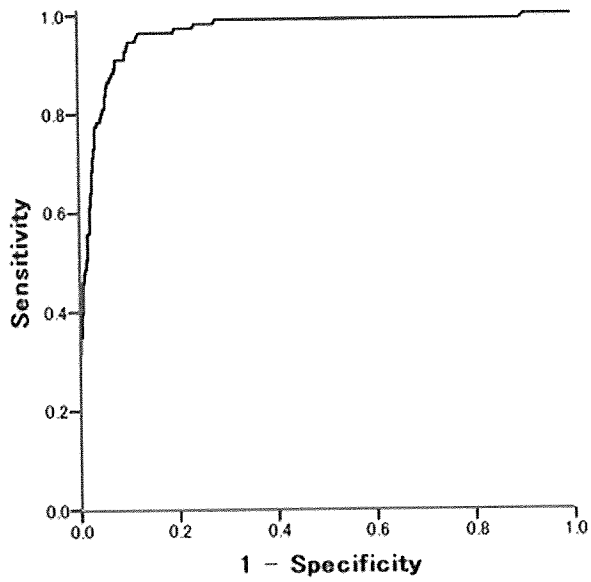

Figure 2. Receiver-operating-characteristic (ROC) curve for the (1→3) β-D-glucan cutoff. The area under the ROC curve for β-D-glucan was 0.964 (95% confidence interval, 0.945–0.984). A β-D-glucan cutoff value of 23.2 pg/mL (which represented the technique's threshold of detection) had a sensitivity of 96.4% and a specificity of 87.8%.

a high sensitivity (96.4%) and specificity (87.8%) for the diagnosis of PCP. Interestingly, serum β-D-glucan levels among those with PCP were not affected by the presence of superficial fungal infection (ie, oral and/or esophageal candidiasis). Deep-seated mycosis other than PCP and cryptococcal infection are quite rare in Japan, and no patients were suspected to have aspergillosis in this study. Hence, we could not analyze the effect of aspergillosis. According to our data and those of others [4], β-D-glucan level increases during cryptococcal infection, but the level is significantly lower than that observed during PCP. The number of *P. jirovecii* organisms in the lungs of patients with AIDS may be significantly higher than that in patients without AIDS [8]. In a meta-analysis of 7 reports in which PCP was diagnosed by staining, the average sensitivity of induced sputum was 56%, whereas that of BALF was >95% [9]. To eliminate false-positive and false-negative results, we analyzed data obtained only from patients who underwent BALF analysis and had a definite diagnosis of PCP.

The second major finding was that the serum level of β-D-glucan does not reflect the severity of PCP in patients with AIDS. Although Shimizu et al [10] reported that β-D-glucan is a negative prognostic marker for PCP in patients with connective tissue diseases, there was no significant difference in β-D-glucan level between survivors and nonsurvivors in our study. Furthermore, Tasaka et al [6] reported that serum levels of LDH correlated with those of β-D-glucan in patients with PCP, whereas our data showed no such relationship. These differences are probably the result of differences in the patient populations studied, especially regarding whether the patients have HIV-1 infection. Considered collectively, these results emphasize the need for further studies to define the exact relationship between β-D-glucan and prognosis as well as LDH.

The third major finding of the present study was that β-D-glucan level did not reflect the effectiveness of therapy. In nearly 85% patients, serum β-D-glucan levels did not decrease to normal despite clinical improvement. Furthermore, 20% of patients had increased levels of β-D-glucan during the early phase of treatment. However, β-D-glucan levels normalized several months or years after treatment in all patients. These results mean that β-D-glucan levels increase transiently early during treatment and decrease thereafter but do not always return to normal during treatment. The transient increase in β-D-glucan level is probably due to lysis of *P. jirovecii* shortly after treatment.

PCP is usually suspected on the basis of chest radiographic findings, clinical symptoms, and low $CD4^+$ cell counts in HIV-infected patients. In the present study, a high serum level of β-D-glucan (especially >23.2 pg/mL by the MK test) was found to be highly indicative of PCP in practically all patients with AIDS. Therefore, the β-D-glucan test is useful for the diagnosis of PCP, especially in HIV-infected patients who are unable to undergo bronchoscopy owing to severe hypoxemia. In conclusion, the present study has demonstrated that β-D-glucan is a useful, noninvasive adjunct marker for the diagnosis of PCP in patients with AIDS. However, its serum levels do not reflect the severity of the disease, and it is not suitable for monitoring response to treatment.

Acknowledgments

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Potential conflicts of interest. All authors: no conflicts.

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ORIGINAL ARTICLE

Interleukin-2 Therapy in Patients with HIV Infection

The INSIGHT–ESPRIT Study Group and SILCAAT Scientific Committee*

ABSTRACT

BACKGROUND

Used in combination with antiretroviral therapy, subcutaneous recombinant interleukin-2 raises CD4+ cell counts more than does antiretroviral therapy alone. The clinical implication of these increases is not known.

METHODS

We conducted two trials: the Subcutaneous Recombinant, Human Interleukin-2 in HIV-Infected Patients with Low CD4+ Counts under Active Antiretroviral Therapy (SILCAAT) study and the Evaluation of Subcutaneous Proleukin in a Randomized International Trial (ESPRIT). In each, patients infected with the human immunodeficiency virus (HIV) who had CD4+ cell counts of either 50 to 299 per cubic millimeter (SILCAAT) or 300 or more per cubic millimeter (ESPRIT) were randomly assigned to receive interleukin-2 plus antiretroviral therapy or antiretroviral therapy alone. The interleukin-2 regimen consisted of cycles of 5 consecutive days each, administered at 8-week intervals. The SILCAAT study involved six cycles and a dose of 4.5 million IU of interleukin-2 twice daily; ESPRIT involved three cycles and a dose of 7.5 million IU twice daily. Additional cycles were recommended to maintain the CD4+ cell count above predefined target levels. The primary end point of both studies was opportunistic disease or death from any cause.

RESULTS

In the SILCAAT study, 1695 patients (849 receiving interleukin-2 plus antiretroviral therapy and 846 receiving antiretroviral therapy alone) who had a median CD4+ cell count of 202 cells per cubic millimeter were enrolled; in ESPRIT, 4111 patients (2071 receiving interleukin-2 plus antiretroviral therapy and 2040 receiving antiretroviral therapy alone) who had a median CD4+ cell count of 457 cells per cubic millimeter were enrolled. Over a median follow-up period of 7 to 8 years, the CD4+ cell count was higher in the interleukin-2 group than in the group receiving antiretroviral therapy alone — by 53 and 159 cells per cubic millimeter, on average, in the SILCAAT study and ESPRIT, respectively. Hazard ratios for opportunistic disease or death from any cause with interleukin-2 plus antiretroviral therapy (vs. antiretroviral therapy alone) were 0.91 (95% confidence interval [CI], 0.70 to 1.18; P=0.47) in the SILCAAT study and 0.94 (95% CI, 0.75 to 1.16; P=0.55) in ESPRIT. The hazard ratios for death from any cause and for grade 4 clinical events were 1.06 (P=0.73) and 1.10 (P=0.35), respectively, in the SILCAAT study and 0.90 (P=0.42) and 1.23 (P=0.003), respectively, in ESPRIT.

CONCLUSIONS

Despite a substantial and sustained increase in the CD4+ cell count, as compared with antiretroviral therapy alone, interleukin-2 plus antiretroviral therapy yielded no clinical benefit in either study. (ClinicalTrials.gov numbers, NCT00004978 [ESPRIT] and NCT00013611 [SILCAAT study].)

Members of the writing group for the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT)–Evaluation of Subcutaneous Proleukin in a Randomized International Trial (ESPRIT) Study Group and the Subcutaneous Recombinant, Human Interleukin-2 in HIV-Infected Patients with Low CD4+ Counts under Active Antiretroviral Therapy (SILCAAT) Scientific Committee (D. Abrams, M.D. [cochair], Y. Lévy, M.D. [cochair], M.H. Losso, M.D. [cochair], A. Babiker, Ph.D., G. Collins, M.S., D.A. Cooper, M.D., J. Darbyshire, M.B., Ch.B., S. Emery, Ph.D., L. Fox, M.D., F. Gordin, M.D., H.C. Lane, M.D., J.D. Lundgren, M.D., R. Mitsuyasu, M.D., J.D. Neaton, Ph.D., A. Phillips, Ph.D., J.P. Routy, M.D., G. Tambussi, M.D., and D. Wentworth, M.P.H.) assume responsibility for the overall content and integrity of the article. Drs. Abrams, Lévy, and Losso contributed equally to the article. Address reprint requests to Dr. Neaton at the Division of Biostatistics, School of Public Health, University of Minnesota, 221 University Ave. SE, Suite 200, Minneapolis, MN 55414, or at jim@ccbr.umn.edu.

