Predictive value of viral load and other markers for progression to clinical AIDS after CD4+ cell count falls below 200/µL

N Carre, F Boufassa, JB Hubert, M Chavance, C Rouzioux, C Goujard, Y Laurian, L Meyer and the SEROCO & HEMOCO Study Group

Background To assess the predictive value of biological and clinical events for progression to AIDS (1993 European classification) when the CD4+ cell count falls below 200/µL (CD4 threshold) in different exposure groups. To investigate whether such markers remain predictive independently of the serum HIV-1 RNA level at the CD4 threshold.

Methods The predictive value of biological and clinical events occurring during the 24 months prior to the occurrence of CD4 threshold (n = 333) was quantified in a Cox model. Another Cox model was carried out in a subset of 77 patients in whom viral load from stored sera was available. Furthermore, changes in viral load during the 24 months preceding the CD4 threshold were assessed in a mixed model according to subsequent development of AIDS.

Results Among the 333 patients, the slope of the CD4+ cell counts, the emergence of p24 antigen, persistent thrush, and age at the CD4 threshold were independent predictors of progression to clinical AIDS (44.7%). Among the subset of 77 patients, the HIV-1 RNA level at the CD4 threshold, persistent thrush and age remained independent predictors of progression to AIDS (45.5%). The increase of the HIV-1 RNA level was moderate, both in non-progressors (24.0% per year) and in those who subsequently developed AIDS (27.1% per year), (P = 0.93). Viral load was consistently higher in the latter group (P = 0.002).

Conclusion At a late stage of infection, age and persistent thrush remain predictive of progression to AIDS, independently of viral load.

Keywords CD4 <200/µL, AIDS onset, markers, viral load, exposure groups

Accepted 23 January 1998

The progression of human immunodeficiency virus type 1 (HIV-1) disease is characterized by a gradual depletion of CD4+ cells. A CD4+ cell count of <200/µL is predictive of clinical AIDS, and prophylaxis of certain opportunistic infections is thus recommended when this threshold is reached. Classically, antiretroviral treatment is required if the immunodepression worsens rapidly. It is therefore important to identify people at higher risk of progression to AIDS, on the basis of biological and clinical parameters collected before this threshold count of 200 CD4+ cells/µL is reached (hereafter referred to as the CD4 threshold). Most known markers of progression reflect the decline of the CD4+ cell counts. Few therefore remain predictive when the CD4 threshold is reached. Markers independent of the CD4 cell count are persistent thrush and weight loss in the months preceding the CD4 threshold. Detectable p24 antigenemia when the CD4 threshold is reached is also associated with more rapid progression to AIDS. However, these reports involved only homosexual men and their important results need to be confirmed in a study including different exposure groups. Furthermore, the recent advent of techniques for quantifying HIV-1 RNA has modified the study of markers of progression. The HIV-1 RNA level is an early marker of the risk of progression to AIDS, but little is known of its predictive value for AIDS at a later stage, when the CD4 cell count reach the value of 200/µL. It is particularly important to know if the HIV-1 RNA level is the only independent marker of progression to clinical AIDS in severely immunodeficient patients. In other
words, do the markers classically used to monitor HIV-infected patients still remain predictive, independently of viral load measured at CD4 threshold?

We first studied the predictive value of clinical and biological markers on the risk of progression to AIDS once the CD4+ cell count has fallen below 200/μL in patients belonging to different HIV exposure groups. In a subset of patients where viral load was quantitated before the use of this measurement in routine clinical practice, we tested the independent effect of HIV-1 RNA level at CD4 threshold.

