

Update on IL-2: Where It's Been and Where It's Going

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PERHAPS NO OTHER DRUG IN THE HISTORY of HIV/AIDS treatment research has been more extensively studied than recombinant interleukin-2 (IL-2). It has been evaluated in numerous proof-of-concept and phase II clinical trials—both alone and in combination with antiretrovirals or with other immune-based therapies—involving a broad spectrum of patients, including those in the acute, chronic, and late stages of HIV disease. Ironically, however, it still lacks a licensed therapeutic indication in HIV. This may change sometime during the next few years. Massive phase III clinical trials are now under way to address fundamental questions regarding the clinical utility of IL-2 treatment. These results—along with other data from pivotal IL-2 clinical trials—will be reviewed by the U.S. Food and Drug Administration and may help carve out a niche for the drug in the standard-of-care for HIV-positive people.

Dr. Richard Davey, Medical Director of the National Institute of Allergy and Infectious Diseases (NIAID) HIV Research Clinic, has long been involved in clinical research of IL-2. To help make heads or tails of IL-2's tortuous history—and to give a glimpse of its future—Dr. Davey provided a meticulous overview at the February 2002 PRN meeting of what will hopefully be the first immune-based therapy approved specifically for use in HIV-positive patients.

The Potential for IL-2: Lessons from Studies Past

AMONG THOSE WHO BELIEVE THAT IL-2 ADMINISTRATION might be clinically beneficial, Dr. Davey acknowledged that there are two distinct schools of thought. One side of the divide is the first-do-no-harm group—researchers such as Dr. Kendall Smith of Cornell University Medical Center who employs daily, low-dose subcutaneous injections of IL-2 to quantitatively and qualitatively boost CD4+ cells with as few side effects as possible (see “Interleukin-2: Use in Immune Restoration and During Structured Treatment Interruption,” a review of a 1999 PRN lecture delivered by Dr. Smith). The other side may be thought of as the “no-pain-no-gain” group, who believe that higher doses which cause more side effects may be needed to induce profound and durable increases in CD4+ cells. The latter approach is, in essence, Dr. Davey's mea culpa: “We tend to follow the theory that gains in immune function do come with a price. There have been data to support both schools of thought and I don't think these are clashing paradigms. They may in fact be complementary paradigms with different applications. But we've had good experience with the higher IL-2 doses and have learned a great deal about how to use them in HIV.”

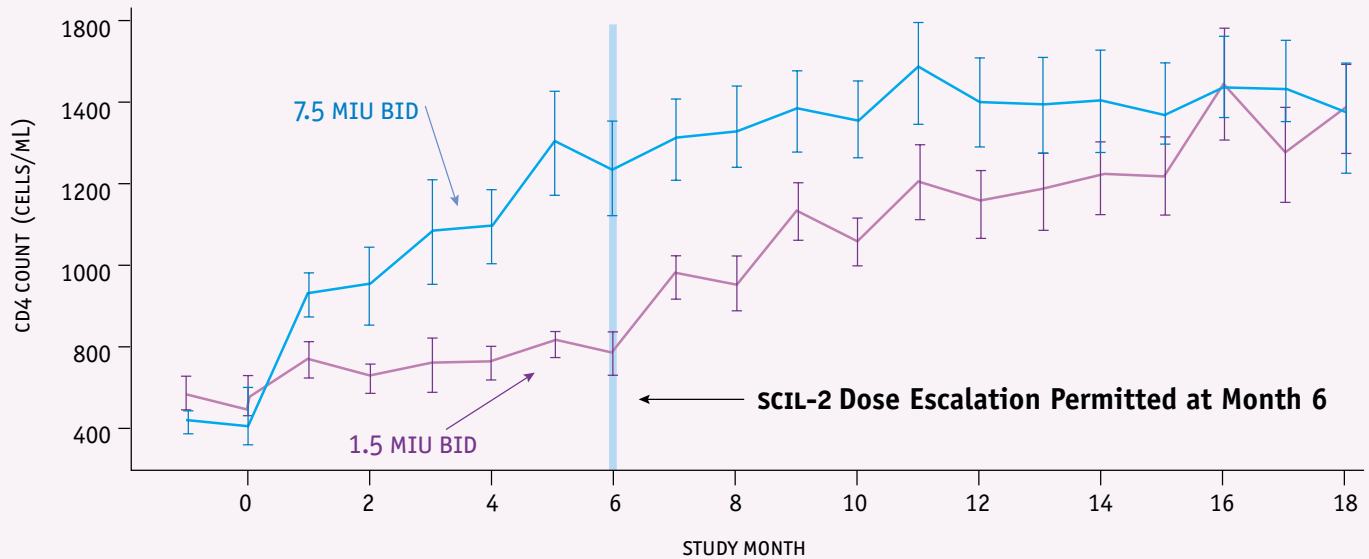
Reviewing IL-2 clinical trial data can be a vexing task. Numerous studies have been conducted over the past seven years and most are not comparable to one another, typified by distinct hypotheses, unique designs, different patient populations, and a range of dosing schedules.