*Affiliations of the writing group are listed in the Appendix, and the members of the Evaluation of Subcutaneous Proleukin in a Randomized International Trial (ESPRIT) and the Subcutaneous Recombinant, Human Interleukin-2 in HIV-Infected Patients with Low CD4+ Counts under Active Antiretroviral Therapy (SILCAAT) study groups are listed in the Supplementary Appendix, available with the full text of this article at NEJM.org.

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THE CD4+ CELL COUNT REMAINS THE BEST single indicator of immunodeficiency related to infection with the human immunodeficiency virus (HIV) and is an important determinant of clinical events defining the acquired immunodeficiency syndrome (AIDS) and other serious diseases.[1,2] Interleukin-2 is a cytokine secreted by activated T cells that regulates the proliferation, differentiation, and survival of T cells. Early studies showed that *Escherichia coli*–expressed recombinant interleukin-2, given intravenously or subcutaneously in combination with antiretroviral therapy, increased the CD4+ cell count significantly as compared with antiretroviral therapy alone.[3-11] The cell expansions occur because of an increase in CD4+ T-cell survival (with half-lives that can exceed 3 years) and are characterized by an increase in numbers of both naive and central memory cells.[12-14] Absolute increases were greater in patients with higher baseline CD4+ cell counts. The level of HIV-associated immune activation, as reflected in T-cell turnover, was decreased in interleukin-2 recipients.[15]

The clinical impact of CD4+ T-cell increases associated with the use of interleukin-2 is unknown. Any possible beneficial effects from interleukin-2 would need to be sufficiently large to mitigate the effect of its known toxicity. Since the net effects might differ between patients with higher CD4+ cell counts and those with lower counts, two trials were conducted involving patients receiving combination antiretroviral therapy.

METHODS

STUDY DESIGN

The Subcutaneous Recombinant, Human Interleukin-2 in HIV-Infected Patients with Low CD4+ Counts under Active Antiretroviral Therapy (SILCAAT) study and the Evaluation of Subcutaneous Proleukin in a Randomized International Trial (ESPRIT) were multicenter, international trials. The studies were open-label because the almost universal and typical side effects of interleukin-2 made blinding impossible. Patients were randomly assigned, in equal numbers, to receive interleukin-2 plus antiretroviral therapy or antiretroviral therapy alone.

Recombinant interleukin-2 was administered subcutaneously in cycles. In the SILCAAT study, one cycle consisted of a dose of 4.5 million IU twice daily for 5 consecutive days. Six cycles of interleukin-2 were planned to be given, approximately 8 weeks apart, within the first 12 months of the study (the induction phase). The induction phase of ESPRIT consisted of three cycles of interleukin-2 given at a dose of 7.5 million IU twice daily. After the induction phase, additional cycles of interleukin-2 therapy were recommended to maintain CD4+ cell counts above the predefined target levels. Guidelines for the management of interleukin-2 toxicity included reductions of the dose of interleukin-2 in decrements of 1.5 million or 3.0 million IU per dose. The minimum dose of interleukin-2 administered was 1.5 million IU twice daily. In the SILCAAT study, after the third cycle, the dose of interleukin-2 could be increased to 6.0 million or 7.5 million IU.

ESPRIT was funded and sponsored by the National Institute of Allergy and Infectious Diseases (NIAID). The SILCAAT study was originally sponsored by Chiron. In February 2003, after completing enrollment, Chiron announced that it would no longer support the trial for business reasons owing to its inability to gain accelerated approval from the Food and Drug Administration on the basis of changes in CD4+ cell count. To complete the study, trial management was transferred to the SILCAAT Scientific Committee and the investigators conducting ESPRIT. NIAID provided regulatory sponsorship, and Chiron — and subsequently Novartis, after acquiring Chiron — provided funds for the SILCAAT study from February 2003 forward. Chiron–Novartis provided the interleukin-2 used in both trials.

The paper was written by a writing group representing the leaders of each study. Neither Chiron nor Novartis was involved in the data analysis or interpretation or in the preparation of the manuscript. Chiron and members of the SILCAAT Scientific Committee designed the SILCAAT study; members of the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) Executive Committee designed ESPRIT. For the entire duration of ESPRIT and since 2003 for the SILCAAT study, oversight of data collection at clinical sites was performed by international coordinating centers working with a central coordinating center at the University of Minnesota, which managed and analyzed the data for both studies. The authors vouch for the accuracy and completeness of the data and analyses.

The ESPRIT design and methods have been reported previously.[16] Additional information on

methods is given in the Supplementary Appendix, available with the full text of this article at NEJM.org.

STUDY POPULATIONS

Both trials included adult patients with confirmed HIV-1 infection. Patients with a CD4+ cell count of 50 to 299 per cubic millimeter (in the SILCAAT study) or 300 or more per cubic millimeter (in ESPRIT) were enrolled. Patients in the SILCAAT study were also required to have an HIV RNA level of less than 10,000 copies per milliliter. Protocols were approved by the institutional review board at each site. Written informed consent was obtained from all patients.

ASSESSMENTS

Patients were seen every 4 months for a targeted history taking and clinical evaluation and measurement of the CD4+ cell count and plasma HIV RNA level. Follow-up continued until a common closing date (November 15, 2008).

DEFINITIONS OF END POINTS

The primary end point of each study was opportunistic disease or death from any cause. Secondary end points included death from any cause and grade 4 clinical events, defined as potentially life-threatening events (excluding opportunistic diseases) requiring medical intervention (see toxicity table at http://rcc.tech-res.com). Grade 4 events were reported irrespective of their perceived relationship to the use of interleukin-2 or antiretroviral therapy and were coded according to the *Medical Dictionary for Regulatory Activities* (version 12.0).

INTERIM MONITORING OF SAFETY AND EFFICACY

An independent data and safety monitoring board reviewed interim analyses from the SILCAAT study and ESPRIT. On November 27, 2007, at their final meeting, the board recommended that ESPRIT continue until its planned completion time (when 320 primary events had occurred) and that the SILCAAT study continue until ESPRIT was closed.

STATISTICAL ANALYSIS

In both trials, the primary analysis was based on the intention-to-treat principle. Time-to-event methods were used to compare the groups receiving interleukin-2 plus combination antiretroviral therapy and combination antiretroviral therapy alone, with regard to major end points.[17] Follow-up data were censored when patients were lost to follow-up before or on November 15, 2008.

The hazard ratios for the comparisons of interleukin-2 plus antiretroviral therapy and antiretroviral therapy alone were estimated from Cox models with a single indicator for treatment group. We tested the proportional-hazards assumption by including an interaction term between treatment group and natural-log–transformed follow-up time.

Data on the primary end point were summarized for prespecified subgroups defined according to baseline characteristics. A total of 12 subgroup analyses were prespecified. The heterogeneity of hazard-ratio estimates between subgroups was assessed by including an interaction term between treatment and subgroup in expanded Cox models. The results of subgroup analyses should be interpreted with caution; a significant interaction could be due to chance, because there was no adjustment made to the type 1 error for the number of subgroups examined.

Cox models were also used to obtain an estimate of the association between the time-updated follow-up CD4+ cell count (the levels last measured before the event, hereafter called the latest levels) after $\log_{10}$ transformation and the primary end point among recipients of antiretroviral therapy alone. Estimates of parameters in Cox models and average differences in the CD4+ cell count between treatment groups during the follow-up period were used to obtain predicted hazard ratios for comparison with observed hazard ratios.

Statistical analyses were performed using SAS software (version 9.1). P values are two-sided.

RESULTS

BASELINE CHARACTERISTICS

A total of 1695 patients (849 receiving interleukin-2 plus antiretroviral therapy and 846 receiving antiretroviral therapy alone) in the SILCAAT study and 4111 patients (2071 receiving interleukin-2 plus antiretroviral therapy and 2040 receiving antiretroviral therapy alone) in ESPRIT were enrolled and had data included in the analysis (Table 1, and Fig. Ia and Ib in the Supplementary Appendix). The two treatment groups were well balanced with respect to baseline characteristics (Tables Ia and Ib in the Supplementary Appendix).

COMPLETENESS OF FOLLOW-UP

Approximately 5700 patient-years and 14,000 patient-years of follow-up were accrued in each group in the SILCAAT study and in ESPRIT, respectively. (The median duration of follow-up was 7.6 years for the SILCAAT study and 7.0 years for ESPRIT.) In the SILCAAT study, the status of the primary end point was unknown for 91 of the 849 patients (10.7%) receiving interleukin-2 and antiretroviral therapy and for 100 of the 846 patients (11.8%) receiving antiretroviral therapy alone. In ESPRIT, the status of the primary end point was unknown for 118 of the 2071 patients (5.7%) receiving interleukin-2 and antiretroviral therapy and for 134 of the 2040 patients (6.6%) receiving antiretroviral therapy alone.

