CSF viral escape in patients without neurological disorders: prevalence and associated factors

Pinnetti C, Lorenzini P, Forbici F, Ammassari A, Libertone R, Giancola ML, Capobianchi MR, Perno CF, Antinori A.

National Institute for Infectious Diseases "Lazzaro Spallanzani", IRCCS, Rome, Italy;

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Carmela Pinnetti, MD
INMI "L. Spallanzani", IRCCS
Via Portuense, 292 - 00149 Roma
Tel: +3906655170369; Fax: +3906655170477
carmela.pinnetti@inmi.it

National Institute for Infectious Diseases "L. Spallanzani" Rome, Italy.

ABSTRACT

Background. CSF viral escape (CVE) is an emerging issue in the HIV setting and has been associated with neurologic symptoms and neurocognitive impairment. Few studies have estimated CVE prevalence and factors associated.
Methodology. Single-center retrospective study on CSF/plasma paired samples obtained from HIV-patients undergoing spinal tap because of neurological signs/symptoms or CNS stage of systemic diseases. Patients with diagnosis of CNS disorders were excluded. Repeated CSF/plasma samples obtained from the same patient were included if collected while receiving different cARTs. CVE was defined: a) detectable CSF HIV-RNA with concurrent plasma levels <50 copies/mL; b) CSF HIV-RNA >1.0 log higher than concomitant plasma RNA level. Adjusted ORs of CVE were calculated by fitting a logistic multivariate regression model.
Results. 303 CSF/plasma pairs collected from 115 patients were included: 88% male, median age 48 (IQR 41-52), HIV acquisition heterosexual in 43%, MSM in 21%, IDU in 27%. CD4 count was <200 cells/mm^3 in 48% and >350 in 25%; 31% were CDC stage C. CSF was collected in 14% during 1994-2004, in 48% during 2004-2008, in 37% during 2009-2013. At the time of collection, 50% were on cART with TDF/FTC, 12% with ABV/3TC, 9% with ZDV/3TC, 33% with EFV, 33% with LPV/r, 12% with ATV/r. CVE was detected in 32/303 samples (10.6%). At multivariable analysis, male gender (OR 0.23; 95%CI 0.07-0.76), CD4 >350 (0.22; 0.06-0.73) and 2009-2013 period (0.05; 0.00-0.25) were all independently associated to a decreased risk of CVE. Fitting a separate logistic model including ARVs and using TDF/FTC as reference, both ABV/3TC (OR 8.20; 1.61-41.65) and ZDV/3TC (OR 11.12; 1.62-76.35) were related to an increased CVE risk. In the same model, having EFV as reference, ATV/r (OR 5.67; 0.98-32.72) was related to a higher risk of CVE. Age, duration of cART and 2010 CPE score were not associated with CVE. A sensitivity analysis including only 151 patients with plasma HIV-RNA <50 copies/mL, found 22 CVE (12.5%). At logistic regression, the protective effect of male gender, CD4 >350, 2009-2013 period was confirmed. Among ARVs, only the increased risk associated with ABV/3TC use when compared to TDF/FTC remained significant.
Conclusions. In this large record of CSF/plasma paired samples from patients without CNS disorders, CVE occurred in about 10% of cases, with a reduced frequency in recent years. Male gender and higher CD4 count had a protective role. Though channeling bias in this cross-sectional study cannot be ruled out, the lack of correlation of CVE and CPE score, and the protective role of TDF/FTC (versus ABV/3TC or ZDV/3TC) and of EFV (versus ATV/r) suggest that effective viral suppression in plasma more than neuropenetrative effectiveness of ARVs may drive the control of HIV replication in CSF.

Background

•HIV invades the Central Nervous System (CNS) during primary infection and is present in this compartment throughout the course of infection suggesting local replication of HIV and replication in reservoirs.

•Although combined antiretroviral therapy (cART) is often effective in suppressing cerebrospinal fluid (CSF) virus, CSF viral escape (CVE) is an emerging issue in the HIV setting and it may be associated with neurologic signs and symptoms as well as HIV-associated neurocognitive disorders (HAND).

•In some reports, persistent viremia has been detected in the CNS despite suppression of viral replication in plasma during cART. Few studies have estimated CVE prevalence and associated factors in neurologically asymptomatic individuals successfully treated with cARV.

