

NRTIs more than boosted PIs exposure enhances virological effective control in cerebrospinal fluid of HIV-1 infected patients affected by neurological disorders

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RESULTS: GENERAL CHARACTERISTICS

Characteristics	IRINA patients (N=1360)	Study Patients (N=363)
Male gender	988 (72.6%)	281 (77.4%)
Age, median years	40 (IQR, 36-45)	41 (IQR, 36-46)
HIV transmission route: IDU	587 (43.2%)	157 (43.3%)
MSM	161 (11.8%)	46 (12.7%)
Heterosexual	432 (31.8%)	111 (30.5%)
Other/unknown	180 (13.2%)	49 (13.5%)
Previous AIDS defining event	430 (31.6%)	109 (30.0%)
CD4 cell/ml, median	63 (IQR, 21-160)	71 (IQR, 22-162)
Plasma HIV-1 RNA log ₁₀ copies/ml, median	4.95 (IQR, 3.91-4.48)	4.98 (IQR, 3.81-5.44)
CSF HIV-1 RNA log ₁₀ copies/ml, median	3.65 (IQR, 2.11-4.81)	3.63 (IQR, 2.17-4.83)
Undetectable CSF HIV-RNA	124 (9.1%)	60 (16.5%)
Experienced	690 (50.8%)	182 (50.1%)
Experienced on ARV at neurological diagnosis	449 (33.0%)	120 (33.1%)
Months on HAART, median	16 (IQR, 3-40)	16 (IQR, 5-41)
>6 months on HAART before diagnosis	418 (30.7%)	118 (32.5%)
At diagnosis pts treated with:		
1 neuroactive drug	78 (5.7%)	16 (4.4%)
2 neuroactive drugs	183 (13.5%)	49 (13.5%)
3-4 neuroactive drugs	179 (13.1%)	55 (15.2%)
Neurological disorders: HIV encephalopathy (HIVE)	278 (20.4%)	103 (28.4%)
PML	168 (12.4%)	56 (15.4%)
encephalopathies of unknown origin (EUO)	84 (6.2%)	37 (10.2%)
Toxoplasmic encephalitis (TE)	383 (28.2%)	36 (9.9%)
cryptococcosis (CM)	135 (9.9%)	35 (9.6%)
cerebral lymphoma (PCNSL)	51 (3.8%)	18 (5.0%)
TB	30 (2.2%)	10 (2.8%)
other diseases	163 (12.0%)	68 (18.7%)

Factors predictive of undetectable CSF HIV-1 RNA. Adjusted logistic regression model