USE OF INTERLEUKIN-2

In the SILCAAT study, 72.3% of patients receiving interleukin-2 plus antiretroviral therapy completed six cycles of interleukin-2 therapy; 2.1% never received interleukin-2. In ESPRIT, 83.4% of the patients receiving interleukin-2 plus antiretroviral therapy completed at least three cycles of interleukin-2 therapy; 3.7% of patients never received interleukin-2. The median number of cycles was 7 (interquartile range, 5 to 9) in the SILCAAT study and 4 (interquartile range, 3 to 6) in ESPRIT.

CD4+ CELL COUNT

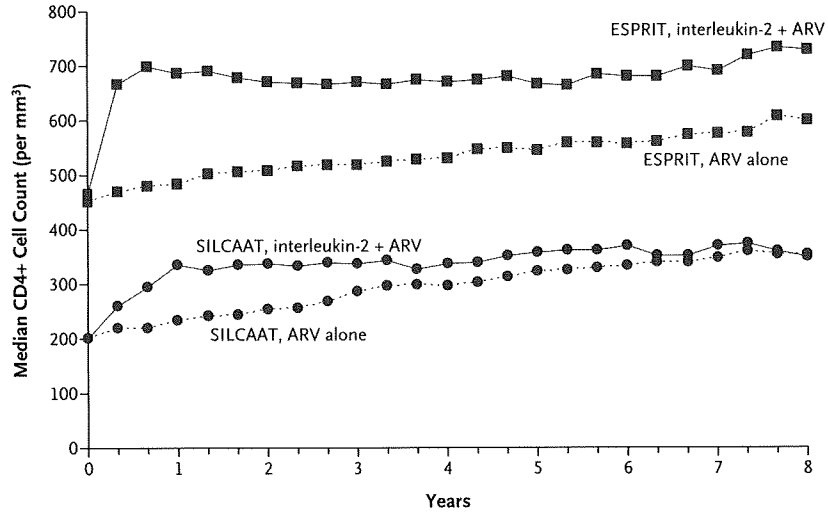
Median CD4+ cell counts are given in Figure 1. In the SILCAAT study, at 1 year, the median CD4+ cell count in the group receiving interleukin-2 plus antiretroviral therapy had increased from the baseline level by 131 per cubic millimeter (interquartile range, 52 to 215). For SILCAAT patients receiving antiretroviral therapy alone, the increase in the CD4+ cell count over the baseline value at 1 year was 32 per cubic millimeter (interquartile range, −11 to 78). The median difference in CD4+ cell count between the two SILCAAT groups declined from 99 per cubic millimeter at 1 year to 38 per cubic millimeter at 6 years. This decline paralleled the percentage of patients receiving interleukin-2 during each year (97.8% in year 1 and 12.0% during year 6). On average, over the follow-up period, the CD4+ cell count was higher with interleukin-2 plus antiretroviral therapy than with antiretroviral therapy alone, by 53 per cubic millimeter (95% confidence interval [CI], 40 to 66).

In ESPRIT, the median CD4+ cell count was increased over the baseline value at 1 year, by 206 cells per cubic millimeter (interquartile range, 55 to 376) in the group receiving interleukin-2 plus antiretroviral therapy as compared with 21 cells per cubic millimeter (interquartile range, −64 to

Table 1. Baseline Characteristics of Participants in SILCAAT and ESPRIT.*

Characteristic	SILCAAT Study (N=1695)	ESPRIT (N=4111)
Age (yr)		
Median	40	40
Interquartile range	36–47	34–46
Female sex (%)	16.5	18.6
Race or ethnic group (%)†		
Black	8.4	9.1
White	79.8	75.3
Other or unknown	11.8	15.5
CD4+ cell count (per mm^3)		
Median	202	457
Interquartile range	151–254	372–584
CD4+ cell-count nadir (per mm^3)		
Median	60	197
Interquartile range	26–107	91–306
HIV RNA ≤500 copies/ml (%)	81.4	79.7
AIDS event (%)	32.5	25.9
Body-mass index‡		
Median	23.9	23.7
Interquartile range	21.8–26.1	21.9–25.9
Previous antiretroviral therapy (%)		
PI	85.5	72.4
NNRTI	57.7	57.9
NRTI, PI, and NNRTI	44.3	38.5
Time since first prescribed antiretroviral drugs (yr)		
Median	3.9	4.2
Interquartile range	1.8–7.2	2.2–6.4
Current antiretroviral regimen (%)		
Includes PI	65.6	49.0
Includes NNRTI	45.8	46.3
Includes NRTI, PI, and NNRTI	13.9	7.9

* AIDS denotes the acquired immunodeficiency syndrome, HIV human immunodeficiency virus, NNRTI nonnucleoside reverse-transcriptase inhibitor, NRTI nucleoside reverse-transcriptase inhibitor, and PI protease inhibitor.
† Race or ethnic group was self-reported.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.



No. of Patients									
SILCAAT, interleukin-2 + ARV	849	722	650	635	648	623	597	447	254
SILCAAT, ARV alone	845	754	679	666	632	632	603	453	233
% Receiving interleukin-2 during yr	97.8	39.8	23.6	18.4	14.8	12.0	7.5	4.2	
ESPRIT, interleukin-2 + ARV	2071	1890	1842	1809	1768	1732	1415	887	297
ESPRIT, ARV alone	2040	1928	1862	1803	1740	1649	1349	831	255
% Receiving interleukin-2 during yr	96.2	37.9	28.7	22.3	17.7	13.7	12.5	9.6	

Figure 1. Median CD4+ Cell Counts during the Study Period, According to Study and Treatment Group.

The median CD4+ cell counts are shown for the groups receiving interleukin-2 plus antiretroviral therapy (ARV) and the groups receiving ARV alone in the SILCAAT study and ESPRIT. The counts during the first 30 days after a cycle of interleukin-2 are not stable and therefore were excluded. Also shown are the percentages of patients assigned to receive interleukin-2 who were taking the drug during each year of the study.

114) in the group receiving antiretroviral therapy alone. This difference between the two ESPRIT groups of 185 cells per cubic millimeter at 1 year declined to 113 cells per cubic millimeter at 6 years. This decrease in the difference between the two groups paralleled the decline in receipt of interleukin-2 — from 96.2% of patients during the first year to 13.7% during the sixth year. On average, during the follow-up period, the CD4+ cell count was higher with interleukin-2 plus antiretroviral therapy, by 159 per cubic millimeter (95% CI, 145 to 174), as compared with antiretroviral therapy alone.

ANTIRETROVIRAL THERAPY AND HIV RNA LEVELS

During the follow-up period, the use of antiretroviral therapy and HIV RNA levels were similar for the groups receiving interleukin-2 plus antiretroviral therapy and the groups receiving antiretroviral therapy alone (Fig. IIa and IIb in the Supplementary Appendix). More than 80% of patients had HIV RNA levels at or below 500 copies per milliliter at each visit.

PRIMARY END POINT AND OTHER MAJOR CLINICAL OUTCOMES

Opportunistic Disease or Death from Any Cause (Primary End Point)

In the SILCAAT study, 110 patients receiving interleukin-2 plus antiretroviral therapy and 119 receiving antiretroviral therapy alone had an opportunistic disease or died (Table 2 and Fig. 2A, and Tables IIa and IIIa in the Supplementary Appendix) (hazard ratio for this primary end point with interleukin-2, 0.91; 95% CI, 0.70 to 1.18; P=0.47). This hazard ratio did not vary significantly over the follow-up period (P=0.34).

