

INTERLEUKIN-2 (IL-2) AND HIV DISEASE



understanding how il-2 may or may not
benefit people living with hiv

Interleukin-2 (IL-2) is a naturally occurring substance made by cells in your immune system. Its main function is to signal cells (most often CD4+ cells) to become active and reproduce.

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Information,
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A man-made version of IL-2 (aldesleukin, Proleukin) has been studied for over 20 years in HIV-positive people as a way to increase the number of CD4+ cells. It is approved by the Food and Drug Administration (FDA) for treating other conditions, though some people living with HIV have found ways to make it part of their overall treatment strategy. Whether or not IL-2 therapy helps people with HIV to live longer or preserves their ability to fight infections is the subject of two large international studies.

CD4+ cells are central to managing your body's response to infections. In HIV disease, these cells become infected with HIV and eventually die or begin to function improperly. Over time, as the total number of these cells declines and their functions fail, the immune system gradually weakens and loses its ability to fight disease.

IL-2 stimulates CD4+ cells to become active and reproduce. This can help restore or maintain a normal number of CD4+ cells and might also improve their function.

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what does the research show?

Researchers have experimented with 3 ways to give IL-2: injection under the skin (subcutaneous, or subQ), injection in the stomach muscles, and infusion into a vein (intravenous or IV). They have tried different schedules—daily, weekly, monthly and every 2 months. They have also experimented with different doses, from very low daily doses (1 million International Units, or *IU*) to higher intermittent doses (18 million IU).

Experimental formulas of IL-2 have been tried and more are being studied. Large studies are underway to evaluate a cycled strategy of twice a day subQ IL-2 injections, at doses of 9 MIU (4.5 twice a day) or 15 MIU (7.5 twice a day), for 5 consecutive days, every 2 months. This approach is effective in producing large increases in the number of CD4+ cells. Increases of 100–400 or more CD4+ cells have been routinely achieved, beyond the improvements seen from standard anti-HIV therapies.

In lab research, IL-2 is often used to stimulate HIV-infected cells to reproduce. When IL-2 is used this way, it causes the infected cells to produce large amounts of new HIV particles. Because of this, some researchers feared using the drug in humans, where they certainly don't want to see increased production of HIV. However, these fears have not been seen in studies.

To the contrary, changes in HIV levels are similar among groups taking IL-2 together with anti-HIV therapy compared to those on anti-HIV therapy alone. After a course of IL-2, there is often a burst of HIV activity, but it's not sustained and there's no evidence that these temporary elevations in HIV levels cause harm. Nonetheless, this concern causes most researchers to use IL-2 only in people using anti-HIV therapies.

Researchers tailor IL-2 dosing and scheduling to fit the individual's needs—trying to optimize CD4+ cell count increases and minimize side effects. If side effects occur, doses are reduced and/or courses are shortened

where to get it?

Treating HIV disease with IL-2 is experimental. It's available through several ongoing studies. For more information about the US sites, call 1-800-TRIALS-A or visit www.clinicaltrials.gov.

Because it's already FDA-approved for treating cancer, some doctors prescribe IL-2 for *off-label* use (giving a drug for purposes other than what it was approved). Insurance companies don't always pay for *off-label* use and IL-2 can be quite expensive. It should be used only under close doctor supervision, and blood should be checked for liver and kidney toxicity and lab abnormalities. For more information on the assistance program, call 1-866-385-4729.

to improve tolerability. If CD4+ cell counts rise to normal ranges, therapy is given less often to maintain those increases. So far in studies, people who started IL-2 therapy while CD4+ cell counts were high (above 400) generally had more immediate and pronounced increases in CD4+ cell counts, resulting in the need for less frequent IL-2 therapy.

One study at the National Institutes of Health included people with CD4+ cell counts around 600. Within the first three cycles, IL-2 recipients experienced CD4+ cell count increases to about 1,200. The average time between cycles that kept CD4+ cell counts at this level was about one year. However, if CD4+ cell counts are below 300 when IL-2 is started, then CD4+ cell count increases are usually less immediate and pronounced. Therefore, to maintain ideal CD4+ cell counts in such people, a much longer time on bi-monthly IL-2 cycles may be required before the period between cycles can be extended.

Using IL-2 as part of structured treatment interruptions (STIs) has also received attention. This is discussed briefly in Project Inform's publication, *Structured Treatment Interruptions*, available at 1-800-822-7422 or www.projectinform.org.

