Outpatient Continuous Intravenous Interleukin-2 or Subcutaneous, Polyethylene Glycol–Modified Interleukin-2 in Human Immunodeficiency Virus–Infected Patients: A Randomized, Controlled, Multicenter Study

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The safety and activity of outpatient-based continuous intravenous interleukin-2 (CIV IL-2) or a slow-release, polyethylene glycol (PEG)–modified IL-2 were studied in human immunodeficiency virus (HIV)–infected persons with CD4 cell counts between 200 and 500/mm^3. One hundred fifteen patients were randomized to antiretroviral therapy plus cyclical CIV IL-2 (n = 27), subcutaneous PEG IL-2 (n = 58), or no IL-2 (n = 30). Toxicity withdrawal rates were low (4% for CIV IL-2 and 7% for PEG IL-2). There were median CD4 cell count increases of 359 and 44 cells/mm^3 and a decline of 46 cells/mm^3 in the 3 groups, respectively, over 1 year ($P < .0001$ for each intergroup comparison). CD4 cell count increases were greatest in those with lower HIV RNA load. Delayed-type hypersensitivity scores increased and HLA-DR expression on CD8 cells decreased significantly with IL-2 therapy. HIV RNA levels were unaffected. IL-2 therapy may expand the existing immune repertoire but not immediately reconstitute lost immune function.

Human immunodeficiency virus (HIV) causes immunodeficiency through progressive destruction of antigen-specific CD4 T lymphocytes. Antiretroviral therapy protects the immune system from damage by inhibiting viral replication and so delays the onset of opportunistic infections and prolongs survival [1–4]. Nevertheless, antiretroviral therapy often fails because of incomplete suppression of viral replication or because of drug intolerance. Other therapies that increase or preserve the reservoir of functional immune cells in HIV-infected patients, even in the absence of an effect on HIV load, might complement antiretroviral therapy and lead to further clinical benefit.

Interleukin-2 (IL-2) is a cytokine secreted by activated T lymphocytes that causes increased proliferation and function of CD4 and CD8 T lymphocytes, B lymphocytes, and NK cells in vitro [5]. HIV infection causes reduced IL-2 production and responsiveness, as well as T cell depletion and dysfunction [6–10]. IL-2 can enhance CD4 T lymphocyte proliferation and the depressed NK and cytomegalovirus-specific cytotoxic activities of lymphocytes from HIV-infected patients [11, 12]. Intermittent cycles of continuous intravenous (CIV) IL-2 resulted in sustained increases in CD4 lymphocyte counts in those with baseline CD4 lymphocyte counts >200/mm^3, with the maximum well-tolerated dose being 12 million IU daily when given as a 5-day infusion every 8 weeks on an inpatient basis [13, 14]. The safety and applicability of IL-2 therapy to widespread clinical use is unclear, however, as IL-2 has not been studied in an outpatient setting.

Polyethylene glycol (PEG)–modified IL-2 is a good candidate for outpatient IL-2 therapy [15]. Two subcutaneous doses of PEG IL-2 given 2 days apart model the pharmacokinetics of a 5-day CIV IL-2 cycle, as subcutaneous PEG IL-2 is well-absorbed and has a 10- to 20-fold slower clearance than does IL-2. Intermittent PEG IL-2 has demonstrated immunologic activity with an acceptable side effect profile, although the maximally tolerated dose was not determined [16–19].

The present trial was designed to evaluate the safety and immunologic activity of IL-2 therapy in an outpatient setting and to define the maximally tolerated dose of intermittent, subcutaneous PEG IL-2. HIV-infected patients receiving antiretroviral therapy and with CD4 T lymphocyte counts between 200 and 500 cells/mm^3 were randomized to receive CIV IL-2, PEG IL-2, or antiretroviral therapy without IL-2 for 1 year.

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Written, informed consent was obtained from each participant, and the study protocol was approved by each institution's research ethics committee.

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Methods

Inclusion criteria. The principal entry criteria were documented HIV infection, age >18 years, CD4 lymphocyte count between 200 and 500 cells/mm^3, Karnofsky score >60, at least 2 months of continuous antiretroviral therapy at study initiation, no prior IL-2 therapy, no AIDS-defining illness apart from untreated mucocutaneous Kaposi's sarcoma, no concurrent experimental or immunomodulating therapy, and no history of autoimmune or inflammatory disease (e.g., psoriasis, inflammatory bowel disease) that might be exacerbated by IL-2. Patients had at least one person available to provide home care during outpatient cycles.