Patients and Methods

Description of the SEROCO & HEMOCO cohorts

Started in 1988 and 1989 respectively, the SEROCO & HEMOCO studies are multicentre prospective cohorts coordinated by the same team and based on identical protocols. Subjects are included in the SEROCO cohort if the diagnosis of HIV-1 seropositivity dates back less than a year or if the date of seroconversion is documented. As of 15 June 1995, 1504 adult volunteers infected by HIV-1 had been enrolled. Except for haemophiliacs, all exposure groups are represented in the cohort. Seventeen centres participate in the recruitment of patients, including 16 hospitals in Paris and the south of France and a network of private practitioners. The HEMOCO cohort is composed of 407 HIV-1-positive haemophiliacs infected by blood products between 1978 and 1985. In both cohorts, clinical and biological data are recorded at enrolment and then every 3 or 6 months according to clinical status. The HIV-1 infection is diagnosed by ELISA methods and confirmed by Western blot. Lymphocytes subsets are determined by flow cytometry. Sera are stored regularly at -180°C in liquid nitrogen. As viral load was not routinely used in the monitoring of HIV infected patients before the cutoff date of analysis (15 June 1995), HIV-1 RNA level was measured in the stored frozen sera of a subset of patients (n = 363) using identical RT-PCR test (Amplicor HIV Monitor test, Roche Diagnostic Systems, Neuilly-sur-Seine, France; cutoff 400 copies/ml). This subset derived from another study on the evolution of viral load in patients with a documented date of infection. The AIDS diagnoses (group C of the 1993 European Classification) were routinely checked on the basis of each participating centre's files, and repeated attempts were made to contact patients lost to follow-up.

Study population

From both cohorts 333 adults had a CD4+ cell count >200/μL at enrolment and subsequently reached the threshold of 200/μL on at least two occasions within 12 months. They constituted the study population. As the endpoint was the onset of a first AIDS-defining condition once the CD4 threshold had been confirmed, people who developed AIDS during the interval between the first and second CD4 cell count <200/μL were excluded from the analysis (n = 19).

Statistical analyses

Qualitative variables were compared by using Pearson's χ² test or Fisher's test (extended version). Quantitative variables were compared by using Student's t-test or the Kruskal-Wallis test, and AIDS-free survival curves since the first CD4 cell counts <200/μL (Kaplan-Meier method) were compared with the log-rank test. Crude (RR) and adjusted relative risks (aRR) of progression to AIDS were quantified in a Cox model.

We first studied the predictive value of markers of progression to AIDS after the CD4 threshold with adjustment for the exposure group (homosexual/bisexual men, heterosexual men, heterosexual women, injecting drug users, and haemophiliacs, this latter group representing the reference group). The slope of the CD4+ cell count in the 24 months preceding the threshold was estimated individually by using the least-squares method, and then categorized according to the median value. During the same period the onset of p24 antigenaemia (Abbott polyclonal or monoclonal ELISA method, defined as >30 pg/ml), and clinical manifestations suggestive of immune deficiency (persistent thrush, seborrhic dermatitis, oral hairy leukoplakia, zoster, weight loss, fever, diarrhoea and night sweating) were also studied. Age at the time of the CD4 threshold was treated as a quantitative variable in the Cox model.

Among those 333 patients HIV-1 RNA level was available for a subset of 77 patients. We thus estimated the predictive value of this measurement in the last available serum sample prior to the CD4 threshold (median 3 months previously). In this subpopulation, multivariate analysis was then used to study the independent effect of markers of progression after adjustment for the HIV-1 RNA level (treated as a quantitative variable). Finally, changes in this latter parameter during the 24 months preceding the CD4 threshold (median: three measures per subject, range: 1–5) were analysed by comparing the slope of the HIV-1 RNA level in subjects who had developed AIDS and those who were AIDS-free at the cutoff date (15 June 1995). Given the correlation of serial measures of viral load in a given subject, we used a mixed model in which a first-order autoregressive process was retained.

SAS software (SAS Institute Inc., Cary, North Carolina) was used for analysis.

