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Antiretroviral-naive and -treated HIV-1 patients can harbour more resistant viruses in CSF than in plasma

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Objectives: The neurological disorders in HIV-1-infected patients remain prevalent. The HIV-1 resistance in plasma and CSF was compared in patients with neurological disorders in a multicentre study.

Methods: Blood and CSF samples were collected at time of neurological disorders for 244 patients. The viral loads were >50 copies/mL in both compartments and bulk genotypic tests were realized.

Results: On 244 patients, 89 and 155 were antiretroviral (ARV) naive and ARV treated, respectively. In ARV-naive patients, detection of mutations in CSF and not in plasma were reported for the reverse transcriptase (RT) gene in 2/89 patients (2.2%) and for the protease gene in 1/89 patients (1.1%). In ARV-treated patients, 19/152 (12.5%) patients had HIV-1 mutations only in the CSF for the RT gene and 30/151 (19.8%) for the protease gene. Two mutations appeared statistically more prevalent in the CSF than in plasma: M41L ($P=0.0455$) and T215Y ($P=0.0455$).

Conclusions: In most cases, resistance mutations were present and similar in both studied compartments. However, in 3.4% of ARV-naive and 8.8% of ARV-treated patients, the virus was more resistant in CSF than in plasma. These results support the need for genotypic resistance testing when lumbar puncture is performed.

Keywords: HIV, ARV, resistance, CSF

Introduction

Infection of the CNS with HIV can lead to the development of HIV-1-associated dementia, HIV-1 encephalitis or neurological disorders. Although treatment with fully active antiretrovirals (ARVs) has reduced the frequency of HIV-1 infection of the CNS, neurological disorder symptoms are still observed in HIV-1 ARV-naive and ARV-treated patients.[1–6]

It is known that HAART has an effect on HIV-1 RNA levels in CSF.[7] Due to the blood–brain barrier, ARV may not be at optimal therapeutic concentrations in the CNS compartment. Low therapeutic concentrations of the ARV could contribute to viral resistance, and consequently, lead to virological failure.[8] Such differences in ARV concentrations in several compartments could result in discordant HIV-1 RNA levels between plasma and CSF and/or ARV drug resistance mutations.[9–12] Differences in ARV drug resistance mutations between plasma and CNS compartments have been reported as case reports or in small cohorts of patients.[9–12]

Currently, little information on the resistance patterns in the CNS is actually available in clinical practice in a large cohort of patients having a viral load (VL) >50 copies/mL in plasma and in CSF. In this study, the resistance of HIV-1 in plasma and CSF was studied and compared in a multicentre study supported by the 'Agence Nationale de Recherche sur le Sida et les Hépatites Virales' (ANRS).

Methods

Patients

We studied all CSF–plasma pairs with detectable VL (>50 copies/mL) between 2000 and 2013 in 22 centres in France and one centre in Switzerland. The indications for lumbar puncture are reserved for people affected by severe cognitive impairment without aetiological orientation. Socio-demographic and clinical data as well as treatment regimen were collected for all studied patients. Participating laboratories belong to ANRS and participate in the ANRS quality control assessment of HIV-1 drug resistance sequencing.[13] The study was approved by the scientific committee of Action Coordonnée 11-AC11 ANRS.

Genotyping resistance testing

The reverse transcriptase (RT) and protease resistance mutations were determined in each laboratory using the ANRS consensus technique (http://www.hivfrenchresistance.org), a Bayer TrueGene Kit, an Abbott ViroSeq Kit or an in-house method. In ARV-naive patients, protease and RT mutations were identified from the consensus statement of the list for genotypic surveillance of transmitted HIV-1 drug resistance.[14] In ARV-treated patients, RT and protease mutations were identified from the last International AIDS Society-USA resistance testing panel (http://www.iasusa.org) and were interpreted with the last ANRS genotypic algorithm (version 23; http://www.hivfrenchresistance.org). According to the ANRS algorithm, the global genotypic susceptibility score (GSS) was calculated on ARV currently available (n=18) as follows: 1 for a sensitive drug and 0 for a resistant or possible resistant drug. The GSS was also calculated according to Standford and Rega algorithms.

Statistical methods

Quantitative variables were summarized by means of median and IQR and qualitative variables by percent. Comparisons between independent groups were performed using the Kruskal–Wallis non-parametric test. The McNemar test was applied to compare the prevalence of mutations in both plasma and CSF in the same group of patients. No correction for multiple testing was made and the analysis was done with SAS (version 9.4).

