervous system may put patients at risk for HIV-Associated Neurocognitive Disorders (HAND).

Two small published studies of efavirenz (EFV) in cerebrospinal fluid (CSF) showed conflicting results, with detectable concentrations in one study (n=10)¹, but undetectable CSF EFV in the other (n=11)².

Emtricitabine (FTC) is a widely-used nucleoside HIV reverse transcriptase inhibitor whose penetration into cerebrospinal fluid (CSF) has not been reported. FTC is similar to lamivudine, which has moderate penetration into CSF (CSF/plasma concentration ratios ~ 0.1 – 0.25)²⁻⁴.

HYPOTHESES

1. Efavirenz concentrations in the CSF will be 0.5% of the plasma concentrations, corresponding to the unbound concentrations of efavirenz in plasma.
2. Emtricitabine concentrations in the CSF will be 10 – 25% of the plasma concentrations, similar to lamivudine.

METHODS

- CHARTER is an on-going, multi-center, observational study to determine the impact of ARV therapy on HIV-Associated Neurocognitive Disorders.
- Single random plasma and CSF samples were drawn within an hour of each other from subjects taking standard doses of emtricitabine (March 2004 – April 2006) or efavirenz (September 2003 – July 2007).

Analysis

- Efavirenz plasma samples were assayed by HPLC (detection limit = 39 ng/mL).
- For EFV CSF samples, after extraction with methyl tert-butyl ether, the lower limit of detection decreased to < 0.1 ng/mL. Without this high degree of assay sensitivity, EFV could not be measured in CSF.
- Emtricitabine plasma and CSF samples were assayed by LC/MS (detection limit = 1 ng/mL).
- Data were analyzed by drug with summary statistics and linear regression.

RESULTS

Table 1. Participants

Characteristic ^a	Efavirenz (n=80)	Emtricitabine (n=21)
DEMOGRAPHICS		
Age (years)	44 ± 8	45 ± 8
Males (%) ^b	60 (75%)	17 (81%)
Weight (kg)	79 ± 15	79 ± 13
Height (cm)	173 ± 10	176 ± 8
Months on Current Regimen	14 ± 19	8 ± 8
LABORATORY TESTS		
Serum Creatinine (mg/dL)	0.9 ± 0.3	1.1 ± 0.4
Albumin (g/dL)	4.3 ± 0.5	4.5 ± 0.5
CD4+ (cells/mm ³)	484 ± 305	371 ± 201
CSF HIV RNA (log ₁₀ copies/mL)	1.9 ± 0.5	1.8 ± 0.5
CSF HIV RNA > 50 copies/mL ^b	13 (16%)	3 (14%)
Plasma HIV RNA (log ₁₀ copies/mL)	2.2 ± 1	2.2 ± 0.8
Plasma HIV RNA > 50 copies/mL ^b	28 (35%)	9 (43%)

^a Mean ± standard deviation unless otherwise noted.

^b n (%)

Efavirenz

- Concentrations are shown and listed in Figures 1-4 and Tables 2 and 3.
- 11 plasma samples were < 39 ng/mL.
- The CSF/wild-type IC_{50} (0.51 ng/mL)⁵ ratio was 26 (IQR 8 – 41). Two CSF concentrations (2.6%) were below the IC_{50} .
- Plasma concentrations were weakly correlated with CSF concentrations ($r^2=0.22$).

Table 2. Efavirenz Concentrations

	Plasma	CSF	CSF/Plasma Ratio
Number of samples	80	80	69
Median EFV (ng/mL)	2145	13.9	0.005
IQR (ng/mL)	1384 – 4423	4.1 – 21.2	0.0026 – 0.0076
Range (ng/mL)	< 39 – 12249	0.2 – 51.8	0.0003 – 0.0275
Time Post Dose (hrs)	12.5 ± 5.4	12.5 ± 5.4	

Emtricitabine

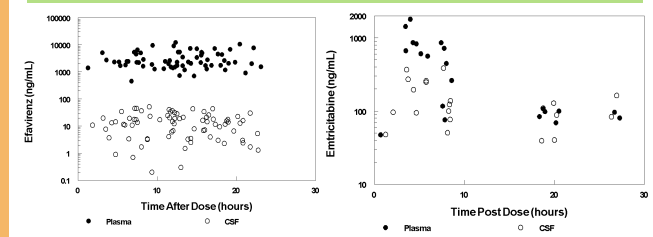
- The CSF/wild-type IC_{50} (70 ng/mL)⁵ ratio was 1.6 (IQR 1.2 – 2.8).
- CSF/plasma ratios correlated with time post dose ($r^2=0.34$).
 > Median ratios drawn < 12 and > 12 hours post dose were 0.36 (IQR 0.21 – 0.45; n=14) and 0.89 (IQR 0.72 – 1.34; n=7), respectively.

Table 3. Emtricitabine Concentrations

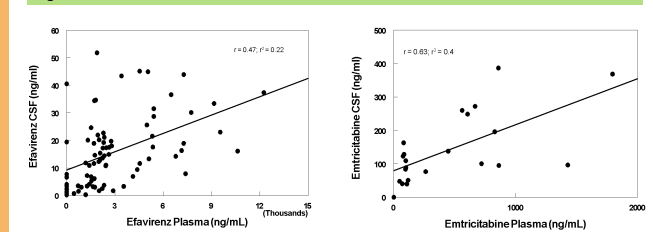
	Plasma	CSF	CSF/Plasma Ratio
Number of samples	21	21	21
Median FTC (ng/mL)	261	109	0.43
IQR (ng/mL)	96 – 720	84 – 196	0.29 – 0.89
Range (ng/mL)	47 – 1795	39 – 386	0.07 – 2.02
Time Post Dose (hrs)	11 ± 8	11 ± 8	

FIGURES

Figures 1 and 2. Plasma and CSF Concentrations versus Time After Dose



Figures 3 and 4. Plasma Concentrations versus CSF Concentrations



CONCLUSIONS

- Efavirenz CSF concentrations were only 0.5% of plasma concentrations, consistent with the unbound fraction in blood and suggesting limited active transport out of the CSF.
- Emtricitabine CSF/plasma ratios ranged from 36% to nearly equal over the dose interval.
 > Plasma concentrations have higher peaks and a greater decline over 24 hours, while CSF concentrations remain relatively stable.
- Concentrations of emtricitabine and efavirenz in CSF exceed the wild-type IC_{50} in most individuals and may inhibit HIV replication in the nervous system.

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