To put these data into perspective, Dr. Davey avoided a review of the historical trajectory of IL-2 studies and instead pointed out seven key points suggested by the cumulative data sets.

1. More Matters: The Immunologic Activity of IL-2 is Dose-Dependent

“ONE OF THE MOST IMPORTANT THINGS WE'VE learned is that IL-2 increases CD4+ cell counts with a strong dose-dependent relationship,” Dr. Davey began. Evidence of this can be seen in a randomized clinical trial conducted by Dr. Davey and his colleagues, the results of which were published in 1999 in the *Journal of Infectious Diseases (JID)* (Davey, 1999). In this study, 49 HIV-infected patients with CD4+ counts >500 cells/mm³—all of whom were receiving stable antiretroviral therapy at the time of enrollment—were randomized to receive five-day cycles of either low-dose (1.5 million IU BID) or high-dose (7.5 million IU BID) subcutaneous IL-2 every four or eight weeks. As illustrated in Figure 1, patients in the high-dose IL-2 group had a mean CD4+ count increase of 116 cells/mm³ per month, whereas low-dose recipients had a mean CD4+ count increase of 26.7 cells/mm³ per month. After six months of treatment, high-dose recipients achieved a 95% increase in mean CD4+ cell counts over baseline, compared with a 19% increase in low-dose recipients. “There were more constitutional side effects in the high-dose group,” Dr. Davey pointed out, “but the CD4+ cell responses we saw clearly support high-dose IL-2 treatment.”

Figure 1. Dose-Response Relationship with IL-2: CD4+ Cell Count Changes in Early Patients Randomized to High- vs. Low-Dose sc IL-2 Tx



Forty-nine HIV-infected patients with CD4+ counts >500 cells/mm³—all of whom were receiving stable antiretroviral therapy at the time of enrollment—were randomized to receive five-day cycles of either low-dose (1.5 million IU BID) or high-dose (7.5 million IU BID) subcutaneous IL-2 every four or eight weeks. Patients in the high-dose IL-2 group had a mean CD4+ count increase of 116 cells/mm³ per month, whereas low-dose recipients had a mean CD4+ count increase of 26.7 cells/mm³ per month. After six months of treatment, high-dose recipients achieved a 95% increase in mean CD4+ cell counts over baseline, compared with a 19% increase in low-dose recipients.

Source: Davey, 1999. Reprinted with permission of the *Journal of Infectious Diseases* and The University of Chicago Press.

2. The Higher the Baseline CD4+ Count, the Bigger the Bang for the Buck

IT IS WELL KNOWN THAT CD4+ CELL RESPONSES TO IL-2 therapy are most pronounced in patients with less immune suppression, loosely defined as a pretreatment CD4+ count of greater than 200 cells/mm³. However, this does not mean that patients with more advanced disease are exempt from immunologic gains that can be achieved with IL-2. One study to demonstrate this was IL-STIM (ANRS 082), a French clinical trial that enrolled 70 patients who, despite prolonged HIV suppression with HAART, were unable to increase their CD4+ counts to a point above 200 cells/mm³ (Katlama, 2000). At the start of the study, 34 patients were randomized to receive IL-2 (4.5 million IU SC BID for five days every six weeks) in combination with HAART; the 36 remaining patients received HAART alone. After six months, IL-2 was offered to both groups.