Results

In total, 244 patients who experienced VL >50 copies/mL in plasma and CSF at the time of neurological disorders were

Table 1. Characteristics of the studied population (n=244)

Characteristic	ARV-naive patients (n=89)	ARV-treated patients (n=155)
Age (years), median (IQR)	42 (37–50)	44 (38–51)
Male, %	68.8	61.0
B subtype in CSF, %	55.8	51.0
B subtype in plasma, %	54.8	51.1
CSF HIV-1 RNA (log_{10} copies/mL), median (IQR)	4.64 (3.78–5.23)	4.09 (3.45–4.71)
Plasma HIV-1 RNA (log_{10} copies/mL), median (IQR)	5.10 (4.54–5.72)	3.70 (2.73–4.69)
Nadir CD4 (cell count/mm^3), median (IQR)	119 (27–332)	59 (18–156)
CD4 (cell count/mm^3), median (IQR)	131 (38–343)	230 (102–413)
Current treatment, %		
NRTIs+PIs	NA	62.6
NRTIs+PIs+INIs+other	NA	11.0
NRTIs+NNRTIs	NA	5.2
PIs	NA	5.2
other	NA	16.0

NA, not applicable; INIs, integrase inhibitors.
The other combinations were present at <5%: NRTIs; NRTIs+PIs+entry inhibitors; PIs+entry inhibitors; NRTIs+PIs+INIs; NRTIs+PIs+INIs+entry inhibitors; NRTIs+NNRTIs+PIs+entry inhibitors; NRTIs+INIs; NRTIs+INIs+other; PIs+INIs; NNRTIs+PIs; NRTIs+NNRTIs+PIs; NRTIs+NNRTIs+PIs+INIs+other.

Table 2. Differential pattern of resistance in ARV-naive and ARV-treated patients

	ARV-naive patients, RT	ARV-naive patients, protease	ARV-treated patients, RT	ARV-treated patients, protease
CSF				
detection of mutations	2.2% (2/89) patients	12.4% (11/89) patients	12.5% (19/152) patients	19.8% (30/151) patients
mutations	K101E, Y181C, M184I, T215Y	L10I/V, V11I, L33F/V, M36I, I62V, L63P, V77I, V82A, L89M	**M41L**, K65R, D67N, T69D, K70R, L74V, K101E, K103N, V108I, F116Y, Q151M, Y181C, M184V, M184I, G190A, L210W, **T215Y**, T215F, H221Y, M230I	L10I, L10F, V11I, K20R, K20I, K20T, M36I, M36L, M46I, F53L, I62V, L63P, I64L, I64V, A71V, A71I, A71L, V77I, V82 T, V82A, L89V, L89M, L90M, I93L, I93M
Plasma				
detection of mutations	2.2% (2/89) patients	9.0% (8/89) patients	10.5% (16/152) patients	13.9% (21/151) patients
mutations	Y181I, M184I	L10I, V11I, G16E, M36I, I62V, L63P, I64V, V77I, I93L	D67N, **T69N**, K70R, K70E, L74V, V90I, V106I, V106M, V108I, E138Q, Y181C, Y188L, M184I, M184V, L210W, K219E, M230L	L10I, L10F, G16E, K20I, L24I, V32I, L33I, L33F, M36I, M36L, M46I, I47V, G48V, I50L, I54V, I54L, I54M, Q58E, D60E, I62V, L63P, I64V, I64M, H69K, A71V, A71T, L76V, V77I, V82A, V82I, V82T, I85V, L89M, L90M, I93L

In bold, mutations appeared statistically more prevalent: in CSF, M41L ($P=0.0455$) and T215Y ($P=0.0455$); and in plasma, T69N ($P=0.0455$).

recruited; 89 and 155 were ARV naive and ARV treated, respectively. The main characteristics of the study population are shown in Table 1. In the regimen of ARV-treated patients, the most frequent NRTIs prescribed were emtricitabine/lamivudine (47.5%), abacavir (25.8%) and tenofovir (25.0%), and the most frequent PIs were lopinavir (20.5%), darunavir (14.7%) and atazanavir (13.1%). Etravirine was the NNRTI most frequently prescribed (13.1%). Overall, non-B subtypes were present in 47.0% of cases with a majority of CRF02_AG (20.6%).

