Abstract number E-118

Antiretroviral CNS Penetration-Effectiveness (CPE) 2010 ranking predicts CSF viral suppression only in patients with undetectable HIV-1 RNA in plasma.

Andrea Antinori[1], Patrizia Lorenzini[1], Maria Letizia Giancola[1], Giovanna Picchi[1], Francesco Baldini[1], Laura Monno[2], Adriana Ammassari[1], Antonella d'Arminio Monforte[3], Paola Cinque[4], Valerio Tozzi[1]

[1]National Institute for Infectious Diseases "Lazzaro Spallanzani", IRCCS, Rome, Italy; [2]University of Bari, Italy; [3]San Paolo Hospital, University of Milan, Italy; [4]HSR San Raffaele Scientific Institute, Milan, Italy

Andrea Antinori, MD
INMI "L. Spallanzani", IRCCS
Via Portuense, 292 - 00149 Roma
Tel: +390655170480;
Fax: +390655170477
andrea.antinori@inmi.it

ABSTRACT

Background. HIV-1 replication in CSF despite viral suppression in plasma has been suggested as associated with neurocognitive impairment and neurological disease. Higher CPE ranking (2010 version) was related to lower proportion of detectable CSF viral load in a retrospective cross-sectional analysis, and lower ranking correlated to time-to-loss-of-viral response in CSF longitudinally. Information on predictive value of CPE ranking according to level of HIV-1 suppression in plasma are still unclear.

Methods. Retrospective analysis of consecutive paired CSF/plasma samples from HIV infected patients followed at four clinical centers in Italy. Plasma and CSF lower limits of quantification were defined by standard methods at the time of collection (range 50-200 cp/mL). Independent predictors of CSF undetectable viral load were assessed by multivariate linear regression method.

Results. A total of 301 paired CSF/plasma samples obtained from 219 HIV-infected patients treated by cART (years 1999-2009) were included in the analysis (male 81%; median age 42; heterosexual 37%, MSM 15%, IVDU 38%; previous AIDS-defining event 65%). Median CD4 count was 129 cells/ml and HIV-1 RNA values in CSF and plasma were 2.39 log10/mL and 2.06 log10/mL, respectively. A neurologic disorder was diagnosed in 56% of patients. Of the 301 paired samples, 107 (35%) had undetectable HIV-1 RNA in plasma, and 155 (51%) undetectable values in CSF. Overall median value of antiretroviral CPE 2010 ranking was 7 (IQR 6-8). Results of multivariate analysis are reported in Table 1. Sensitivity analysis indicated CPE ranking cut-off of 6 as highly predictive. Age, gender, HIV transmission route, number of ARV drugs, ARV drug class (PI/r, PI, or NNRTI) did not correlate in univariate analysis and were not included in the final model.

Table 1. Factors predictive of undetectable HIV-1 RNA in CSF by multivariable linear regression according to plasma HIV-1 RNA at the time of CSF collection.

	Beta coefficient	95%CI	p-value
Plasma HIV-1 RNA above detection limit at time of CSF collection (n=194)			
Previous AIDS defining event	-5688,3	-34592,9 23216,3	0.69
Latest CD4 cells (per 50 cells increase)	-661,0	-4745,9 3423,9	0.75
CPE (6 cut-off)	2496,9	-39240,0 44233,8	0.91
Presence of neurologic disorders	5134,5	-24887,9 35156,9	0.74
Plasma HIV-1 RNA undetectable at time of CSF collection (n=107)			
Previous AIDS defining event	848,9	-1476,1 3173,8	0.47
Latest CD4 cells (per 50 cells increase)	-52,4	-331,7 226,9	0.71
CPE (6 cut-off)	**-4927,1**	**-8389,1 -1465,1**	**0.006**
Presence of neurologic disorders	1295,6	-823,8 3415,0	0.23

Conclusions

CPE 2010 ranking strongly predicts HIV-1 replication in CSF during plasma viral suppression, but does not have the same predictive value in individuals with plasma active replicating virus. This could be explained by other factors, such as HIV drug resistance, poor adherence or immune activation that may offset CPE in the context of virological failure. These results may have relevant implications for clinical strategy in order to define patients at higher risk of CSF/plasma discordant HIV-1 suppression.

Introduction

Combined Antiretroviral Therapy (cART) is been demonstrated to be effective in reducing HIV viral load in plasma as well as in CSF.