A few completed studies looked at using IL-2 as part of an eradication strategy. So far, they have not shown that completely removing HIV from a person's body is possible—with or without IL-2.

Studies of low dose daily injections of IL-2 have not resulted in the dramatic CD4+ cell increases seen with the higher dose cycle, although this approach may cause fewer side effects. Following less than remarkable results from a moderately sized study, the company developing IL-2 at that time (Chiron Corporation) stopped major development efforts on low dose IL-2. Nonetheless, some individuals and doctors still experiment with this approach, hoping to find an ideal balance between potential benefits and known side effects.

Finally, a moderate size study in people with very low CD4+ cell counts (below 200) and controlled HIV replication (below 1,000 copies HIV RNA) showed that IL-2 therapy could lead to modest increases in CD4+ cell counts. Results have led the French regulatory agency to approve a Compassionate Use Program for IL-2 for people with low CD4+ cell counts and HIV levels below 1,000. These data, combined with other study results, provided French authorities with enough confidence to make IL-2 more widely available to people with more advanced-stage HIV disease. The FDA in the US has taken a more conservative approach and has not approved access to IL-2 in the same way. Despite this, some people in the US manage to get IL-2; since once a drug is approved by the FDA, doctors have the right to use it however they choose. However, private insurance and other payers may not be willing to pay for the drug.

who should use it?

IL-2 is not currently approved or proven for use in treating HIV. Use in people with HIV is experimental. IL-2 has been studied in people with a wide spectrum of CD4+ cell counts. Emerging information suggests that a person's CD4+ cell count at the time of starting IL-2 might be useful in predicting the outcome of therapy. This information may indicate how quickly the CD4+ cell count might rise and how high it will reach. Still, even people with low CD4+ cell counts when starting IL-2 appear to experience higher CD4+ cell increases than those seen from anti-HIV therapy alone.

Studies suggest that IL-2 therapy can be used safely (though with significant side effects) by people at all levels of CD4+ cell counts. IL-2 provides the greatest increases in CD4+ counts when it is used together with anti-HIV therapy. The most pronounced and immediate increases in CD4+ cell counts are seen among people who start IL-2 therapy together with anti-HIV therapy while their CD4+ cell counts are above 300, and preferably when their lowest ever CD4+ cell count (*nadir count*) has never been below 200.

There are several situations in which IL-2 therapy should be avoided or approached with extreme caution. As a general rule, it is discouraged for people with high detectable viral loads, since IL-2 can at least temporarily cause the viral load to increase even more. Some doctors urge caution using IL-2 in anyone who has a detectable viral load at all. However, this strict position seems unnecessary to others, since all early studies of IL-2 that

showed benefit were conducted before potent three-drug anti-HIV therapy made it possible to reduce viral load to undetectable levels.

People with an active infection (e.g. opportunistic infection) should avoid IL-2 or use it carefully. IL-2 can produce temporary immune suppressive effects. Therefore, anyone with an infection should wait until the condition has resolved before using IL-2.

This also applies to people currently on an IL-2 regimen. If you have an infection, consider waiting until it's resolved before starting your next IL-2 cycle. If you're taking IL-2 and develop an infection, delay IL-2 therapy until it's resolved.

People with heart problems should also be cautious since IL-2 decreases blood pressure. People on medicine to lower blood pressure should consider either avoiding IL-2 therapy or consider stopping blood pressure medication, in consultation with a doctor, during the five-day courses of IL-2. The combination of IL-2 with blood pressure lowering medication could result in dangerously low blood pressure levels that could be fatal.

IL-2 should not be used by people with lung disease. People with autoimmune diseases, including Crohn's disease, psoriasis and rheumatoid arthritis should not use IL-2, or use it with great caution because it may worsen these conditions. There are concerns that IL-2 therapy might also worsen diabetes, so people with diabetes and people with signs of insulin resistance should be cautious. Because IL-2 side effects include flu-like symptoms, including fatigue, people experiencing extreme fatigue are encouraged to seek treatment for its cause and delay IL-2 therapy until the condition has resolved. In rare instances, IL-2 has caused hypothyroidism and thus should not be used by people with thyroid problems.



Pregnant women and children

IL-2 has not been studied in pregnant women. In studies, women who become pregnant must stop IL-2 but can remain in the study. IL-2 can raise bilirubin levels which may cause serious harm to the developing child. Studies of IL-2 in children are ongoing.

what about side effects?