In ESPRIT, 159 patients receiving interleukin-2 plus antiretroviral therapy and 165 receiving antiretroviral therapy alone had an opportunistic disease or died (Table 2, and Tables IIb and IIIb in the Supplementary Appendix). The hazard ratio for

Table 2. **Hazard Ratios for the Primary End Point and Major Secondary End Points in SILCAAT and ESPRIT, According to Treatment Group.**

End Point*	Interleukin-2 + Antiretroviral Therapy	Antiretroviral Therapy Alone	Hazard Ratio for Interleukin-2 (95% CI)	P Value
	no. of patients (rate/100 person-yr)			
SILCAAT				
Primary end point: opportunistic disease or death from any cause	110 (1.94)	119 (2.13)	0.91 (0.70–1.18)	0.47
Death from any cause	81 (1.38)	77 (1.31)	1.06 (0.77–1.44)	0.73
Opportunistic disease	49 (0.86)	66 (1.18)	0.73 (0.51–1.06)	0.10
Grade 4 event	203 (3.93)	186 (3.58)	1.10 (0.90–1.34)	0.35
ESPRIT				
Primary end point: opportunistic disease or death from any cause	159 (1.14)	165 (1.21)	0.94 (0.75–1.16)	0.55
Death from any cause	107 (0.75)	116 (0.83)	0.90 (0.69–1.17)	0.42
Opportunistic disease	68 (0.49)	63 (0.46)	1.05 (0.75–1.48)	0.78
Grade 4 event	466 (3.80)	383 (3.09)	1.23 (1.07–1.41)	0.003

* Grade 4 clinical events were defined as potentially life-threatening events (excluding opportunistic diseases) requiring medical intervention (see toxicity table at http://rcc.tech-res.com).

this primary end point with interleukin-2 was 0.94 (95% CI, 0.75 to 1.16; P=0.55) (P=0.40 for test of the proportional-hazards assumption).

We predicted the hazard ratios for the primary end point with interleukin-2 therapy on the basis of the overall differences in the CD4+ cell count between the two treatment groups in each study (on the $\log_{10}$ scale, 0.065 cells per cubic millimeter for the SILCAAT study and 0.099 cells per cubic millimeter for ESPRIT) and the relationship between the latest $\log_{10}$-transformed CD4+ cell count and the risk of opportunistic disease or death in the group receiving antiretroviral therapy alone in each study (Cox coefficient [±SE], −3.339±0.233 for the SILCAAT study and −3.049±0.187 for ESPRIT). The predicted hazard ratios for the SILCAAT study and ESPRIT were 0.80 (95% CI, 0.78 to 0.83) and 0.74 (95% CI, 0.71 to 0.77, respectively). Each of the predicted hazard ratios is smaller than the corresponding observed hazard ratio (which was 0.91 for the SILCAAT study and 0.94 for ESPRIT).

Death from Any Cause

In the SILCAAT study, 81 patients receiving interleukin-2 and antiretroviral therapy and 77 receiving antiretroviral therapy alone died (hazard ratio with interleukin-2, 1.06; 95% CI, 0.77 to 1.44; P=0.73) (Table 2, Fig. 2B, and Table IIIa in the Supplementary Appendix). The hazard ratio for deaths not attributable to opportunistic diseases (which occurred in 70 patients receiving interleukin-2 plus antiretroviral therapy and 60 receiving antiretroviral therapy alone) was 1.17 with interleukin-2 (95% CI, 0.83 to 1.66; P=0.36).

In ESPRIT, 107 patients receiving interleukin-2 and antiretroviral therapy and 116 receiving antiretroviral therapy alone died (hazard ratio with interleukin-2, 0.90; 95% CI, 0.69 to 1.17; P=0.42) (Table 2, and Table IIIb in the Supplementary Appendix). The hazard ratio for deaths not attributable to opportunistic diseases (which occurred in 97 patients receiving interleukin-2 and antiretroviral therapy and 106 receiving antiretroviral therapy alone) was 0.89 (95% CI, 0.68 to 1.17; P=0.41) with interleukin-2.

Opportunistic Diseases

In the SILCAAT study, an opportunistic disease developed in 49 patients receiving interleukin-2 and antiretroviral therapy and 66 receiving antiretroviral therapy alone (hazard ratio with interleukin-2, 0.73; 95% CI, 0.51 to 1.06; P=0.10). In ESPRIT, an opportunistic disease developed in 68 patients receiving interleukin-2 and antiretroviral therapy and 63 receiving antiretroviral therapy alone (hazard ratio with interleukin-2, 1.05; 95% CI, 0.75 to 1.48; P=0.78) (Table 2, and Fig. III in the Supplementary Appendix).

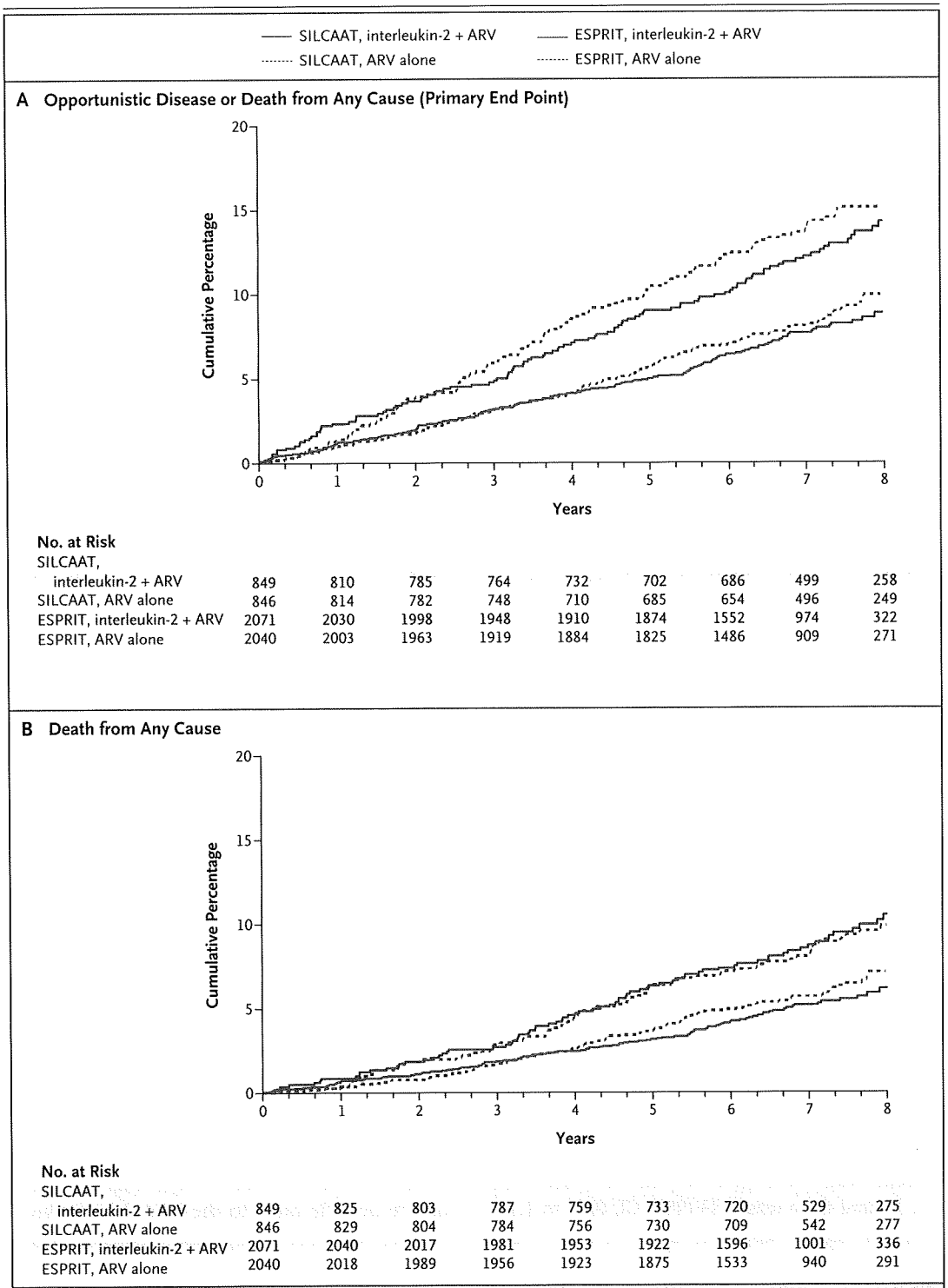


Figure 2. Cumulative Percentages of Patients with Opportunistic Disease or Death from Any Cause, According to Study and Treatment Group.

Panel A shows data for opportunistic disease or death from any cause (primary end point); and Panel B, for death from any cause. ARV denotes antiretroviral therapy.

Grade 4 Events

In the SILCAAT study, 203 patients receiving interleukin-2 and antiretroviral therapy and 186 receiving antiretroviral therapy alone had a grade 4 event (hazard ratio with interleukin-2, 1.10; 95% CI, 0.90 to 1.34; P=0.35) (Table 2, and Fig. IV in the Supplementary Appendix). In the interleukin-2 and antiretroviral therapy group, the 203 patients had a total of 342 grade 4 events, 78.4% of which occurred more than 60 days after the last dose of interleukin-2 was administered. Gastrointestinal disorders and psychiatric disorders were more common in the interleukin-2 group (P=0.02 and P=0.03, respectively) (Table IVa in the Supplementary Appendix).

