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Concentrations of Human Immunodeficiency Virus Type 1 (HIV-1) RNA in Cerebrospinal Fluid after Antiretroviral Treatment Initiated during Primary HIV-1 Infection

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In 6 patients with primary human immunodeficiency virus type 1 (HIV-1) infection, concentrations of HIV-1 RNA and β2-microglobulin were monitored in cerebrospinal fluid (CSF) and in plasma during antiretroviral therapy. Four patients had neurological symptoms. At baseline, the CSF of 5 patients had detectable levels of HIV-1 RNA (median, 3.68 log_{10} copies/mL; range, <2.60–5.67 log_{10} copies/mL), and the CSF of 3 patients had elevated levels of β2-microglobulin. After 8 weeks of treatment, the median concentrations of HIV-1 RNA in CSF had decreased to <2.60 log_{10} copies/mL (range, <1.60–3.00 log_{10} copies/mL; P = .04) and in plasma to 3.07 log_{10} copies/mL (range, 2.57–3.79 log_{10} copies/mL; P = .03). Median concentration of β2-microglobulin in CSF had decreased to 1.2 mg/L (range, 0.9–1.7 mg/L; P = .06) and in plasma, to 1.7 mg/L (range, 1.1–2.2 mg/L; P = .03). After 48 weeks, HIV-1 RNA concentrations in 1 patient were still 1.97 log_{10} copies/mL in CSF and 1.51 log_{10} copies/mL in plasma, although β2-microglobulin concentrations in CSF and plasma had normalized after 8 weeks.

Primary HIV-1 infection is frequently associated with a transient flulike illness that is often undiagnosed or misdiagnosed [1, 2]. Neurological manifestations may occur, ranging from mild viral meningitis to encephalitis [2, 3]. The incidence of symptoms consistent with viral meningitis during primary HIV-1 infection is 9% [2]. Neurological symptoms generally resolve in several weeks [2]. HIV-1 and HIV-1 p24 have been detected in CSF specimens obtained from such patients [3, 4]. Very few longitudinal data are available on CSF findings for patients receiving antiretroviral treatment that was initiated at the time of primary HIV-1 infection [5, 6]. Because the investigation of CSF provides a window on what is happening in the brain parenchyma [7], we longitudinally measured HIV-1 RNA and β2-microglobulin in CSF and plasma from 6 patients who started receiving regimens of 5 or of 6 antiretroviral drugs at about this time.

PATIENTS AND METHODS

Since November 1997, 6 patients with primary HIV-1 infection have been enrolled in an open-label trial to evaluate the efficacy of a 5-drug treatment regimen
Table 1. Findings in CSF and in plasma for 6 patients with primary HIV-1 infection.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Neurological symptoms</th>
<th>Time to treatment, wk</th>
<th>CD4 count, cells/μL</th>
<th>HIV-1 RNA level, copies/mL</th>
<th>Leukocyte count, cells/μL</th>
<th>HIV-1 RNA level, copies/mL</th>
</tr>
</thead>
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<tr>
<td></td>
<td></td>
<td></td>
<td>CSF</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>16</td>
<td>Severe</td>
<td>6</td>
<td>390</td>
<td>19a</td>
<td>1800</td>
<td>280,000</td>
</tr>
<tr>
<td>18</td>
<td>Severe</td>
<td>4</td>
<td>340</td>
<td>59</td>
<td>470,000</td>
<td>300,000</td>
</tr>
<tr>
<td>20</td>
<td>Mild</td>
<td>4</td>
<td>350</td>
<td>5</td>
<td>20,000</td>
<td>930,000</td>
</tr>
<tr>
<td>21</td>
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<td>4</td>
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<td>4</td>
<td>&lt;400</td>
<td>44,000</td>
</tr>
<tr>
<td>23</td>
<td>Mild</td>
<td>2</td>
<td>730</td>
<td>203</td>
<td>7700</td>
<td>340,000</td>
</tr>
<tr>
<td>24</td>
<td>None</td>
<td>6d</td>
<td>670</td>
<td>40</td>
<td>620</td>
<td>25,000</td>
</tr>
</tbody>
</table>

NOTE. ND, not determined.

a Time from first symptoms of acute HIV-1 infection to the start of antiretroviral treatment.
b Data were available only for patients 16 and 18 at week 48.
c First CSF examination was done in another hospital.
d Time to treatment from documented seroconversion, no symptoms of acute HIV-1 infection.

differences were considered significant.