Objective

Aim of our study was to analyze prevalence and predictors of CSF viral escape in HIV patients without neurologic disorders assuming combined antiretroviral therapy (cART).

Methods

•We retrospectively analyzed 303 CSF/plasma pairs collected in 115 HIV patients without neurologic disorders. Lumbar puncture (LP) was performed if the patient presented with new neurological symptoms or for CSF staging in patients with systemic lymphomas. All patients were receiving cART and were monitored at our clinical center.
•CVE was defined as:
- CSF HIV-1 RNA > threshold of detectability and plasma HIV-1 RNA <50 copies/mL
- CSF HIV-1 RNA > 1.0 $\log_{10}$ higher than concomitant plasma HIV-1 RNA level.

•According with definition, 32 CVEs were detected (overall prevalence 10.6%), 31 asymptomatic and 1 symptomatic. For the analysis, only the 31 symptomatic CVEs were considered.

Statistical analysis
Comparisons between groups of samples with and without viral escape were made using Chi square test for categorical variables and Wilcoxon Mann-Whitney test for continuous variables.
Logistic regression model was fitted to determine factors associated with CVE.
Multivariable analysis was carried out also on a subgroup of samples with plasma HIV-1 RNA<50 copies/mL

Results

CSF Viral escape N=31 (10.3%)	N
CSF HIV-1 RNA >threshold of detectability and plasma HIV-1 RNA<50 copies/mL	22 (71.0%)
CSF HIV-1 RNA >1.0 $\log_{10}$ higher than concomitant plasma HIV-1 RNA level	9 (29.0%)

***1 patient with symptomatic viral escape were excluded from the statistical analysis**

Patients' characteristics (N=114*)	CSF samples (N=302*)	samples with CVE (N=31*, 10.3%)	samples without CVE (N=271, 89.7%)	P-value
Male gender, n (%)	267 (88.1)	26 (83.9)	241 (88.9)	0.405
Age, yrs, median (IQR)	48 (41-52)	49 (39-61)	48 (41-52)	0.517
Mode of HIV transmission, n (%):				0.802
Heterosexual contacts	128 (42.4)	15 (48.4)	113 (41.7)	
MSM	63 (20.9)	7 (22.6)	56 (20.7)	
IVDU	81 (26.8)	7 (22.6)	74 (27.3)	
Other/unknown	30 (9.9)	2 (6.4)	28 (10.3)	
Previous AIDS defining event, n (%)	93 (30.8)	6 (19.3)	87 (32.1)	0.145
HCV Ab positivity, n(%)	118 (39.1)	11 (35.5)	107 (39.5)	0.546
CD4 count at the LP, cell/mm^3, median (IQR)	206 (86-375)	131 (41-227)	210 (93-390)	0.022
Plasma HIV-1 RNA at the LP, $\log_{10}$cp/ml, median (IQR)	1.71 (1.60-2.58)	1.70 (1.70-1.81)	1.78 (1.60-2.78)	0.366
CSF HIV-1 RNA at the LP $\log_{10}$cp/ml, median (IQR)	2.00 (1.30-2.11)	2.30 (2.15-3.49)	2.00 (1.30-2.00)	<0.001
Months of total cART exposure, median (IQR)	11.0 (2.8-59.3)	15.4 (3.4-56.6)	10.8 (2.8-69.8)	0.927
Months of current regimen, median (IQR)	3.9 (1.6-11.0)	4.1 (2.1-15.4)	3.8 (1.5-10.9)	0.617
Current cART regimen third drug, n(%)				0.006
EFV	90 (29.8)	4 (12.9)	86 (31.7)	
LPV/r	95 (31.5)	13 (41.9)	82 (30.3)	
ATV/r	31 (10.3)	8 (25.8)	23 (8.5)	
DRV/r	13 (4.3)	0	13 (4.8)	
other	73 (24.2)	6 (19.4)	67 (24.7)	
NRTIs, n (%)				0.242
TDF+FTC	158 (52.3)	13 (41.9)	145 (53.5)	
TDF+3TC	20 (6.6)	4 (12.9)	16 (5.9)	
ABV+3TC	36 (11.9)	6 (19.3)	30 (11.1)	
AZT+3TC	22 (7.3)	2 (6.5)	20 (7.4)	
other combinations	66 (22.1)	6 (19.3)	60 (22.1)	
CPE ranking 2010, median (IQR)	7 (6-7)	7 (5-7)	7 (6-7)	0.566
Calendar year of LP, n (%)				0.001
1999-2003	31 (10.3%)	5 (16.1%)	26 (9.6%)	
2004-2008	129 (42.9%)	21 (67.7%)	108 (40.0%)	
2009-2013	141 (46.8%)	5 (16.1%)	136 (50.4%)	
Presence of symptoms	15 (5.6%)	0	15 (6.3%)	0.342

