

# IMMUNE THERAPY: CYTOKINES



immune chemicals may hold hope  
for new treatments in hiv disease

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Immune cells communicate through chemical messages. For example, one chemical might direct cells to where they are needed to fight off an infection. Another may make cells reproduce, cloning themselves to build an army to combat a specific infection. These chemicals are called *cytokines*.

Scientists have been trying to decipher the chemical language of the immune system to learn how to harness it for use in the fight against AIDS. This publication provides a general picture of cytokine therapy to date—approved therapies, those currently in large studies, those entering studies in HIV soon, and a glimpse at tried and failed approaches.

## **Cytokines: the past or the future?**

One of the great clichés of popular writings about medicine is the claim that some products “boost the immune system”. This is far easier said than done, nor is it always clear that the goal, even in HIV disease, should be to “boost” any aspect of the system. Just as often, the real goal may be to suppress or modulate some aspect of the immune response.

Therapies designed to influence the immune system are called immune-based therapies (IBTs). The field IBTs is still in its infancy, but not so new that the reality of IBTs is outside the grasp of day-to-day use in the practice of medicine. There are currently approved and proven cytokine therapies that are routinely used by people living with HIV.

These include cytokines like interferon-alpha, granulocyte colony stimulating factor and erythropoietin-alpha.

## **Interferon-alpha**

Interferon-alpha (Infergen, Roferon, Intron-A, Peg-Intron) is a cytokine with broad antiviral properties. It has been researched and proven useful in treating viral hepatitis. It is also used in treating an AIDS-related cancer, Kaposi's Sarcoma (KS), which is triggered by human herpes virus 8 (HHV-8), also called KS Herpes Virus (KSHV).

Interferon-alpha is most known in the setting of HIV as a broad spectrum antiviral. While test tube studies show some anti-HIV activity of interferon-alpha, studies in people have been conflicting. Other facets of its impact on immune functions are also being explored. For example, studies are underway to see if its use can prevent diabetes. It has also been proven to be useful in treating non-viral cancers, such as malignant melanoma. It is available in standard and “PEG” (pegylated) forms. These forms combine it with PolyEthylene Glycol, which stabilizes the interferon and keeps it in the bloodstream longer, thus improving its effectiveness.

**Granulocyte colony stimulating factor**

Granulocyte colony stimulating factor (G-CSF, neupogen, Filgrastim) is used by people with low neutrophil cell counts (*neutropenia*). Neutrophils are important in fighting bacterial infections. When these counts are very low (below 750), people are at increased risk for severe and potentially life-threatening bacterial infections. Drugs to treat HIV and related conditions, particularly anti-CMV drugs, can cause neutropenia. It has also been associated with HIV disease progression. G-CSF mobilizes neutrophil cells and causes them to reproduce.

**Erythropoetin-alpha (epoetin-alpha, Epogen)**

Erythropoetin-alpha (epoetin-alpha, Epogen) is used for treating mild-to-moderate AZT-associated anemia. Anemia is a decrease in red blood cell counts. Red blood cells carry oxygen throughout the body. Severe anemia is treated with blood transfusion. Symptoms of anemia may include fatigue, dizziness, difficulty concentrating, menstrual abnormalities and/or decreased sex drive. Anemia can be caused by HIV, HIV-related conditions and/or by drugs used to treat HIV.

**On the horizon****Interleukin-2 (IL-2, Proleukin)**

Of the cytokines being researched in the setting of HIV, IL-2 is the most widely studied and furthest along in development. Also known as T cell Growth Factor, IL-2 stimulates CD4+ cells to reproduce. An emerging body of research suggests that IL-2-stimulated cells thrive better in the face of HIV infection than other CD4+ cells. IL-2 induces increases in CD4+ cell count levels that far surpass those achieved by any other therapy researched for HIV. Two very large studies are underway to see if IL-2, in addition to anti-HIV therapy, reduces disease progression and prolongs life. For more information on IL-2, read the publications, *IL-2* and *Managing Its Side Effects*, available from through Project Inform's info-line and website.

IL-2 is also being evaluated for its potential to heighten responses to therapeutic HIV vaccines. A few small studies are including IL-2 as part of acute infection and early disease treatment and structured treatment interruption (STI).

**The bleeding edge**

Two cytokines are drawing increased interest from researchers for their potential in treating HIV infection. These are interleukin-7 (IL-7) and interleukin-15 (IL-15).

**Interleukin-7**

A healthy adult will maintain a CD4+ cell count generally from 500–1,500. What keeps cell counts from falling below 500 or from reproducing out of control remains something of a mystery. When CD4+ cell counts drop below normal ranges, other cells begin producing IL-7 (among other things), which in turn stimulates CD4+ cells to reproduce and causes the thymus (where new CD4+ cells come from) to produce more CD4+ cells. Low CD4+ cell counts have been correlated to increases in IL-7 levels in people with or without HIV (bone marrow transplant patients, etc.). It's theorized that the body produces more IL-7 as CD4+ cell counts fall as a way to prompt the regeneration of CD4+ cells to normal levels. For this reason it is believed to be a potentially important HIV therapy.

