

Structured Treatment Interruptions



Structured Treatment Interruption Workshop

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The Foundation for AIDS and Immune Research (FAIR), in partnership with Project Inform and Treatment Action Group (TAG), co-sponsored a workshop in Boston at the end of July on structured therapy interruptions. Researchers from around the world attended to discuss preliminary data and plan future studies. People living with HIV/AIDS and representatives from industry and government also attended.

The goals of the meeting were to:

- identify gaps in the research agenda for testing the safety and effectiveness of structured treatment interruptions which meet a minimum of three known objectives across the spectrum of HIV infection;
- develop new study concepts and/or specific studies to fill identified gaps to coordinate a comprehensive research agenda; and
- encourage collaboration to enhance current, planned and future studies to learn as much as possible about the risks and benefits of therapy interruption.

In general, the current goals behind structured treatment interruptions (STI) focus around three basic theories:

- STIs may make it possible to *preserve or strengthen immune responses against HIV*; this is primarily being studied in people with very early infection.
- STIs might *restore a useful degree of sensitivity to anti-HIV therapies* in people who are resistant to several available therapies.
- STIs might give people who are experiencing *treatment fatigue or severe side effects a break from therapy long enough to permit some degree of healing, both physically and psychologically—if it can be done without creating long-term harm in a person's fight against HIV*.

Research and interest in the area of STIs, however, *should not* indicate that stopping therapy, in any of these settings, is so far known to be either safe or beneficial. To the contrary, it could be found that STIs cause undue harm in some or all people. The goal of this research is to identify who (if anyone) might benefit from this approach and to shed light on potential harms of stopping therapy.

Most data presented at the Boston meeting were considered very preliminary and not ready for public distribution. Everyone carefully avoided drawing premature conclusions. Researchers agreed to present

these early data only with the understanding that the forum was closed to the press. Major themes, however, came out of the workshop.

First and foremost, everyone agreed that people living with HIV and their providers should be aware that the benefit of STI has not been established in any setting and that stopping therapy involves numerous potential risks. People considering a therapy interruption are strongly encouraged to do so in the context of a planned study, where intensive monitoring of the immune system and virus is available to minimize risks.

There was at least one anecdote of a patient on effective anti-HIV therapy with full viral suppression who, upon stopping therapy, experienced increases in HIV levels and decreases in CD4+ cell counts. Upon re-starting therapy, this individual never again achieved optimal viral suppression with a potent anti-HIV therapy regimen. While no broad conclusions can be drawn from this single case, it underscores the potential risks of stopping therapy.

Secondly, workshop participants agreed that clear messages of what an STI is and is not should be clearly conveyed to people living with HIV and their health care providers. Stopping therapy for one or two days (what is commonly meant by a *drug holiday*) every now and then is neither strategic nor structured and will almost certainly increase the risk of developing anti-HIV drug resistance.

A Structured Treatment Interruption will include stopping therapy for some extended and defined period of time (usually at least a month or more). Depending on the goals of the STI, re-starting therapy may sometimes be done according to a specific time frame (e.g. start after one month) or be based on certain viral load or CD4+ cell count changes.

Finally, based on preliminary data from observations and studies, even if therapy interrup-

Table of Contents

Additional Information 4/99	3
New Information 8/00	6
New Information 10/00	8
New Information 8/01	9



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Structured Treatment Interruptions

tions prove useful in some settings, they will not be useful for all people. In every setting, observations have been made of possible harm from therapy interruptions. These include:

- CD4+ cell count losses that might not be regained after re-initiating therapy;
- viral load increases that might not be brought back under control;
- the risk of resistant virus emerging and taking hold after stopping therapy; and,
- for those with resistant virus, lack of a shift toward a predominant drug-sensitive (wild type) form of virus.

For a few people, preliminary evidence suggests improved immune responses against HIV after an STI. Among people with multi-drug resistant virus, some seem to show a shift toward drug sensitive virus after stopping therapy. For people who can't fathom a lifetime of anti-HIV therapy, at the very least some information on long-term consequences is necessary to enable informed decision-making. With all these considerations, STI research proceeds with caution.