In ESPRIT, grade 4 adverse events occurred in 466 patients receiving interleukin-2 and antiretroviral therapy and 383 receiving antiretroviral therapy alone (hazard ratio with interleukin-2, 1.23; 95% CI, 1.07 to 1.41; P=0.003) (Table 2). In the interleukin-2 and antiretroviral therapy group, the 466 patients had a total of 711 grade 4 events, 82.4% of which occurred more than 60 days after the last dose of interleukin-2 was given. Differences between the two treatment groups were seen for the category of vascular disorders as well as the category of general disorders and administration site conditions (Table IVb in the Supplementary Appendix). Vascular events were seen in 40 patients receiving interleukin-2 and antiretroviral therapy and in 14 receiving antiretroviral therapy alone (hazard ratio with interleukin-2, 2.80; 95% CI, 1.53 to 5.15; P<0.001). The most frequent type of vascular event was deep-vein thrombosis (affecting 10 patients receiving interleukin-2 and antiretroviral therapy and 2 receiving antiretroviral therapy alone).

SUBGROUP FINDINGS

In both studies, hazard ratios for the primary end point with interleukin-2 were similar across demographic subgroups (Fig. 3). In ESPRIT, among patients with a baseline CD4+ cell count below 450, the hazard ratio was 0.83 (95% CI, 0.62 to 1.12), whereas among those with counts of 450 or more, the hazard ratio was 1.09 (95% CI, 0.79 to 1.50) (P=0.04 for the interaction between the CD4+ cell count and treatment group) (Fig. 3B). For these two baseline CD4+ cell-count subgroups in ESPRIT, the hazard ratios for death with interleukin-2 also differed significantly (P=0.003): 0.68 (95% CI, 0.47 to 0.98) for a count below 450 and 1.25 (95% CI, 0.85 to 1.84) for a count of 450 or more.

DISCUSSION

These studies confirm that intermittent use of interleukin-2 is associated with substantial, sustained increases in CD4+ cell count. However, despite the increases in the CD4+ cell count, there was no clinical benefit, as measured by the reduction in the risk of opportunistic diseases or death, with interleukin-2 plus antiretroviral therapy as compared with antiretroviral therapy alone.

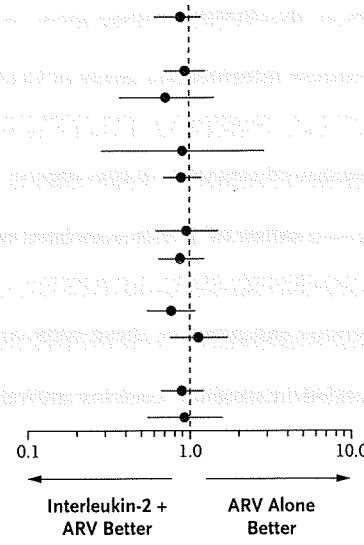
On the basis of the associations between the latest CD4+ cell count and the occurrence of opportunistic disease or death in the groups receiving antiretroviral therapy alone, the difference in the CD4+ cell count between the groups receiving interleukin-2 and antiretroviral therapy and those receiving antiretroviral therapy alone resulted in predicted hazard ratios for the primary end point with interleukin-2 of 0.80 for the SILCAAT study and 0.74 for ESPRIT. The predicted hazard ratios would be even smaller with adjustment for regression dilution bias resulting from variability in the measurement of the CD4+ cell count.[18] It is unlikely that treatment differences of these predicted magnitudes were missed.

There are at least two hypotheses that could explain our results. The first and simplest is that the CD4+ T cells induced by interleukin-2 have no role in host defense. The second is that the cells are at least partially functional or that interleukin-2 has some modest beneficial effect not mediated through CD4+ cells but negative effects of interleukin-2 neutralize any improvements in host defense conferred by the therapy.

The value of a given CD4+ T cell to its host is the net sum of the predetermined antigenic specificity of that cell and the effector functions it expresses once activated by its antigen. T cells with receptors for irrelevant antigens or T cells that fail to exert protective effector functions on activation are of little value to the host. Interleukin-2 is known to induce a polyclonal expansion of preexisting CD4+ T cells that have predominantly naive or central-memory phenotypes. Antiretroviral therapy leads to expansions of preexisting effector memory, central memory, and naive cells. In this regard, it is possible that, despite the capacity to respond in vitro to certain antigens and

A SILCAAT

Subgroup	Difference in CD4+ Cell Count (per mm³)	Interleukin-2 + ARV	ARV alone	Hazard Ratio for Interleukin-2 (95% CI)	P Value for Interaction
		no. with an event (rate/100 person-yr)			
All patients	53.0±6.5	110 (1.94)	119 (2.13)	0.91	0.47
Sex					0.47
Male	56.1±6.1	96 (2.01)	98 (2.12)	0.94	
Female	40.3±13.8	14 (1.58)	21 (2.19)	0.72	
Race or ethnic group					0.98
Black	75.4±20.2	5 (1.21)	7 (1.33)	0.91	
White or other	52.4±5.8	105 (2.00)	112 (2.22)	0.90	
Age					0.98
<40 yr	46.9±8.3	41 (1.56)	41 (1.62)	0.96	
≥40 yr	59.2±7.4	69 (2.26)	78 (2.56)	0.88	
Baseline CD4+ cell count (per mm³)					0.12
<200	30.3±7.5	59 (2.19)	75 (2.86)	0.77	
≥200	75.1±8.1	51 (1.71)	44 (1.49)	1.14	
HIV RNA (copies/ml)					0.92
≤500	63.5±6.1	83 (1.79)	92 (2.00)	0.90	
>500	17.6±11.7	27 (2.61)	27 (2.79)	0.93	



B ESPRIT

Subgroup	Difference in CD4+ Cell Count (per mm³)	Interleukin-2 + ARV	ARV alone	Hazard Ratio for Interleukin-2 (95% CI)	P Value for Interaction
		no. with an event (rate/100 person-yr)			
All patients	159.2±7.4	159 (1.14)	165 (1.21)	0.94	0.55
Sex					0.83
Male	154.5±8.3	135 (1.19)	141 (1.28)	0.92	
Female	179.3±16.8	24 (0.91)	24 (0.92)	0.98	
Race or ethnic group					0.54
Asian	247.4±21.6	7 (0.44)	10 (0.63)	0.70	
Black	195.6±26.7	10 (0.74)	14 (1.13)	0.64	
White or other	142.9±8.2	142 (1.28)	141 (1.30)	0.98	
Age					0.21
<40 yr	170.7±10.7	50 (0.71)	59 (0.87)	0.81	
≥40 yr	147.0±10.1	109 (1.57)	106 (1.55)	1.01	
Baseline CD4+ cell count (per mm³)					0.04
<450	127.3±7.8	78 (1.23)	97 (1.48)	0.83	
≥450	176.0±10.5	81 (1.06)	68 (0.96)	1.09	
HIV RNA (copies/ml)					0.64
≤500	160.4±8.3	104 (0.94)	107 (0.98)	0.97	
>500	154.8±16.2	55 (1.87)	57 (2.16)	0.87	

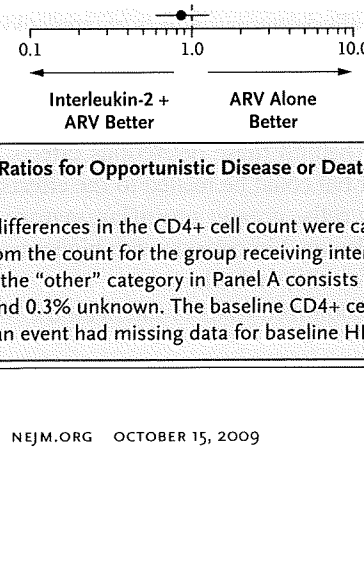


Figure 3. Between-Group Differences in the CD4+ Cell Count and Hazard Ratios for Opportunistic Disease or Death from Any Cause (Primary End Point), According to Subgroup.

Panel A shows data for the SILCAAT study; and Panel B, for ESPRIT. The differences in the CD4+ cell count were calculated by subtracting the count for the group receiving antiretroviral therapy (ARV) alone from the count for the group receiving interleukin-2 plus ARV and are expressed as means ±SE. Race or ethnic group was self-reported; the "other" category in Panel A consists of 1.2% Asians, 9.7% Hispanics, 0.8% other, and 0.1% unknown and in Panel B of 4.4% other and 0.3% unknown. The baseline CD4+ cell count is the approximate median value. In ESPRIT, one patient receiving ARV alone who had an event had missing data for baseline HIV RNA level.

mitogens[10] the antigenic specificities of cells expanded with the use of interleukin-2 contribute little to the immediate needs of the host, whereas cells expanded as a result of antiretroviral therapy include those of greatest current value — namely, those in the effector memory pool. In addition, the CD4+ cells expanded by means of interleukin-2 express intermediate levels of CD25+, the alpha chain of the interleukin-2 receptor, as well as moderate levels of the transcriptional regulator forkhead box P3 (FOXP3). In this regard, the CD4+ cells are similar, but not identical, to regulatory T cells — a subset of T cells associated with suppressor-cell activity. Thus, it is possible that even if correct antigenic specificities are present, effector functions exhibited by these cells could be different from those provided by CD4+ cells that are expanded in patients receiving antiretroviral therapy.