Prior to the initiation of HAART, the median CD4+ count in these 70 patients was less than 70 cells/mm³. Prior to the initiation of IL-2 (but while receiving HAART), the

average CD4+ count was less than 150 cells/mm³ in both groups. After six months, there was a median increase of 65 CD4+ cells/mm³ in the IL-2 group, compared with an 18 CD4+ cell/mm³ median increase among patients who received HAART alone. After 48 weeks, the median CD4 count had increased to 330 cells/mm³ in the patients originally randomized to receiving IL-2. “Obviously, the CD4+ cell gain in the IL-2 group was far from rip-roaring,” Dr. Davey commented, “but the fact remains that they did see impressive gains in a population of patients in which such a response would not otherwise have been anticipated. Patients with higher baseline CD4+ cell counts do the best, but these results suggest possible benefit even for those starting therapy later in the course of HIV.”

3. More Matters (Part II): Toxicities Are Predictable and Dose-Dependent

AS HAS BEEN SEEN IN NUMEROUS CLINICAL trials, the most common side effects of

IL-2 therapy are fatigue/malaise, myalgias, headache, and nausea. Their frequencies are related to the dose of IL-2 administered, either intravenously or subcutaneously (see Table 1).

4. On Again, Off Again: Five-Day Cycles Every Eight Weeks Appears Best

CLINICAL TRIALS HAVE DETERMINED THAT OPTIMAL increases in CD4+ cell counts are achieved when IL-2 is delivered in five-day cycles, administered every eight weeks. In a 1996 study reported at the 36th Interscience Conference on Antimicrobial Agents and Chemotherapy, 81 HIV-positive patients with CD4+ counts between 100 and 300 cells/mm³ were randomized to receive antiretroviral therapy alone or in combination with intermittent IL-2 (12 million IU/day) for three, four, or five days every eight weeks. After one year of treatment, patients who received antiretroviral therapy alone had lost a median of 45 CD4+ cells/mm³ compared to a median loss of 16

CD4+ cells/mm³ in the three-day cycle IL-2 group and median CD4+ gains of 14 and 80 CD4+ cells/mm³ for the four- and five-day cycle groups, respectively.

To further explore the duration and frequency of IL-2 cycles, a rather complex randomized study was conducted at the NIH in which patients who received the "standard" five-days-every-eight-weeks regimen were compared to patients who received cycles of variable duration (based on individual patterns of cell-cycle progression) and to patients who received cycles of variable frequency (based on individual CD4+ cell response in the previous cycles) (Miller, 2001). Twenty-two patients with CD4+ counts > 200 cells/mm³ were randomized to one of three treatment groups: eight patients received five-day IL-2 cycles every eight weeks (a total of four cycles); seven patients received four cycles of longer duration (mean 7.7 days); and another seven patients received an increased frequency of five-day cycles (approximately every 4 weeks). After 32 weeks of treatment, all three groups had significant increases in CD4+ cell counts. There were no statistically significant differences between the three groups. "In other words," Dr. Davey added, "taking IL-2 every eight weeks was just as good as taking it more often or for a longer period of time."

5. Don't Mind the Virus: Viral Load Increases Are Blunted and Transient During IL-2 Therapy

A LONG-STANDING CONCERN HAS BEEN THE potential for IL-2 to increase HIV-RNA levels. "Some consternation arose from early data demonstrating that IL-2 administered by intravenous infusion was associated with a rise in viral load above baseline," Dr. Davey said. "These viral load increases typically peaked at day five of a cycle and then declined back to baseline after the cycle was completed. The concern was that IL-2 might be perturbing the system against the host." Indeed, studies have established that IL-2 treatment is associated with increases in proinflammatory cytokine production, most notably interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α), which can contribute to an upsurge in HIV replication (Sereti, 2001). "But we now have data to show that viral load increases are transient and do not have a long-term effect on HIV-RNA levels," Dr. Davey

added. "In fact, we have data to suggest that HIV-RNA levels may actually decrease, over time, with the use of IL-2."

Referring to his 1999 *JID* paper (discussed above), Dr. Davey pointed out that the 49 patients who entered the dose-ranging IL-2 study were all on antiretroviral therapy but still began IL-2 treatment with a baseline HIV-RNA level of approximately 3.5 log (Davey, 1999). While some patients experienced transient increases in their viral loads during their IL-2 cycles, after six months of follow-up HIV-RNA levels were, on average, lower than baseline levels after six months of follow-up. In the 7.5 million IU IL-2 group for example, HIV-RNA levels were -0.036 log below baseline after 24 weeks.