Results

In the study population (n = 333), 52.0% of the patients were homosexual or bisexual men, 21.0% were heterosexual women, 9.6% were heterosexual men, 10.2% were haemophiliacs, and 7.2% were injecting drug users (Table 1). The median age when the CD4 threshold was reached was 32.9 years (range: 18.2–66.1). During the 24 months prior to this CD4 threshold, the median slope of individual CD4+ cell count (n = 328) was (-)9.7 cells/month (10th–90th percentiles: -64.3/month to +2.1/month), a positive p24 antigenaemia, detected in 40.5% of subjects, was not related to the CD4 cell slope (P = 0.74), a higher frequency of thrush in injecting drug users (45.8%) than in the other exposure groups (21.0%) was the only noteworthy difference in clinical parameters among the different exposure groups (P = 0.04).

Among the 149 (44.7%) patients in whom a first AIDS-defining condition was diagnosed (median follow-up: 24.5 months), 97 had an opportunistic infection (Pneumocystis carinii pneumonia: n = 21), 36 had Kaposi’s sarcoma, 7 had a wasting syndrome, 7 had AIDS-related dementia and 2 had non-Hodgkin’s lymphoma.

Markers of progression to clinical AIDS

Progression to AIDS was significantly related to the slope of the CD4+ cell count prior to the CD4 threshold (log-rank test:...
Table 1 Description of the study population. SEROCO & HEMOCO cohorts (1988–1995)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Exposure group</th>
<th>n</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homosexual men</td>
<td>173</td>
<td>52.0%</td>
<td></td>
</tr>
<tr>
<td>Heterosexual women</td>
<td>70</td>
<td>21.0%</td>
<td></td>
</tr>
<tr>
<td>Heterosexual men</td>
<td>32</td>
<td>9.6%</td>
<td></td>
</tr>
<tr>
<td>Haemophiliacs</td>
<td>34</td>
<td>10.2%</td>
<td></td>
</tr>
<tr>
<td>Injecting drug users</td>
<td>24</td>
<td>7.2%</td>
<td></td>
</tr>
<tr>
<td>CD4 cell slope (median, 10⁸−9⁰ b)</td>
<td>-9.7 cells/month (−64.3→2.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p24 positive antigenaemia a</td>
<td>135</td>
<td>(40.5%)</td>
<td></td>
</tr>
</tbody>
</table>

Clinical events b

<table>
<thead>
<tr>
<th>Event</th>
<th>n</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrush</td>
<td>77</td>
<td>23.1%</td>
</tr>
<tr>
<td>Seborrhic dermatitis</td>
<td>107</td>
<td>32.1%</td>
</tr>
<tr>
<td>Oral hairy leukoplasia</td>
<td>41</td>
<td>12.3%</td>
</tr>
<tr>
<td>Zoster</td>
<td>33</td>
<td>9.9%</td>
</tr>
<tr>
<td>Other conditions</td>
<td>56</td>
<td>(16.9%)</td>
</tr>
</tbody>
</table>

a In the 24 months prior to the threshold of 200 CD4 cells/μL.

b Fever and/or weight loss and/or diarrhea and/or night sweating.

The median value of the last serum HIV-1 RNA level before the CD4 threshold was 4.68 log₁₀, i.e. 47 550 copies/ml (25–75th percentiles: 11 700–111 000 copies/ml). The crude RR of progression to AIDS associated with a 1-log₁₀ increase in the HIV-1 RNA level was 2.24 (95% CI: 1.30–3.87). For example, in patients whose viral load was above the median at the CD4 threshold, the cumulative incidence of AIDS at 12 months since the CD4 <200/μL (Figure 1) was 35.2%, compared to 16.7% in the remainder (log-rank test: P = 0.06). In a Cox model in which this measurement of viral load was not included, the aRR associated with p24 antigenaemia was also of borderline statistical significance (RR = 1.91, 95% CI: 0.92–3.40), but fell to 1.35 (95% CI: 0.70–2.62) when Kaposi's sarcoma was excluded from the definition of AIDS.