In ARV-naive patients, 17.9% (16/89) of patients had at least one HIV-1 resistance mutation in plasma and 17.9% (16/89) in CSF. Mutations were associated with resistance in 11.2% (10/89) and 12.4% (11/89) of patients in plasma and CSF, respectively. The concordance between CSF and plasma sequences was evidenced in 85/89 (95.5%) and 88/89 (98.9%) patients for the studied positions in RT and protease gene, respectively. The detection of mutations in CSF and not in plasma viruses was reported in 2/89 (2.2%) patients for the RT gene and in 1/89 (1.1%) patients for the protease gene (Table 2). Some mutations were also present in plasma and not in CSF in 2/89 (2.2%) patients for the RT gene (Table 2). Furthermore, 96.6% (86/89) of ARV-naive patients had viruses with a similar global GSS in the two compartments, 3.4% (3/89) with a global GSS in CSF < GSS in plasma, and none with a global GSS in CSF > GSS in plasma (Figure 1).

In ARV-treated patients, the RT and protease amplification was successful for 152 and 151 cases, respectively, resulting in complete paired sequences for 148 patients. Mutations induced HIV-1 resistance at least for one drug for 111/148 (75.0%) patients and 110/148 (74.3%) in CSF and plasma, respectively. Nineteen of 152 (12.5%) patients had HIV-1 mutations only present in the CSF for the RT gene and 30/151 (19.8%) patients for the protease gene (Table 3). Two mutations were statistically more prevalent in the CSF in comparison with the plasma for the RT gene: M41L ($P=0.0455$) and T215Y ($P=0.0455$). There was no statistically significant difference for the presence of protease gene mutations. Some patients also presented HIV-1 mutations in plasma and not in CSF: 16/152 (10.5%) and 21/151 (13.9%) for RT and protease gene, respectively (Table 2). One mutation for the RT gene was statistically significantly more prevalent in plasma than in CSF: T69N ($P=0.0455$). Furthermore, 79.7% (118/148) of ARV-treated patients had viruses with a similar global GSS of current treatment in the two compartments whatever algorithm was used, 11.5% (17/148) with a global GSS in CSF < GSS in plasma and 8.8% (13/148) with a global GSS in CSF > GSS in plasma (Figure 1). No correlation of CNS-penetration effectiveness (CPE) score and any studied parameters was evidenced.

Discussion

In this multicentre study, the ARV resistance in 244 HIV-1 patients with neurological disorders and HIV-1 RNA load >50 copies/mL in plasma and CSF was studied in both compartments. In most cases, HIV-1 resistance was similar in plasma and CSF. However, we identified some cases where HIV-1 was more resistant in CSF than in plasma, reducing the number of future therapeutic options, in the studied population.

In ARV-naive patients, the prevalence of transmitted drug resistance was 11.2% in plasma. Similar results (9.0%) were described in the national sentinel surveillance of transmitted drug resistance in ARV-naive chronically HIV-1-infected patients in France over a decade (2001–11).[15] The prevalence of HIV-1 drug resistance in ARV-treated patients in this study was superior to that previously shown in 2009 in a French nationwide study (59%), possibly because the present study population was more advanced with higher VL (3.70 versus 2.57 $\log_{10}$ copies/mL) and lower CD4 (230 versus 390 cells/mm^3).[16]

Overall, a good concordance of resistance pattern was observed in CSF and plasma, but some resistance mutations can

(a)

	GSS in CSF									
GSS in plasma	9	10	11	12	14	15	16	17	18	Patients (*n*)
9	1									1
11			1							1
12				1						1
14		1			2					3
15						3				3
16							2			2
17								1		1
18								2	75	77
Patients (*n*)	1	1	1	1	2	3	2	3	75	89

(b)

	GSS in CSF															
GSS in plasma	2	3	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Patients (*n*)
2	1																1
3		1															1
4			1														1
5			2														2
6				2					1*								3
7					2												2
8						2											2
9							1										1
10							1	1			1						3
11									4								4
12								1		4	1	1			1		8
13							1				7						8
14			1	1							1	14				1	18
15													9	1		1	11
16										1		1		13	1	1	17
17												1	2		23	2	28
18													1		5	32	38
Patients (*n*)	1	1	4	3	2	2	3	2	5	5	10	17	12	14	30	37	148