To be sure of this observation, an NIH team headed by Dr. Joe Kovacs conducted an extensive virologic evaluation of 11 patients undergoing IL-2 treatment. Six patients showed a greater than 0.5 log increase in plasma HIV during at least one IL-2 cycle, and two experienced an increased viral load in >50% of cycles. Three of the remaining five patients had a >0.5 log decrease during at least one IL-2 cycle, and the remaining patients exhibited <0.5 log decrease. No change in lymphoid (tonsil) level of HIV was seen during the year of IL-2 treatment. Quasispecies analysis in a separate cohort demonstrated that the transient bursts in viral load involved virus that most commonly resembled pre-IL-2 plasma quasispecies. "In other words," Dr. Davey commented, "intermittent IL-2 does not result in sustained increases in either plasma or tissue levels of HIV and it does not result in sustained expression of latent mutated HIV quasispecies."

6. HAART Helps: Making a Good Thing Better for Patients with Advanced HIV Disease

AS DISCUSSED IN POINT TWO ABOVE, A patient's baseline CD4+ cell count is often predictive of his/her immunologic response to IL-2 treatment. Historical experience suggests that patients with severely suppressed immune function typically do not benefit from IL-2 therapy and may, in fact, be harmed by the drug. "In the past," Dr. Davey recalled, "if you gave IL-2 to someone with a CD4+ count below 100 cells/mm³, you would likely not see a CD4+ rise and might see substantial side effects.

In many cases, those concerns have since been obviated with the advent of HAART."

In the largest clinical trial to date involving HIV-positive patients with advanced disease, the AIDS Clinical Trials Group treated 204 protease inhibitor-naive patients with baseline CD4+ counts between 50 and 350 cells/mm³ with indinavir and two NRTIs for 12 weeks (ACTG 328). Provided that the viral loads were below 5,000 copies/mL after three months of antiretroviral therapy, patients were randomized to receive a continuation of HAART alone, HAART plus IL-2 administered intravenously at a dose of 9 million IU/day for five days every eight weeks, or HAART plus IL-2 administered subcutaneously at a dose of 7.5 million IU twice a day for five days every eight weeks. Sixty weeks after entering the study, patients who continued on HAART alone had a median CD4+ cell increase of 97 cells/mm³. Among IL-2 recipients, the median CD4+ cell increase was 309 cells/mm³ in the intravenous group and 240 cells/mm³ in the subcutaneous group. The difference between the IL-2 groups and the HAART alone group was statistically significant.

7. Few and Far Between: Induction/Maintenance Dosing on the Horizon

PERHAPS ONE OF THE MOST ENCOURAGING findings coming out of Dr. Davey's clinic are data involving a possible induction- and maintenance-therapy approach to using IL-2. "In one of our earliest IL-2 cohorts, started back in 1993, we now have 37 patients who began subcutaneous IL-2 therapy with a median CD4+ count of 629 cells/mm³. We used 7.5 million IU twice a day in these patients, and after several five-day cycles every eight weeks we saw a nice doubling of baseline CD4+ counts. What we've been doing is using lower maintenance doses of IL-2, on average 5.8 million IU per injection for five days. But we're using it less frequently, such as every year or every two years, to keep their CD4+ cell numbers up. After 55 months, our cohort still averages CD4+ counts between 1100 and 1200, with a mean interval between cycles of 33 months. This is a very promising concept."

Table 1. IL-2 Toxicities Are Dependent on Route of Administration and Dose

	Percentage of Grade 3 or 4 Toxicities		
	18 MIU CIV QD	7.5 MIU SC BID	1.5 MIU SC BID
Fatigue/malaise	90%	75%	20%
Myalgias	61%	4%	12%
Headache	35%	17%	0%
Nausea	59%	8%	0%

Current Studies and Controversies

Does IL-2 Therapy Yield a Significant Antiviral Effect?

