

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

■
a concern for people
who are starting hiv therapy

A PUBLICATION FROM

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Information,
Inspiration and
Advocacy for People
Living with HIV/AIDS

APRIL 2008



It's a mouthful of a phrase, but *immune reconstitution inflammatory syndrome* (IRIS) is a serious condition that can be challenging to diagnose and treat. The main concern with IRIS is the inflammation that it causes. Though research is beginning to sort out the condition, it is still not well understood.

It's not clear who will more likely experience IRIS, though it most often occurs in people with severely

damaged immune systems shortly after they start taking HIV therapy. More study needs to tease out its risk factors and to find screening tools to help predict and manage the condition.

The symptoms are also found in HIV-negative people. However, this publication provides an overview of IRIS within the context of HIV disease. It presents ways to assess your risk and identify the condition.

What is inflammation?

Inflammation means *to put on fire*, and it's a complex response that results when your body attacks germs or repairs damaged tissue. A simple example of it is the redness, swelling and soreness that emerges around a cut as it's healing. For your immune system to repair the damage and clear any infection that's present, cells and fluids are recruited to the site of the damage. This shows up as swelling, redness and pain.

Inflammation can appear nearly anywhere in your body. It can occur in an organ like the liver, in lymph nodes, in nerve fibers, and even in areas outside organs like your immune system. Inflammation can be *acute* or *chronic*.

Acute inflammation is when your body first responds by sending white blood cells to the damaged area. Your circulatory and immune systems assist in the process. For the most part, acute inflammation is normal and healthy.

By contrast, *chronic* inflammation persists over time. In this case, your body shifts the types of cells that are present. This causes a situation where cells and tissues are healed and destroyed at the same time. While it's not well understood, chronic inflammation is thought to be unhealthy and possibly linked to a number of serious diseases including heart disease and Alzheimer's.

What is IRIS?

IRIS is a serious condition that can occur shortly after a person starts HIV therapy for the first time. It can also occur in people who restart their meds after a time being off them. IRIS happens when your immune system recovers too quickly. It can start to "overwork" and respond to other infections that may or may not have been diagnosed before starting therapy, even ones that may have already been under control.

When your immune system responds in this way it results in inflammation, and the inflammation that flares up can cause symptoms, sometimes severe. For some, these symptoms can be life-threatening. Though most cases of IRIS resolve after a few weeks, the symptoms may be mistaken by you or your doctor as HIV disease progression or another condition. IRIS is a *paradoxical* situation because, as your immune system responds to an infection, the inflammation that occurs actually makes your symptoms worse.

Most people who start their first regimens do not develop IRIS. And of those who do, many cases resolve on their own. However, it's wise to report these symptoms to your health provider as soon as possible.

When IRIS does occur, it happens more often in people with TB and other *mycobacterial* infections, accounting for about 2 in 5 of the total IRIS cases. However, many other bacteria and viruses can contribute to IRIS. The box at right provides a list of the known infections. Some chronic conditions, particularly autoimmune disorders like rheumatoid arthritis, lupus or Grave's disease, may become aggravated by IRIS.

List of known infections that contribute to IRIS

- CMV, or cytomegalovirus
- Cryptococcal meningitis, or *Cryptococcus*
- Eosinophilic folliculitis
- Hepatitis B and C
- Herpes, or HSV
- Herpes zoster, or Shingles, Varicella-zoster, VZV
- Human papillomavirus, or HPV
- Kaposi sarcoma and Castleman's disease, or HHV8
- MAC, or *Mycobacterium avium* complex
- PCP, or *Pneumocystis jiroveci* pneumonia
- PML, or progressive multifocal leukoencephalopathy (caused by the JC virus)
- TB, or *Mycobacterium tuberculosis*



How is it diagnosed?

A *differential diagnosis* is normally used to identify IRIS. This is when the diagnosis is narrowed down from a list of possibilities until one emerges as the best. A differential diagnosis will consider the failed treatment of the current infection, a possible new infection or malignancy, and drug side effects (especially with hepatitis).

One important thing to consider after starting therapy is the amount of decrease in HIV levels (*viral load*). IRIS tends to occur when there's a large drop in HIV levels. An example of this would be going from 100,000 copies of HIV down to about 500, which shows a strong response to therapy but an increased risk for IRIS.

This is another paradox about IRIS, because getting viral load to an undetectable level as soon as possible is one goal of HIV therapy. Should this happen, it's the most likely time that IRIS will occur. Therefore, closely checking HIV levels is an important way to help diagnose possible IRIS. Other tests can also assist the diagnosis, such as white blood count and C-reactive protein, which indicate inflammation. The higher the levels, the more likely major inflammation is taking place.

Who is at risk?

In general, people with more severely damaged immune systems before starting HIV therapy are most at risk for IRIS. You and your doctor should be aware that IRIS is *possible* after starting therapy; especially if it's known that another infection was or is present and even under control. Possible risk factors are listed below. The more of these risks you have, the more likely that IRIS can result.

- People with CD4 counts below 100 before starting therapy.
- People who start HIV therapy for the first time, or re-start therapy after a time off their meds.
- People with greater drops in HIV levels (2.5 logs or more) due to therapy, though IRIS has been seen in people with drops of 1.0 log.
- People with a diagnosis of another infection before starting therapy. (See box on page 2.) The closer the appearance or diagnosis is to starting therapy, the higher the risk.
- People who start on protease inhibitor regimens boosted with Norvir (some evidence).

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What are the symptoms?

Symptoms of IRIS can be dangerous. They usually appear within 2–6 weeks of starting HIV therapy. For some, the symptoms may improve and resolve on their own. For others, the symptoms may persist or get worse and become life-threatening. In any of these cases, these symptoms should be brought to the attention of your health provider.