With regard to the second hypothesis, that benefits of interleukin-2 are counteracted by negative effects of interleukin-2, in both the SILCAAT study and ESPRIT, patients who were receiving interleukin-2 plus antiretroviral therapy had more grade 4 events than those receiving antiretroviral therapy alone. Although many grade 4 events occurring in the interleukin-2 group occurred more than 60 days after the completion of an interleukin-2 cycle, they nonetheless appear to be related to receipt of interleukin-2. The association between occurrence of thromboembolic events and use of interleukin-2 found in ESPRIT, coupled with the association between elevated D-dimer levels and death from any cause in patients with HIV infection[19] suggests a possible mechanism for a negative effect of interleukin-2 on clinical outcome. In ESPRIT, patients with higher baseline CD4+ cell counts had the greatest expansions of CD4+ T cells but also had a greater relative risk of having the primary end point or death from any cause. If this finding is not due to chance, it suggests that there may be clinically deleterious effects of interleukin-2 that are more pronounced in patients with higher baseline CD4+ cell counts or greater increases in CD4+ T cells after the use of interleukin-2. The mechanisms behind these deleterious effects remain unclear but could be related to the effects of T regulatory cells, greater proinflammatory effects of interleukin-2 in patients with higher numbers of CD4+ cells, or both.

Earlier randomized trials of interleukin-2 were conducted in patients receiving mono- or dual-nucleoside therapy, a different setting from that in the SILCAAT study and ESPRIT. In these earlier studies, most patients had HIV RNA levels above 10,000 copies per milliliter, and the groups receiving antiretroviral therapy alone had declining CD4+ cell counts.[4,20,21] A pooled analysis of the results from these earlier studies suggested that patients treated with interleukin-2 plus antiretroviral therapy, as compared with antiretroviral therapy alone, had higher CD4+ cell counts, lower viral loads, and a trend toward fewer opportunistic infections and death.[22] A more recent study in patients with advanced HIV infection also showed a trend toward fewer AIDS-defining illnesses with the use of interleukin-2.[23] One possible explanation for the differences between findings in the previous studies and our results is that interleukin-2 has some net beneficial effect in a small subgroup of patients who have ongoing viral replication and a lower CD4+ cell count. A more likely explanation is that the treatment differences in the earlier studies were chance findings. This emphasizes the importance of conducting adequately powered, randomized trials to evaluate novel therapeutic strategies.

Surrogate markers often do not accurately predict the clinical effects of a treatment. The peripheral-blood total CD4+ cell count only partially explains the beneficial effects of antiretroviral therapy.[24,25] These studies reaffirm that effects of a novel intervention that positively perturb levels of prognostic markers need to be assessed and validated in trials with clinical end points before those markers can be deemed reliable surrogates regarding that intervention. This requirement is consistent with experiences in other diseases.[26]

In summary, the results of the SILCAAT study and ESPRIT indicate that interleukin-2 offers no clinical benefit as compared with antiretroviral therapy alone. Whether these findings are relevant to other immunotherapies, such as interleukin-7,[27] is uncertain. The precise role of the immune system in the pathogenesis of HIV infection may benefit from a reevaluation as a consequence of our results. Our data indicate that all CD4+ cells may not be equal with respect to host defense and that improvement in the prognostic or surrogate value of CD4+ counts requires refinement in measurement.

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APPENDIX

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Raltegravir-associated perihepatitis and peritonitis: a single case report

Raltegravir, the first approved HIV integrase inhibitor, has demonstrated an excellent safety and tolerability profile in several clinical trials [1] and is currently used widely as one of the key components of salvage regimens. However, the duration of clinical use is relatively short, and unknown adverse effect may occur. Here, we report one case of peritonitis associated with use of raltegravir. Abdominal symptoms appeared within 2 weeks of commencement of treatment, and raltegravir had to be stopped due to worsening of clinical condition.

Case report

The patient was a 49-year-old Japanese hemophiliac coinfected with HIV and hepatitis C virus (HCV). HIV-RNA was undetectable, and $CD4^+$ cell count was above 500 cells/μl for more than 5 years under the combination of abacavir, nevirapine and lopinavir/ritonavir. In January 2009, lopinavir/ritonavir was replaced with raltegravir because of bleeding tendency related to the use of a protease inhibitor. Abacavir and nevirapine were continued, and no other drugs were modified. The patient visited the hospital on day 18 after the use of raltegravir, complaining of a gradually worsening pain in the right upper abdomen and lower chest wall for 3 days. A nonsteroidal anti-inflammatory drug was not effective, and a computed tomography (CT) scan performed 11 days after the onset of the symptom revealed contrast enhancement of the liver surface (Fig. 1a) and fatty stranding of the greater omentum (Fig. 1b), which are findings compatible with perihepatitis and peritonitis. Oral prednisone (60 mg/day for 3 days, then 30 mg/day for 3 days) was prescribed, and all the symptoms resolved immediately. However, abdominal symptoms developed again after withdrawal of prednisone, necessitating its reintroduction on day 31 at 30 mg/day. Attempts to taper prednisone led to worsening of abdominal pain and development of stomatitis, resulting in continuation of treatment at 20 mg/day. Raltegravir was switched to lopinavir/ritonavir 11 weeks after the onset of abdominal pain and, finally, all antiretroviral drugs were terminated 4 days later because of diarrhea and bleeding related to lopinavir/ritonavir. Abdominal symptoms gradually improved, and prednisone could be tapered to 10 mg/day within 2 weeks. A CT scan performed 10 days after cessation of antiretroviral therapy showed an improvement of perihepatic enhancement. C-reactive protein levels increased to 1.42 mg/dl during raltegravir use and fell to normal levels 6 days after discontinuation of raltegravir. Other laboratory data including transaminase levels showed no changes, and $CD4^+$ cell count and HIV-RNA were stable throughout the course.

This is the first reported case of severe peritonitis associated with raltegravir use. Although not described here, we have experienced several other cases with similar abdominal symptoms that disappeared after raltegravir termination. Several case reports have recently described previously unknown adverse effects related to raltegravir, such as rhabdomyolysis [2] and exacerbation of depression [3]. However, to our knowledge, raltegravir-associated peritonitis has not been reported. In the BENCHMRK

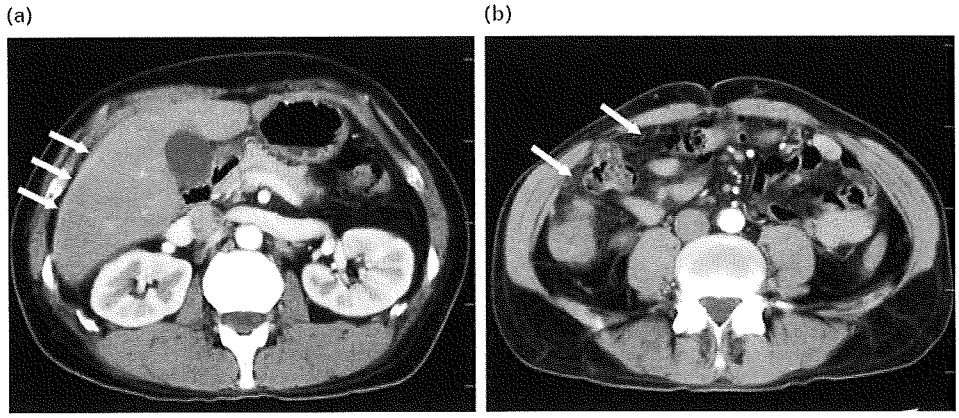

Fig. 1. A computed tomography scan performed 11 days after the onset of the symptoms. A computed tomography scan shows contrast enhancement around the liver surface (a) and fatty stranding of the greater omentum (b).

(Blocking integrase in treatment Experienced patients with a Novel Compound against HIV: MeRcK, MK-0518) study [1], abdominal symptoms, such as diarrhea and nausea, were noted in patients on raltegravir, and some of which might be associated with mild peritonitis.

Fortunately, raltegravir-associated peritonitis seemed reversible, at least to some extent. However, the longer use of raltegravir after onset of symptoms may lead to irreversible and lethal sequelae. Cessation of antiretroviral therapy as a result of severe abdominal symptoms is a potential risk for re-emergence of acute retroviral syndrome or the further accumulation of HIV-resistant mutations.