HIV-1 RNA level at CD4 cell count <200/μL and AIDS onset

Among the 77 patients in whom serum HIV-1 RNA values were available during the 24 months prior to the CD4 threshold, 35 (45.5%) subsequently progressed to AIDS. In this subset of participants and before the CD4 threshold: 42.9% received zidovudine monotherapy alone (median: 9.9 months previously), 6.5% switched from zidovudine to another reverse transcriptase inhibitor (didanosine or zalcitabine), and 3.8% received combination therapy including zidovudine. Among those who subsequently progressed to AIDS, 40.0% had received antiretroviral treatment compared to 54.7% of the remainder (P = 0.20).
Table 3  Adjusted relative risks (RR) of progression to AIDS after the CD4 threshold of 200/µL. Value of viral load measured at the CD4 threshold (n = 77)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Adjusted RR (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at CD4 threshold*</td>
<td>1.54 (1.05-2.26)</td>
</tr>
<tr>
<td>CD4 cell slope**</td>
<td></td>
</tr>
<tr>
<td>&gt;(-) 9.7 cells/months</td>
<td>1.00</td>
</tr>
<tr>
<td>&lt;=(-) 9.7 cells/months</td>
<td>1.72 (0.79-3.73)</td>
</tr>
<tr>
<td>p24 antigenaemia**</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1.00</td>
</tr>
<tr>
<td>Positive</td>
<td>1.88 (0.92-3.84)</td>
</tr>
<tr>
<td>Thrush**</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>1.00</td>
</tr>
<tr>
<td>Present</td>
<td>2.98 (1.21-7.33)</td>
</tr>
<tr>
<td>Serum HIV-RNA**</td>
<td>1.94 (1.05-3.58)</td>
</tr>
</tbody>
</table>

* Per 10-year increase.
** During the 24 months prior to the CD4 cell threshold of 200/µL.
*** Per 1-log_{10} increase.

The HIV-1 RNA level was 1.94 (95% CI: 1.05-3.58). Adjustment for antiretroviral treatment (aRR = 1.01, P = 0.94) prior to the CD4 threshold did not affect the results. The individual slopes of viral load (least-squares method) during the 24 months prior to this threshold were not significantly associated with the risk of progression to AIDS (aRR = 1.08, 95% CI: 0.40-2.92).

HIV-1 RNA level before CD4 cell count <200/µL according to subsequent AIDS onset

In the mixed model, the HIV-1 RNA level during the 24 months preceding the CD4 threshold was relatively stable (average slope: 0.0082 log_{10} per month, 95% CI: -0.0015 to +0.0178), corresponding to a mean increase of 25.4% per year. This stability of the viral load (Figure 2) was observed not only in the patients who had not progressed to AIDS at the cutoff date (+24.0% per year), but also in those who developed AIDS (+27.1% per year), and the difference between the two slopes was not significant (P = 0.93). During the same period a persistent difference (estimated at 0.49 log_{10}) was observed between these two groups (P = 0.002), with HIV-1 RNA levels three times higher in patients who developed AIDS before the cutoff date. Adjustment for antiretroviral treatment did not modify the mean slopes of viral load and the difference in the HIV-1 RNA level between these two groups was only reduced to 0.44 log_{10} (P < 0.02).

Discussion

Markers predictive of progression to AIDS once the threshold count of 200 CD4 cell/µL is reached were initially described in homosexual men, but were also found to carry a poor prognosis in this study involving different exposure groups. The individual slope of the CD4+ cell count in the 24 months preceding the CD4 threshold was predictive of progression to AIDS, as were p24 antigenaemia and thrush. The risk of progression did not differ significantly according to the exposure group, especially when Kaposi's sarcoma was excluded from the definition of AIDS.