Common symptoms of IRIS include fever, swollen lymph nodes, skin lesions and rashes, changes in breathing, pneumonia, hepatitis, abscesses and eye inflammation. Although less common, some people can experience short-term cognitive or mental changes, including memory problems and personality shifts. Though IRIS can react to a specific infection like TB, IRIS symptoms may not appear like the symptoms originally did for the TB. This can hold true for other infections.



IRIS symptoms are mostly different than and should not be confused with the possible side effects from starting HIV drugs, like fever or skin rash. If side effects do occur, they usually appear soon after starting your meds. Within a few weeks your body usually adjusts to them and they go away. However, there may be some overlap of time between drug side effects and IRIS symptoms, which is one reason it's challenging to diagnose IRIS. It's wise to pay close attention to and report any and all symptoms to your health provider.

How do you treat IRIS?

No standard of care is currently in place for treating IRIS, so the best way to treat it is unknown at this time. However, it's important to address the condition as soon as symptoms appear. Current treatment is based mostly on case reports and other anecdotal data.

Treating IRIS usually starts by treating the active infection, like TB or herpes. HIV therapy is usually continued as well, unless IRIS becomes life-threatening. To reduce the inflammation, you may be prescribed NSAIDs and/or corticosteroids. More research is currently looking at this issue.

Starting HIV therapy while an active infection persists is a controversial issue, and it may be dangerous. However,

there are not a lot of data to help guide this type of decision. In fact, several studies show that the closer another infection is diagnosed before starting HIV therapy, the more likely IRIS will occur.

Therefore, deciding to start therapy can be especially troubling for you and your doctor if the infection becomes severe or if your immune system doesn't respond. Still, if the immune system is stable and other health markers suggest treatment could be successful, holding off on starting HIV therapy may be the best option until the active infection has been resolved.

Special concerns for people living with HIV

Before starting HIV therapy, especially if you have a severely damaged immune system (low CD4 count and high HIV level), it may be wise to aggressively diagnose any possible infections. Some infections may appear as though they're well under control, such as TB disease. Some may have resolved many months or even years ago.

However, other infections may have occurred without you noticing their symptoms, like herpes or HPV. This is called a *subclinical* infection—something that hasn't been diagnosed or noticed yet. Talking to your doctor, taking a thorough medical history, and checking a full range of blood tests can go a long way in diagnosing other possible infections.



Special concerns for women, children and people over 50

Few if any data show that women, children or people over 50 have any special concerns around IRIS. So far, it does not appear to affect these populations more often or severely.

What can help to ask about at a doctor's visit?

- Am I at risk for IRIS? How many risk factors do I have?
- What types of symptoms should I be aware of? What should I do if I have them?
- How do I tell the difference between IRIS symptoms and side effects from the HIV drugs?
- Is there a regimen I can take that is less associated with IRIS?
- Can starting HIV therapy make my herpes (or other infection) worse? How do we manage that?

Commentary

If another infection besides HIV is present before starting therapy, IRIS is more likely to develop. As well, the greater the drop in HIV levels (2.5 logs or more) and the fewer CD4s before starting therapy (below 50), the more likely it will occur. However, IRIS has also been seen in people with somewhat higher CD4s (below 100) and less dramatic drops in HIV levels (1.0 logs or more).

Much has been learned about IRIS, though a good deal more still needs to be understood. Current research is

answering more of these questions, especially ways to test for whom is more likely to develop IRIS and more specific answers for knowing when it may happen. It's wise for those who face first line therapy to understand your risks, especially if your immune system is severely damaged. Reporting your symptoms can help inform your doctor of a situation that may need to be more closely managed and treated.

What does the research show?

The research on predicting and diagnosing IRIS is still in its early stage, though more discovery releases new information every few months. Below is some recent study information.



Asthma medicine

A type of immune chemical, called a *leukotriene*, causes different types of inflammation. Drugs that reduce these levels in the body, called *leukotriene inhibitors*, are commonly used to treat asthma. Since it's thought that leukotriene inhibitors affect other inflammation in the body, they may be useful for treating IRIS.

Encouraging results have been reported by doctors in London who used a common asthma medicine, Singulair (montelukast), to treat IRIS in a 59-year-old man. After five months off therapy, he restarted on a protease inhibitor regimen boosted with Norvir. IRIS appeared a few weeks later as a skin rash, and prednisone was used. His health improved somewhat but then the rash returned along with a fever and rapid heart beat. Singulair was prescribed and within five days his symptoms had settled.

The doctors suggest that leukotrienes may play a role in IRIS. Although this case does not prove that this therapy works, it may open up new research into using leukotrienes to treat IRIS. If this turns out to be true, then already approved drugs may be easily adapted to treat the condition.

Gene markers

Finding ways to diagnose earlier who will develop IRIS will allow for better strategies for its prevention and treatment. One study at CROI 2008 reported results of 28 people with and 38 without recent cryptococcal meningitis who started HIV therapy. Researchers looked at 85 genes that were related to cells of the immune response and reproduction of the meningitis. Results showed that using certain gene markers may help predict IRIS before it becomes a problem. More study is needed.

Immune markers in TB disease

One study at CROI 2008 reported disappointing results of finding immune markers that would adequately predict IRIS in TB disease. A Thai study showed that IL-12 and serum IL-2, among other markers, did not show differences between those who did and did not develop IRIS. However, a second study reported that they're looking at other markers, such as regulatory and effector T cells, monocytes and macrophages. Results will be forthcoming.

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