RESULTS

Five patients (patients 16, 18, 20, 21, 23) experienced an acute illness consistent with primary HIV-1 infection and had peak plasma HIV-1 RNA concentrations of ≥5 log10 copies/mL. For 4 of these 5 patients (patients 16, 18, 21, 23), the results of Western blotting were indeterminate during their first visit but evolved toward positive during follow up. One patient (patient 20) had a peak plasma HIV-1 RNA concentration of 6.4 log10 copies/mL, and the HIV-1 antibody level increased 4-fold after the acute illness. For 1 patient (patient 24), results of HIV-1 antibody screening were negative 6 months before study entry, but the patient was found to be HIV-1–seropositive 6 weeks before enrollment.

Two patients (patients 16 and 18) had severe neurological symptoms. Patient 16 had meningoencephaloradiculitis due to primary HIV-1 infection. The first CSF examination (done elsewhere) revealed the following values: leukocyte count, 130 cells/μL; protein level, 2.89 g/L; and glucose level, 2.2 mg/dL. The following tests yielded negative results: cultures for bacteria and virus, Ziehl-Neelsen staining, and PCR analysis for herpesviruses. Patient 18 had viral meningitis due to primary HIV-1 infection; symptoms gradually resolved over several weeks. Two patients (patients 20 and 23) had mild neurological symptoms (headache and fever), and 2 patients had no neurological symptoms (table 1).
At baseline, 5 patients had detectable HIV-1 RNA in CSF (median, 3.68 log_{10} copies/mL; range, <2.60–5.67 log_{10} copies/mL); the 2 patients without neurological symptoms had either low (2.79 log_{10} copies/mL) or undetectable levels (figure 1; table 2). In CSF, neither leukocyte level nor protein levels correlated with levels of HIV-1 RNA (data not shown). Concomitant plasma levels of HIV-1 RNA were 5.46 log_{10} copies/mL (range, 4.40–5.97 log_{10} copies/mL). Levels of HIV-1 RNA in CSF were not significantly correlated with plasma HIV-1 RNA levels (r = .77; P = .07). After 8 weeks of treatment, levels of HIV-1 RNA in CSF decreased significantly, to a median of <2.60 log_{10} copies/mL (range, <1.60–3.00 log_{10} copies/mL; P = .04; figure 1; tables 1 and 2).

For 2 patients, data were available for week 48. The patient who had the highest level of HIV-1 RNA in CSF at baseline (5.67 log_{10} copies/mL; plasma HIV-1 RNA level, 5.48 log_{10} copies/mL) still had detectable HIV-1 RNA after 8 weeks (in CSF, 3.00 log_{10} copies/mL; in plasma, 3.52 log_{10} copies/mL) and after 48 weeks (in CSF, 1.97 log_{10} copies/mL; in plasma, 1.51 log_{10} copies/mL). The plasma HIV-1 RNA level remained <0.70 log_{10} copies/mL from week 71 onwards, but follow-up measurement of concentrations in CSF was not planned to be performed until week 96. The other patient’s HIV-1 RNA levels in CSF were <1.60 log_{10} copies/mL at both week 8 and 48. Plasma HIV-1 RNA levels decreased significantly, from 5.46 log_{10} copies/mL (range, 4.40–5.97 log_{10} copies/mL) to 3.07 log_{10} copies/mL (range, 2.57–3.79 log_{10} copies/mL; P = .03) after 8 weeks of treatment (figure 1).

In addition, the CSF inflammatory response was evaluated during treatment. After 8 weeks of treatment, the median leukocyte count in CSF decreased from 30 cells/µL (range, 4–203 cells/µL; >90% lymphocytes in all patients) to 4 cells/µL (range, 2–13 cells/µL; P = .03). The median protein level in CSF decreased slightly, from 0.58 g/L (range, 0.32–1.36 g/L) to 0.48 g/L (0.22–0.68 g/L; P = .10). At baseline, β_{2}-microglobulin levels in CSF were significantly higher in patients infected with HIV-1 than levels in HIV-1–seronegative control subjects (P = .002), and they were elevated in 3 patients (table 2).