The HIV-1 RNA level is predictive of progression to AIDS at an early stage of the infection, as well as in more immunodeficient patients (CD4+ cell counts between 200 and 500/µL). In our study, in which all the patients were severely immunodeficient (CD4 <200/µL on two occasions), viral load just prior to the CD4 threshold was also associated with the risk of
progression. The RR associated with an increase of one-log_{10} in the HIV RNA level was close to 2, a value lower than in previous studies.\textsuperscript{19,30} Inclusions of cases of AIDS diagnosed between the first and the confirmatory CD4 cell count <200/μL did not modify the results (data not shown). Exclusion of earlier AIDS-defining conditions occurring before the first CD4 count <200/μL threshold probably explains this result. Although viral load was highly predictive of progression to AIDS, we think it did not entirely account for the risk of AIDS at an advanced stage of the infection in the multivariate model.\textsuperscript{31} Indeed, the effect of individual CD4 cell slope and p24 antigenemia were of borderline significance probably owing to a lack of statistical power. The occurrence of thrush before the CD4 threshold remained an important risk factor, underlining the predictive value of clinical signs at this stage of the disease. Other group B-defining conditions were not predictive of AIDS. This was somewhat surprising, but is in keeping with a study involving 620 immunodeficient subjects (median CD4+ cell count 274/μL)\textsuperscript{32} and is probably explained by the fact that all our patients were severely immunodepressed. Age at the CD4 threshold was also independently predictive of AIDS, confirming the clear effect of this risk factor in the late stages of HIV disease.\textsuperscript{33,34} This result is probably not due to a longer time since infection among the older subjects, leading eventually to a more severe immunodeficiency when the CD4+ cell count fell below 200/μL. Indeed, in order to match patients for the degree of immunodeficiency when they reached this threshold count, we selected those who reached it at least twice in a 12-month period. It is still unclear why older subjects progress more rapidly to AIDS. It is possible that the capacity for lymphocyte production or available CD4+ lymphocyte reserves decline with age,\textsuperscript{35} but the fact that the effect of age is independent of the decline in the CD4+ cell counts and the HIV-1 RNA level\textsuperscript{19} rather points to a functional deficiency of residual CD4 lymphocytes. Although viral load was only measured on a subset of patients, these results are unlikely to be biased. Indeed, the RR associated with markers of AIDS before adjustment for HIV-1 quantitation and the rate of progression to AIDS were very similar between this subset and the overall study population.

Interestingly, the individual slopes of the HIV-1 RNA level during the 24 months prior to the CD4 threshold were not related to the subsequent risk of AIDS onset. Indeed, the HIV-1 RNA level appeared relatively stable both in the patients who developed AIDS before the cutoff date (+27.1% per 12 months) and in the other patients (+24.0% per 12 months). The absence of a clear rise in viral load at this stage of the infection in patients who subsequently develop AIDS contrasts with the marked fall in the CD4+ cell count. Although slightly less patients who developed AIDS had been treated with antiretroviral agents (mainly zidovudine alone), the transient effect of zidovudine on the HIV-1 RNA level\textsuperscript{36} does not explain this relative stability of the HIV-1 RNA level. Adjustment for the effect of antiretroviral treatment did not affect the slopes of the HIV-1 RNA level. Despite the lack of any clear increase in viral load in the 24 months prior to the CD4 threshold in the patients who subsequently developed AIDS, their HIV-1 RNA level were consistently 2.7 times higher (0.44 log_{10}) than in patients who remained free of AIDS at the cutoff date. The persistent gap between these two groups suggests that the difference probably arises earlier in the natural history of the infection. Indeed, HIV-1 RNA level measured some months after seroconversion already differs significantly between patients who go on to develop AIDS in subsequent years and those who remain AIDS-free.\textsuperscript{12}

In conclusion, despite the important predictive value of viral load for progression to clinical AIDS when the CD4 cell count
falls below the threshold of 200/μL, clinical events such as the
onset of thrush before this threshold remain valuable for
monitoring immunodeficient patients. Older patients should
be monitored closely, whatever their rate of decline in the CD4 cell
count and their level of HTV-1 RNA.