Treatments. Patients continued antiretroviral therapy and were randomized to CIV IL-2 (Proleukin, Aldesleukin for injection; Chiron, Emeryville, CA), subcutaneous PEG IL-2, or no IL-2 (i.e., antiretroviral therapy alone) on a 1:2:1 basis (the unequal randomization allowed for determination of the maximally tolerated dose of PEG IL-2 as well as its efficacy). Randomization was stratified by site and screening CD4 lymphocyte count ($\geqslant$300 or <300 cells/mm^3). The initial dose of CIV IL-2 was 12 million IU daily for 5 days every 8 weeks [13, 14]. The initial dose of PEG IL-2 was 1.0 million IU per cycle in equal, divided doses on days 1 and 3 every 8 weeks [15–18]. Dose increments of 0.5 million IU of PEG IL-2 per cycle occurred after 3 patients had successfully completed a treatment cycle at a given dose until a dose of 6.5 million IU per cycle was reached; after a protocol amendment, increments were increased to 1.0 million IU per cycle because of the minimal toxicity associated with lower-dose PEG IL-2. The maximally tolerated dose (MTD) of PEG IL-2 was defined by the highest dose at which at least 4 of 6 patients did not develop a toxicity sufficient to preclude repeated dosing at that dose.

IL-2 recipients were hospitalized for the first 5–6 days of cycle 1 to familiarize patients and caregivers with the toxicities of IL-2 and to determine the optimum prophylaxis and therapy for common toxicities, such as fever, fatigue, myalgias, stomatitis, nausea, diarrhea, anxiety, and insomnia, in subsequent cycles. Patients were advised to maintain a fluid intake of at least 2.5 L daily and a urine output of at least 1.5 L daily. Patients receiving PEG IL-2 were reviewed on days 1, 3, 5, and 8 of each cycle, and those receiving CIV IL-2 on days 1–6 and day 8. Dose-limiting adverse events during treatment (including hospitalizations after cycle 1) resulted in termination of therapy for that cycle. Mid-cycle assessments (week 4 or 5) were done to ensure that treatment-related adverse events had resolved. Dose reductions for toxicity were 3 million IU/day for CIV IL-2 and 1 million IU per cycle for PEG IL-2. IL-2 therapy could be delayed for up to 4 weeks for acute medical events.

All patients received at least one of the following antiretroviral agents for the entire study: zidovudine, 250 mg twice daily; didanosine, 125 mg twice daily; and zalcitabine, 0.375 mg three times daily. To determine if improved suppression of HIV replication might augment IL-2 responsiveness, all patients started lamivudine at 150 mg twice daily at cycle 4, week 6.

Assessments. Safety assessments included complete blood cell count, renal and hepatic function tests, and creatine kinase, calcium, phosphate, magnesium, and glucose determinations. Other assessments included CD4 and CD8 lymphocyte counts (including CD25$^+$ and HLA-DR$^+$ subsets) by three-color flow cytometry, batched plasma HIV RNA levels, determined by a branched-chain DNA assay with a sensitivity of 10,000 copies/mL of plasma (Quantiplex; Chiron), plasma IL-2 and PEG IL-2 levels (data not shown), IL-2 and PEG IL-2 antibody levels (data not shown), and delayed-type hypersensitivity (DTH) skin testing (CMI Multitest; Pasteur Mérieux, Lyon, France). In an attempt to control for prior antigen exposure, all patients received adult diphtheria-tetanus vaccine (ADT Vaccine; Commonwealth Serum Laboratories, Melbourne, Australia) at screening (3 weeks before initial DTH testing and 4 weeks before cycle 1). DTH was scored as the sum of all indurated responses of a mean diameter of $\geqslant$2 mm (a positive score) to each of the seven antigens in the test [20]. Patients anergic to tetanus toxoid at baseline DTH testing received booster ADT vaccinations midway during cycles 3 and 4.

The study was designed to recruit 120 patients. Two interim analyses to evaluate safety and efficacy were specified in the study protocol. A Lan-DeMets α spending rule was used to specify the significance levels for the interim and final efficacy analyses. The study was terminated prematurely in November 1995, when the second, interim analysis showed differences among treatment groups in CD4 cell counts exceeded a predefined stopping rule. The Data and Safety Monitoring Board recommended cessation of the study and provision of IL-2 to all trial participants.

