Immune reconstitution inflammatory syndrome

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 or predicted.

It’s not clear who will more likely experience IRIS, though it most often occurs shortly after the start of HIV therapy in people with more damaged immune systems. More study needs to tease out its risk factors and to find screening tools to help predict and manage 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 heals. 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 — in 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 lasts a short amount … a normal process that promotes healing. By contrast, chronic inflammation persists over time. Here, cells and tissues are healed and destroyed at the same time. It’s thought to be unhealthy and possibly linked to serious diseases like heart disease and Alzheimer’s.

What is IRIS?
IRIS 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 been under control.

This results in inflammation throughout the body, sometimes flaring up as severe disease. IRIS is a paradoxical situation because, as your immune system does its job, the inflammation that occurs actually makes your symptoms worse. 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.

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.

FACING NEW DECISIONS? WONDERING WHAT’S THE NEXT STEP?
HIV Health InfoLine: 1-800-822-7422 (toll-free)
10a–4p, Monday–Friday, Pacific Time
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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. 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 Cryptococcosis
- Eosinophilic folliculitis
- Hepatitis B and C
- Herpes, or HSV
- Herpes zoster, or Shingles (VZV)
- Human papillomavirus, or HPV
- Kaposi sarcoma, or HHV8
- MAC, or *Mycobacterium avium* complex
- PCP, or *Pneumocystis jiroveci* pneumonia
- PML, or progressive multifocal leukoencephalopathy
- TB, or *Mycobacterium tuberculosis*

**Who is at risk?**

In general, people with poorer 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 you know 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.

- CD4s below 100 before starting HIV therapy.
- Starting HIV therapy for the first time, or re-starting therapy after a time off meds.
- Large drops in HIV levels (2.5 logs or more) due to therapy, (IRIS has been seen in people with drops of 1.0 log).
- Diagnosis of another infection before starting therapy. The closer that is to starting therapy, the higher the risk.
- Starting on protease inhibitors boosted with Norvir (some evidence).

**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. This diagnosis will consider the failed treatment of the current infection, a possible new infection or malignancy, and drug side effects (especially with hepatitis).

**IRIS** tends to occur when there’s a large drop in HIV levels (viral loads). An example of this would be going from 100,000 copies of HIV down to about 500 in just a few weeks, which shows a strong response to therapy but an increased risk for IRIS. So 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 show inflammation. The higher the levels, the more likely major inflammation is taking place.

**What are the symptoms?**

Symptoms of IRIS can vary and 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, they may persist or get worse and become life-threatening. In any of these cases, these symptoms should be told to your health provider.

Common symptoms include fever, swollen lymph nodes, skin lesions...
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and rashes, changes in breathing, pneumonia, hepatitis, abscesses and eye inflammation. Although less common, some people can experience short-term mental changes, like memory problems. Though IRIS can react to a specific infection like TB, IRIS symptoms may not appear like the symptoms originally did for the TB, or 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 drug side effects do occur, they usually appear soon after starting your meds. Within a few weeks your body usually re-adjusts to them and they go away. However, drug side effects may overlap IRIS symptoms, which makes it challenging to diagnose IRIS.

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. Treatment options are 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. The goal here is to stop the mounting inflammation. You may be prescribed NSAIDs and/or corticosteroids.

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 treating the actual infection, 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 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. Talking to your doctor, doing a thorough medical history, and checking a full range of blood tests can go a long way in diagnosing other possible infections.

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?
• Can starting HIV therapy make my herpes (or other infection) worse? How do we manage that?
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What does recent research show?

**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 5 months off therapy, he restarted with a protease inhibitor boosted with Norvir. IRIS appeared a few weeks later as a skin rash, and prednisone was used. His health improved somewhat but the rash returned along with a fever and rapid heart beat. Singulair was prescribed and within 5 days his symptoms had settled.

Although this case does not prove that this therapy would work for everyone, it may open up new research into using these drugs 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 inflammation. Results showed that using certain gene markers may help predict IRIS before it becomes a problem, but 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.