Acknowledgements

This research was supported by the Agence Nationale de
Recherche sur le SIDA, France. A grant from SIDACTION,
France. We thank the members of both cohorts for participating
for so many years.

References

1 Fauci AS. The human immunodeficiency virus: infectivity and
2 Polk BF, Fox R, Brookmeyer R et al. Predictors of the acquired
immunodeficiency syndrome developing in a cohort of seropositive
3 Levy JA. Pathogenesis of human immunodeficiency virus infection.
4 Lee CA, Phillips A, Elford J et al. The natural history of human immuno-
deficiency virus infection in a haemophilic cohort. Br J Haematol
1989;73:228-34.
5 Fahey JL, Taylor JM, Detels R et al. The prognostic value of cellular
and serologic markers in infection with human immunodeficiency
6 Lange JMA, de Wolf F, Goudsmit J. Markers for progression in HTV
7 Phair J, Muñoz A, Detels R, Kaslow R, Rinaldo C, Saah A, and the
multicenter AIDS cohort study group. The risk of pneumocystis
carinii pneumonia among men infected with human immunodeficien-
8 Gallant JE, Moore RD, Chaisson RE. Prophylaxis for opportunistic
120:932-44.
9 Carpenter CC, Fischl MA, Hammer SM et al. Antiretroviral therapy for
HIV infection in 1996: Recommendations of an International Panel.
JAMA 1996;276:146-54.
10 Moss AR, Bacchetti P. Natural history of HIV infection. AIDS 1989;3:
55-61.
11 Goedert JJ, Kessler CM, Aledort LM et al. A prospective study of human
immunodeficiency virus type 1 infection and the development of
12 Farzadegan H, Henrard DR, Kleeberger CA et al. Virologic and
serologic markers of rapid progression to AIDS after HIV-1 serocon-
13 Schellekens PT, Koot M, Roos MT, Tersmette M, Miedema F.
Immunologic and virologic markers determining progression to AIDS.
14 Yong FH, Taylor JMG, Bryant JL, Chmiel JS, Gange SJ, Hoover D.
15 Hoover DR, Rinaldo C, He Y, Phair J, Fahey J, Graham NM. Long-
term survival without clinical AIDS after CD4+ cell counts fall below
16 Keet IP, Król A, Koot M et al. Predictors of disease progression in HIV-
infectected homosexual men with CD4+ cells <200 x 10⁶/L but free of
Prognosis in HIV-1 infection predicted by the quantity of virus in
18 Mellors JW, Kingsley LA, Rinaldo CH Jr et al. Quantification of HIV-1
RNA plasma predicts outcome after seroconversion. Ann Intern Med
19 O'Brien TR, Blattner WA, Waters D et al. Serum HIV-1 RNA levels and
time to development of AIDS in the multicenter hemophilia cohort
study. JAMA 1996;276:105-10.
20 Coombs RW, Welles SL, Hooper C et al. Association of plasma human
immunodeficiency virus type 1 RNA level with risk of clinical pro-
gression in patients with advanced infection. J Infect Dis 1996;174:
704-12.
21 Bucquet D, Deveau C, Belanger F et al. Cohortes française multi-
centrique d’adultes infectés par le VIH: description et évolution après
22 Boufassa F, Carré N, Deveau C et al. Hemocc: a French prospective
study of haemophiliacs infected by human immunodeficiency virus
23 Carré N, Deveau C, Belanger F et al. Effect of age and exposure group
on the onset of AIDS in heterosexual and homosexual HIV-infected
patients. AIDS 1994;8:797-802.
manifestations of primary human immunodeficiency virus infection on
26 Hoover DR, Graham NM, Chen B et al. Effect of CD4+ cell count
measurement variability on staging HIV-1 infection. J Acquir Immune
27 Giorgi JV, Cheng HL, Margolick JB et al. Quality control in the flow
cytometric measurement of T-lymphocyte subsets: The Multicenter
55:173-86.
28 Lee MT, Rosner BA, Yokonas PS, Weiss ST. Longitudinal analysis of
29 Operskalski EA, Stram DO, Lee H et al. Human immunodeficiency
virus type 1 infection: relationship of risk group and age to rate of
30 O’Brien WA, Hartigan PM, Daar ES, Simberkoff MS, Hamilton JD.
For the VA cooperative study group on AIDS. Changes in plasma HIV
RNA levels and CD4+ lymphocyte counts predict both response to
antiretroviral therapy and therapeutic failure. Ann Intern Med
1997;126:939-45.
31 Katzstein DA, Hammer SM, Hughes MD et al. The relation of virologic
and immunologic markers to clinical outcomes after nucleoside therapy in
HIV-infected adults with 200 to 500 CD4 cells per cubic millimeter. AIDS
Clinical Trials Group Study 175 Virology Study Team. N Engl J Med
1996;335:1091-98.
32 Phillips AN, Eron JJ, Bartlett JA et al. HIV-1 RNA levels and the
33 Darby SC, Ewart DW, Giangrande PFL, Spooner RJD, Rizza CR, for
the UK Haemophilia Centre Directors’ Organisation. Importance of age at
infection with HIV-1 for survival and development of AIDS in UK
34 III Croft A, Johnson MA, Phillips AN. Factors affecting survival in
patients with the acquired immunodeficiency syndrome. AIDS
35 Phillips AN, Lee CA, Elford J et al. More rapid progression to AIDS in
older HIV-infected people: the role of CD4+ T-cell counts. J Acquir
36 Welles SL, Jackson JB, Yen-Lieberman B et al. Prognostic value of
plasma human immunodeficiency virus type 1 (HIV-1) RNA levels in
patients with advanced HIV-1 disease and with little or no prior zido-
vu dine therapy. AIDS Clinical Trials Group Protocol 116A/118/117
Appendix