Factors	Crude OR (95%CI)	P-value	MODEL 1		MODEL 2		MODEL 3	
			Adjusted OR (95%CI)	P-value	Adjusted OR (95%CI)	P-value	Adjusted OR (95%CI)	P-value
Age (10 years increase)	1.00 (0.74-1.34)	n.s.	0.86 (0.59-1.30)	n.s.	0.85 (0.56-1.30)	n.s.	0.78 (0.54-1.18)	n.s.
Male gender	1.35 (0.85-2.08)	n.s.	1.38 (0.84-2.08)	n.s.	1.78 (0.89-3.58)	n.s.	1.84 (0.74-4.62)	n.s.
HIV transmission route: IDU	1.00		1.00		1.00		1.00	
MSM	0.64 (0.23-1.79)	n.s.	0.33 (0.06-1.26)	n.s.	0.34 (0.09-1.25)	n.s.	0.37 (0.10-1.31)	n.s.
Heterosexual	1.38 (0.74-2.58)	n.s.	1.28 (0.65-2.58)	n.s.	1.92 (0.78-4.74)	n.s.	2.15 (0.89-5.18)	n.s.
Other/unknown	0.88 (0.36-2.18)	n.s.	1.55 (0.44-5.31)	n.s.	1.30 (0.39-4.93)	n.s.	1.19 (0.36-3.93)	n.s.
Plasma HIV-RNA (log ₁₀ copies/ml)	0.57 (0.47-0.68)	<0.01	0.71 (0.52-0.97)	0.03	0.70 (0.51-0.96)	0.03	0.68 (0.51-0.90)	0.007
CD4 at diagnosis (50 cells increase)	1.05 (0.97-1.14)	n.s.	0.97 (0.86-1.11)	n.s.	0.96 (0.85-1.09)	n.s.	0.96 (0.86-1.08)	n.s.
Drugs at diagnosis:								
AZT	3.67 (1.83-7.08)	<0.01	1.83 (0.47-6.68)	n.s.				
DDI	2.30 (0.93-6.04)	<0.01	1.54 (0.34-7.0)	n.s.				
DAT	3.52 (1.63-7.63)	<0.01	1.33 (0.35-4.8)	n.s.				
ATC	4.53 (1.54-13.10)	<0.01	1.73 (0.42-7.07)	n.s.				
BVC	1.17 (0.32-4.25)	n.s.	0.24 (0.01-0.85)	n.s.				
NVP	1.19 (1.07-1.28)	n.s.	5.18 (1.16-23.44)	0.03				
EFV	7.38 (3.21-16.95)	<0.01	5.59 (1.29-24.27)	0.02				
RTV	3.20 (1.21-8.51)	0.02	2.24 (0.57-8.73)	n.s.				
IDV	2.22 (0.88-5.62)	n.s.	1.9 (2.42-4.13)	n.s.				
NFV	1.66 (0.63-4.35)	n.s.	0.80 (0.19-3.41)	n.s.				
LPV	2.21 (0.75-6.51)	n.s.	1.02 (1.09-13.2)	n.s.				
Drug classes:								
NO ARV	1.00		1.00		1.00		1.00	
PI	14.32 (6.13-33.44)	<0.01	1.42 (0.47-4.71)	<0.01	12.46 (4.47-41)	<0.01	12.46 (4.47-41)	<0.01
PI+NNRTI	3.50 (1.54-7.96)	<0.01	2.48 (0.75-8.22)	n.s.	2.48 (0.75-8.22)	n.s.	2.48 (0.75-8.22)	n.s.
PI+NNRTI+boosted PI	3.22 (0.83-12.53)	<0.01	1.25 (0.09-17.10)	n.s.	1.25 (0.09-17.10)	n.s.	1.25 (0.09-17.10)	n.s.
PI+NNRTI	7.07 (3.46-14.47)	<0.01	10.42 (1.59-68.46)	0.02	10.42 (1.59-68.46)	0.02	10.42 (1.59-68.46)	0.02
Number of neuroactive drugs:								
0	1.00		1.00		1.00		1.00	
1	3.22 (0.83-12.52)	n.s.	0.47 (0.27-0.83)	<0.01	0.36 (0.16-0.88)	0.02	0.38 (0.16-0.88)	0.03
2	6.07 (2.87-12.85)	<0.01	2.22 (0.92-5.34)	n.s.	2.18 (0.83-5.16)	n.s.	2.00 (0.86-4.64)	n.s.
3-4	7.07 (3.46-14.47)	<0.01	1.12 (0.41-3.10)	n.s.	1.12 (0.41-3.10)	n.s.	0.84 (0.32-2.23)	n.s.
>6 months of HAART before diagnosis	0.47 (0.27-0.83)	<0.01	0.36 (0.16-0.88)	0.02	0.38 (0.16-0.88)	0.03	0.43 (0.19-1.01)	0.052
Cognitive symptoms	1.13 (0.60-2.11)	n.s.	2.22 (0.92-5.34)	n.s.	2.18 (0.83-5.16)	n.s.	2.00 (0.86-4.64)	n.s.
Abnormal mental status	1.13 (0.60-2.11)	n.s.	2.22 (0.92-5.34)	n.s.	2.18 (0.83-5.16)	n.s.	2.00 (0.86-4.64)	n.s.
Cerebral atrophy	1.22 (0.69-2.14)	n.s.	1.54 (0.63-3.73)	n.s.	1.49 (0.63-3.55)	n.s.	1.32 (0.57-3.08)	n.s.
Neurological diagnosis:								
HIVE	1.00		1.00		1.00		1.00	
PML	1.85 (0.76-4.53)	n.s.	1.41 (0.44-4.49)	n.s.	1.41 (0.44-4.50)	n.s.	1.34 (0.44-4.17)	n.s.
TE	1.52 (0.38-6.02)	n.s.	0.98 (0.17-5.59)	n.s.	1.09 (0.20-6.08)	n.s.	1.06 (0.20-5.33)	n.s.
PCNSL	0.95 (0.29-3.15)	n.s.	0.68 (0.14-3.22)	n.s.	0.72 (0.16-3.29)	n.s.	0.88 (0.20-3.69)	n.s.
Other Encephalop.	1.77 (0.84-3.50)	n.s.	0.71 (0.18-2.88)	n.s.	0.86 (0.22-3.29)	n.s.	0.99 (0.28-3.54)	n.s.
CM/TE	0.74 (0.23-2.43)	n.s.	0.31 (0.06-1.45)	n.s.	0.37 (0.09-1.70)	n.s.	0.39 (0.09-1.73)	n.s.
Other	2.94 (1.32-6.56)	<0.01	1.31 (0.43-3.97)	n.s.	1.50 (0.51-4.46)	n.s.	1.58 (0.54-4.56)	n.s.