The type of side effects produced by IL-2 is generally predictable, though their severity varies widely. Nearly everyone experiences flu-like symptoms during the time therapy is administered. When the body fights off infections, cells produce IL-2 to stimulate other cells necessary to control the infection. It's the natural production of IL-2 and other immune chemicals that result in the aches and fevers associated with the flu.

Unlike anti-HIV therapy where only a relatively small percentage of people may experience a particular side effect, flu-like symptoms are both predictable and expected among the vast majority of IL-2 users. This side effect may be lessened by taking antihistamines and ibuprofen *before* taking IL-2. (NOTE: Some antihistamines may have serious interactions with protease inhibitors.)

People who are careful to follow side effect pre-treatment guidelines report that the first few days of IL-2 therapy are relatively easy. If side effects emerge, they usually are worst on the last two or three days of a five-day course. To minimize interference with day jobs, some people begin their five-day course of IL-2 on a Wednesday. This plan helps time the worst side effects to occur over a weekend or at a time when a person is not working.

People who take IL-2 recommend that you ask someone to stay with you overnight if possible, through the first five-day course. If that's not possible, ask a friend to check on you periodically. If you have children, see if a friend or family member can take care of them for a few days as you may not feel up to the task yourself.

Experienced IL-2 users say that the more prepared you are, the easier it is and less likely that you'll experience severe side effects. The worst side effects seem to happen when you let your guard down, aren't prepared and don't pre-treat for side effects. Ask for your

doctor's emergency number in the event you need or want support through the side effects.

Another relatively common side effect is swelling, red marks or lumps where you inject yourself. Long-time IL-2 users note that putting an ice pack on the injection site before and after injections can help diminish the development of swelling and bumps. The cold temperature has an effect that is identical to that of non-steroidal anti-inflammatory agents, such as ibuprofen, although it's more concentrated at the site of the injection. Sometimes these lumps, or nodules at the site of injection, can last as long as a few months and they may even produce a scab. In nearly all cases they go away over time.

Other less frequent side effects include sinus congestion, low blood pressure, liver toxicity, swelling due to water retention, nausea and vomiting, diarrhea, peeling skin, changes in mental status and altered blood levels including albumin, potassium, magnesium, calcium, red blood cells and platelets. Nearly all side effects diminish quickly when the drug is stopped, usually at the end of a five-day course. In rare cases, IL-2 has been linked to hypothyroidism, vision problems (including blindness) and depression leading to suicide. There is a long list of potential side effects associated with IL-2. The most serious of these occur relatively rarely in doses used in people living with HIV.

As mentioned earlier, IL-2 can also temporarily stimulate HIV replication. Studies show that this viral activity can be controlled with the use of anti-HIV therapy. More importantly, these temporary increases don't appear to have negative long-term consequences.

For more information on IL-2 side effects and side effects management, read the attached publication, *Taking IL-2 and Managing Its Side Effects*.

Certain side effects are potentially more severe and of greater concern than others. Contact your healthcare provider immediately if:

- ▶ You notice that you are making less than normal amount of urine or if you stop urinating altogether;
- ▶ You have shortness of breath;
- ▶ You have fever over 102° F that doesn't go away with over-the-counter drugs;
- ▶ You experience major changes in mental status, like confusion;
- ▶ You faint; or
- ▶ You have major swelling in your face, neck and/or feet.





how to use il-2

IL-2 is given by injection under the skin in starting doses ranging from 4.5 million international units (MIU) twice daily (total daily dose of 9 MIU) to 7.5 MIU twice daily (total daily dose of 15 MIU), over a period of five consecutive days.

This five-day course is repeated every eight weeks.

To manage toxicity and side effects, individuals reduce the daily dose of IL-2 in three MIU increments. For example, if 15 MIU daily schedule was very difficult for an individual to take, then the next five-day course dose would be 6 MIU twice daily (total daily dose of 12 MIU), for five consecutive days. Unlike anti-HIV therapy, lowering the dose of IL-2 does not lead to drug resistance.

Studies show that people who tolerate the higher starting doses (15 MIU) for three cycles are most likely to see immediate CD4+ cell count increases. People who start with the lower 4.5 MIU twice daily dose (total daily dose of 9 MIU) still get substantial increases in CD4+ cell count, but these increases usually take longer. In this situation, it often takes a number of cycles before any significant change is seen.

