

STRUCTURED TREATMENT INTERRUPTIONS



a discussion of the research for using an s.t.i. as therapy

The reasons that someone may want to take a structured treatment interruption (STI) can vary from treatment fatigue to struggling with adherence to avoid side effects. Various STIs have been studied since the late 1990s with mixed results. While significant questions still remain, taken as a whole STI research suggests that their risks greatly outweigh their possible benefits. This publication reviews various STI strategies.

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A general caution on STIs

Taking an STI involves going off HIV therapy for a period of time in a strategic way. This is usually paired with more frequent lab and health monitoring. Taking an STI is considered experimental since there are no conclusive data to recommend it as standard care.

Given the types of STIs presented in this publication, should you wish to try one, you should only do so with the full knowledge and support of your doctor(s) who are experienced with them. Most STIs are generally unsafe and some may only be safe for certain people.

Someone who takes an STI may face the typical symptoms seen in acute infection. These can occur within the first few weeks after starting an STI. Symptoms are flu-like in nature and can include fever, muscle aches, swollen lymph nodes and rash.

It's important to check CD4 counts and HIV levels before and after starting an STI and resume HIV therapy according to the Federal Guidelines, as well as prevent opportunistic



infections (OIs). For more information, read Project Inform's publications, *Strategies for First Line HIV Therapy*, *Strategies for Third Line HIV Therapy* and *Strategies for Managing Opportunistic Infections*.

The most notable research to date

The most notable research to date on STIs comes from the SMART study. It compared two strategies in nearly 6,000 people worldwide: continuous treatment vs. regularly interrupted treatment guided by CD4 counts. The researchers had expected that by keeping people off medicines for periods of time, there would be lower rates of long-term problems like heart disease, which have been linked to HIV drugs.

The opposite was true. SMART was stopped early when the data showed that people who interrupted treatment had higher rates of illness and death. This finding was quite unexpected. Some believe these results are so bad that STIs have been proven to be risky and should be avoided in most cases. Others feel that SMART raises some concerns, but reasons still remain to study other kinds of STIs.



SMART isn't the only study to highlight the dangers of STIs. Others — like PART, DART and TRIVICAN — have shown similar results. However, a recent Swiss study found that STIs may be safe for people who started HIV treatment with higher CD4 counts.

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Using an STI to reinvigorate the immune response

Some observations suggest that HIV disease progression may be due in part to the loss of a potent type of immune cell, called an *HIV-specific cytotoxic lymphocyte* (CTL). These cells seek out and destroy HIV-infected cells. Some findings indicate that some long-term non-progressors — people who stay well for many years without HIV therapy — maintain their CTLs while those who progress more rapidly do not.

Although not all research supports the loss of CTLs as a cause for disease progression, several studies were planned or started.

These included giving treatment within the first few weeks or months after infection (*acute infection*) followed by an STI as well as STIs taken with therapeutic vaccines to enhance a person's immune response against HIV.

Ultimately, the goal of this type of STI is to preserve and enhance the body's natural immune responses in early HIV infection. In theory, this would help a person's immune system to better control HIV on its own for longer, and perhaps indefinitely, without therapy. For those with established HIV infection, the goal is to enhance or restore their immune responses, hopefully doing better in the long-term.

By starting and stopping therapy at regular intervals, it was hoped that with each STI the immune

system would become more able to control HIV on its own. This is sometimes called *auto-immunization*, when enhancing a person's exposure to HIV in a controlled manner can create a more potent and effective response against it.

However, the results of this research were the opposite of what was expected. People living with HIV the longest were actually more likely to have broader and more potent CTL increases. Those who had started therapy just before or after acute infection

had fairly weak responses with CTLs. The CTLs were boosted somewhat during the STI but then decreased back to lower levels after restarting treatment. Similar results were found in several other studies in

people with long-term infection.

Several studies combined STIs with immune therapies, like IL-2 (Interleukin-2) or therapeutic vaccines. The hope here is that these therapies, when used with an STI, would provide the needed "lift" to coordinate a stronger immune response to HIV. The results are not promising. Therefore, people who hope to "boost" their immune systems should not look to STIs as a proven treatment.

IN THE END, PEOPLE WHO HOPE TO "BOOST" THEIR IMMUNE SYSTEMS SHOULD NOT LOOK TO STIs AS A PROVEN TREATMENT.

2 Using an STI to help people with treatment fatigue

Simply put, treatment fatigue is when a person is “tired” of taking HIV medicines. This could be due to physical and/or emotional tiredness.

For people who wish to stop their therapy for this reason, the data are somewhat conflicting. Various results show that some people can take a break without developing drug resistance, treatment failure or disease progression.

Several factors can help predict when a person may have a poorer outcome. These are:

- low CD4 count before starting therapy (below 200),
- high HIV level before starting therapy (above 55,000),
- poor control of virus while on therapy or other signs of drug resistance, and
- history of opportunistic infections (OIs).

There’s a significant difference between studies looking at a single STI than several of them. Numerous studies used CD4 counts and HIV levels as a guide for when to restart therapy after one STI. Nearly all were done in people who had reached undetectable HIV levels in the last 12 months or longer and CD4 counts above 350 in the last six months.

