Poster 444

CROI 2015
Seattle, WA
February 23-26, 2015

Neurocognitive Decline is Associated with Antiretroviral Concentrations in Cerebral Spinal Fluid and Blood

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Abstract

Background: Therapeutic antiretroviral therapy (ART) drug concentrations in the central nervous system are likely important for controlling HIV replication in the brain although their relationship to neurocognitive impairment (NCI) remains controversial. The objective was to investigate associations between drug concentrations with incident NCI in a randomized clinical trial comparing two regimens, tenofovir-lamivudine-efavirenz (TDF-3TC-EFV, T3E) and zidovudine-lamivudine-nevirapine (ZDV-3TC-NVP, Z3N), in China.
Methods: A total of 23 HIV+ adults were evaluated in a nested case-control substudy: 11 who developed NCI (decliners) after 48 weeks of ART and 12 who did not (non-decliners). Cases and controls were matched by sex, education, ethnicity, and baseline NC performance (but not treatment arm). Plasma and CSF were sampled at a median of 12.4 hours post-dose. Drug concentrations were measured by LC/MS/MS.
Results: Subjects were all Han Chinese men with a mean age of 32.9 years. All subjects had plasma HIV RNA levels below 50 c/mL. Similar to the findings of the parent trial (presented in a separate abstract), decliners were more frequently randomized to T3E (58.3% vs. 36.4%, RR 1.53). Decliners had markedly higher plasma TDF concentrations (d=2.2, p=0.004) and lower TDF CSF-to-Plasma Ratios (CPRs, d=1.3, p=0.028) than non-decliners with a trend towards higher EFV CPRs (d=1.0, p=0.09). Recursive partitioning identified that none of the 5 subjects who had plasma TDF concentrations < 33.5 ng/mL were decliners while all 6 subjects who had plasma TDF concentrations ≥ 33.5 ng/mL and EFV CPRs ≥ 0.46% were (p=0.0004).
Conclusions: In this small, nested case-control study, incident NCI was associated with TDF and EFV drug concentrations. The observed association with low TDF CPRs may reflect suboptimal antiviral efficacy in the CNS while the association with high EFV CPRs may reflect neurotoxicity. Together, the observed CPR associations may indicate disturbances in the permeability and drug transport properties of the blood-brain barrier that predispose to development of HIV-associated NCI.

Background and Objective

- HIV neurocognitive Impairment (NCI) is prevalent despite the use of combination antiretroviral therapy.
- Therapeutic antiretroviral therapy (ART) drug concentrations in the central nervous system (CNS) are likely important for controlling HIV replication in the brain.
  - Prolonged suppression of viral replication was related to drug exposure of ZDV, 3TC, and NVP in CSF. (van Praag RM, et al., 2002)
  - Tenofovir concentrations in the CSF are 5% of plasma, suggesting limited transfer into the CSF, which may not effectively inhibit viral replication in the CNS. EFV concentrations in the CSF exceed the wild-type IC50 suggesting therapeutic concentrations in brain tissue. (Best BM, et al., 2011, 2012)
- The relationship between CNS penetration effectiveness (CPE) of ART and improvement of NCI remains controversial.
  - A positive relationship between NCI improvement and CPE was identified in well controlled patients. (Ciccarelli N, et al., 2013)
  - HIV-CAUSAL reported an increased risk of HIV-associated dementia in patients receiving ART with high CPE. (Caniglia EC, et al., 2014)
- The objective was to investigate associations between drug concentrations with incident NCI in a randomized clinical trial comparing ART regimens, tenofovir-lamivudine-efavirenz (TDF-3TC-EFV, T3E) and zidovudine-lamivudine-nevirapine (ZDV-3TC-NVP, Z3N).
  - T3E and Z3N, available as fixed dose combinations, are recommended by WHO as the first-line treatment, and commonly used in resource-limited settings. (Maek-a-Nantawat W, et al., 2012)

Results

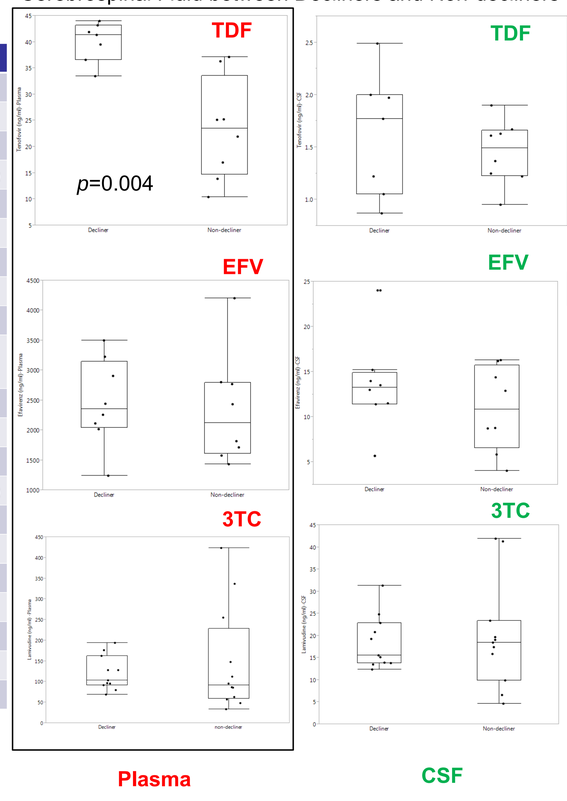
- A total of 30 Chinese male patients were enrolled and 23 (77%) provided blood and CSF samples for further evaluation. Table 1 summarized the clinical and demographic characteristics of NCI (decliners) and control (non-decliners).
- Drug concentrations in CSF and plasma were summarized in Table 2 and Figure 1.
- No statistically significant differences in EFV or 3TC (ng/ml) were noted in plasma, CSF or CSF-plasma ratio (CPR) between two groups. Decliners had a trend towards higher EFV CPRs (d=1.0, p=0.09).
- Decliners had markedly higher plasma TDF concentrations (d=2.2, p=0.004) and lower TDF CPR (d=1.3, p=0.028) than non-decliners.
- TDF CPR was correlated with 48-week GDS (r=-0.550, p=0.034) and change of GDS (r=0.611, p=0.015, Figure 2).
- Recursive partitioning identified that none of the 5 subjects who had plasma TDF concentrations < 33.5 ng/mL were decliners while all 6 subjects who had plasma TDF concentrations ≥ 33.5 ng/mL and EFV CPRs ≥ 0.46% were (p=0.0004, Figure 3).

