CD4 Cell Count and HIV DNA Level Are Independent Predictors of Disease Progression after Primary HIV Type 1 Infection in Untreated Patients

Cécile Goujard,1,3 Mojgan Bonarek,1 Laurence Meyer,7 Fabrice Bonnet,1 Marie-Laure Chaix,4 Christiane Deveau,2 Martine Sinet,7 Julie Galimand,6 Jean-François Delfraissy,1,3 Alain Venet,3 Christine Rouzioux,4 Philippe Morlat,5 and the Agence Nationale de Recherche sur le Sida PRIMO Study Group*

1Service de Médecine Interne and 2INSERM-INED/Paris XI U569, Service d’Épidémiologie, Bicêtre Hospital, Assistance Publique–Hôpitaux de Paris (AP-HP), and 3INSERM E109, Faculté de Médecine Paris-Sud, Le Kremlin Bicêtre, 4Laboratoire de Virologie et Equipe d’Accueil–Ministère de la Recherche et des Technologies 3620, Necker-Enfants Malades Hospital, AP-HP, Paris, and 5Service de Médecine Interne et Maladies Infectieuses, Saint André Hospital, Bordeaux, France

Background. Treatment initiation at the time of primary human immunodeficiency virus (HIV) type 1 (HIV-1) infection has become less frequent in recent years.

Methods. In the French prospective PRIMO Cohort, in which patients are enrolled at the time of primary HIV-1 infection, 30% of the 552 patients recruited during 1996–2004 did not start receiving antiretroviral treatment during the first 3 months after diagnosis. We analyzed the patients’ clinical and immunological outcomes and examined potential predictors of disease progression. Progression was defined as the occurrence of an acquired immunodeficiency syndrome (AIDS)–related clinical event or a CD4 cell count <350 cells/mm3.

Results. Fifty-six (34%) of the untreated patients experienced immunological progression during a median duration of follow-up of 24 months, and 1 of these patients had an AIDS-related event. The estimated risks of progression were 25%, 34%, and 42% at 1, 2, and 3 years after enrollment, respectively. Compared with patients who did not have progression, those with progression had significantly lower CD4 cell counts at diagnosis (455 vs. 738 cells/mm3), higher plasma HIV RNA levels (4.9 vs. 4.5 log10 copies/mL), and higher HIV DNA levels (3.3 vs. 3.0 log10 copies/106 peripheral blood mononuclear cells [PBMCs]). All 3 parameters were significantly associated with progression in univariate analysis. In multivariate analysis, only the CD4 cell count and HIV DNA level were independently predictive of disease progression (relative hazard for CD4 cell count, 1.84 per decrease of 100 cells/mm3; relative hazard for HIV DNA level, 2.73 per increase of 1 log10 copies/106 PBMCs).

Conclusions. Both a low initial CD4 cell count and a high HIV DNA level are predictive of rapid progression of untreated primary HIV-1 infection. Affected patients may therefore benefit from close clinical and laboratory monitoring and/or early administration of treatment.

The potential benefit of starting antiviral therapy during primary HIV infection is still controversial [1–4]. Administration of combination antiretroviral therapy at this stage may reduce the initial spread of the virus through the body, attenuate T cell activation, and preserve HIV-specific immune responses [5–11]. Early treatment is also as efficient as later treatment with regard to viral replication, CD4 cell count, and progression to AIDS [12–14]. However, the benefits of treatment initiation during primary HIV infection have not yet been examined in a controlled clinical trial. Because of the toxicity and complexity of long-term antiretroviral regimens, treatment interruptions and suboptimal adherence to therapy are common [15–17]. In addition, viral rebound is common when the patient interrupts treatment that had been started during the acute phase of infection [18]. Recent guidelines state that therapy is optional for patients with ongoing acute infection and for those who had seroconversion <6 months earlier [19–21].
In the French PRIMO Cohort, in which HIV-1–infected patients are recruited at the time of primary HIV infection, the proportion of initially untreated patients increased markedly from 1996 to 2004 [17]. This raises issues concerning the prognosis for such patients and the predictive value of initial immunological and virological parameters. Long-lasting and intense symptoms during primary HIV infection are associated with poorer subsequent outcomes, but unlike during the chronic phase of infection, it is less established whether virological and/or immunological factors during primary HIV infection are predictive of disease progression [22–24].