Statistical analysis. The primary safety variables were the safety and MTD of CIV IL-2 and PEG IL-2 in an outpatient setting. The primary efficacy variable was the percentage of change in CD4 lymphocyte counts. An analysis of variance of the ranked observations was used with effects for treatment group, CD4 cell count stratum, and study center. The significance of baseline variables on response was assessed by adding to the model effects for that variable and its interaction with treatment. Similar methods were used to analyze HIV RNA and immunologic response variables, including changes in DTH scores, from pretreatment to posttreatment values.

Longitudinal plots were used to evaluate temporal trends in immunologic and virologic variables. To account for potential biases due to early patient withdrawals, a modified last-value-carried-forward approach was used, in which each patient withdrawing early for toxicity or patient request (but not because of the study's premature termination) had their last value carried forward (imputed) until 31 December 1995, using an expected 8-week cycle duration.

Results

Subjects. One hundred forty-three patients were screened, and 115 patients were randomized between July 1994 and November 1995, 27 to the CIV IL-2 group, 58 to the PEG IL-2 group, and 30 to the control group. Twenty-six of the 28 persons not selected were rejected on the basis of CD4 cell counts. One patient was randomized with prior non-Hodgkin's lymphoma in complete remission since 1987. Baseline clinical and laboratory characteristics did not differ significantly among groups (table 1).

Treatments. Table 2 shows patient disposition and dose reductions. The mean number of treatment cycles received was 4.9 in the CIV IL-2 group (total, 131 cycles) and 4.6 in the PEG IL-2 group (total, 265 cycles); these reduced means reflect the study's premature termination.

Table 1. Baseline characteristics of patients receiving CIV IL-2, PEG-modified IL-2, or no IL-2 (controls).

	CIV IL-2 (n = 27)	PEG IL-2 (n = 58)	Controls (n = 30)
Age (mean years)	38	39	38
Male sex	27 (100)	56 (97)	30 (100)
Risk factor(s) for HIV infection*			
Homosexual or bisexual sex	25 (92)	55 (95)	29 (96)
Injecting drug use	2 (7)	6 (10)	2 (7)
Blood product exposure pre-1985	0 (0)	1 (2)	1 (3)
Occupational exposure	1 (4)	1 (2)	1 (3)
Duration of HIV infection (mean years)	6.4	6.3	6.3
Antiretroviral therapy			
Monotherapy	18 (67)	30 (52)	15 (50)
Double therapy	9 (33)	28 (48)	15 (50)
Karnofsky score (mean)	98	99	96
Weight (mean kg)	74	73	76
HIV disease category			
A (asymptomatic)	13 (48)	28 (48)	15 (50)
B (symptomatic, not AIDS)	13 (48)	28 (48)	15 (50)
C (AIDS)	1 (4)	2 (4)	0 (0)
CD4 lymphocyte count (median cells/mm^3)	305	347	336
$<$300	251	265	280
$\geqslant$300	367	403	391
CD4 % (median)	19	19	18
CD8 lymphocyte count (median cells/mm^3)	893	980	1003
CD8 % (median)	59	58	60
Delayed-type hypersensitivity			
Score (mean mm)	13.7	10.9	13.7
Positive antigens (mean no.)	2.2	2.2	2.4
Positive tetanus toxoid response (mean no.)	18 (67)	37 (64)	20 (67)
HIV RNA load (median log copies/mL of plasma)	4.15	4.23	4.28

NOTE. Where not specified, data are no. (%).
* Some patients had $>$1 risk factor for HIV infection.

The median daily CIV IL-2 dose throughout the study was 12 million IU/day at the commencement of each cycle. Twelve (44%) CIV IL-2 patients had dose reduction to 9 million IU/day (10 after the first IL-2 cycle); 2 patients had further dose reduction to 6 million IU/day, and 1 patient returned to the 12 million IU/day dose.

The median dose of PEG IL-2 in cycle 1 was 5.0 million IU and progressively increased to 8.5 million IU at cycle 6. The MTD was 11.5 million IU per cycle. No single adverse event determined the MTD of PEG IL-2; a constellation of constitutional symptoms, including severe and prolonged fatigue, fever, and mental status changes, were judged to contraindicate repeated outpatient administration. Sixteen (28%) PEG IL-2 patients required dose reductions for adverse events at or below the MTD.