- **However, cARTcould be not sufficient to control HIV replication in CNS for a lot of reasons, such as the variable concentrations that antiretroviral drugs reach into the anatomical reservoirs. A compartmentalization between plasma and CNS has been demonstrated.**
- **In fact some evidences show that in some patients HIV replication in CSF continues inspite of a long and complete viral suppression in their plasma and neurological and neurocognitive disorders could be recognized.**
- **In the most recent years some efforts to identify antiretroviral drugs or regimens that could be more effective than others in controlling HIV replication in CSF have been done.**
- **Antiretroviral CSF Penetration-Effectiveness (CPE) score has been proposed by CHARTER Group in order to evaluate the relationship between CSF HIV-RNA, antiretroviral penetration in CSF, and neurocognitive impairment.**
- **Higher CPE ranking (2010 version) has been related to lower proportion of detectable CSF viral load in a retrospective cross-sectional analysis, and lower ranking correlated to time-to-loss-of-viral response in CSF longitudinally.**
- **Information on predictive value of CPE ranking according to level of HIV-1 suppression in plasma are still unclear.**

Objectives

- **To analyze the effect of cART on CSF HIV –RNA replication in a large group of HIV-infected patients.**
- **To identify predictive factors associated to CSF HIV-RNA load in the study group.**
- **To explore the predictive value of CPE ranking according to level of HIV-1 suppression in plasma.**

Methods

- **A retrospective analysis on consecutive paired CSF/plasma samples from HIV infected patients attending four clinical centers in Italy was conducted**
- **Plasma and CSF lower limits of quantification were defined by standard methods at the time of collection (range 50-200 cp/mL).**
- **Independent predictors of CSF viral load were assessed by multivariate linear regression method.**
- **CPE score considers pharmacokinetics characteristics of antiretrovirals and classifies the drugs into 4 classes; the rank varies from 1 to 4 (table 1). A 6 cut-off was choosen according to a sensitivity analysis.**

CNS Penetration-Effectiveness (CPE) Ranks (2010)

Table 1.	4	3	2	1
NRTIs	Zidovudine	Abacavir	Didanosine	Tenofovir
		Emtricitabine	Lamivudine	Zalcitabine
			Stavudine	
NNRTIs	Nevirapine	Delavirdine	Etravirine	
		Efavirenz		
PIs	Indinavir-r	Darunavir-r	Atazanavir-r	Nelfinavir
		Fosamprenavir-r	Atazanavir	Ritonavir
		Indinavir	Fosamprenavir	Saquinavir-r
		Lopinavir-r		Saquinavir
				Tipranavir-r
Fusion/Entry Inhibitors		Maraviroc		Enfuvirtide
Integrase Inhibitors		Raltegravir		

Letendre S. et al. , 17th Conference on Retroviruses and Opportunstic Infections, poster n° 430

Results

Characteristics	Patients (N=301)	Patients with plasma HIV-RNA undetectable (N=107, 35.5%)	Patients with plasma HIV-RNA detectable (N=194, 64.5%)
Male gender , n(%)	244 (81.1)	89 (83.2)	155 (79.9)
Age, median years (IQR)	42 (37-48)	44 (37-50)	41 (37-46)
HIV transmission route, n(%):			
IVDU	114 (37.9)	39 (36.4)	75 (38.7)
MSM	45 (15.0)	11 (10.3)	34 (17.5)
Heterosexual	111 (36.9)	41 (38.3)	70 (36.1)
Other/unknown	31 (10.2)	16 (15.0)	15 (7.7)
Previous AIDS defining event	196 (65.1)	73 (68.2)	123 (63.4)
CD4 cell/mmc, median (IQR)	129 (65-287)	167 (75-338)	124 (60-265)
Plasma HIV-1 RNA log_{10}cp/ml, median (IQR)	2.39 (1.70-4.19)	-	3.40 (2.46-5.00)
CSF HIV-1 RNA log_{10}cp/ml, median (IQR)	2.06 (1.69-3.05)	2 (1.90-2.13)	2.30 (2.00-3.56)
CSF HIV-1 RNA undetectable, n(%)	155 (51.5)	80 (74.8)	75 (38.7)
Neurological disorders, n(%)	169 (56.2)	49 (45.8)	120 (61.9)
Antiretroviral therapy			
third drug class			
nnrti	73 (24.2)	39 (36.4)	34 (17.5)
pi/r	124 (41.2)	34 (31.8)	90 (46.4)
pi	80 (26.6)	31 (29.0)	49 (25.3)
only nrti	5 (1.7)	3 (2.8)	3 (1.5)
2 classes	19 (6.3)	-	18 (9.3)
nucleoside analogues			
azt+3tc	73 (24.2)	33 (30.8)	40 (20.6)
d4t+3tc	69 (22.9)	20 (18.7)	49 (25.3)
d4t+ddi	55 (18.3)	25 (23.4)	30 (15.5)
tdf+3tc	30 (10.0)	14 (13.1)	16 (8.2)
tdf+ftc	18 (6.0)	0	18 (9.3)
abv+3tc	12 (4.0)	6 (5.6)	6 (3.1)
other combinations	44 (14.6)	9 (8.4)	35 (18.0)
CPE 2010, mean	6.90	6.86	6.93

