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Antiretroviral Distribution in Cerebrospinal Fluid and Viral Resistance in HIV-Infected Patients

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ABSTRACT

Background: The central nervous system is a potential reservoir of HIV. Differences exist in CSF drug penetration between antiretrovirals (ARVs), which may influence the development of resistant virus. CSF concentrations have been described for some ARVs but not for multiple drugs in a large patient population.

Methods: Patients receiving HAART had concomitant CSF and plasma samples collected. Samples were analyzed for plasma concentrations using LC/MS/MS. In patients with detectable virus, virtual Phenotype was performed on both CSF and plasma.

Results: Sixty-three patients (median age 39 yrs, 76% male, 25% IDU, 59% heterosexual; 62% previous AIDS, 78% neurologic diseases) had paired CSF/plasma samples collected at a median of 8 wks from starting last ARV regimen (IQR 3-25). At time of sample collection median CD4 count, HIV-1 RNA in plasma and CSF were 111/ml (53-275), 3.34 $\log_{10}$/ml (2.23-4.84), and 2.00 $\log_{10}$/ml (1.90-3.11), respectively. Samples included 356 drug concentrations (178 each in plasma and CSF). CSF concentrations were undetectable for didanosine, efavirenz, and nelfinavir. Only 1 of 8 samples for ritonavir had detectable CSF levels. CSF concentrations were highest for nevirapine with a median CSF/plasma ratio of 0.63 (n=16), followed by lamivudine (0.23; n=55), stavudine (0.20; n=31), and indinavir (0.11; n=18). Virtual phenotype in CSF and plasma was available for 40 patients. In 18 patients, differences in fold-change resistance between the CSF and the plasma virus were noted for at least one drug. Factors associated with having differences in fold-change resistance were number of drug exposures (*P*=0.02) and presence of neurologic disease (*P*=0.05). A significant association was found between duration of therapy and fold-change resistance in CSF (*P* at Spearman's=0.02) and plasma (*P*=0.002).

Conclusions: Differences in CSF penetration exist between ARVs, with a number of drugs having limited CSF concentrations. Different resistance profiles exist in CSF isolates compared to those in plasma. Treatment decisions for CNS manifestations may require knowledge of drug penetration and susceptibility of HIV in CSF.

INTRODUCTION

Reservoirs of HIV infection may harbor viruses with resistance patterns that are different than those observed in the plasma. The central nervous system is one such reservoir in which the blood-brain barrier is effective in reducing antiretroviral drug delivery to the brain for some agents. The decreased ability of some drugs to achieve adequate concentrations in the CSF and the resistance prifile in the CSF may need to be considered if CNS manifestations are present.

STUDY METHODS

- All consecutive HIV-1 infected patients undergoing lumbar puncture between March 1999 and June 2000 because of neurological signs and symptoms or CNS staging of non-Hodgkins lymphoma were included
- Concomitant CSF and plasma samples were collected at steady-state (median 8 weeks from starting last ARV regimen)
- CSF and plasma concentrations were determined by a validated LC/MS/MS method
- CSF samples were collected according to a standardized protocol: 8 ml of CSF were obtained from each patient, and a defined panel of diagnostic examinations was carried out. At the same time, a blood sample was drawn each patient for virological and immunological assessment.
- CSF and plasma viral load determined by Nuclisens HIV-1 QT assay
- Patients with detectable virus had a VirtualPhenotype' performed on both CSF and plasma

RESULTS

Demographic Data

- Sixty-three HIV-infected patients receiving HAART
- Median age: 39 years (IQR 35-43)
- Gender: 76% male
- HIV risk factor: 25% IVDU, 59% heterosexual
- Previous AIDS diagnosis: 62%
- Neurologic disease: 78%

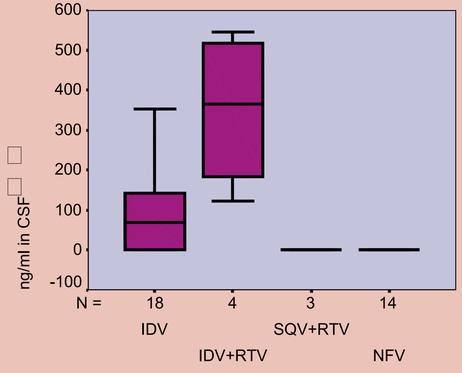
Table 1
CD4 and viral load data at time of sample collection

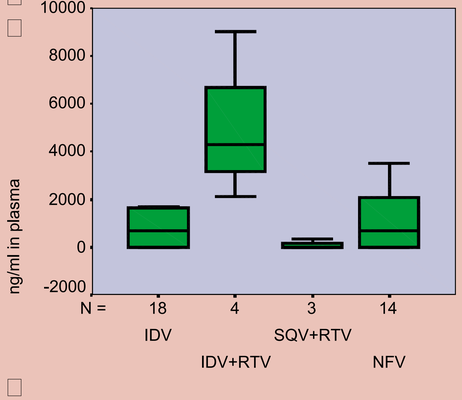
Parameter	Median (range)
CD4 (cells / l)	111 (53-275)
Plasma viral load (log10/ml)	3.34 (2.23-4.84)
CSF viral load (log10/ml)	2.00 (1.90-3.11)

Table 1
CSF/Plasma ratios

Drug	N	Median CSF/Plasma ratio	Range
Abacavir	4	0.039	0 - 2.36
Didanosine	5	0.0	0.0 - 0.0
Efavirenz	11	0.0	0.0 - 0.0
Indinavir	18	0.111	0.0 - 0.47
Lamivudine	55	0.229	0.0 - 4.90
Nelfinavir	9	0.0	0.0 - 0.0
Nevirapine	16	0.626	0.41 - 0.77
Ritonavir	8	0.0	0.0 - 0.52
Stavudine	31	0.204	0.0 - 0.204
Zidovudine	18	0.02	0.0 - 6.74

Figures 1 and 2
Protease inhibitor concentrations in CSF and plasma





RESISTANCE TESTING IN CSF AND PLASMA

- In 40 patients with paired Virtual Phenotypes in CSF and plasma, 18 patients had a different fold change for at least one drug
- Fold change differences were most common for:
  - Efavirenz: 11/18
  - Nevirapine 9/18
  - Nelfinavir and stavudine: 7/18
  - Indinavir, amprenavir, ritonavir: 5/18

Table 2
Predictors of phenotypic difference between CSF/Plasma paired samples

Parameter	No fold change differences between CSF and plasma (n=22)	At least one fold-change difference between CSF and plasma (n=18)	P
CSF log10 HIV-1 RNA	5.38	5.25	0.73
Plasma log10 HIV-1 RNA	5.48	5.17	0.34
Plasma/CSF ratio	1.29 1.31	0.88	
ART exposure (%)	36	72	0.03
Years of ART	1.18	1.43	0.73
Number of drugs	4.0	5.8	0.02
Days of PI	170	462	0.003
Days of NRTI	433	578	0.58
Neurologic disease (%)	68	94	0.05

CONCLUSIONS

- Differences in CSF penetration exist between antiretrovirals with a number of drugs having limited CSF concentrations.
- Highest CSF concentrations were observed for nevirapine, indinavir, stavudine, and lamivudine
- Different resistance profiles for at least one drug in CSF isolates compared to those in plasma were observed in 45% of patients
- Treatment decisions for CNS manifestations may require knowledge of drug penetration and susceptibility of HIV in CSF