Thirty-seven (32%) patients changed antiretroviral therapy during the study in addition to commencing lamivudine, 13 (48%) in the CIV IL-2 group, 14 (25%) in the PEG IL-2 group, and 10 (33%) controls ($P > .2$). Patients switched, added, and ceased various antiretroviral agents because of declining CD4 lymphocyte counts, toxicities, and pill burden, but these changes did not influence the immunologic responses to IL-2 therapy (data not shown).

Adverse events. The termination rates due to adverse events were 4% in the CIV group and 7% in the PEG IL-2 group. The frequency and severity of grade 3 and 4 adverse events (National Cancer Institute Common Toxicity Criteria) were similar for both IL-2 groups, with the exception of the local erythema and induration associated with subcutaneous PEG IL-2 injections (table 3). Fever, fatigue, stomatitis, erythema, gastrointestinal symptoms, and mood alterations constituted the majority of clinically significant toxicities, although these reached grade 4 toxicity in only 4 (5%) IL-2 recipients. The majority of adverse events resolved by day 8–15 of each cycle.

Several unusual side effects developed that were not dose-dependent. One PEG IL-2 patient with a history of heroin abuse was newly diagnosed with a cardiomyopathy during his second treatment cycle. His cardiac ejection fraction improved but did not normalize after IL-2 withdrawal. A second PEG IL-2 patient with a psychiatric history attempted suicide during his second cycle and was removed from study. One PEG IL-2 and 1 CIV IL-2 patient had worsening of preexisting diarrhea during therapy and were removed from study; 1 patient had a colonoscopy, and biopsies were consistent with a diagnosis of ulcerative colitis. One patient who was hepatitis B virus surface antigen–negative but core antibody–positive had a clinical flare of hepatitis B after four cycles of PEG IL-2; this resolved during treatment with lamivudine and did not recur. Finally, 4 patients developed tinnitus, 2 with sustained hearing loss; in 3 patients (2 CIV IL-2 patients and 1 control), this followed the

Table 2. IL-2 dosing and premature study terminations.

	CIV IL-2 (n = 27)	PEG IL-2 (n = 58)*	Controls (n = 30)
IL-2 dose reduction	12 (44)	16 (28)†	—
Completed protocol	14 (52)	31 (53)	19 (63)
No dose reduction	8 (30)	20 (34)	—
With dose reduction	6 (22)	11 (19)	—
Terminated prematurely	13 (48)	27 (47)	11 (37)
Termination by DSMB‡	9 (33)	19 (33)	11 (37)
IL-2 adverse event	1 (4)	4 (7)	—
Patient request	3 (11)	4 (7)*	0
No dose reduction	7 (26)	22 (38)	—
With dose reduction	6 (22)	5 (9)	—

NOTE. Data are no. (%).
* Includes 1 patient who was randomized to but did not receive any PEG IL-2 therapy.
† Does not include 5 patients who had dose reduction from 12.5 million IU per cycle after maximally tolerated dose of PEG IL-2 was determined to be 11.5 million IU per cycle.
‡ Patients receiving randomized therapy at study premature termination after Data and Safety Monitoring Board recommendation.

Table 3. Summary of grade 3 or 4 adverse events and hospitalizations.

	CIV IL-2 (n = 27)	PEG IL-2 (n = 58)	Controls (n = 30)
Any adverse event	21 (78)	52 (91)	3 (10)
Constitutional symptoms	13 (48)	47 (82)	3 (10)
Fatigue	9 (33)	21 (37)	2 (7)
Fever	4 (15)	7 (12)	0
Myalgias/arthralgias	0	4 (7)	0
Injection site reaction	—	38 (67)	—
Gastrointestinal			
Stomatitis	0	4 (7)	0
Mouth ulcers	1 (4)	1 (2)	0
Nausea	4 (15)	5 (9)	1 (3)
Vomiting	5 (19)	7 (12)	1 (3)
Diarrhea	3 (11)	2 (4)	1 (3)
Central nervous system	5 (19)	13 (23)	3 (10)
Somnolence	4 (15)	10 (18)	2 (7)
Mood changes	2 (8)	4 (7)	0
Laboratory parameters			
Bilirubin $>1.5 \times$ ULN	13 (48)	13 (22)	3 (10)
Serum ALT $>5 \times$ ULN	7 (26)	18 (31)	4 (13)
Serum creatinine $>3 \times$ ULN	1 (4)	0	0
Thrombocytopenia $<50 \times 10^9$/L	2 (8)	4 (7)	0
Neutrophils $<0.5 \times 10^9$/L	2 (7)	3 (5)	0
Hospitalizations, no. (mean days)*	0.48 (2.0)	0.43 (1.6)	0.21 (1.5)

NOTE. Data are no. (%) unless otherwise indicated. ALT, alanine aminotransferase; ULN, upper limit of normal. Only two grade 4 events were reported in each IL-2 group.