Here, we describe the outcomes for patients enrolled in the prospective PRIMO Cohort who received a diagnosis of primary HIV-1 infection during the HAART era and who did not immediately begin taking antiretroviral treatment. We also report baseline factors predictive of subsequent clinical and immunological progression.

PATIENTS AND METHODS

The PRIMO Cohort. The ongoing multicenter French PRIMO Cohort enrolled 552 patients with primary HIV infection between November 1996 and October 2004. The median duration of follow-up of these patients is currently 30 months (interquartile range, 16–54 months). The PRIMO study protocol was approved by the Paris Cochin Ethics Committee. After giving their written informed consent, patients are enrolled if they had seroconversion to HIV-1 infection between November 1996 and October 2004. The median duration of follow-up of these patients is currently 30 months (interquartile range, 16–54 months). The PRIMO study protocol was approved by the Paris Cochin Ethics Committee.

Here, we describe the outcomes for patients enrolled in the prospective PRIMO Cohort who received a diagnosis of primary HIV-1 infection during the HAART era and who did not immediately begin taking antiretroviral treatment. We also report baseline factors predictive of subsequent clinical and immunological progression.

Results

Characteristics of the patients. Among the 552 patients enrolled in the PRIMO Cohort during the study period, 163 (30%) did not start receiving antiretroviral therapy at or soon after enrollment. Clinical progression was defined by the occurrence of death or an AIDS-defining event (on the basis of Centers for Disease Control and Prevention category C from 1993). Immunological progression was defined by the occurrence of a CD4 cell count <350 cells/mm³ at or after the 3-month visit (because immunological fluctuations can occur during the acute phase of HIV infection). We chose this value because it represents the threshold at which treatment is generally indicated during both primary HIV infection and the chronic phase of infection.

Statistical analysis. Times to events were calculated by constructing Kaplan-Meier survival curves from the date of enrollment to the date of progression. For patients who did not experience the event, data were censored at their last visit before 30 June 2005 (n = 93) or at the initiation of treatment, regardless of the reason for initiation (n = 14). Statistical comparisons were based on the nonparametric Wilcoxon test or Student’s t test for continuous variables. Percentages were compared by using the χ² test or Fisher’s exact test. Relative hazards (RHs) of progression, according to baseline characteristics, were estimated using a Cox proportional hazards model, after checking that the assumption of proportionality held. The following characteristics were considered: age, sex, the presence or absence of symptoms, CD4 and CD8 cell counts, and plasma HIV RNA and HIV DNA levels at study enrollment. Variables associated with the risk of progression in univariate analysis (P<.25) were included in the final multivariate model. Data were analyzed using SAS software (SAS Institute).

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counts were 599 and 662 cells/mm³ \((P = .05)\), and the respective HIV DNA levels were 3.3 and 2.8 log\(_{10}\) copies/10\(^6\) PBMCs \((P = .0002)\).

**Disease progression among untreated patients.** During follow-up, 56 patients (34%) had immunological progression, as defined by a CD4 cell count of <350 cells/mm³. Only 1 patient had an AIDS-defining event (recurrent bacterial pneumonia; CD4 cell count, 222 cells/mm³). The median HIV RNA level was 5.0 log\(_{10}\) copies/mL (range, 3.0–5.9 log\(_{10}\) copies/mL) at the time of disease progression. The median time to progression among these 56 patients was 6.7 months after enrollment.