Table 1 Median (IRQ)	Decliners	Non-Decliners
n	11	12
Age, yr	35 (26-40)	32 (28-37)
Education, yr	9 (6-12)	11 (9-13)
GDS baseline	0.125 (0-0.375)	0.125 (0-0.250)
GDS 48-week* $p<0.001$	0.875 (0.563-1)	0.0625 (0-0.281)
HIV RNA baseline, log_{10} copies/ml	4.4 (3.8-5.0)	4.4 (4.2-4.6)
CD4+ baseline, cells/mm^3	244 (216-323)	219 (168-255)
CD4+ 48-week, cells/mm^3	395 (370-490)	348 (297-400)
T3E, n (%)	7 (64)	7 (58)
Z3N, n (%)	2 (18)	3 (25)
HBcAb, n (%)	4 (36)	8 (67)

Table 2		Decliners	Non-Decliners
Efavirenz	**Plasma**		
	Median (ng/ml)	2350	2125
	Interquartile range	2088-2990	1678-2778
	Time post dose (hr)	12.0 (11.6-23.0)	13.0 (10.3-16.8)
	CSF		
	Median (ng/ml)	13.25	10.84
	Interquartile range	11.48-14.30	8.01-14.85
	CSF/Plasma Ratio[1]		
	Median (ng/ml)	0.00565	0.00450
	Interquartile range	0.00505-0.00605	0.00358-0.00550
Tenofovir	**Plasma[2]**		
	Median (ng/ml)	41.30	23.50
	Interquartile range	38.05-42.55	16.23-27.98
	Time post dose (hr)	12.0 (11.6-23.0)	13.0 (10.3-16.8)
	CSF		
	Median (ng/ml)	1.770	1.490
	Interquartile range	1.135-1.985	1.243-1.640
	CSF/Plasma Ratio[3]		
	Median (ng/ml)	0.0430	0.061
	Interquartile range	0.0315-0.0455	0.0483-0.0963

[1] $p=0.09$, [2] $p=0.004$, [3] $p=0.028$

Figure 1 Antiretroviral Drug Concentrations in Plasma and Cerebrospinal Fluid between Decliners and Non-decliners



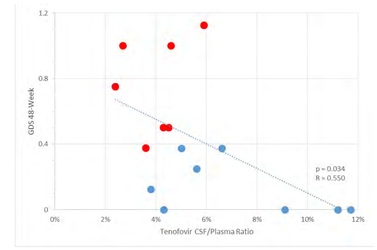


Figure 2 Correlation between Tenofovir CSF/Plasma Ratio and Global Deficit Score (GDS) 48-Week (Decliners-red, Non-Decliners-blue)

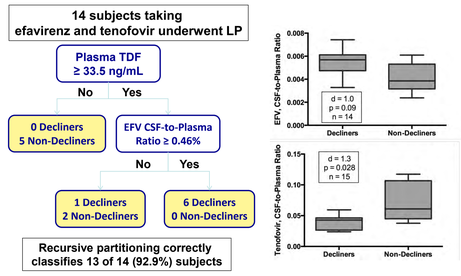


Figure 3 Cases and Controls Differed by CSF-Plasma Ratios of EFV and TDF

Summary and Conclusions

- Incident NCI was associated with TDF and EFV drug concentrations in plasma and CSF.
- The observed association of NCI with low TDF CSF/Plasma Ratio may reflect suboptimal antiretroviral efficacy in the CNS while the association with high EFV CPR may reflect neurotoxicity.
- Together, the observed CPR associations may indicate disturbances in the permeability and drug transport properties of the blood-brain barrier that predispose to the development of HIV-associated NCI.

Methods

- A total of 30 HIV+ Chinese male adults were enrolled and 23 provided samples for further evaluation: 11 who developed NCI (decliners) after 48 weeks of ART and 12 who did not (non-decliners).
- Cases and controls were matched by sex, education, and baseline NC performance (but not treatment arm).
- Plasma and CSF were sampled at a median of 12.4 hours post-dose. Drug concentrations and measured by LC/MS/MS.

Acknowledgements

The authors gratefully acknowledge the volunteers, research staff, and support from the National Institute of Mental Health (R01 MH092225, K08 MH098794, K24 MH097673) as well as the National Science Foundation in China to support the Clinical Pharmacology Supplement Project.