WHILE THERE ARE DATA TO CONCLUDE THAT IL-2 therapy does not have a lasting negative effect on HIV-RNA levels or on HIV quasi-species (see above), questions remain as to whether IL-2 may actually work to reduce viral load—either of its own accord or synergistically with antiretroviral drugs. “The results of early studies prompted us to look more closely at the antiviral effects of IL-2,” Dr. Davey said. “It’s still a controversial issue, but we do have some encouraging data to consider.”

In one study reported in the *Journal of the American Medical Association*, Dr. Davey and his colleagues evaluated the rate and magnitude of viral suppression and CD4+ cell recovery in patients using HAART alone or HAART combined with IL-2 (7.5 million IU BID SC for five days every eight weeks). Eighty-two HIV-positive individuals were enrolled in the study, all of whom had CD4+ cell counts between 200 and 500 cells/mm³ and viral loads lower than 10,000 copies/mL. After one year of follow-up, individuals who received IL-2 plus HAART had HIV-RNA levels approximately 0.28 log below baseline, compared with a median HIV-RNA increase of 0.09 log among patients receiving HAART alone. What’s more, 20/30 (67%) evaluable patients receiving IL-2 plus HAART ended the study with HIV-RNA levels below 50 copies/mL, compared with 13/36 (36%) patients who received only HAART. Both of these differences were statistically significant. “A 0.3 log difference doesn’t really compare to the better antiretrovirals that are out there,” he commented. “But we did have statistically significant differences. The fact is, HAART is so potent that it likely obscures much of our ability to detect any potential effect of IL-2 on viral suppression.”

Does IL-2 Therapy Affect the Latently Infected, Resting CD4+ Cell Pool?

AS DISCUSSED ABOVE, IL-2 THERAPY IS ASSOCIATED with an upregulation of proinflammatory cytokines (e.g., IL-6 and TNF- α). Because these cytokines stimulate the activation of CD4+ cells and hence induce the transient increases in viral load seen in early clinical trials of IL-2, it has been hypothesized that IL-2 may “turn on” quiescent, latently infected CD4+ cells harboring integrated and unintegrated proviral DNA and, as a result, possibly enable antiretroviral agents to more effectively eliminate HIV from the host (see “Studies of HIV Latency: Implications for Treatment and Virus Eradication,” published in the June 1999 issue of *The PRN Notebook*).

To assess the impact of IL-2 on this HIV viral reservoir, Dr. Tae-Wook Chun of the NIH and his colleagues conducted a non-randomized study of 14 patients receiving HAART (Chun, 1999). Patients received 3 million to 18 million units of IL-2 over a five-day infusion period, followed by an eight-week period of rest. The average CD4+ count among these patients was 453 cells/mm³; HIV-RNA was less than 50 copies/mL for all patients.

A non-randomized concurrent control group of 12 patients receiving HAART had a mean CD4+ T-cell count of 360 cells/mm³; all patients had viral loads less than 50 copies/mL. To establish the effectiveness of these patients’ antiretroviral therapy, the number of resting CD4+ T-cells latently infected with HIV was determined. Among IL-2-treated patients, 8 of 14 had detectable virus, compared with all 12 non-IL-2 patients. To further study the six aviremic IL-2/HAART patients, a virus detection assay using an increased number of CD4+ cells—ranging from 100 million to 360 million cells—was employed. Three of the six pa-

tients had no detectable virus even by this intensified technique. Lymph node biopsies were available from two of these three culture-negative patients; the third patient was excluded from the biopsy procedure because of other health problems. No evidence of viral RNA or viral replication was detected from multiple tissue samples from the three patients. Even after stimulation of lymphocytes derived from lymph nodes of these patients, no HIV was cultured.

The next step was to conduct a clinical trial in which long-term responders to HAART were provided with the opportunity to stop antiretroviral drug treatment (Davey, 1999a). Eighteen patients with CD4+ counts greater than 350 cells/mm³ and undetectable viral loads (<500 copies/mL for at least one year, as well as HIV-RNA levels below 50 copies/mL on at least two determinations immediately before enrollment) were enrolled. Of these 18, 12 had received prior IL-2 therapy and had low frequencies of resting, latently infected CD4+ cells.