Overall, the median time to disease progression estimated from Kaplan-Meier curves was 42 months after enrollment. Estimates of the risk of progression were 16% at 6 months (95% CI, 10%–22%), 25% at 1 year (95% CI, 18%–32%), 34% at 2 years (95% CI, 25%–42%), and 42% at 3 years (95% CI, 32%–52%) (figure 1).

Twenty-one patients (38%) were “early progressors,” because they had CD4 cell counts <350 cells/mm³ at month 3. Of these patients, 16 had CD4 cell counts <350 cells/mm³ at enrollment \((n = 11)\) or at the month 1 visit \((n = 5)\).

**Factors predictive of disease progression.** At baseline, patients with disease progression had a significantly lower median CD4 cell count than did those without progression (455 vs. 738 cells/mm³; \(P < .0001\)), and they also had a higher median HIV RNA level (4.9 vs. 4.5 log\(_{10}\) copies/mL; \(P = .03\)) and a higher median HIV DNA level (3.3 vs. 3.0 log\(_{10}\) copies/10\(^6\) PBMCs; \(P = .003\)). Age, sex, time since infection, clinical features of primary HIV infection, and CD8 count did not influence the risk of progression.

Kaplan-Meier estimates were then made for strata established according to different threshold values of laboratory parameters (figure 2). As shown in figure 2A, a CD4 cell count <500 cells/mm³ was associated with a 77% risk of progression at 2 years (95% CI, 62%–93%), compared with only 5% (95% CI, 0%–12%) when the CD4 cell count was >750 cells/mm³. A HIV RNA level >5.0 log\(_{10}\) copies/mL was associated with a 55% risk of progression at 2 years (95% CI, 44%–80%), compared with 8% (95% CI, 0%–17%) among patients with levels <4.0 log\(_{10}\) copies/mL (figure 2B). An HIV DNA level >3.4 log\(_{10}\) copies/10\(^6\) PBMCs (corresponding to the 66th percentile value) was associated with a 62% risk of progression at 2 years (95% CI, 44%–80%), compared with 13% (95% CI, 2%–23%) among patients with values <2.9 log\(_{10}\) copies/10\(^6\) PBMCs (corresponding to the 33rd percentile value) (figure 2C). The significant prognostic value of these parameters persisted when cutoffs established according to the 33rd and 66th percentile of CD4 cell counts and HIV RNA were used.

Cox modeling was used to further quantify the impact of these factors (table 2). The relative risks of progression were 1.95 per decrease in the CD4 cell count of 100 cells/mm³ \((P < .0001)\), 1.70 per increase in the HIV RNA level of 1 log\(_{10}\) copy/mL \((P = .0001)\), and 4.03 per increase in the HIV DNA level of 1 log\(_{10}\) copy/10\(^6\) PBMCs \((P < .0001)\).

Table 2 shows the results of multivariate analysis including age, the baseline CD4 cell count, and baseline HIV RNA and HIV DNA levels. A low CD4 cell count and a high HIV DNA level remained independently associated with an increased risk of progression, with relative risks of 1.84 per decrease in the CD4 cell count of 100 cells/mm³ \((P < .0001)\) and 2.73 per increase in the HIV DNA level of 1 log\(_{10}\) copy/10\(^6\) PBMCs \((P = .003)\). In contrast, HIV RNA was no longer associated with progression.