Commentary

The meeting in Boston culminated with a review of ongoing efforts and a list of recommendations by the scientists for modifying current studies, initiating specific studies and exploring existing data sets to gather more information on STIs. This would include developing an STI *case definition* and then applying that definition to large observational studies.

In addition to examining the experiences of people who may have already stopped therapy, the *case definition* can be applied and additional monitoring and data collection could take place. To achieve this goal, a Task Force is being created, including representatives from large studies around Europe and North America.

Project Inform has previously written on structured therapy interruption. For additional information, call Project Inform's National HIV/AIDS Treatment Hotline.

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The Basic Message

- Learn about HIV testing options and choose one that fits your needs! Be sure your privacy is protected!
- If you're positive, don't panic. If you make your health a priority, chances are you will be reasonably healthy for many years.
- Learn about your healthcare options and local support services.
- Get a complete physical and blood tests for CD4+ cell count & HIV level. Repeat quarterly and watch for trends. Women should get GYN exams and Pap tests every six months, more often if abnormal.
- Work with a doctor to develop a long-term strategy for managing HIV disease.
- If the CD4+ cell count is below 350 or falling rapidly, consider starting anti-HIV therapy. Test at least twice before taking action.
- If anti-HIV therapy fails to reduce your HIV level below the "limit of detection" or below 5,000 copies within 3–6 months, consider a different or more aggressive therapy.
- If the CD4+ count trend stays below 300, consider treatment for preventing PCP. If it stays below 200, start treatment for preventing PCP (if you haven't already done so) and reconsider anti-HIV therapy if not on one. Learn about drug interactions and preventive treatments for opportunistic infections.
- If you started preventive therapies and your CD4+ cell count rises in response to anti-HIV therapy, ask your doctor whether it might be safe to stop certain preventive therapies.
- If your CD4+ cell count stays below 75, consider more frequent blood work—perhaps even monthly. Consider therapies for preventing MAC/MAI and CMV.
- Regularly seek support for your personal, spiritual and emotional needs. It takes more than medicines to keep you well.

HELPFUL READING FROM PROJECT INFORM

Day One; Building a Doctor/Patient Relationship; Making Decisions; and Anti-HIV Therapy Strategies

Structured Treatment Interruptions Addenda Sheet



Pulsed Therapy and Structured Interruptions of Treatment

reprinted from
P I Perspective 27, April 1999

The first approach, best described as a form of pulsed or intermittent therapy, aims at stimulating a stronger immune response against HIV. Researchers speculate that this will empower the person's own immune system sufficiently to control HIV replication without the continual use of anti-HIV drugs.

The second approach, a type of structured interruption of treatment (or *drug holiday*), can take a number of different forms. On one level, it can be little more than taking people off therapy, after successfully suppressing HIV for a year or more, to simply see what happens. On another level, it assumes that measurable HIV replication will begin again sometime after treatment is stopped but tests whether this is necessarily bad. This kind of therapy interruption compares the benefits and drawbacks of constantly staying on drug therapy against those of periodically taking time off.

While each approach is getting serious attention as a research project, no one suggests that we know enough to recommend these strategies for anyone's personal use. They are experimental strategies whose overall harm or benefits are simply not yet known.

Pulsed Therapy

The *pulsed therapy* approach assumes that people should always maintain viral loads below the limit of detection to be healthy. In this approach, a person who has been treated since the earliest stage of HIV infection is taken off all therapy once viral load remains undetectable for some pre-determined length of time, perhaps six months to a year or longer.

While off therapy, the person would be carefully monitored for the return of measurable virus. If and when viral load becomes detectable again, the person would be put back on aggressive antiviral therapy. Typically, this results in the rapid disappearance of measurable viral load for the second time. After another pre-determined period on therapy, the cycle is repeated—taking the person off therapy while monitoring for return of measurable viral load.