* Does not include protocol-required 5 days for inpatient administration of IL-2 in cycle 1.

addition of lamivudine. The fourth case occurred in a PEG IL-2 recipient who did not receive lamivudine. The relationship of these events to IL-2 or lamivudine therapy is uncertain, as they have not been reported previously with either therapy.

Development of grade 3 or 4 adverse events did not correlate with plasma levels of either form of IL-2 (data not shown).

Immunologic responses. The median percentage increases in CD4 cell counts before lamivudine were 72% in the CIV IL-2 group and 6% in the PEG IL-2 group, versus a decline of 18% in the controls ($P < .0001$ for each intergroup comparison). The percentages of all patients who had at least a 25% increase in CD4 lymphocyte count before lamivudine were 89%, 28%, and 7%, respectively. There were median (mean) CD4 lymphocyte increases of 359 (417) cells/mm^3 and 44 (57) cells/mm^3 and a decline of 46 (61) cells/mm^3 in CIV IL-2, PEG IL-2, and control patients, respectively, over the entire study (figure 1A).

CD4 lymphocyte responses were analyzed according to baseline CD4 cell count stratum (figure 1B), baseline HIV RNA burden (median, 4.23 log copies/mL of plasma; figure 1C), and baseline $CD4^+CD25^+$ cell percentage (median, 1.8%; data not shown). The only positive predictor of response was lower baseline virus load. Even in patients with virus load >4.23 log/mL of plasma, however, the CD4 cell count outcome was significantly higher in both IL-2 groups than in controls ($P = .0001$). Changes in CD4 cell counts did not correlate with plasma levels of either form of IL-2 nor with the development of IL-2 antibodies, the latter being uncommon (data not shown).

Total CD8 and $CD25^+CD8^+$ (data not shown) lymphocyte counts did not change in any group over six cycles. There was a significant decline in the percentage of CD8 lymphocytes expressing the activation marker HLA-DR in the CIV IL-2 group versus the control group (mean decline of 26% and mean increase of 52%, respectively; $P = .03$).

DTH scores increased by a mean (median) diameter of 3.6 (3.0) mm in the CIV IL-2 group and 3.3 (2.8) mm in the PEG IL-2 group and declined by 3.7 (3.0) mm in the control group ($P = .001$ for CIV IL-2 group vs. controls and $P = .004$ for PEG IL-2 group vs. controls; figure 2). There was no significant increase in the number of new positive DTH responses in any group, including to tetanus and diphtheria antigens; the increased scores mostly represented an increase in the diameters of responses positive at baseline.

Virologic responses. Figure 3 shows changes in mean log HIV load by treatment group. Before lamivudine therapy, HIV RNA load did not significantly change in or between any groups (median change, 0.00 log in each group; $P > .2$ for all intergroup comparisons). The median (mean) transient increase in HIV RNA from day 1 to day 7 of cycles 1 and 3 was 0.16 (0.24) log in the CIV IL-2 group and 0.11 (0.15) log in the PEG IL-2 group ($P > .2$ for comparison of CIV IL-2 vs. PEG IL-2 groups).

The addition of lamivudine during cycle 4 resulted in mean 0.19 to 0.30 log declines in HIV RNA load in the 3 groups. Lamivudine did not diminish the transient burst in HIV viremia seen with IL-2 therapy during cycle 5 (data not shown).

Clinical outcome. There was no significant change in mean weight, Karnofsky score, or any biochemical or hematologic parameter (apart from lymphocyte counts and subsets) over the study in any group (data not shown).

Progression to AIDS (CDC category C disease) occurred in 5 patients, 1 (4%) CIV IL-2 recipient (cryptococcal meningitis at a CD4 cell count of 10/mm^3 after six cycles), 2 (4%) PEG IL-2 recipients (each with asymptomatic esophageal candidiasis and CD4 cell counts of 224 and 240/mm^3), and 2 (7%) controls (1 with pulmonary *Mycobacterium avium* infection and a CD4 cell count of 255/mm^3 soon after randomization, the other with presumed cerebral toxoplasmosis and a CD4 cell count of 160/mm^3).