Baseline levels of β_{2}-microglobulin in CSF were significantly correlated with the leukocyte count in CSF (r = .83; P = .04) and protein levels in CSF (r = .83; P = .04). Baseline levels of β_{2}-microglobulin in plasma also were higher in case patients than they were in control subjects (P = .002). Baseline levels of β_{2}-microglobulin in CSF and plasma were significantly correlated (r = .78; P < .001); 4 patients had levels of β_{2}-microglobulin in CSF that exceeded the levels in plasma. After 8 weeks of treatment, levels of β_{2}-microglobulin in CSF decreased from 2.5 mg/L (range, 0.9–5.5 mg/L) to 1.2 mg/L (range, 0.9–1.7 mg/L; P = .06; figure 2).

For 2 patients, data were available for week 48. For patient 16, the β_{2}-microglobulin level in CSF decreased from 2.0 mg/L at baseline to 1.2 mg/L at week 8 and to 0.8 mg/L at week 48; the level in plasma decreased from 1.7 mg/L at baseline to 1.1 mg/L at week 8 and 1.0 mg/L at week 48. At baseline, patient 18 had elevated levels of β_{2}-microglobulin in CSF and in plasma (5.5 and 3.1 mg/L, respectively), which decreased to 1.4 and 1.9 mg/L, respectively, after 8 weeks and to 0.9 and 1.1 mg/L, respectively, after 48 weeks. After 8 weeks, levels of β_{2}-microglobulin in plasma had decreased from 2.6 mg/L (range, 1.4–3.1 mg/L) to 1.7 mg/L (range, 1.1–2.2 mg/L; P = .03; figure 2).

### DISCUSSION

Measuring the level of HIV-1 RNA in CSF may indicate what is happening in the brain [7]. HIV-1 RNA is detectable in the

Figure 1. β_{2}-microglobulin concentrations at baseline and at week 8 in CSF and in plasma from patients with HIV-1 infection who were receiving regimens of 5 or 6 antiretroviral drugs to treat primary infection.
CSF of most untreated asymptomatic HIV-1–infected persons [9–11], and over several years a small but significant increase is seen in the level [11]. The concentration of HIV-1 RNA in CSF varies widely (range, <2.30–5.10 \log_{10} \text{ copies/mL}), but it is generally lower than the concentration in plasma [9–12]. However, levels of HIV-1 RNA in CSF may surpass levels in plasma [9, 10, 12]. The CSF HIV-1 RNA concentration is correlated with the CSF lymphocyte count but not necessarily with the plasma HIV-1 concentration [9, 10, 12, 13]. Therefore, it is assumed that lymphocytes are the main source of HIV-1 in the CSF of asymptomatic patients. Leakage of HIV-1 from plasma is improbable, because in these patients the integrity of the blood-brain barrier has generally been preserved. However, lymphocyte transport across an intact blood-brain barrier is known to occur [9, 10, 13]. In neurologically symptomatic patients, CSF HIV-1 RNA concentrations correlate with the presence and severity of cognitive impairment, neuropathologic abnormalities, and with high levels of HIV-1 RNA in the brain [14–17]. In these patients, CSF HIV-1 RNA levels are independent of CSF lymphocyte counts, a finding that strongly supports the hypothesis that brain macrophages are the source of HIV-1 RNA in the CSF [7, 18]. In asymptomatic patients, the levels of HIV-1 RNA in CSF and in plasma are seen to decrease at the same rate after the initiation of antiretroviral therapy; whereas in demented persons, the level decreases more slowly in CSF than in plasma, which suggests that HIV-1 replication in the CNS becomes increasingly independent in patients with advanced HIV-1 infection [18].