Research has begun on two new strategies for long-term treatment of HIV disease. Although both theories involve taking people off treatment in some way, they have different goals and expectations. These two strategies are known as *pulsed therapy* and structured interruptions of treatment (sometimes called *drug holidays*).

An interesting phenomenon has been noted in a few cases of pulsed therapy, either as a structured experiment or simply as a matter of patient choice. The first time a person went off therapy, viral breakthrough (return of measurable levels of viral load) occurred after a relatively short period of time, ranging from a few days to a few weeks. After restarting therapy, viral load plummeted again, below the level of detection. Then after staying on therapy for varying periods, they stopped therapy a second time. This time, viral load remained undetectable for considerably longer than the first time, despite the lack of continued treatment.

A few people who cycled on and off therapy twice now have no return of measurable viral load, while off therapy, for periods ranging from 6 to 21 months. Researchers theorize that each cycle of pulsed therapy led to a progressively longer period for the body to fully control viral replication without the help of anti-HIV drugs. In a few cases, people treated with two or more cycles of pulsed therapy have been able to control viral replication with continued therapy for as long as two years (and still counting).

It is hard to draw any clear conclusions from these observations since nearly every patient involved has done something differently from others. For the most part, they were simply choosing to go on and off therapy for personal reasons. They each had varying times on and off therapy, and varied considerably in how quickly they returned to treatment when viral load reappeared. Researchers carefully studied the consequences of their actions, and were understandably surprised by the results.

What is Going on Here?

Researchers at the Aaron Diamond AIDS Research Institute and the RIGHT group have proposed a theory: the periods in which a person is taken off therapy and viral replication is allowed to resume may be beneficial. They suspect that the returned viral load is acting somewhat like a vaccination. HIV is aggressively presented to the immune system once again, stimulating a more powerful immune response.





Structured Treatment Interruptions Addenda Sheet

This makes some sense because we know when people use antiviral drugs that work for them, HIV is no longer being presented to the immune system. In theory this might allow the normal immune response against HIV to gradually decline. In turn, occasional interruptions in therapy as proposed here may reintroduce HIV into the immune system, thus stimulating a renewed immune response against the virus.

If this is indeed what is happening—and there is promising initial evidence that it is—this approach might be used to help people become less dependent on anti-HIV drugs and more reliant on their immune systems for control of HIV. Such a response might resemble the tiny percentage of HIV-infected people known as “long-term non-progressors.” Such people appear able to control HIV replication without the use of anti-HIV drugs and usually have an abnormally strong immune response against HIV, very similar to that being seen in people who are treated with pulsed therapy.

Still, pulsed therapy is far more theory than reality at this point. The only thing known for sure is that a few people seem to respond in a way that resembles the theory, including the widely discussed “Berlin patient” reported by Dr. Franco Lori’s group. Studies of many more people are necessary and already planned.

Even proponents of pulsed therapy warn that there is no evidence so far that this will work in typical, chronically infected people. The case reports noted have all come from people who began anti-HIV treatment extremely early after initial HIV infection. Such people are known to still be able to mount strong HIV-specific immune responses.

In contrast, many people with more typical chronic HIV infection (where treatment began six months or later after initial infection) frequently show no evidence of this kind of immune response. Some researchers believe that the natural capacity for this immune response is lost fairly early in the course of HIV infection. Thus, for now, the only realistic target for pulsed therapy research is in people treated from the earliest or *acute* stage of HIV infection, also known as *primary infection*.

Structured Interruptions of Treatment

The second strategy, *structured interruptions of treatment*, responds to a different set of goals and concerns. It assumes that people taken off therapy are likely to see a rebound of measurable viral load. What’s not clear is how high the rebound will go and whether it will initially shoot up and then fall back to some lower “set point” level (a viral load level lower than that seen before the person began therapy).

In this approach, people are not automatically put back on antiviral therapy the minute viral load becomes detectable again. Instead, a person stays off drugs for awhile despite the presence of detectable

viral load. So then a question begs to be asked: “Is the harm caused by a return of measurable viral load a greater or lesser danger than constant therapy, and all the attendant side effects and development of resistance to treatment?”

