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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)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ARV-naive patients (n=89)</th>
<th>ARV-treated patients (n=155)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (IQR)</td>
<td>42 (37–50)</td>
<td>44 (38–51)</td>
</tr>
<tr>
<td>Male, %</td>
<td>68.8</td>
<td>61.0</td>
</tr>
<tr>
<td>B subtype in CSF, %</td>
<td>55.8</td>
<td>51.0</td>
</tr>
<tr>
<td>B subtype in plasma, %</td>
<td>54.8</td>
<td>51.1</td>
</tr>
<tr>
<td>CSF HIV-1 RNA (log_{10} copies/mL), median (IQR)</td>
<td>4.64 (3.78–5.23)</td>
<td>4.09 (3.45–4.71)</td>
</tr>
<tr>
<td>Plasma HIV-1 RNA (log_{10} copies/mL), median (IQR)</td>
<td>5.10 (4.54–5.72)</td>
<td>3.70 (2.73–4.69)</td>
</tr>
<tr>
<td>Nadir CD4 (cell count/mm³), median (IQR)</td>
<td>119 (27–332)</td>
<td>59 (18–156)</td>
</tr>
<tr>
<td>CD4 (cell count/mm³), median (IQR)</td>
<td>131 (38–343)</td>
<td>230 (102–413)</td>
</tr>
<tr>
<td>Current treatment, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRTIs+PIs</td>
<td>NA</td>
<td>62.6</td>
</tr>
<tr>
<td>NRTIs+PIs+INIs+other</td>
<td>NA</td>
<td>11.0</td>
</tr>
<tr>
<td>NRTIs+NNRTIs</td>
<td>NA</td>
<td>5.2</td>
</tr>
<tr>
<td>PI</td>
<td>NA</td>
<td>5.2</td>
</tr>
<tr>
<td>other</td>
<td>NA</td>
<td>16.0</td>
</tr>
</tbody>
</table>

NA, not applicable; INIs, integrase inhibitors.
The other combinations were present at <5%; NRTIs; NRTIs+PIs+entry inhibitors; PI+entry inhibitors; NRTIs+PIs+INIs; NRTIs+PIs+INIs+entry inhibitors; NRTIs+NNRTIs+PIs+entry inhibitors; NRTIs+INIs; NRTIs+INIs+other; PI+INIs; NNRTIs+PIs; NRTIs+NNRTIs+PIs; NRTIs+NNRTIs+PIs+INIs+other.
In bold, mutations appeared statistically more prevalent: in CSF, M41L ($P = 0.0455$) and T215Y ($P = 0.0455$); and in plasma, T69N ($P = 0.0455$).

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 selected.


discussion

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 selected.

Overall, a good concordance of resistance pattern was observed in CSF and plasma, but some resistance mutations can be more prevalent in CSF than in plasma, reducing the number of future therapeutic options, in the studied population.
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. 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, previous discontinuation of treatment, independent replication and evolution of resistance in the CNS, or previous virological failure in plasma allowing archiving of ARV-resistant HIV-1 strains in the CNS compartment. The CNS drug penetration appeared to be an important factor in the pathogenesis of CSF viral escape. The CPE score was developed by Letendre 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 ARV 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.

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.

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

<table>
<thead>
<tr>
<th>Patient</th>
<th>Treatment</th>
<th>CPE</th>
<th>Subtype</th>
<th>CSF</th>
<th>Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>f3TC, ddI, NVP</td>
<td>8.5</td>
<td>CRF01_AE</td>
<td>4.31112, VL108I</td>
<td>5.15921, K20R, L63P</td>
</tr>
<tr>
<td>2</td>
<td>f3TC, TDF, ETR</td>
<td>5.5</td>
<td>B</td>
<td>4.30103, 4.54845</td>
<td>6.63347, 6.4138Q</td>
</tr>
<tr>
<td>3</td>
<td>f3TC, TDF, ETR</td>
<td>5.5</td>
<td>D</td>
<td>4.51805</td>
<td>5.71850, M230L</td>
</tr>
<tr>
<td>4</td>
<td>f3TC, ABC, TDF, NVP</td>
<td>10.5</td>
<td>B</td>
<td>5.45618, M41L, L74V, Y181C, M184V, V82T, L210W, T215Y, H221Y</td>
<td>5.55630, Y188L</td>
</tr>
<tr>
<td>5</td>
<td>f3TC, ABC, DRV</td>
<td>8.5</td>
<td>C</td>
<td>4.93952, K20R</td>
<td>5.32248, M361</td>
</tr>
<tr>
<td>6</td>
<td>f3TC, ABC, fAPV</td>
<td>8.5</td>
<td>B</td>
<td>3.64345, L10F, L10I</td>
<td>2.32428, V82I</td>
</tr>
<tr>
<td>7</td>
<td>f3TC, TDF, fAPV</td>
<td>6.5</td>
<td>B</td>
<td>5.45618, M41L, L74V, Y181C, M184V, L210W, T215Y, K103N</td>
<td>2.90741</td>
</tr>
</tbody>
</table>

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**37** ETR, DRV, RAL, T20

38 d4T, ETR, DRV,

39 d4T, T20

40 d4T, TDF, LPV

41 d4T, TDF, ATV

42 d4T, TDF, ATV

43 d4T, TDF, ATV

44 d4T, TDF, ATV

The mutations described in this table are only those discordant between the HIV-1 sequence in plasma and in CSF. The mutations described in this table are only those discordant between the HIV-1 sequence in plasma and in CSF.

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Transparency declarations
None to declare.

References