Discussion

Outpatient treatment of HIV-infected patients with CD4 cell counts between 200 and 500 cells/mm^3 with CIV IL-2 or subcutaneous PEG IL-2 every 8 weeks is safe, feasible, and well-tolerated. Outpatient IL-2 therapy generally resulted in significant and sustained increases in CD4 cell counts over a period of up to 1 year of therapy when added to nucleoside analogue

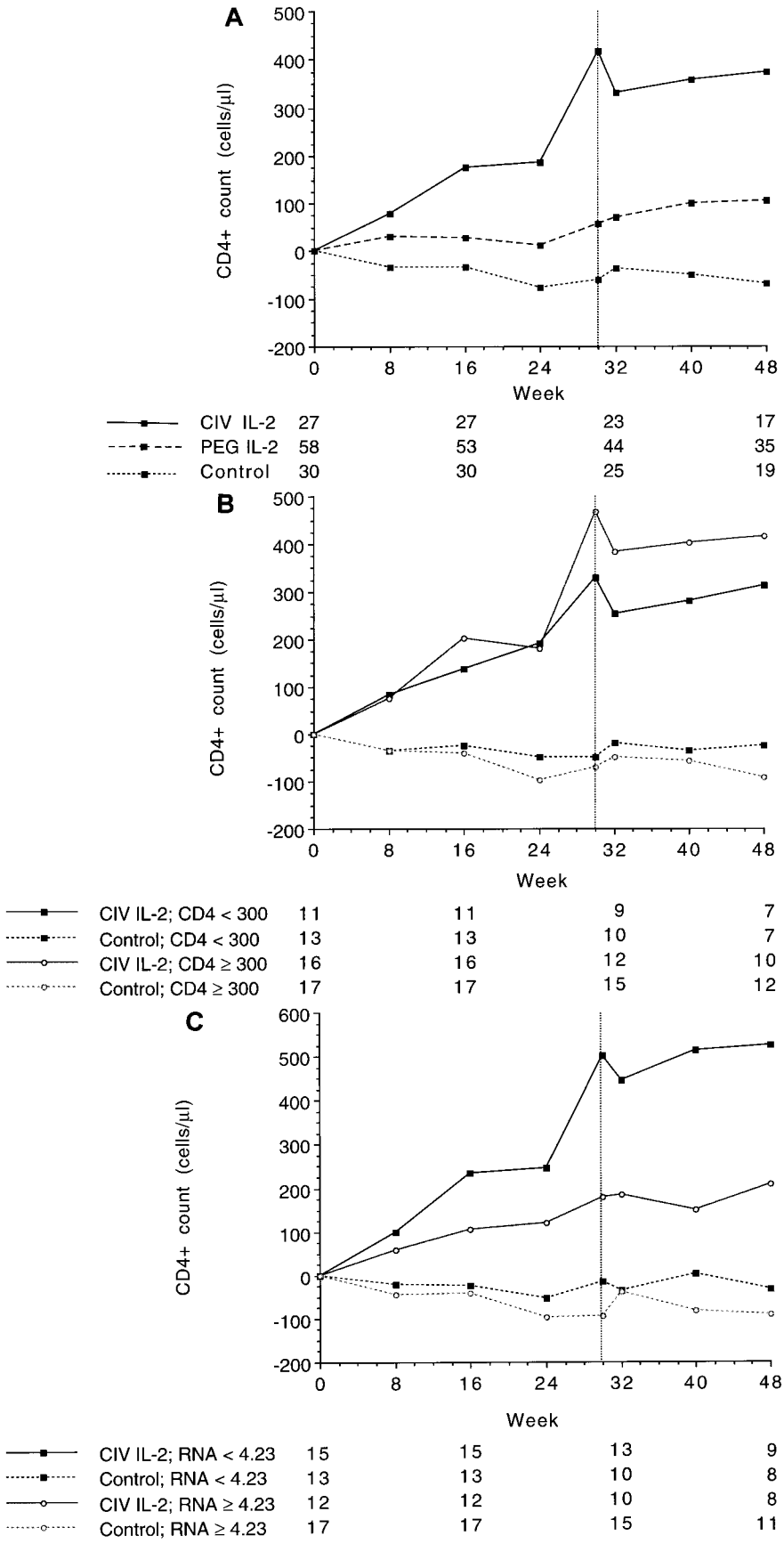

Figure 1. Mean changes from baseline in CD4 lymphocyte counts (cells/mm^3) in patients receiving antiretroviral therapy plus CIV IL-2, PEG IL-2, or no IL-2 (controls). **A** shows all patients, **B** shows CIV IL-2 and control patients by baseline CD4 cell counts ($\geq$300 or $<$300 cells/mm^3), and **C** shows CIV IL-2 and control patients by baseline HIV RNA ($\geq$4.23 or $<$4.23 log copies/mL of plasma). Modified last-value-carried-forward approach was used. Numbers under *x* axis refer to no. of patients evaluated at each cycle. Vertical line shows protocol-specified time point of addition of lamivudine to antiretroviral therapy (cycle 4, week 6).

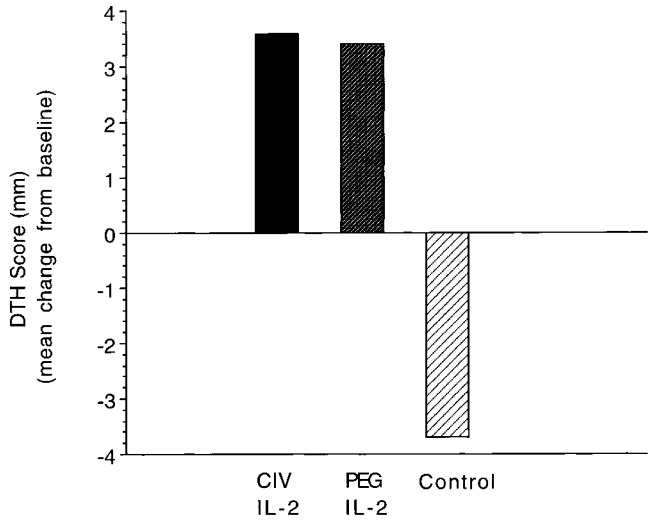

Figure 2. Mean changes in delayed-type hypersensitivity (DTH) scores from baseline to study completion in patients receiving antiretroviral therapy plus CIV IL-2, PEG IL-2, or no IL-2 (P = .001 for CIV IL-2 group vs. controls and P = .004 for PEG IL-2 group vs. controls).

antiretroviral therapy. Markers of T cell function (DTH scores and HLA-DR expression on CD8 lymphocytes) also improved in IL-2 recipients.