CSF cerebrospinal fluid, CVE CSF viral escape, IQR interquartile range, MSM men who have sex with men, IVDU intravenous drug users, LP lumbar puncture, cART combined antiretroviral therapy, CPE CNS penetration effectiveness

Multivariable logistic regression model (dependent variable: CSF viral escape)

	Univariable				Multivariable			
	OR	(95%CI)		P-value	AOR	(95%CI)		P-value
Male gender vs female	0.65	0.23	1.81	0.408	0.26	0.07	0.94	0.039
CD4 count, cell/mm^3								
0-200	1.00				1.00			
201-350	0.41	0.15	1.13	0.086	0.25	0.08	0.83	0.023
>350	0.23	0.07	0.78	0.019	0.28	0.07	1.13	0.074
Calendar year of LP, n(%)								
1999-2003	0.99	0.34	2.87	0.984	2.10	0.43	10.29	0.360
2004-2008	1.00				1.00			
2009-2013	0.19	0.07	0.52	0.001	0.09	0.02	0.41	0.002
Nucleoside analogues								
TDF+FTC	1.00				1.00			
TDF+3TC	2.79	0.81	9.58	0.103	1.52	0.33	7.11	0.592
ABV+3TC	2.23	0.79	6.34	0.132	3.52	1.02	12.18	0.047
AZT+3TC	1.12	0.23	5.31	0.891	1.49	0.16	13.96	0.727
other combinations	1.12	0.41	3.07	0.833	0.94	0.20	4.27	0.931
Third drug								
EFV	1.00				1.00			
LPV/r	3.41	1.07	10.88	0.038	1.44	0.32	6.47	0.638
ATV/r	7.48	2.07	27.04	0.002	12.70	2.33	69.22	0.003
DRV/r	n.e.*	-	-		n.e.*	-	-	
Other	1.61	0.44	5.92	0.472	0.79	0.15	4.14	0.782
Months of current cART	0.99	0.97	1.01	0.265	1.00	0.97	1.03	0.917

*not evaluable due to lack of CVE in pts treated with DRV/r

Multivariable logistic regression model (dependent variable: CSF viral escape)

Subgroup of samples with plasma HIV-1 RNA undetectable (N=151)

	AOR	(95%CI)		P-value
Male gender vs female	0.08	0.01	0.62	0.016
Cd4 count, cell/mmc				
0-200	1.00			
201-350	0.16	0.03	0.85	0.031
>350	0.20	0.02	1.83	0.154
Calendar year of LP, n(%)				
1999-2003	2.57	0.24	27.92	0.439
2004-2008	1.00			
2009-2013	0.04	0.00	0.39	0.006
Nucleoside analogues				
TDF+FTC	1.00			
TDF+3TC	0.48	0.03	6.74	0.583
ABV+3TC	3.15	0.52	19.17	0.212
AZT+3TC	0.55	0.03	10.51	0.689
other combinations	0.54	0.04	7.20	0.644
Third drug				
EFV	1.00			
LPV/r	1.71	0.17	16.94	0.646
ATV/r	11.24	0.89	141.86	0.061
DRV/r	n.e.*	-	-	-
other	0.89	0.08	9.32	0.920
Months of current cART	1.00	0.97	1.04	0.802

