

Immune Therapy: In Brief



Immune Therapy

A number of very small studies of immune-based therapies have reported data. The most that can be concluded on the basis of small studies is whether or not a therapy is safe and if it warrants further study. It may be years before large studies of these types of approaches are launched. The following are brief summaries of results from studies of these novel approaches to treating HIV.

HIV Vaccines for People Living with HIV

The goal of giving an HIV vaccine to someone living with HIV is to enhance the immune system's ability to control the virus. Many such approaches have been tried with limited success in the past. A new approach attempts to enhance the ability of immune cells to seek out and destroy HIV-infected cells (called cellular immunity). The new vaccine combines a previously studied vaccine (called rgp160) with a live virus vaccine carrying four HIV genes. The live virus used in this study (called canarypox) is a virus that birds get that does not cause disease in humans. The product is called vCP1452. The study included eight volunteers who had started taking anti-HIV medication within 90 days of initial HIV infection. At the time of the study, participants had sustained control of HIV levels for at least two years. Researchers presented results of the first six people who completed four injections with the vCP1452/rgp160 vaccine over a six-month period.

All volunteers demonstrated increases in anti-HIV immune responses over time, though not all had the same magnitude or breadth of response. There were no reported side effects and the vaccine approach was deemed safe. Future studies will assess whether or not these improved immune responses lead to decreased risk of HIV disease progression or improved outcomes, over time.

G-CSF (Neupogen) Enhances Function of Neutrophils

Neutrophils are important cells in fighting bacterial infections. The function of these cells is impaired in people with AIDS. Also, many commonly used therapies for HIV can cause a decrease in neutrophil counts. Granulocyte colony stimulating factor (G-CSF, Neupogen) is commonly used to treat people with HIV who have low neutrophil counts (neutropenia).

A small study including 30 people with CD4+ cell counts below 200 who did not have low neutrophil counts evaluated three different doses of G-CSF. Volunteers received G-CSF, given by daily injection

in doses of 75, 150 or 300mg for seven days. Neutrophils were examined and shown to have increased ability to destroy bacteria in a dose dependent manner (i.e. the larger the dose, the more effective the neutrophils are in killing bacteria). Also, cells were less likely to self-destruct (undergo programmed cell death) as higher doses were used. The benefits of G-CSF therapy lessened within three days of stopping G-CSF therapy, however, suggesting that turning this into a practical therapy would require daily injections.

Immune Suppression for Treating HIV

As a person's HIV disease progresses, their levels of immune cell activation increase, most likely in response to increases in HIV viral load. Markers of immune activation have been associated with HIV disease progression and increased HIV replication. It is well established that inactive infected cells produce very little new HIV. Some researchers believe that much of the harm attributed to HIV infection may be linked to excessive immune activation. The concepts have led to the study of cyclosporine (CsA, Neoral), an immune suppressive drug that is commonly used in organ transplant patients to prevent their immune systems from rejecting the newly transplanted organ.

A recent study included 28 people with CD4+ cell counts above 400 and low but measurable HIV levels. They received CsA (4mg/kg daily) or placebo for three months. Volunteers were either on no anti-HIV therapy or on two-drug therapy with NARTI anti-HIV drugs. (This study was started before the time three-drug therapy was standard-of-care).

Levels of immune activation decreased in people receiving CsA and either remained stable or increased in those receiving placebo. Measures of immune function, however, also slightly decreased in those receiving CsA. The impact of CsA on both immune activation and immune function was only modest. In general, the therapy was deemed safe and worthy of further evaluation, especially among people with HIV undergoing organ transplantation.





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New Form of Interferon-alpha May Be Useful in Treating HIV

Interferon-alpha (INF- α) is a naturally occurring immune chemical with antiviral activity. A man-made form of the chemical is currently approved for treating Kaposi's Sarcoma, an AIDS-related cancer. It is also one of the therapies used for treating hepatitis C virus. In the past, injectable INF- α was studied as an anti-HIV therapy, but side effects were deemed too severe to warrant continued research. The most common side effects include flu-like symptoms and depression.

Interest re-emerged in INF- α when studies of third-line therapy indicated that it may be a useful addition to anti-HIV therapy in people who need mega-HAART type regimens to control viral load. A new form of INF- α , called PEG Intron, binds INF- α with a chemical that makes the INF- α stay in the blood for longer periods of time requiring less frequent dosing.

A study of 31 people on stable anti-HIV therapy with CD4+ cell counts greater than 200 and viral levels greater than 500 copies per/ml assessed varying doses of PEG intron. Doses evaluated included 1, 1.5, 2.25 or 3.5mg/kg, delivered by injection under the skin (subcutaneously) once per week for eight weeks.

PEG Intron seemed to cause nearly a 1 log (10-fold) drop in HIV RNA levels at the end of the study. There appeared to be no effect on CD4+ cell count (or percentages) over time. Volunteers who started with high levels of immune activation were least likely to experience HIV RNA decreases resulting from PEG Intron therapy. Higher doses were correlated to greater decreases in viral load. Since this was a pilot study and it did not compare treated patients to a control group, it is not yet possible to conclude that the drug was responsible for the changes in outcome. Larger studies using PEG intron will begin in the near future.

CD4+ Cell Expansion

CD4+ cell counts decrease over the course of HIV infection, as do their function. Researchers have identified a method to grow CD4+ cells, outside the body, in a way that may make them somewhat resistant to HIV infection. To evaluate the safety of CD4+ cell expansion in people with HIV, a small eight-person study was conducted through the U.S. military.

Dr. Carl June expanded cells and delivered increasing numbers of cells, every six weeks for three courses of therapy. After the first three courses, volunteers received cell infusions every eight weeks for one year. Side effects included fevers, chills and fatigue. Side effects were more severe when higher numbers of cells were infused. Overall, people experienced no changes in viral load associated with cell

therapy. Seven of the eight volunteers experienced increases in CD4+ cell numbers, and all experienced increases in CD4+ percentages.

The use of aggressive anti-HIV therapy became more widely available during the course of this study. As it did, people made adjustments in their anti-HIV therapies. It is therefore impossible to note what (if any) changes in CD4+ cell counts are due to CD4+ cell therapy and which are due to anti-HIV therapy.

The new CD4+ cell expansion approach used in this study has since been adopted as a part of other cell therapy studies that include gene therapy (e.g. modifying cells with genes that may help protect them from HIV infection). The researchers conclude that this approach is safe. Whether it is financially feasible is another matter.

HIV-specific CD8+ Cell Therapy

HIV-specific CD8+ cells (also called HIV-specific cytotoxic lymphocytes, or CTL) are cells that seek out and destroy HIV-infected cells. Researchers in Seattle have been studying HIV-specific CTL therapy in people with HIV.

Most recently this group has reported on a study of five people with CD4+ cell counts between 200 and 500, on stable anti-HIV therapy, without prior history of opportunistic infection, who received two infusions of HIV-specific CTLs at one-week intervals.

The researchers expanded the cells and "marked" them with a gene that would show them where the cells went in the body after they were re-infused. The cells were detected in the blood as well as other organs (e.g. lymph nodes) for 18 days after infusions. Sporadic detection of cells was noted 4 - 6 weeks after the second infusion of cells. The cells appear to travel to the lymph nodes appropriately and maintain their anti-HIV capacity.

In Conclusion ...

Most immune-based therapies are still in very early stages of research. The most that can be concluded about small studies like those described above are that the approaches appear safe and warrant further investigation. These types of studies pave the way for future directions in HIV research.

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