Figure 1. Comparison of global GSS of HIV-1 viruses in plasma and CSF compartments in (a) ARV-naive patients and (b) ARV-treated patients. The results are expressed in the table as the number of patients having a global GSS in plasma and in CSF. *This patient had a global GSS at 11 in CSF and 6 in plasma.

be detected only in CSF or in plasma. In addition, some attention should also be paid to patients with similar global GSS in both compartments, because the resistance mutation set could be different, resulting in different ARV resistance. Our results were similar to a systematic review pooling 35 reports with heterogeneous design and methods.[17] Several factors could explain the discordant presence of HIV-1 mutations and/or ARV resistance between the plasma and the CSF, such as insufficient drug exposure,[9] previous discontinuation of treatment,[18] independent replication and evolution of resistance in the CNS,[19] CNS infection leading to local immune activation[20,21] or previous virological failure in plasma allowing archiving of ARV-resistant HIV-1 strains in the CNS compartment.[10] The CNS drug penetration appeared to be an important factor in the pathogenesis of CSF viral escape.[22] The CPE score was developed by Letendre[23] to calculate a CPE score adjusted for each regimen. In case of neurological disorders, the ART should be based not only on drug penetration but also on HIV-1 resistance in CSF. It should be mentioned that these cases of discordance between blood and CSF remain relatively uncommon. Furthermore, analysis of plasma and CNS samples also by Ultra Deep P Sequencing can provide a deeper characterization of drug resistance mutations and HIV-1 quasi-species in both compartments. This new-generation sequencing could highlight either some additional discordances or concordances with different percentages in both compartments.

It is noteworthy that the two mutations statistically significantly more prevalent in CSF than in plasma were M41L and T215Y. This may be related to thymidine analogues that have a good penetration into the CNS compartment, allowing appearance of the virus mutation, probably due to drug pressure.[8] More attention has to be paid to pharmacological CNS drug penetration not only to treat neurological disorders but also to prevent ARV resistance, despite the difficulties of evaluati individual CNS drug concentration.

In conclusion, these results from a large cohort from clinical routine care evidenced discordance in HIV-1 mutations and/or resistance between the plasma and the CSF in HIV-1 patients with neurocognitive symptoms. Furthermore, in 3.4% of ARV-naive and 8.8% of ARV-treated patients, the virus was more resistant in CSF than in plasma. These results support the need to perform genotypic resistance testing when VL is >50 copies/mL in CSF.

Table 3. Description of treated patients with discordant mutations between the CSF and plasma HIV-1 sequences