INTRODUCTION

- The levels of HIV-1 RNA in cerebrospinal fluid (CSF) are considered a biological marker of infection, as well as in plasma, and an indirect tool to evaluate active infection in the brain
- CSF and plasma HIV-1 dynamics can evolve independently, leading to virological compartmentalization of HIV infection in the central nervous system
- Elevated HIV-1 RNA levels in CSF have been associated with HIV associated dementia and have been found in neurocognitively impaired patients with late-stage HIV disease
- High CSF HIV-1 RNA levels predict the subsequent progression to neuropsychological impairment in HIV-infected patients
- Highly Active Antiretroviral therapy (HAART) is demonstrated to effectively reduce HIV-1 RNA levels in CSF as well as in plasma
- The incidence of dementia presented a significant decline in HIV-infected patients following the introduction of HAART
- However the penetration of specific antiretroviral drugs in CSF is variable and some drugs reach inadequate concentrations in CSF
- The neuroactive role of single antiretroviral drugs and the protective effect of different drug classes in patients treated with HAART has to be conclusively defined

OBJECTIVES

- To analyze the effect of antiretroviral therapy, single antiretroviral agents and different classes of drugs on HIV-RNA levels in CSF in a large cohort study group of HIV-infected patients affected by neurological disorders
- To identify factors related to undetectable levels of CSF HIV-1 RNA in HIV-patients with neurological disorders

METHODS

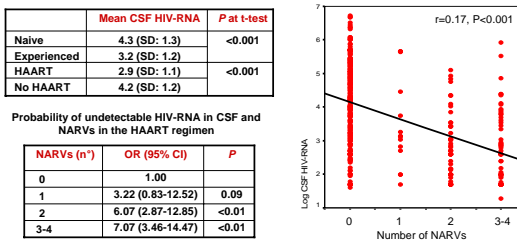
Analyses were conducted on paired CSF/plasma data collected from Italian Registry Investigative NeuroAIDS (IRINA)

IRINA is a longitudinal multicentric study collecting data of neurological cases from 45 Italian Infectious Diseases Centres including: demographic and epidemiological variables, natural history of HIV infection and antiretroviral therapy, clinical-radiological features at diagnosis, diagnostic criteria, availability of biological samples

CSF HIV-RNA level was considered undetectable if it was below the detection limit of the used tool

AZT, DAT, 3TC, ABC, NVP, EFV, IDV are known to have high level of penetration in CSF or effectively suppress HIV-1 RNA in CSF and were considered "neuroactive drugs" (NARVs)

Statistical analysis: crude and adjusted logistic regression model was used to analyze predictive factors of undetectable CSF viral load and t-Student test was employed to compare values of CSF HIV-RNA in different categories of a factor



Factors predictive of undetectable CSF HIV-1 RNA. Adjusted logistic regression model in the subgroup of 120 patients on HAART

Factors	Crude OR (95%CI)	P-value	Adjusted OR (95%CI)	P-value
CD4 cell count ≥ 200	1.80 (0.79-4.10)	0.162	3.27 (0.87-12.28)	0.079
Drug classes				
PI	1.00		1.00	
NNRTI	4.08 (1.54-10.84)	<0.01	5.38 (1.52-19.00)	0.01
NRTI	0.92 (0.22-3.88)	0.91	0.29 (0.02-4.18)	0.37
PI+NNRTI	2.02 (0.42-8.20)	0.38	1.47 (0.15-14.09)	0.74
boosted PI	1.96 (0.62-6.20)	0.25	1.68 (0.40-7.04)	0.48

The multivariate model was also adjusted for age, gender, HIV transmission route, plasma HIV-RNA, cognitive symptoms, abnormal mental status, cerebral atrophy, HAART exposure before diagnosis and neurological disorder.

CONCLUSIONS

- Antiretroviral therapy significantly reduces HIV burden in CSF of HIV-infected patients with neurological disorders
- Including a higher number of neuroactive drugs in the HAART regimen results in a more effective control of HIV-1 replication in neurological impaired patients
- Exposure to NNRTIs and, in lower measure, to boosted-PI increases the probability of suppression of HIV-1 in CSF during therapy
- Uncontrolled HIV replication in CSF usefully predicts neurocognitive impairment also in this setting of high prevalence of HAART exposure

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