What is the harm of constant therapy? Even if viral load remains undetectable for long periods, there are many possible long-term consequences to constant therapy. The risks of cumulative side effects and tissue damage are perhaps the greatest concerns. This encompasses problems such as fat redistribution (*lipodystrophy*), high cholesterol and triglycerides, diabetes, heart disease and liver problems. These come in addition to the side effects of the older generation of drugs, such as pain in the feet, legs, and/or hands (*peripheral neuropathy*), red and white blood cell suppression (*anemia*), pancreatitis, rash, etc.

Suppression of viral load through anti-HIV drug therapy can produce improvements in overall health and prolonged survival. The challenge is to find the best possible balance—to get the most from therapy without experiencing its down sides which includes the emergence of possible long-term negative effects. For some, this might mean periodically structuring time away from the drugs, for the body to recover from side effects. Some researchers believe that periodic interruptions of therapy may not only be possible, but necessary to help people live out a normal lifetime with HIV disease.

Since we only have about three years of experience treating people with today’s potent three- and four-drug combinations, it remains highly uncertain just how long people will tolerate constant use of the drugs. Few researchers, however, have enough confidence in the drugs to believe that people could use them continually for the 20 to 50 years needed to live a normal life span.

In contrast, we have long known that most people can tolerate long periods of untreated HIV infection without irreparable harm. On the average, people using no treatment at all can usually go for roughly ten years without progression to AIDS. For some, this period is longer, for others it’s shorter. Part of the goal of treatment interruptions is to give some of this time back to people, in effect letting them coast along with the virus for awhile. They then return to medication only when signs of disease progression become apparent. Similar strategies employing periodic interruptions of treatments are routinely used for other chronic illnesses that require long-term therapy.

Another concern caused by constant therapy is simply the weariness it causes people. The longer many people remain on constant therapy the more likely they begin to miss doses or take short unstructured drug holidays. That can do harm by encouraging development of viral resistance. If structured interruptions of treatment can be of-

Structured Treatment Interruptions Addenda Sheet



ferred to people in ways that are unlikely to hasten resistance, with little or no downside, commitment to proper use of therapy may increase during those periods when people use the drugs. This approach offers a compromise, but hopefully one that will provide long-term benefits.

Since we know that short or frequently repeated drug holidays speed the development of viral resistance, the model here focuses not on casual weekend holidays but rather on carefully planned, structured interruptions. An additional benefit already demonstrated in initial studies is that the break from drugs may help a person's virus increase its sensitivity to some previously used drugs. In theory, this might restore their ability to use drugs to which they had developed resistance. This would greatly enhance their options for future therapy.

Structured Treatment Interruption Research Programs

Treatment interruption programs are just beginning and plan to start with people who have undetectable levels of HIV for six months to a year or more (though this may change after more experience is gained). After that, the approaches vary. Four are outlined below.

1. Some plan to take people off therapy and monitor them to measure the immune and viral responses when therapy is stopped. Here, a person will usually restart anti-HIV therapy as soon as viral load again becomes measurable. The hope is that this may identify the people in whom this approach would be safest and most productive. Such a study is underway at the National Institutes of Health (NIH).
2. Some plan to take people off therapy and monitor them, but not immediately restart therapy if viral load reappears. These seek to determine whether viral load will rise to and maintain a high level peak, perhaps even higher than before the person started therapy. Or they may find that such a peak is followed by a gradual reduction back to a lower and stable level (a *set point*). If viral load comes back down to a modest set point, researchers may choose to withhold therapy as long as viral load remains stable with no major decline in CD4+ cell counts. Such a study is planned at the NIH.
3. Still another approach, perhaps targeted to people with more advanced disease or those who have developed resistance to most available drugs, will keep people off therapy, regardless of viral load, for a period of a few to several months. At some fixed point, anti-HIV therapy will be restarted. The hope of this approach—sometimes called a *washout period*—is to see if the time off allows the virus to return to its natural state (often called *wild-type virus*) and regain sensitivity to previously used

drugs. Restarting therapy with a mix of old and new drugs might then kick off another long period of effective viral control.