In most studies, at least 1 in 3 of the volunteers could stay off therapy for at least one year. The average time off therapy for the others ranged from 8–12 weeks. However, it should be noted that people who interrupted their treatment had large drops in their CD4 counts (on average dropping 50%). These decreases could be dangerous for people whose counts drop below 200, especially without proper preventive medicine for OIs.

Also, most studies were unable to consistently measure meaningful improvements in cholesterol and triglycerides in people on STIs. Dropout rates also tended to be higher among those on STIs. This indicates that STIs may actually be more difficult to manage than taking pills every day.

For people who wish to take a break from therapy because of treat-

ment fatigue, certain guidelines can be followed. Because of higher risks for disease progression and OIs, careful monitoring by your doctor is critical during this time. People should check their health care programs (private and public) to ensure that the cost of additional lab tests would be covered if needed.

Testing your HIV level and CD4 count should be done before the STI and three months after it, if not sooner. You and your doctor should decide beforehand what factors would lead you to resume therapy. At a minimum, most people would recommend using the Federal Guidelines as a guide to restart therapy.

Also, drug resistance testing should be conducted when HIV levels are at their highest to determine whether a person should change to a new regimen when and if they resume treatment.

If your CD4 count was ever below 200, or you ever had an OI, it’s risky to take an STI to deal with treatment fatigue. People taking an STI usually see their CD4 counts fall fairly quickly to pre-treatment levels.

Some data show it may be safe for people who started therapy early in

I've taken meds now for five years. I'm really tired of it. I wonder if I can safely take an STI.



their infection to go off treatment safely. Swiss researchers looked at a group of people who began taking HIV drugs when their CD4 counts were over 500. These people had the option to stop or continue their HIV treatment. The researchers found no evidence of harm in the group of people who stopped treatment.

Other recent research suggests the opposite. An analysis from SMART found that people who restarted their HIV meds when the study was stopped continued to have higher rates of heart, liver and kidney problems compared to those on continuous treatment.

People who started HIV treatment with higher CD4 counts are the most likely to be able to stop HIV therapy safely. On average, roughly one-third to one-half of people treated early in their disease who participated in STI research have been able to stay off treatment for months. Some were able to control their HIV levels during the first STI; others needed two or three. For people who started HIV treatment somewhat later, the results have been less promising.

3

Using an STI before starting third line therapy

When a person tries to construct a new regimen which may contain drugs that had failed before, the regimen is often referred to as *third line* or *salvage therapy*. Because salvage also means “to save”, some people call salvage regimens rescue therapy. In this publication, third line therapy describes a new regimen that typically contains four or more HIV drugs, some of which a person may be resistant to.

The theory behind using STIs in this way is to increase HIV’s response to treatments that it had become resistant to. Studies conducted in the early days of HIV therapy found that when a person goes off therapy to which HIV has become resistant, the new virus will rapidly revert to what is called *wild-type*. Wild-type HIV is the strain that reproduces most easily and responds to HIV therapy. The earlier studies found that when wild-type HIV takes over as the

dominant form in the body, a drug that had stopped working could sometimes regain some of its potency.

For this reason, several studies looked at how STIs impact third line therapy. A Barcelona study found

that a three-month STI before starting third line therapy did not provide any advantage. The French gigaHAART study, using a shorter interruption, showed that

people taking an STI had larger reductions in HIV when they started their next regimen than those who started their next regimen without an STI.

San Francisco researchers conducted a similar study using a four-month STI before starting salvage therapy to others who started their third line regimens immediately. In contrast to the French study, these results showed no benefits in viral response to treatment in those who were on the STI. In fact, people were more likely to develop an OI or die.

IN THEORY,
TAKING AN STI BEFORE
STARTING A THIRD LINE REGIMEN
MAY MAKE HIV SENSITIVE
TO DRUGS AGAIN.

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Using an STI to reduce the costs and side effects of therapy

Another form of STI studied was one designed mainly to cut the time a person spent on treatment. This was the basis for SMART, and several other studies. As mentioned, SMART found higher rates of heart and other problems, and importantly poorer quality of life for people on STIs. Another study, where volunteers went off and on therapy every 14 days, resulted in some of them developing drug-resistant virus and losing control of their HIV levels.

Another small study, this time with cycles of seven days off and seven days on therapy, resulted in fewer side effects and better quality of life for people on STIs than those on continued therapy. As well, their HIV levels were well controlled. However, a similar study in Thailand conflicted with these results, so it’s impossible to state for certain whether STIs of this type work.

A final word on STIs

It's fair to say that the trend in research has been solidly against STIs for some time now. While it might be safe for people who began their HIV treatment with high CD4 counts, for most people the research suggest the risks of STIs probably outweigh their benefits.

Some have called for an outright halt to all STI research. Project Inform does not share this belief. The burdens of lifelong treatment are significant, as is the challenge of adherence. If safer ways of managing STIs can be developed, they should be studied.

We also more clearly understand the conditions when taking these treatment breaks can result in problems. However, there simply aren't enough data yet to say that any study will benefit those attempting an STI. Still, there are reasons to remain hopeful and to examine every

We now know
when taking time off
therapy can result
in problems.



piece of new information as the possible thread that will lead us one day to a cure.

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