When trying to measure how IL-2 affects CD4+ counts, it's important not to take the CD4+ test too quickly after using IL-2, as this produces exaggerated and false results. Immediately after taking IL-2, CD4+ cells initially are depressed and then are highly stimulated and stirred up in the blood, causing potentially meaningless changes in the CD4+ count. Great increases might be seen a few days to a few weeks after IL-2, but these immediate changes generally decline rapidly after that.

Changes in the CD4+ count are only real and meaningful when the CD4+ test is taken a month or more after the last use of IL-2. For many people, no significant change is seen for several months, despite the short-term "bursts" of CD4+ activity seen right after IL-2 is taken. Over time though, the average level of CD4+ cells begins to rise and remains consistently above the levels seen before IL-2 use began.

Once someone has reached a goal in terms of CD4+ cell count increase, the time between courses of IL-2 therapy will be increased by four-week periods or longer if CD4+ cell counts are sustained. Blood work for CD4+

cell counts and HIV levels should be run two weeks *before* an IL-2 cycle. (Note: Lab test results done within four weeks after a cycle are considered unreliable.)

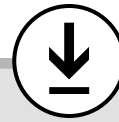
When IL-2 is prescribed as part of a study or through off-label use, it's important that a doctor or nurse teach you how to:

- ▶ prepare the IL-2 (it may or may not come in pre-filled syringes, other times you will have to prepare the syringe yourself),
- ▶ inject yourself,
- ▶ safely dispose of used syringes, and
- ▶ monitor for and manage side effects (and provide you with prescriptions for side effects management medications).

For more information on IL-2 side effects and side effects management, read the attached publication, *Taking IL-2 and Managing Its Side Effects*.

Some people using subQ IL-2 who failed to achieve CD4+ cell increases over time attained these increases when they switched to continuous intravenous (CIV) therapy. Early studies of IL-2 involved five-day continuous intravenous (in the vein) infusions, every eight weeks. Starting doses ranged from 9–18 MIU, daily. In general, the 15–18 MIU CIV daily doses were not well tolerated. Starting doses of 9–15 MIU were slightly more tolerable in CIV IL-2 studies.

CIV IL-2 side effects are more common and severe than side effects seen with the subcutaneous injection dosing. A large percentage of people taking IL-2 will see sizable CD4+ cell count increases with the less toxic and easier-to-use subQ approach. However, for those who don't experience CD4+ cell count increases with subQ injections, CIV IL-2 represents another option. Optimally, the first few CIV IL-2 cycles should be done in a hospital or clinic setting with skilled staff to support with side effects management. For more information, see the *Dosing Considerations* box on page 8.



commentary

In recent years it has become obvious that preserving the immune system is necessary for people with HIV to live longer lives. IL-2 shows much promise as part of a total treatment plan for people living with HIV, and it is currently the only immune based therapy to produce such significant and easily measured results. It may eventually become standard care to use an immune modulator (like IL-2) with anti-HIV therapies in order to maintain a person's immune system at healthy levels. However, as with any drug, the benefits of IL-2 must be weighed against the severity of its side effects.

Two major obstacles in developing IL-2 for HIV disease are the difficulty of taking the therapy and its side effects. Some people may not be willing to undergo twice daily injections for five days, every two months. Moreover, people who otherwise feel good might be unwilling to endure the flu-like symptoms. Because IL-2 has had such a pronounced and sustained increase on CD4+ cell counts, enthusiasm for it continues despite the challenges that taking the drug and side effects pose.

Despite pronounced and significant increases in CD4+ cell counts induced by IL-2 therapy, there is as yet no clear proof that these increases result in longer life or longer disease-free time. At the heart of the debate is whether increased CD4+ cells from IL-2 therapy function properly. So far, data overwhelmingly suggest that these cells do function properly, and in general those with sustained CD4+ cell increases have not experienced opportunistic infections at abnormally high CD4+ cell counts. When the cells are tested they appear normal and functioning, yet researchers readily admit that the tests to measure cell function leave a lot to be desired. These tests, however limited, suggest that the cells work at least as well as new CD4+ cells produced through anti-HIV therapy.