				CSF			Plasma		
Patient	Treatment	CPE	Subtype	VL (log_{10} copies/mL)	RT	protease	VL (log_{10} copies/mL)	RT	protease
1	f3TC, ddI, NVP	8.5	CRF01_AE	4.31112	V108I		4.15921		
2	f3TC, TDF, ETR	5.5	B	4.30103		K20R, L63P	5.63347	E138Q	
3	f3TC, TDF, ETR	5.5	D	4.54845	M41L, L210W, T215Y	V82T		M230L	L33I, I50L, I64V
4	f3TC, ABC, TDF, NVP	10.5	B	3.61805	Y181C, M184V, T215Y, H221Y		5.71850		
5	f3TC, ABC, DRV	8.5	C	4.93952		K20R	3.55630	Y188L	V82I
6	f3TC, ABC, fAPV	8.5		3.64345		L10F, L10I	2.32428		M36I
7	f3TC, TDF, fAPV	6.5	B	5.45618	M41L, L74V, Y181C, M184V, L210W, T215Y, K103N		2.90741		
8	f3TC, TDF, ATV	5.5	B	4.64640	K103N		4.22272	T69N	
9	AZT, SQV, LPV	8	CRF02_AG	4.96480		L90M	3.75664		
10	AZT, f3TC, SQV	7.5	B	3.89209			3.98677		Q58E, I62V, V82I, I85V, L90M
11	f3TC, TDF, ATV	5.5	B	3.31492		A71V, L90M	5.13374		Q58E, A71T
12	f3TC, TDF, LPV	6.5	CRF02_AG	3.44592	M184V		2.21484	V90I	
13	AZT, ABC, LPV	10	CRF06_CPX	5.14993		M46I	2.07555		
14	f3TC, d4T, ddI, ABC, SQV, NFV, LPV	14.5	B	3.21958			4.53842	D67N, K70R, Y181C, L210W, K219E	M46I, L63P, A71V, V77I
15	f3TC, ABC, LPV	8.5	CRF02_AG	3.41497			4.59356	M184I, M184V	K20I, M36I, H69K, L89M
16	f3TC, TDF, LPV	6.5	B	3.20683		M36I	6.78056		I93L
17	ddI, TDF, ATV	5	B	3.68422		A71L, A71V	2.27416		A71T
18	f3TC, ABC, ATV	7.5	B	3.29667		M46I, I93M	3.58894		
19	f3TC, ddI, ATV	6.5	B	4.02612		V77I	3.20466		A71T
20	ddC, TDF, fAPV	5	C	3.27875		L89M	3.64345		M46I, I47V, I54M
21	f3TC, TDF, ATV	5.5	B	3.00346	Q151M		2.81158	V90I	
22	f3TC, TDF, LPV	6.5	A	5.23553	M184I		5.53921		
23	f3TC, TDF, DRV	6.5	B	2.14613	T69D	F53L, V82A	5.41497	T69N	L10F, V82T
24	AZT, f3TC, ATV	8.5	B	4.76641		M36I, V77I	3.75694		
25	f3TC, ABC, IDV	9.5	B	4.77815		M46I	2.45637		
26	ABC, TDF, DRV	7	ind	4.63347			3.43136	L74V, V106I, V106M	
27	f3TC, ddI, SQV	5.5	CRF02_AG	4.36736	D67N		4.51720	M184I	
28	AZT, f3TC, LPV	9.5	CRF02_AG	3.64738		I64L	5.41159		L63P
29	f3TC, ddI, NFV	5.5	CRF09_cpx			I62V	2.54283		
30	f3TC, ABC, IDV	9.5	B	3.61278	M41L, L74V		3.88480		
31	f3TC, ETR, DRV, RAL	10.5	B	4.56820	H221Y		4.60206		
32	AZT, f3TC, IDV, T20	11.5	B	3.96848		M36L	2.62325	T69N	M36I
33	AZT, f3TC, NVP, LPV	13.5	B	2.40140	M230I	M36I	2.37107		
34	ETR, DRV, RAL	8	B			M36I, I64V, I93L	3.69992		L10I, L24I, L33F, M36L, M46I, I50L, Q58E, I62V, I64M, V82A, L89M
35	f3TC, ABC, DRV	11.5	B	3.87679		K20I, A71L, A71V	2.80140	D67N, T69N, K70R, Y181C, K219E	
36	AZT, f3TC, ABC, TDF	10.5	B	4.57287			2.36361		V82A

37	ETR, DRV, RAL, T20	9	A		3.76343	F116Y		4.68772		
38	d4T, ETR, DRV, DTG, T20	8	B		4.08998		L10I, A71L, I93L, L89M	2.31387		V32I, I54L, A71V, L76V
39	f3TC, TDF, DRV, T20	7.5	A		3.41830	D67N, T69D, K70R, M184V, T215F		2.48572	V108I	
40	f3TC, TDF, LPV, T20	7.5	CRF02_AG		4.68124			4.46240	K70E	D60E, L89M
41	SQV, ATV	3	B		3.60606		K20T	2.70329		
42	f3TC, ddI, ABC	7.5	B		4.29226	M41L, D67N, K101E, Y181C, M184I, L210W, T215Y, G190A	L63P, A71V, V77I, L90M, I93L	3.70070	L74V, M184V	G16E, M36I, M46I, I54V, H69K, V82A, L89M
43	AZT, f3TC, LPV, T20	10.5	CRF02_AG		3.33846	D67N	V11I	3.80161		G16E
44	TDF, fAPV, TPV, T20	6	CRF06		3.93862		M46I			G16E, G48V

The mutations described in this table are only those discordant between the HIV-1 sequence in plasma and in CSF.
NRTIs: f3TC, emtricitabine/lamivudine; ddI, didanosine; TDF, tenofovir; ABC, abacavir; AZT, zidovudine; d4T, stavudine. NNTIs: NVP, nevirapine; ETR, etravirine. PIs: DRV, darunavir; fAPV, fosamprenavir; ATV, atazanavir; SQV, saquinavir; LPV, lopinavir; NFV, nelfinavir; IDV, indinavir; TPV, tipranavir. INIs: RAL, raltegravir; DTG, dolutegravir. Fusion inhibitor: T20, enfuvirtide.

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Transparency declarations

None to declare.

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