Members of the SEROCO & HEMOCO Study Group

C Rouzioux, M Bary, M Burgard (ACCTES-Paris); J Dormont, F Boué, A Lévy (Hôpital Antoine Béclère-Clamart); P Dellamonica, I Perbost, M Carles, V Mondain (Hôpital L'Archet-Nice); L Guillemin, B Jarousse, B Trogoff (Hôpital Avicenne-Bobigny); JF Delfraissy, P Lebras, C Goujard, Y Quertainmont (Hôpital de Bicêtre-Le Kremlin-Bicêtre); JL Vilde, C Leport, U Colassante (Hôpital Bichat-Paris); M Kazatchkine, A Vellay, M Buisson (Hôpital Broussais-Paris); JP Cassuto, B Reboulot, M Quaranta (Hôpital Cimiez-Nice); D Séréri, V Gomez, C Bachmeyer (Hôpital Cochin-Paris); H Gallais, ME Mars, J Gallais (Hôpital de la Conception-Marseille); A Sobel, J Duval, C Majerhole, I Deforges (Hôpital Henri Mondor-Créteil); JJ Lefrère, J Lerable, L Joubert (Institut National de Transfusion Sanguine-Paris); B Dupont, C Beuzelin, S Fournier (Institut Pasteur-Paris); D Vittecoq, C Bollot, MT Pechalat (Hôpital Paul Brousse-Villejuif); S Herson, A Cauterlier (Hôpital Pitié-Salpêtrière-Paris); C Katlama, F Bricaire (Hôpital Pitié-Salpêtrière-Paris); JA Gastaut, C Dhiver, MP Drogoul (Hôpital Ste Marguerite-Marseille); Y Sultan, N Stieltjes (Hôpital Cochin-Paris); C Gazengel, C Rothschild, M F Torchet (Hôpital Necker Enfants Malades-Paris); Y Laurian, A Blanc, R d'Oiron, A Rafowicz, L Kebedjis (Hôpital de Bicêtre-Le Kremlin-Bicêtre); J Peynet, C Laux (Hôpital Mignot-Le Chesnay).