The first human study of IL-7 is recruiting volunteers in the setting of cancer. HIV researchers are watching this study and will learn about dose, schedule and side effects that will be further evaluated in HIV studies. While there is increasing interest in using IL-7 for HIV, there are concerns about safety. IL-7 activates HIV and particularly a very aggressive form of HIV, called syncytia inducing (SI) or R4-dependent virus. It's possible that this concern could be lessened by giving IL-7 with anti-HIV medications. Some research in animals suggest that short-term activation of HIV by IL-7 might be a good thing as it may decrease the reservoir of HIV lurking in resting cells. The major barrier to moving this research forward is that no company committed to HIV research currently makes a form of quality controlled IL-7 suitable for large human studies.

## Interleukin-15

Interleukin-15 (IL-15) appears to preferentially enhance CD8+ cell number, function and survival in animal and lab studies. These cells are important in cell-to-cell killing of virally infected cells. While IL-2 stimulates CD4+ cells to reproduce, IL-15 stimulates CD8+ cells. Also, IL-15 appears to inhibit cell death caused by activation. Immune activation and a cascade of activation-induced cell death are increasingly believed to be part of the immune dysfunction of HIV disease (the “sink and drain” notion that HIV simply kills billions of cells each day is no longer widely held). Increases in IL-15 levels have been associated with better control of HIV infection, though which is the cause and which is the effect have not been clearly determined. An IL-15 study for treating HIV has been in development for years and never materialized. The major barrier to moving this research forward is that the company who owns IL-15 (Amgen) is not committed to HIV research.

## Tried and failed and tried again?

Several cytokines have been looked at in the context of HIV. Interferon-gamma enhances the function of cells that control mycobacterial infections, including tuberculosis and MAC. It has been studied together with anti-TB treatment in people with TB and HIV. It is also being looked at as an adjunctive therapy to enhance vaccine effects. Early studies suggest that low doses of interferon-gamma may control HIV whereas high doses may promote HIV replication. Interferon-gamma, however, is also associated with cell activation, which isn't necessarily a good thing. Over the years, increased interferon-gamma levels have alternately been described as both a good thing and a bad thing.

This point is important when considering the challenges of researching cytokines. In the body, cells are producing these chemicals at very, very small—nanomolar—concentrations and together with other cytokines. The combination of cytokines, in varying concentrations, elicits different immune responses. At low doses IL-2 preferentially stimulates natural killer cells, while at higher doses, delivered intermittently, it stimulates CD4+ cells to reproduce. When IL-2 is given at high dose daily it produces no appreciable effect on CD4+ cell count. When it is given for five days every eight weeks, the effect is profound and pronounced. The challenge

with cytokine research is not merely to understand the various biologic functions of the cytokine, but also how best to give the therapy to achieve the desired responses.

## Interleukin-12

Interleukin-12 (IL-12) was researched in the early 1990s because it's believed to enhance cellular immune responses (the type of responses associated with killing HIV-infected cells, as opposed to killing free virus in blood). Results from small studies suggest it had no effect on either HIV levels or CD4+ cell counts at doses that were tolerable. However, dosing and schedules of doses may not have been fully explored to truly understand the potential of this therapy.

## Granulocyte macrophage colony stimulation factor

Granulocyte macrophage colony stimulation factor (GM-CSF) was evaluated in a large study to see if adding it to anti-HIV therapy would decrease risks for opportunistic infections among people with more advanced HIV disease. While there were some interesting observations of decreases of specific bacterial infections among those receiving GM-CSF compared to placebo, the differences were not significant overall.

## Interleukin-10

Interleukin-10 (IL-10) is an immune suppressive cytokine that suppressed HIV replication in test tubes. One study in people showed no impact on HIV replication, positive or negative when IL-10 was given at 1, 4 or 8µg/kg daily compared to placebo. Another study suggested that IL-10 therapy may decrease HIV levels.

## Interleukin-4

Interleukin-4 (IL-4) has been researched for activity against the AIDS-related cancer Kaposi's sarcoma (KS) and its impact on HIV was monitored. At a dose of 1µg/kg daily, IL-4 had no effect on HIV levels and little to no impact on KS.

These are a handful of cytokines that have been studied in the setting of HIV. While they failed to show benefit, it may be that at different doses, given intermittently as opposed to daily, or combined



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with other cytokines, they will one day be researched again and show promise.

### Conclusion

As research advances and tools are improved to understand the immune system, more is being learned about cytokines. There is increased interest in harnessing the language of the immune system to direct its responses and improve health. This research holds great potential, though the road to realizing it will likely be riddled with failed experiments and confounding results. Cytokine therapy is not merely a tool of the future—years from the grasp of our medicine cabinets. To the contrary, several cytokine therapies are now routinely used by many peo-

ple living with HIV.

Furthest along in the research pipeline is IL-2. Answers about the value of IL-2 in combination with anti-HIV therapy are expected within the next 2–3 years. The hottest new tickets in the cytokine town are IL-7 and IL-15. Although neither has made a debut in studies of people with HIV, there's not an immunology conference in HIV where they're not the buzz. Activist involvement is needed to ensure these two therapies are researched in HIV.

A handful of other cytokines have been tested in HIV, with either negative or confounding results. They may make comebacks as more is learned about the language of the immune system and how it acts.

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