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**Table 1. Baseline characteristics of the 552 patients in the PRIMO Cohort, according to therapeutic approach.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treated patients ((n = 389))</th>
<th>Untreated patients ((n = 163))</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median years (IQR)</td>
<td>34 (28–42)</td>
<td>33 (28–40)</td>
<td>.44</td>
</tr>
<tr>
<td>Male sex</td>
<td>82</td>
<td>78</td>
<td>.24</td>
</tr>
<tr>
<td>Exposure category</td>
<td></td>
<td></td>
<td>.16</td>
</tr>
<tr>
<td>Homosexual contact</td>
<td>62</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>Heterosexual contact</td>
<td>29</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Period of enrollment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1996–2001 ((n = 306))</td>
<td>82</td>
<td>18</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>2002–2004 ((n = 246))</td>
<td>57</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Time since infection, median days (IQR)</td>
<td>40 (33–54)</td>
<td>68 (47–96)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Duration of follow-up, median months (IQR)</td>
<td>40 (19–66)</td>
<td>24 (12–38)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Symptomatic primary HIV infection</td>
<td>90</td>
<td>80</td>
<td>.001</td>
</tr>
<tr>
<td>CD4 cell count, median cells/mm³ (IQR)</td>
<td>478 (351–628)</td>
<td>628 (460–813)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Plasma HIV RNA level, median log(_{10}) copies/mL (IQR)</td>
<td>5.3 (4.7–5.8)</td>
<td>4.6 (3.8–5.2)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>HIV DNA level, median log(_{10}) copies/10(^6) PBMCs (IQR)</td>
<td>3.4 (3.0–3.7)</td>
<td>3.2 (2.7–3.5)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

**NOTE.** Data are percentage of patients, unless otherwise indicated. IQR, interquartile range.
Figure 1. Progression-free survival among untreated patients in the French PRIMO Cohort. Progression was defined as a CD4 cell count <350 cells/mm³.

Figure 2. Progression-free survival among untreated patients, according to the baseline CD4 cell count (in cells/mm³), plasma HIV RNA level (in log₁₀ copies/mL), and HIV DNA level (in log₁₀ copies/10⁶ PBMCs). Kaplan-Meier estimates were made for 3 classes of CD4 cell count (A), HIV RNA level (B), and HIV DNA level (C). Progression was defined as a CD4 cell count <350 cells/mm³.

with the risk of disease progression. To better define the respective impacts of the CD4 cell count and HIV DNA level, we also made Kaplan-Meier estimates for patients with values greater than and less than the overall baseline median CD4 cell count (628 cells/mm³); patients in each subgroup were further stratified according to the median HIV DNA level (3.2 log₁₀ copies/10⁶ PBMCs). The risk of progression was very low when the CD4 cell count was >628 cells/mm³, regardless of the HIV DNA level (figure 3A). When the CD4 cell count was ≤628 cells/mm³ (figure 3B), a high HIV DNA level added significant weight to the predictive value of the CD4 cell count. The estimated risk of progression among these patients within the first 2 years ranged from 41% (95% CI, 21%–60%) among those with a HIV DNA level <3.2 log₁₀ copies/10⁶ PBMCs to 83% (95% CI, 67%–99%) among those with higher HIV DNA levels (P = .006, by log rank test).

DISCUSSION

An increasing proportion of patients enrolled in the French PRIMO Cohort do not start receiving antiretroviral treatment within 3 months after the diagnosis of primary HIV-1 infection. Here, we examined the risk of clinical and immunological progression among the 163 untreated patients recruited from November 1996 to October 2004. During the follow-up period, only 1 patient had an AIDS-related clinical event, whereas 34% of the patients experienced immunological progression, as defined by a CD4 cell count <350 cells/mm³.

The prognostic value of CD4 cell count and HIV RNA level has been analyzed in untreated patients who have had HIV-1 seroconversion, but these studies were performed before the HAART era and rarely included patients who received a diagnosis at the time of primary infection, and progression was defined by either a clinical event or a CD4 cell count <200 cells/mm³ [27–30]. Because immediate treatment initiation is now considered to be optional for patients who receive diagnoses during acute HIV-1 infection, treatment is generally indicated when the CD4 cell count decreases to <350 cells/mm³ [20, 21]. We therefore used this threshold value as an end point for the analysis of progression.