Whether the described side effects are universal or related to Asians, hemophiliacs or those who have underlying liver disease is unknown at present. Careful monitoring of abdominal symptoms and the consideration of an appropriate radiographic examination are warranted after commencement of raltegravir-containing regimens.

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第22回日本エイズ学会シンポジウム記録

HAARTとNeuroAIDS

HAART and NeuroAIDS

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はじめに

HIV感染症は，高活性抗レトロウイルス療法（HAART）により「死に至る病い」から「コントロール可能な慢性疾患」へと変貌した。HAARTによりエイズ脳症を含むHIV感染による神経合併症（NeuroAIDS）の頻度は著明に低下したが[1]，免疫再構築症候群，薬剤耐性例での日和見感染，薬剤関連末梢神経障害，脳血管障害などが増加しており，その病態の解明・治療戦略が今後の重要な課題である。また，エイズ脳症の病態もいまだ未解明な点が多い[2]。

本稿では，以上の点を踏まえて，臨床的立場から，1）神経病変を示すHIV症例の診断の進め方，2）HAART下における神経日和見感染症，3）免疫再構築症候群とエイズ脳症に関して，診療の現場を踏まえた研究を，基礎研究の立場からは，1）エイズ脳症の小動物モデル，2）ヒト剖検例，サルエイズモデルにおける中枢神経サイトカインの動態に関して，第一線で活躍している研究者に述べて頂いた。なお，本稿の内容は，第22回日本エイズ学会学術集会（2008年11月，大阪）のシンポジウムで発表された内容をまとめたものである。

中枢神経病変のある症例の診断の進め方

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HIV感染症患者に合併する脳内病変は多彩で，難治性の疾患から治癒が可能な疾患まであり，適切な診断と治療が患者の予後を大きく左右する。しかし，いずれも画像所見は類似しており，確定診断が困難な場合も多い。血液，髄液，画像検査を実施しても確定診断が困難な場合では，脳生検で重要な情報が得ることができれば，適切な治療方針の選択に役立つと考えられる。当院でも，画像上は脳原発リンパ腫と思われたケースでも，脳生検で悪性リンパ腫が否定された例もあり，脳生検は非常に有用であった。しかし，脳生検を実施できない症例や，脳生検でも確定診断が難しい症例もある。そこで，脳内病変の診断に際し，血液，髄液，画像検査に加えて脳生検を施行した症例を紹介し，中枢神経病変の診断の進め方について考える。

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画像検査の必要性

HIV関連で中枢神経病変をきたす疾患の診断をすすめていくにあたり，頭痛，意識障害，認知機能低下，麻痺，不明熱など何らかの神経疾患の存在が疑われる場合や特に症状がなくてもCD4値が非常に低値（CD4値＜100～200）の症例では日和見疾患の合併を疑い，脳MRI，CT検査などの画像検査を行うことがすすめられる。

中枢神経病変の診断の進め方（図1）

まず，画像検査で脳に占拠性病変の有無をみる。占拠性病変無い例の多くは髄膜炎疾患であり，髄液検査が診断に有用である。

次に，脳占拠性病変が有る例では，腫瘤による周辺部位へのMass effectの有無を見る。Mass effectを認めない疾患では，主として進行性多巣性白質脳症（以下PML），脳血管病変がある。これらは，特徴的な画像所見を呈するが，PMLでは髄液検査でJCVが検出されることも診断に役立

表 1　名古屋医療センターにおける中枢神経合併症の内訳

疾　患	～2000年7月	2000年8月～2007年12月
トキソプラズマ脳炎	3例	5例
HIV脳症		6例
進行性多巣性白質脳症	2例	3例
脳原発リンパ腫	1例	4例
クリプトコッカス髄膜炎	1例	3例
無菌性髄膜炎		2例
結核性髄膜炎		1例
HSV髄膜炎		1例
VZV髄膜炎		1例
CMV脳炎		1例
アメーバ脳炎		1例
海綿静脈洞症候群		1例
水頭症		1例
原因不明		1例
計	7例	31例
HIV症例数（うちAIDS）	106（19）例	614（199）例
AIDSでの中枢神経合併率	36.8%	14.6%

示した。最多はトキソプラズマ脳炎8例，以下HIV脳症6例，進行性多巣性白質脳症5例，クリプトコッカス髄膜炎4例，悪性リンパ腫4例と，日和見感染症が大きな比重を占めている。これら中枢神経日和見感染症の実地臨床上の問題点について検討した。

HIV感染による日和見感染の特徴

第一に，HIV感染症の前提がないと診断が困難であることが挙げられる。とりわけトキソプラズマ脳炎や進行性多巣性白質脳症，HIV脳症はいずれの疾患もHIV感染症という情報がないと，脳腫瘍や細菌性脳膿瘍，脳梗塞，ウェルニッケ脳症，ADEM等と鑑別が難しい。診断に難渋した結果，適切な治療開始が遅れることとなる。逆に，HIV感染症と診断がついていれば，診断手順に従って鑑別をすすめることが可能である。

第二にNeuroAIDSをいったん発症した際の予後が不良であることである。自施設でのNeuroAIDS 36例に対し，その転帰について検討したところ，後遺症なく回復した症例は4例（11.1%）に過ぎず，後遺症を残したものが16例（44.4%），死亡は16例（44.4%）にのぼった。生命予後について既報告と同様に不良であることはもちろん，機能予後としても不良であるといえる。

トキソプラズマ脳炎

個々の中枢神経疾患について問題点を挙げると，トキソプラズマ脳炎は外国人症例が多く，社会的要因により治療継続が困難となることがあること，治療薬の副反応が挙げられる。トキソプラズマ脳炎の8例は，日本人2例に対し，南米出身者が6例と多数を占めた。その背景として，抗体保有率に注目し検討を行った。当院を継続受診したHIV感染症例連続518例を対象として，トキソプラズマ抗体保有率について検討したところ，トキソプラズマ抗体を測定した419症例中，日本人の抗体陽性率は9.8%であったのに対し，ブラジル人での抗体陽性率は56.1%と高率であった。抗体保有率の地域差から患者層の地域的な偏りを生じていると推定された。金銭的問題や帰国のタイミング，家族との連絡手段，言語の障壁等，社会的要因から治療継続性を困難なものとしている。後者の治療薬の副反応については，骨髄抑制を3例に，輸血を必要とする貧血を1例，腎機能障害を2例に認めた。また，副反応のため治療を中断したものを3例認め，重度の骨髄抑制がその理由であった。サルファジアジンとピリメサミンの併用療法の有効性は確立しているが，副反応のためやむを得ずクリンダマイシンに切り替える際のタイミング，葉酸の補充方法等，検討の余地があると思われた。また，トキソプラズマ脳炎の症例で，転移性脳腫瘍や出血性梗塞と当初診断され，適切な治療のタイミングを逸した症例もあり，HIV感染症と判明していない状況での診断の難しさが挙げられた。

進行性多巣性白質脳症（PML）

PMLは，HAART導入後に改善を示し長期生存例が存在する一方で，急速に進行する症例があること，特異的治療がないことが問題である。PMLは特異的治療法がないため，当院ではPMLを強く疑った症例に対して，他の日和見感染症を可及的速やかに除外しHAARTを導入している。HAART時代に経験したPMLは3例全例でHAART開始1ヶ月間に急激に神経症状が進行した。うち2例は死亡し，1例は剖検を行ったところ，強い炎症細胞浸潤があり，免疫再構築による増悪が示唆された。急性増悪を乗り超えて現在も在宅療養を継続している1例については，発症1年後の髄液検査でJCウイルスが検出されなかった。いかに免疫再構築による増悪をおさえるかがPML診療における今後の課題と考える。

HIV感染の中枢神経合併症においては，その予後が不良

であるだけに予防に勝るものはないが，不幸にして生じた場合もHIV感染症自体の早期診断が必要不可欠である。トキソプラズマ脳炎についてはより副反応の軽い治療法を，PMLについては早期HAARTの導入と免疫再構築の治療についての知見の蓄積が望まれる。HAARTによりNeuroAIDSについても長期生存が可能となってきており，長期療養を支える仕組みも必要である。

神経免疫再構築症候群とエイズ脳症

(東京都立駒込病院脳神経内科　岸田修二)