As of February 2007, one of the two largest studies of IL-2 is in jeopardy. Despite nearly two decades of drug developing in HIV under the auspices of Chiron Corporation, another company (Novartis Pharmaceuticals) bought out Chiron. Novartis originally seemed to suggest it would honor its obligations to the HIV affected community and complete these studies. In the eleventh hour, however, they seem not committed to carrying this important research to fruition and will abandon years of effort and turn their backs on the HIV affected communities. If this should be the case, it should not be allowed to happen without large public outcry.

the bottom line on IL-2

Benefits:

- › IL-2 shows greater CD4+ cell increases than almost any anti-HIV therapy, particularly when used together with anti-HIV therapy.
- › Those who have had dramatic and sustained increases end up dosing less frequently (maybe as little as one or two times a year) and retain high CD4+ cell numbers.
- › Opportunistic infections have not generally occurred at unusually high CD4+ cell counts, suggesting that IL-2 may preserve or improve immune function.

Concerns:

- › Side effects associated with IL-2 can be severe.
- › IL-2 requires under the skin injection or, more rarely, in the vein injection, both of which are invasive.
- › Studies to confirm the benefits of IL-2 are ongoing, and it's currently unknown if IL-2 will slow disease progression or prolong survival.
- › IL-2 should not be used by people with other autoimmune diseases (like rheumatoid arthritis, psoriasis and Crohn's disease), heart disease or diabetes.
- › IL-2 should be used with caution by people taking medicine to lower blood pressure.
- › Not everyone taking IL-2 experiences immediate CD4+ cell increases. Especially for those who start therapy with lower CD4+ cell counts, CD4+ cell increases may take up to 6 months.

How to get it:

- › IL-2 is available through several ongoing studies.
- › IL-2 is approved for use in kidney cancer and is available through *off label* use.
- › IL-2 is available through an assistance program for those whose insurance will not cover it and/or for people without third party payer (e.g. insurance) coverage, based on income eligibility. People should call 1-866-385-4729 for more information.

dosing considerations

Studied doses that appear to greatly impact CD4+ cell increases:

- ▶ Daily subcutaneous injection (under the skin) with starting doses of 9–15 MIU (4.5–7.5 MIU, twice daily), five consecutive days, every eight weeks. Lower doses have been used, resulting in less significant CD4+ cell count increases.
- ▶ Continuous IV (in the vein) infusion of 9–12 MIU, daily, five consecutive days, every eight weeks. This approach is associated with greater and more severe side effects and may only be desirable for people who fail to achieve CD4+ cell count increases using subcutaneous injections. People using IL-2 in this way are encouraged to do so in a hospital setting. This IV approach is rarely if ever used today, though it was standard for the lion's share of early research on IL-2.

Dosing strategies to consider:

- ▶ Reduce dosing to manage side effects in increments of three million IU (15 to 12, 12 to 9, etc.). You should also take antihistamines and ibuprofen before starting IL-2.
- ▶ If you use subQ IL-2 and experience no CD4+ cell increases, in studies some success has been seen in those switching to CIV IL-2. (*Note: People who start IL-2 with lower CD4+ cell counts may take longer to experience increases in CD4+ cell counts; in any case, people should not assume a dose isn't working unless it has been used for six months or longer.*)
- ▶ If you use CIV IL-2 and experience pronounced and sustained CD4+ cell increases, consider switching to maintenance therapy with subQ injections.

- ▶ If CD4+ cell counts are high and sustained (above 600), consider increasing the time between IL-2 dosing in four-week increments (e.g., every twelve weeks instead of eight). If CD4+ cell counts remain high after lengthening time between IL-2 therapy for three cycles, consider increasing it again, in four-week increments (8 to 12 weeks, 12 to 16 weeks, etc.).

IL-2 and CD4+ cell count, viral load and general health

- ▶ Measure CD4+ cell and viral levels *before* taking IL-2 (preferably getting results before starting a five-day course).
- ▶ If viral levels are high or increasing, consider re-evaluating your anti-HIV regimen (read Project Inform's publication, *Anti-HIV Therapy Strategies*). Consider delaying IL-2 therapy until viral levels are under control.
- ▶ If you experience an active infection or condition, consider delaying five-day IL-2 course of therapy until it's resolved. IL-2 therapy temporarily suppresses the immune system and may interfere with your body's ability to fight off infection in the short-term.

IL-2 and other therapy

- ▶ Maintain optimal anti-HIV therapy while on IL-2, preferably a three-drug combination.
- ▶ Regardless of CD4+ cell impact from IL-2, consider continuing preventive therapy for OIs (PCP, etc.) if it was warranted before starting IL-2. Be cautious and conservative about stopping preventive therapy when CD4+ cell counts rise. The value of IL-2 therapy and CD4+ cell count increases realized as a result of therapy is still not known.

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