The very low rate of clinical progression is likely to be the result of early treatment initiation for patients with severe acute infection. In contrast, immunological progression was frequent, occurring in 34% of patients. The estimated risks of progression were 25%, 34%, and 42% at years 1, 2, and 3, respectively—values close to those observed elsewhere during the natural course of HIV-1 infection [31]. These rates of progression are surprisingly high, because untreated patients generally had less severe primary infection than did treated patients.
When the HIV RNA level reaches its plateau after seroconversion, its predictive value for progression to AIDS is well established [32]. In contrast, the prognostic value of HIV RNA level in the early phase of infection is more controversial [7, 28, 33–35]. This apparent discrepancy may be because of the strong variability of HIV RNA levels, a phenomenon that may undermine their predictive value [27–31]. In our study, the predictive value of HIV RNA level for immunological progression disappeared when the CD4 cell count and HIV DNA levels were taken into account.

The HIV DNA level in PBMCs provides an estimate of the cellular HIV reservoir, which is established soon after infection [36, 37]. We found that HIV DNA level was predictive of the risk of progression, independently of CD4 cell count and HIV RNA level. This is consistent with previous studies showing that HIV DNA level is an important predictor of CD4 cell loss, AIDS, and death, both in patients with recent or chronic infection [25, 37].

As expected, we found that the baseline CD4 cell count was the most potent predictor of progression in patients with recent seroconversion. Among the 47 patients who had a CD4 cell count <500 cells/mm³ during the first 3 months after enrollment, 77% had disease progression within 2 years. Very few patients who had a CD4 cell count <350 cells/mm³ during primary HIV infection experienced a spontaneous increase thereafter. Conversely, patients whose CD4 cell counts were >750 cells/mm³ had only a 5% risk of progression at 2 years.

The predictive value of the CD4 cell count has major significance for the therapeutic management of primary HIV-1–infected patients. In the PRIMO Cohort, treatment now tends to be withheld until the CD4 cell count decreases to 350 cells/mm³. This treatment-sparing strategy is currently being compared with an initial short-course therapy in the Spartac trial, which is described on the Web site of The National Research Register (http://www.nrr.nhs.uk/ViewDocument.asp?ID=N0241121238). Our results suggest that patients with CD4 cell counts >750 cells/mm³ during acute infection should not be treated immediately, given the potential adverse effects of therapy. This may also apply to patients with CD4 cell counts of 500–750 cells/mm³, who have a 25% risk of progression within 2 years; however, the additive predictive value of HIV DNA level observed here may also be of assistance in the decision-making process. Finally, immediate treatment appears to be warranted for most patients with CD4 cell counts <500 cells/mm³. This is particularly the case for patients with a high HIV DNA level and/or a CD4 cell count <350 cells/mm³ during the first 3 months after diagnosis. It should be noted that patients with baseline CD4 cell counts <500 cells/mm³ represented 47% of the PRIMO Cohort population.

This study underlines the fact that immunological status can worsen rapidly in the absence of early treatment during primary HIV infection, even in a selected population of patients with relatively mild acute symptoms. Such patients must receive close clinical and laboratory monitoring if it is decided to postpone treatment. In addition to the CD4 cell count, the HIV DNA level may be a useful tool for making decisions regarding

Table 2. Risk factors for progression in the 163 patients untreated at the time of primary infection.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Crude RH (95% CI)</th>
<th>P</th>
<th>Adjusted RH (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 cell count (per 100-cell decrease)</td>
<td>1.95 (1.63–2.32)</td>
<td>&lt;.0001</td>
<td>1.84 (1.52–2.23)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>HIV RNA level (per 1-log₁₀ increase)</td>
<td>1.70 (1.30–2.22)</td>
<td>.0001</td>
<td>0.94 (0.67–1.32)</td>
<td>.73</td>
</tr>
<tr>
<td>HIV DNA (per 1-log₁₀ increase)</td>
<td>4.03 (2.29–7.08)</td>
<td>&lt;.0001</td>
<td>2.73 (1.40–5.32)</td>
<td>.003</td>
</tr>
<tr>
<td>Age at inclusion (&gt;33 years)</td>
<td>1.56 (0.90–2.70)</td>
<td>.11</td>
<td>1.55 (0.88–2.73)</td>
<td>.13</td>
</tr>
</tbody>
</table>

NOTE. RH, relative hazard.