HAARTがHIV感染治療に導入された後，抗レトロウイルス剤を服用している患者の神経疾患発症は原発・日和見疾患とも極めて少なくなり，発症者のほとんどが抗ウイルス剤未治療者か治療中断者である[2]。HAARTはHIV感染患者の日和見感染症発症を抑制し，生命予後を改善する一方，これまでみられた亜急性進行性脳症に替わって慢性脳症の発症や抗レトロウイルス剤の副作用から生じる脳血管障害の増加，延命に伴い老化に関連した疾病などの出現が危惧されている。その上HAART開始に伴いHIVが抑制され，免疫が回復してくるとともにこれまで潜伏していた感染症が顕症化したり，すでに治療を受けた感染症が一時的に増悪する病態，すなわち免疫再構築症候群が新たな疾患概念として出現してきた。治療法の進歩とともにHIV/AIDS患者の病像は臨床・病理学的に複雑に修飾されてきている。1997年～2008年6月までに経験したNeuroAIDS症例でHAARTにより免疫再構築症候群を発症した症例の臨床的検討ならびに他施設で発症した免疫再構築症候群症例の病理学的検討，そしてHAART導入中に発症したエイズ脳症3例の病態を検討した（表2)。

HAART導入後の神経合併症

①HAART導入後免疫再構築症候群発症例はエイズ脳症0/15例，クリプトコッカス症3/7例，サイトメガロウイルス脳炎2/5例，トキソプラズマ脳炎1/9例，進行性多巣性白質脳症（PML）6/6例であった。②神経免疫再構築症候群は，病原体ではJCウイルス，クリプトコッカス，サイトメガロウイルス感染によるものが多かった。③クリプトコッカス髄膜炎では免疫再構築症候群を発症した症例のHAART導入前のクリプトコッカス抗原価は128～1024倍であり，発症しなかった症例の抗原価4～64倍に比べ高い傾向を認め，免疫再構築症候群発症時HAART中断が必要であった。④PMLはHAART導入により全例免疫再構築症候群を発症し，免疫再構築症候群重症例にはステロイドパルス療法の併用が有効であった。さらに免疫再構築症候群は延命と関係していた。⑤免疫再構築症候群を発症した症例の髄液では発症時髄液IL-6が高値を示し，診断の一助になるものと思われた。⑥免疫再構築症候群を発症して死亡したPML2例ならびに白質脳症1例の神経病理学的検討では血管周囲性にCD8陽性T細胞の顕著な浸潤がみられた。

HAART治療中エイズ脳症発症者3例を経験した。2例は末梢でのHIV抑制が不十分でうち1例は髄液HIV＞血漿HIV負荷量であり，1例はCD4が300台，末梢HIV負荷量は検出限界以下でありながら髄液HIVは不十分に抑制された状態で発症した。臨床症状は軽症から中等症であるが，髄液中でのHIV抑制不十分例は抑制例に比べ認知障害が高度であった。また画像上白質脳症，髄液検査異常を示すものがあり，慢性脳症を示唆する例があった。中枢神経移行性の高いHAART処方に変更し，臨床症状の改善をみた。

表2　1997年～2008年6月までの主な自験NeuroAIDS症例（都立駒込病院）

疾　患	症例数	HAART導入数	免疫再構築症候群発症数			死亡数	HAART導入例の死亡数
			顕性化	逆説性	計		
クリプトコッカス髄膜炎	15	8	0	3	3 (40%)	4 不明4	1 (13%)
サイトメガロ脳炎	11	5	1	1	2 (40%)	10	4 (80%)
トキソプラズマ脳炎	17	9	1	0	1 (11%)	6 不明3	1 (11%)
進行性多巣性白質脳症	6	6	2	4	6 (100%)	1	1 (HAART中止) (17%)
HIV脳症	20	15	0	0	0	9 不明1	4 (27%) 不明1

HAART 導入後の問題点

HAART は HIV/AIDS 患者にとって延命効果とともに，様々な合併症をも来す諸刃の剣のような面を持っている。新たな疾患概念として発症した免疫再構築症候群もその一つである。免疫再構築症候群の定義もコンセンサスを得られたものは未だなく，従って免疫再構築症候群の正確な発症頻度やどのような症例に発症する危険性があるのか充分解明されていないし，発症したときの対策も個々の疾患により異なっている。今回の検討では神経免疫再構築症候群はクリプトコッカス性髄膜炎，進行性多巣性白質脳症，サイトメガロウイルス感染症に発症頻度が高く，クリプトコッカス髄膜炎では HAART 導入時点での高抗原価に発症危険性が高いことが示された。免疫再構築症候群の剖検例からは致死的免疫再構築症候群では CD8 陽性細胞傷害性 T 細胞が急速に中枢神経系に浸潤することが重要な役割を演じていると思われた。神経免疫再構築症候群重症例ではステロイド併用が有効かもしれない。一方エイズ脳症は HAART 導入後重篤な脳症が減少してきた。しかしながら米国での ACTG での ALLRT 調査にみるように HAART 服用者でも軽症の認知障害患者が相当数いること，免疫の改善により認知機能の改善の見込みがあること，逆に軽症認知障害が残存したり，抗ウイルス療法が成功しても新たに認知障害が発症する場合のあること，特に AIDS の既往のある場合や，CD4 陽性 T 細胞が回復してこない例に多いことなどが指摘されている。今回の検討例はいずれも免疫不全の進行した時期からの HAART 開始であり，さらに末梢や髄液で十分 HIV が抑制されていない状態であった。薬剤選択如何により中枢神経に残存した HIV により神経病理学的異常が進行している可能性があり，特に AIDS 発症後の HAART 処方は中枢神経移行性を考慮する必要性があると考えられた。

わが国では HIV 感染患者が増加，特に HIV 感染を知らないで，あるいは治療を自己中断して AIDS を発症してくる患者の割合が増加し続けている。これらの患者は原発性あるいは日和見性神経疾患を初発症状として受診するかも知れない。神経疾患の多彩さは HAART 導入前と同様である。神経障害の発症は致死的あるいは高度に機能障害を後遺症とする率が高く，また HAART 導入により臨床的・病理学的に従来より診断・治療が複雑性を増してきている。神経合併症は今後も重要な HIV 合併症であり，Neuro-AIDS の発症機構の解明と治療戦略は，延命化した HIV 感染症にとって最も重要な課題である。

エイズ脳症の小動物モデル（埼玉県総合リハビリテーションセンター神経内科　三浦義治，京都大学ウイルス研究所ウイルス病態研究領域　小柳義夫，東京医科歯科大学大学院脳神経病態学分野　水澤英洋）

エイズ脳症とはヒト免疫不全ウイルス（HIV）により引き起こされる認知運動障害であり，主にエイズ発症時期に著明となり，亜急性に進行する。しかし，HAART によりエイズ脳症患者数は著明に減少した。そして近年ではエイズ脳症の軽症型である軽微認知運動障害（milder cognitive and motor disorder, MCMD）が深刻な問題となってきている[4]。このエイズ脳症の病態の中心は，感染して脳内に侵入した血管周囲に存在する HIV-1 感染マクロファージとミクログリアである。そしてエイズ脳症患者の脳より検出されるウイルスは CCR5 をコレセプターとして使用する R5 ウイルス，マクロファージ指向性 HIV である。ここにおいて神経細胞とオリゴデンドログリアが主に障害を受ける。このように細胞への直接の感染増殖によらない間接的細胞障害が病態の中心であると考えられている。

マウスを用いたエイズ脳症研究の歴史

HIV-1 はヒトとチンパンジーにしか感染しないことがその特徴である。このウイルスによる脳障害すなわちエイズ脳症はげっ歯類などの小動物モデルで病態の再現が可能かどうかが議論となってきた。これまでマウスを用いたエイズ脳症研究は，①トランスジェニックマウスを用いた研究，②重症複合型免疫不全マウスである重症複合免疫不全（severe combined immunodeficiency）SCID マウスを用いた研究があり，他に HIV に近縁のマウス白血病ウイルス（murine leukemia virus, MuLV）を用いた研究に分けられる。トランスジェニックマウスを用いた研究は，ウイルスゲノムあるいはウイルス産生タンパクを遺伝子導入した実験系と，宿主因子であるサイトカイン等を組み込んだマウスに大別される。前者では Tomas らが 1994 年に HIV-1 ゲノム全長を neurofilament protein-L をプロモーターにして神経細胞に発現するマウスと，Toggas らが 1994 年に発表した GFAP をプロモーターとしてアストロサイトに HIV-1X4 ウイルスの産生蛋白である gp120 を発現させたマウスが有名である。他に Wang らが R5 ウイルスである JR-CFS 全長を T 細胞と単球に発現させたマウス，gp160, Tat, Vpr のトランスジェニックが報告されている。サイトカインでは IL-6, TNF, MCP-1 のトランスジェニックマウスが報告されている。

SCID マウスを用いた実験系は脳内移植の実験系と，腹腔内移植の 2 系統の実験系に大別される。1993 年 Tyor らは SCID マウスにヒト末梢血単核球を脳内移植し，その後