Viral load relapses to >50 copies/mL occurred in all 18 patients, regardless of whether or not they received prior treatment with IL-2. The mean relapse rate was 0.20 log a day, which was very similar to the mean viral clearance rate after drug resumption of 0.15 log a day. “We didn’t see any significant differences,” Dr. Davey explained. “Viral rebounds occurred rapidly, even in patients with a markedly diminished pool of resting, latently infected CD4+ cells at the start of the study.”

What about using IL-2 to boost HIV-specific immune responses? To evaluate this possibility, Dr. Davey’s colleague Mark Dybul, MD, headed up a study to determine whether HIV-specific immune responses preserved after HAART are augmented by the administration of IL-2 (Dybul, 2002). The study involved nine patients who had been infected with HIV for less than six months and who were randomized to receive HAART alone or HAART plus three cycles of IL-2 over the course of a year. Although HAART combined with IL-2 significantly increased total and naive CD4+ cell counts, there was no increase in either CD4+ or CD8+ HIV-specific immune responses. “We saw a nice increase in CD4+ cells,” added Dr. Davey. “We just didn’t see CD4+ cell responses that were largely restricted to protection against HIV.”


Future Directions with IL-2

THERE IS MUCH TO BE SAID FOR THE GOOD SHOWING of IL-2 in early clinical trials. But the fact remains that its day in court has yet to come, most notably in a review of its hefty data set by the U.S. Food and Drug Administration (FDA). While the eventual submission of a new drug application (NDA) by Chiron in support of its IL-2 formulation, aldesleukin (Proleukin), would mark the first-ever immune-based therapy to be reviewed by the FDA, the central questions it must address are quite basic. "The FDA will grant licensure if either of two criteria are met," reckoned Dr. Davey. "First, IL-2 must be shown to have a direct clinical benefit, meaning a delay in the onset of AIDS-defining illnesses or death. Another possibility is for IL-2 to be used as an antiretroviral-sparing agent—that is using IL-2 either to reduce or eliminate the need for continuous antiretroviral therapy."

A glimpse at IL-2's direct clinical benefit can be seen in a meta-analysis published in *JMD* by Dr. Sean Emery and others of the University of New South Wales in Sydney (Emery, 2001). This study evaluated disease progression, survival, CD4+ cell counts, and viral loads in 157 participants in three randomized clinical trials of IL-2 that commenced before 1995. Median follow-up was about 30 months. During this follow-up period, 16 control patients died, compared to nine among patients who received IL-2. "This pooled analysis wasn't sufficiently powered to reach any statistically significant conclusions," Dr. Davey commented, "but we did see a nice trend toward survival in the IL-2 groups, which was quite encouraging."

Clearly, more data illustrative of statistically significant clinical benefits observed in prospective clinical trials are needed. To obtain such data, attention has now turned to two phase III clinical trials: ESPRIT (Evaluation of Subcutaneous Proleukin in a Randomized International Trial) and SILCAAT (Study of Interleukin-2 in People with Low CD4+ T-Cell Counts on Active Anti-HIV Therapy). The NIH-sponsored ESPRIT trial (www.espritstudy.org) continues to enroll patients with CD4 counts >300 cells/mm³ who are receiving at least two antiretrovirals prior to entry (there is no viral load requirement). IL-2 is administered subcutaneously at a starting dose of 7.5 million IU BID for five days every eight weeks for a total of three cycles and is being compared to antiretroviral therapy alone. The target

accrual is 4,000 patients—as of February 2002, approximately 2600 patients have enrolled—and the trial is being conducted in the United States and in select locations throughout Asia, Australia, South America, Europe, and the Middle East.

SILCAAT (www.silcaat.com), sponsored by Chiron Corporation, is enrolling patients with CD4+ counts between 50 and 300 cells/mm³ and HIV-RNA levels less than 10,000 copies/mL. All patients must be on an antiretroviral regimen consisting of at least three drugs for at least six months prior to entering the study. Patients will be randomized to receive IL-2 (4.5 million IU BID for five days every eight weeks) for a total of six cycles in combination with HAART and will be compared to patients receiving HAART alone. There are 135 sites throughout the world participating in the study, and even though the target enrollment was originally set at 1400, more than 1650 patients are already enrolled. As with ESPRIT, the primary endpoint for SILCAAT is time to the first AIDS-defining event or death, the surest of all efficacy variables. 

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