There is a preliminary report on the monitoring of HIV-1 RNA in CSF in 4 patients who were receiving combination antiretroviral treatment that was started during primary HIV-1 infection, which demonstrated that the level of HIV-1 RNA in CSF had become undetectable after 8 weeks [5]. In 2 patients for whom baseline data were unavailable, HIV-1 RNA was unde-

tectable in CSF after 2 and 2.5 years of triple-nucleoside therapy that was initiated at the time of primary HIV-1 infection [6]. HIV-1 replication may mediate an inflammatory response in the CNS that is reflected in an increased CSF lymphocyte count, a higher IgG index, and elevated levels of markers of immune activation, including \( \beta_2 \)-microglobulin and neopterin [19]. \( \beta_2 \)-microglobulin levels are the more interesting of the latter 2 markers, because neurologically asymptomatic patients with elevated concentrations of \( \beta_2 \)-microglobulin in CSF have a much higher risk of eventually developing AIDS dementia [20]. Longitudinal data have shown that the CSF \( \beta_2 \)-microglobulin concentration slightly increases over time in untreated persons infected with HIV-1 [19]. Elevated \( \beta_2 \)-microglobulin concentrations in CSF have been reported in 3 patients with primary HIV-1 infection [21]; \( \beta_2 \)-microglobulin had become undetectable 10 weeks after therapy was initiated but had increased 11 months after.

We monitored HIV-1 RNA and \( \beta_2 \)-microglobulin concentrations in the CSF of 6 patients who initiated antiretroviral treatment within 6 weeks of first symptoms of primary HIV-1 infection or documented HIV-1 seroconversion. We chose to use the 5-drug regimen described above in this open-label study because its antiviral effect is superior to that of a 3-drug regimen [8]. Many data support the initiation of antiretroviral treatment during primary HIV-1 infection. Initiating aggressive treatment at this stage may facilitate the HIV-1–specific CD4 T cell response and may lead to a greater reduction in HIV-1 viremia than that in persons who start treatment during chronic infection [22, 23].

HIV-1 RNA was detectable (>400 copies/mL) in CSF samples of 5 of our 6 patients. The level of HIV-1 RNA in CSF surpassed the level in plasma in 1 patient who had severe neurological symptoms before the start of treatment. The lowest CSF HIV-1 RNA concentrations were seen in the 2 patients who did not have neurological symptoms. An inflammatory response was seen in some patients: 4 patients had elevated leukocyte counts in CSF, which is consistent with viral meningitis; levels of \( \beta_2 \)-microglobulin in CSF were elevated in 3 patients and were significantly higher than levels in control subjects.

After 8 weeks of treatment, the concentration of HIV-1 RNA, the leukocyte count, and the levels of \( \beta_2 \)-microglobulin in CSF decreased at the same rate as levels of HIV-1 RNA and \( \beta_2 \)-microglobulin in plasma. Of note, in 1 patient, HIV-1 RNA was still detectable in CSF (1.97 \log_{10} \text{ copies/mL}) after 48 weeks of treatment, and the concentration exceeded that in plasma (1.51 \log_{10} \text{ copies/mL}). This patient began with the 5-drug regimen and changed to the 6-drug regimen at week 14. His CSF \( \beta_2 \)-microglobulin concentration was elevated at baseline but had normalized after 8 weeks of treatment. Our findings demonstrate that clearance of HIV-1 RNA from CSF (and plasma) may not be complete after 48 weeks of aggressive treatment initiated within 6 weeks of a diagnosis of primary HIV-1 in-

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**Figure 2.** HIV-1 RNA concentrations at baseline and at week 8 in CSF and in plasma from patients with HIV-1 infection who were receiving regimens of 5 or 6 antiretroviral drugs to treat primary infection.
fection. Eleven patients from our institution started treatment with 2 nucleoside analogues (if necessary, augmented with a protease inhibitor) during chronic HIV-1 infection and had CSF HIV-1 RNA levels of <50 copies/mL after 48 weeks, even when plasma response was not complete [24].

Several explanations can be given for the slow decrease in HIV-1 RNA levels in patient 18. The drug combination used was not the culprit, because it included all of the drugs administered in a previous study [24]. A discordant HIV-1 response in CSF and blood may be explained by divergent resistance patterns in these compartments [25]. There is no reason to doubt that these highly motivated patients adhered to their therapeutic regimens; furthermore, patient 18 eventually had an undetectable plasma HIV-1 RNA concentration. The very high concentration of HIV-1 RNA in CSF at baseline may be a contributing factor. Another explanation could be that, at this early stage of HIV-1 infection, the immune response is still immature. Clearance of HIV-1 RNA from the CSF may be slow in patients who start therapy during primary HIV-1 infection. Similar data have been found with regard to levels in plasma [26].

References

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