Figure 3. Progression-free survival among untreated patients, according to the baseline HIV DNA level (in log₁₀ copies/10⁶ PBMCs), after stratification for the median baseline CD4 cell count. Kaplan-Meier estimates were made for patients with a high CD4 cell count (A) and a low CD4 cell count (B).
the optimal time to prescribe treatment to a patient with primary HIV-1 infection.

THE AGENCE NATIONALE DE RECHERCHE SUR LE SIDA PRIMO COHORT STUDY GROUP

J. Beylot, P. Morlat, D. Malvy, M. Bonarek, and F. Bonnet (St. André, Bordeaux); C. Caulin, E. Badsy, J. Cervoni, V. Vincent (Lariboisière, Paris); J.M. Molina and D. Ponscarme (St. Louis, Paris); A. P. Blanc and T. Allégre (Aix en Provence); J. F. Delfraissy, C. Goujard, and Y. Quertainmont (Bicêtre, Le Kremlin Bicêtre); F. Raffi, V. Reliquet, E. Billault, and J. L. Esnault (Hôtel-Dieu, Nantes); J. Reynes, V. Baillat, and V. Le Moing (Gu de Chauliac, Montpellier); J. M. Livrozet, F. Jeanblanc, and P. Chiarello (E. Herriot, Lyon); F. Bricaire, C. Katlama, J. Ghosn, H. Ait Mohand, and C. Duvivier (Pitié-Salpêtrière, Paris); B. Dupont and J. P. Viard (Necker, Paris); E. Rouveix, S. Morelon, and C. Dupont (A. Paré, Boulogne); C. Trepo, N. Benmaklouf, and C. Augustin-Normand (Hôtel-Dieu, Lyon); A. Cabié and S. Abel (CHU, Fort de France); R. Thomas, F. Souala, and C. Peaucelle (Pontchaillou, Rennes); J. L. Vildé, J. Jestin, and C. Jadad (Bichat, Paris); G. Piaoux, W. Rosenbaum, L. Slama, and C. Chakvetadze (Tenon, Paris); P. Yéni, E. Bouvet, and I. Fournier (Bichat, Paris); D. Séréné and C. Lascoux (St. Louis, Paris); E. Pichard, P. Fialaire, and J. M. Cheneubault (Angers); J. Beytout and C. Jacomet (Hôtel Dieu, Clermont-Ferrand); P. Henon, G. Beck-Wirth, and C. Beck (Emile Muller, Mulhouse); M. Kazatchkine, D. Batisse, and J. Derouineau (HEGP, Paris); D. Sicard, D. Salmon, and A. Brunet (Cochin, Paris); A. Sobel, P. Lesprit, and A. S. Lascaux (H. Mondor, Créteil); H. Aumaitre, B. Delmas, and M. Saada (Joffre, Perpignan); A. Devidas, P. Chevojon, and P. Kousignian (Corbeil); R. Verdon and M. Six (CHR Côte de Nacre, Caen); P. Massip and M. Obadia (Purpan, Toulouse); S. Herson and A. Simon (Pitié-Salpétrière, Paris); H. Gallais, I. Ravaux, and C. Tomei (La Conception, Marseille); P. Morel and F. Timsit (St. Louis, Paris); P. M. Girard, D. Samaan-Bollens, and P. Campa (St. Antoine, Paris); P. Galanaud, F. Boué, and J. Polo de Veto (A. Béclère, Clamart); P. Choutet, P. Nau, and F. Bastides (Bretonneau, Tours); C. Miodovski (Paris); G. Guermonprez and A. Duplioust (Bligny, Briis s/Forges); and P. Boudon and D. Malbec (Aulnay s/Bois).

HIV/AIDS

10. Alfeld M, Rosenberg E, Shankarappa R, et al. Cellular immune re-