Outpatient safety and tolerability were demonstrated by the low rates of discontinuation, hospitalization, and grade 4 adverse events, preserved weights and Karnofsky scores, and the stable CIV IL-2 dose and plasma HIV RNA levels over time. Safety and tolerability were dependent on several factors: the administration of the first cycle as an inpatient; the liberal use of medications designed to minimize toxicity; and the availability of home care during treatment. The side effect profiles of PEG IL-2 and CIV IL-2 at maximally tolerated doses were substantial and similar and included fever, fatigue, nausea, diarrhea, and stomatitis. While home-based delivery of care improved treatment and patient acceptance, evaluation of lower doses and subcutaneous administration of non-PEG IL-2 is warranted.

IL-2 therapy resulted in increases in CD4 cell counts generally greater than those seen with combination antiretroviral therapy. The gradual and sustained increases over time suggest that these increases are due to increased production and/or survival rather than to altered CD4 cell trafficking. Although 90% of CIV IL-2 recipients had at least a 25% increase in CD4 cell count, there was variability in the magnitude of the responses. Baseline HIV load predicted IL-2 responsiveness; identification of other predictors is desirable so that potentially toxic therapy can be avoided in patients unlikely to respond.

Two results suggest that the CD4 lymphocytes generated by IL-2 therapy are functional. First, significant increases were seen in diameters of preexisting DTH responses, whereas DTH scores declined in controls. Second, in CIV IL-2 recipients, there was reduced HLA-DR expression on CD8 lymphocytes, suggestive of a more normal phenotype [13, 14, 21–24]; elevated levels of HLA-DR on CD8 lymphocytes is a marker of more rapid HIV disease progression [23, 24].