*not evaluable due to lack of CVE in pts treated with DRV/r

Samples	Gender	Age	Mode of HIV transmission	CDC stage	Calendar year	CD4 count, cell/mm^3	Plasma HIV-1 RNA, copies/mL	CSF HIV-1 RNA, copies/mL	Months of ARV therapy	Months of current regimen	NRTIs in the current regimen	Third drug in the current regimen	CPE ranking 2010
1	M	39	IVDU	A/B	2003	30	<50	140	11.1	4.2	d4T+3TC	LPV/r	7
2	M	46	Other/unknown	C	2005	323	249	116992	4.8	4.8	d4T+3TC	LPV/r	7
3	M	66	Other/unknown	A/B	2004	28	<50	1724	9.4	9.4	TDF+3TC	EFV	6
4	M	58	IVDU	A/B	2011	150	48	200	171.4	62.2	AZT+3TC+ABV	-	9
5	M	34	hetero	A/B	2003	287	<50	314	12.9	12.9	AZT+3TC	IDV	9
6	M	44	IVDU	A/B	2003	28	<50	200	98.1	8.8	AZT+3TC	NVP	10
7	M	44	IVDU	C	2004	43	67	1444	1.9	1.9	TDF+3TC	EFV	6
8	M	37	MSM	A/B	2003	27	1343	22354	1.3	1.3	d4T+3TC	IDV	7
9	M	37	MSM	A/B	2004	31	522	8536	2.1	2.1	d4T+3TC	IDV	7
10	M	45	hetero	A/B	2007	563	<50	120	118.8	29.5	ABV+3TC	EFV	8
11	F	44	IVDU	A/B	2005	170	<50	134	4.9	4.9	TDF+3TC	EFV	6
12	F	43	IVDU	A/B	2005	338	<50	150	20.6	2.3	TDF+3TC	LPV/r	6
13	M	50	MSM	A/B	2005	113	<50	128	56.6	1.2	TDF+FTC	LPV/r	7
14	M	50	MSM	A/B	2005	197	<50	162	57.9	2.5	TDF+FTC	LPV/r	7
15	M	50	MSM	A/B	2005	197	<50	150	58.6	3.2	TDF+FTC	LPV/r	7
16	M	50	MSM	A/B	2005	115	<50	114	59.3	3.9	TDF+FTC	LPV/r	7
17	F	33	hetero	C	2003	- -	<50	504	37.3	6.3	ABV+ddI	LPV/r	8
18	M	43	IVDU	A/B	2007	256	<50	134	116.6	1.3	TDF+FTC	LPV/r	7
19	M	61	hetero	A/B	2007	50	167	15382	1.6	1.6	TDF+FTC	ATV/r	6
20	M	61	hetero	A/B	2007	25	78	3064	2.6	2.6	TDF+FTC	ATV/r	6
21	M	61	hetero	A/B	2007	25	<50	2396	3.4	3.4	TDF+FTC	ATV/r	6
22	F	28	hetero	A/B	2007	539	<50	152	1.6	1.6	TDF+FTC	LPV/r	7
23	M	38	MSM	C	2006	136	<50	150	3.6	3.6	TDF+FTC	LPV/r	7
24	M	49	hetero	C	2008	139	<50	150	15.4	15.4	ABV+3TC	LPV/r	8
25	M	51	hetero	A/B	2007	41	<50	200	4.7	4.1	TDF+FTC	LPV/r	7
26	F	33	hetero	C	2008	435	<50	110	0.5	0.5	TDF+FTC	LPV/r	6
27	M	69	hetero	A/B	2008	227	65	38434	17.5	17.5	ABV+3TC	ATV/r	7
28	M	69	hetero	A/B	2009	120	<50	2318	18.3	18.3	ABV+3TC	ATV/r	7
29	M	70	hetero	A/B	2009	128	40	1510	19.0	19.0	ABV+3TC	ATV/r	7
30	M	70	hetero	A/B	2009	129	70	3606	19.6	19.6	ABV+3TC	ATV/r	7
31	M	70	hetero	A/B	2009	133	53	5164	20.3	20.3	ABV+3TC	ATV/r	7

Conclusions

In this large record of CSF/plasma paired samples from HIV patients without CNS disorders, asymptomatic CVE occurred in 10.3% of cases, with a reduced frequency in recent years.

Male gender and higher current CD4 T-cell count had a protective role, even though channeling bias in this cross-sectional study cannot be ruled out.

The effects of ARVs over CVE occurrence seem to be related both to general effectiveness (ABV/3TC compared to TDF/FTC) and specifically drug-associated CSF penetration/effectiveness properties (ATV/r compared to EFV).

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