Patients with plasma HIV-RNA undetectable (N=107)				
	N	Mean	P at t-test	P at multivariable linear regression
CPE <6	11	5344	0.005	0.006
CPE>=6	96	450		
CPE <7	41	1901	0.169	0.224
CPE>=7	66	365		
CPE <8	77	1261	0.366	0.386
CPE>=8	30	165		
CPE <9	100	1011	0.691	0.613
CPE>=9	7	133		

Patients with plasma HIV-RNA detectable (N=194)				
	N	Mean	P at t-test	P at multivariable linear regression
CPE <6	25	79418	0.961	0.906
CPE>=6	169	23976		
CPE <7	65	24813	0.806	0.808
CPE>=7	129	25820		
CPE <8	130	23283	0.954	0.853
CPE>=8	64	26903		
CPE <9	175	25972	0.286	0.319
CPE>=9	19	25118		

Linear regression models

(dependent variable: number of CSF HIV-RNA copies/ml)

Subgroup of patients with plasma HIV-RNA undetectable (N=107)

	Univariate				Multivariate			
	Beta coefficient	(95%CI)		P-value	Beta coefficient	(95%CI)		P-value
Previous AIDS defining event	947.7	-1090.5	2986.0	0.359	848.9	-1476.1	3173.8	0.471
CD4 cell/mmc (50 cell increase)	-120.8	-398.1	156.4	0.389	-52.4	-331.7	226.9	0.711
Concomitant neurological disorders, n(%)	999.9	-976.4	2976.2	0.318	1295.6	-823.8	3415.0	0.228
CPE 2010 >6	-4924.2	-8179.1	-1669.4	0.003	-4927.1	-8389.1	-1465.1	0.006

Subgroup of patients with plasma HIV-RNA detectable (N=194)

	Univariate				Multivariate			
	Beta coefficient	(95%CI)		P-value	Beta coefficient	(95%CI)		P-value
Previous AIDS defining event	-3496.7	-29569.9	22576.4	0.792	-5688.3	-34592.9	23216.3	0.698
CD4 cell/mmc (50 cell increase)	-880.2	-4754.8	2994.3	0.655	-661.0	-4745.9	3423.9	0.750
Concomitant neurological disorders, n(%)	8079.9	-17700.7	33860.4	0.537	2496.9	-39240.0	44233.8	0.906
CPE 2010 >6	-1222.5	-40371.1	37926.1	0.951	5134.5	-24887.9	35156.9	0.736

Conclusions

- **CPE 2010 ranking strongly predicts HIV-1 replication in CSF during plasma viral suppression, but does not have the same predictive value in individuals with plasma active replicating virus.**
- **This could be explained by some factors, such as HIV drug resistance, poor adherence or intrathecal immune activation that may offset CPE in the context of virological failure and could lead to a compartmentalization between plasma and CNS.**
- **These results may have relevant implications for clinical strategy in order to define patients at higher risk of CSF/plasma discordant HIV-1 suppression and could be useful for the clinicians to choose the more effective antiretroviral therapy for subsets of patients**
- **Including neuroactive drugs in the cART regimen could be considered in the group of patients with complete virological suppression in plasma in order to better control the HIV replication in CSF and preserve CNS from neurocognitive and neurological disorders.**

References

1. Harrington PR, Schnell G, Letendre SL, et al. Cross-sectional characterization of HIV-1 env compartmentalization in cerebrospinal fluid over the full disease course. AIDS 2009;23, 907-15
2. Simioni S, Cavassini M, Annoni JM, et al. Cognitive dysfunction in HIV patients despite long-standing suppression of viremia. AIDS 2010; 24:1243-50
3. Canestri A, Lescure FX, Jaureguiberry S, et al. Discordance between cerebral spinal fluid and plasma HIV replication in patients with neurological symptoms who are receiving suppressive antiretroviral therapy. Clin Infect Dis 2010;50:773-8.
4. Letendre S, Ellis R, Deuthsch R, et al. 17th Conference on Retroviruses and Opportunstic Infections, San Francisco (poster n°430)
5. Smurzynski M, Wu K, Letendre S, et al. Effects of central nervous system antiretroviral penetration on cognitive functioning in the ALLRT cohort. AIDS. 2011;25:357-65
6. Tozzi V, Balestra P, Salvatori MF, et al. Changes in cognition during antiretroviral therapy: comparison of 2 different ranking systems to measure antiretroviral drug efficacy on HIV-associated neurocognitive disorders. JAIDS 2009;52:56-63.