The CD4 cell responses to PEG IL-2 were less impressive than those to CIV IL-2. Despite their similar pharmacokinetic profiles and low rates of IL-2 antibody induction (data not shown), duration and severity of treatment-related side effects, and qualitative immunologic responses, PEG IL-2 was quantitatively less active. Overall dose is unlikely to explain the

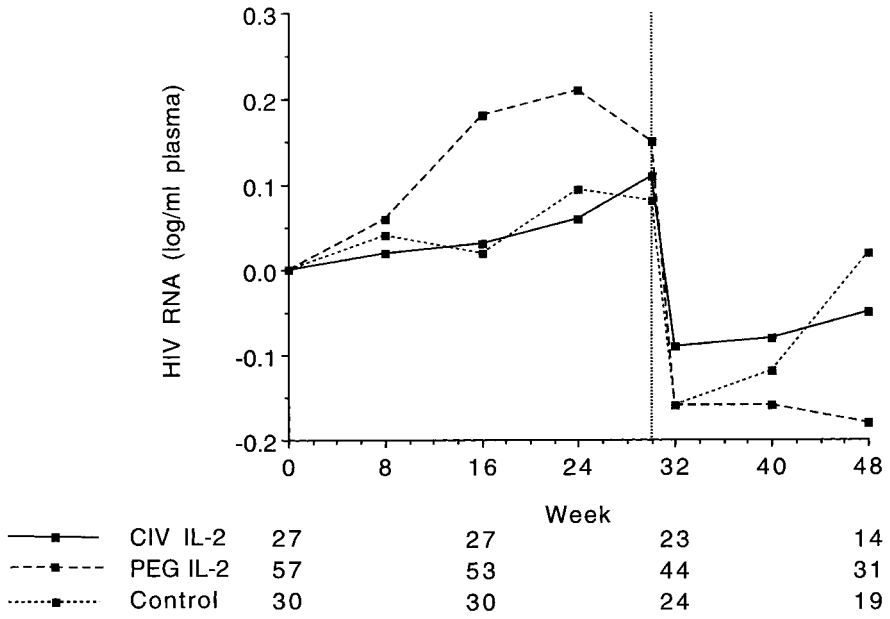

Figure 3. Mean changes from baseline in log plasma HIV RNA levels in patients receiving antiretroviral therapy plus CIV IL-2 (solid line), PEG IL-2 (dashed line), or no IL-2 (controls; dotted line). Modified last-value-carried-forward approach was used. Numbers under x axis refer to no. of patients evaluated at each cycle. Vertical line shows protocol-specified time point of addition of lamivudine to antiretroviral therapy (cycle 4, week 6).

reduced activity of PEG IL-2, since there was no greater CD4 cell count response with increasing doses of PEG IL-2 (data not shown). The explanation may lie in PEG IL-2's lower binding affinity for the IL-2 receptor or may be because its larger molecular weight changes its biodistribution within the body [25].

The transient burst of HIV load observed 7 days after commencing a cycle of IL-2 did not translate to greater virus load over time. The lack of decline in HIV RNA levels suggests, however, that IL-2 did not improve the host immune response to HIV. Higher baseline virus load reduced the mean CD4 lymphocyte increases to IL-2, although patients with high virus burden did derive a CD4 cell count benefit from IL-2 therapy (figures 1B, C).

The addition of lamivudine to stable background antiretroviral therapy did not appear to augment the CD4 lymphocyte responses to IL-2, despite lamivudine's benefit in delaying disease progression and death [26]. It should be noted, however, that lamivudine was not evaluated in a randomized fashion.

Although IL-2 led to increases in CD4 cell counts, most IL-2 recipients did not develop new positive DTH responses (despite vaccination with two of the DTH test antigens), and their HIV load did not decline. IL-2 therapy may serve best, therefore, to preserve the immune repertoire rather than to restore lost immunity. Responses beyond 1 year, however, have not been evaluated. The data suggest that IL-2 therapy may be of greatest benefit when administered early in disease, before irreparable damage to the immune system, and in conjunction with antiretroviral therapy. Preliminary evaluation of patients with CD4 lymphocyte counts $>500/mm^3$ has shown that moderate doses of subcutaneous IL-2 can increase CD4 lymphocyte numbers substantially [27]. The data also suggest that IL-2 may be beneficial in more advanced HIV disease, especially if used in conjunction with potent combination antiretroviral regimens including a protease inhibitor [28, 29]. However, any role for IL-2 therapy in patients with sustained complete suppression of HIV replication by highly active antiretroviral therapy remains to be determined.

If IL-2 therapy prevents attrition of immune specificities, prolonged therapy should delay HIV disease progression. The present study was not powered to evaluate clinical efficacy, and the number of new AIDS-defining illnesses was small. This hypothesis can be addressed only in trials powered to assess clinical end points.

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Data and Safety Monitoring Board

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