4. Another approach takes people off therapy for a fixed period, such as two to six months or longer. This is done to let the body heal from drug side effects and rest from the constant rigor of daily therapy. Either at a fixed point in time, or after some permissible level of CD4+ cell count decreases and/or viral load increases occur, the person may be put back on anti-HIV therapy. If successful, this could theoretically be repeated over many years or even throughout a normal lifetime. The hope is that the mix of time on and off therapy might lead to the increased tolerance of therapy and the longest possible life expectancy for HIV-infected people, short of an outright cure.

Commentary

Many important new strategies for the use of anti-HIV therapy must be tested. Until recently, most research focused only on how well individual drugs worked over a period of a few months to a few years. Many people are already coming to the end of the hope offered by such narrowly defined, product-driven strategies.

Today, new strategy research on pulsed therapy or structured interruptions of treatment may well be what's needed. Such research may extend our knowledge of how to best get HIV-infected people through a lifetime, or at least well into the new millennium and not just the next few years. *These strategies should not yet be considered recommendations for medical practice, nor should the fact that they are being tested encourage people to try them on their own.*

We don't have enough information to know whether these procedures will help people live longer or instead cut precious time off what a person has left. If we knew, there would be no need for the research. The right approach is in the context of well-designed studies. Self experimentation seldom leads to knowledge, since there is never a way to know whether what happens to an individual is due to the strategy or drugs used, or whether it is a mere coincidence.

The next several months will see a rash of new strategy studies asking whether and how it might be possible for people to get off therapy, at least temporarily. The more people who volunteer to participate in these studies, the sooner we will know what is and isn't possible.

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Structured Treatment Interruptions Addenda Sheet



The Latest on Structured Treatment Interruptions

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During unstructured interruptions, people are not closely monitored for viral load and CD4+ cell counts. The interruption follows no particular plan. However, people taking STIs are usually tested very frequently for viral load, CD4+ cell count and sometimes resistance. This way, when they're ready to restart therapy, the decision can be made based on data and the achievement of goals while minimizing the risks.

Early results have recently been reported from several STI studies, but it's still too early to know how safe or effective an STI treatment strategy may be. STIs are now being studied in three different scenarios:

1 Primary or chronic/established HIV infection in people with well controlled viral replication.

The goal in either group is to improve the natural immune response against HIV, hopefully making it possible to control viral replication with less aggressive treatment. In primary infection (someone infected very recently, from a few days to a few months), the body usually mounts a vigorous immune response against HIV. Over time, though, this response often fades. In chronic/established HIV infection (someone living with HIV for at least a year), this natural immune response is often very weak or missing altogether. In both cases, the decline is thought to be associated with the success of anti-HIV therapies, which dramatically reduces the amount of new virus being produced. Because of this lowered viral activity, the immune system sees less and less of the virus and thus does less to mount a defense against it. By periodically permitting HIV to replicate, an STI permits the immune system to once again "see" and react against the virus, perhaps resulting in a strong natural anti-HIV response. See Fig. 1, next page.

2 Chronic/established HIV infection in people who have developed resistance to all or most of the available antiviral drugs.

The potential goal of STI here is to replace drug-resistant virus with non-resistant virus, called "wild type." This might restore a person's

interest in structured treatment interruptions (STIs) (sometimes mistakenly called drug holidays) continues to increase. Though research in this area is relatively new and so far inconclusive, many people are already taking unplanned or unstructured treatment interruptions due to problems with drug side effects, treatment failure and adherence problems.

sensitivity to drugs that had previously become ineffective due to resistance and allow the drugs to work again, at least temporarily.

3 Chronic/established HIV infection in people who have become physically or psychologically intolerant to currently available anti-HIV drugs.

The goal of STI in this context is give the person—mind, body and spirit—a chance to rest and recover from the stress of anti-HIV therapy. Some people develop bothersome side effects to anti-HIV drugs, either quickly or after years of use. Side effects such as liver and kidney problems can become serious, even life-threatening, and limit a person's ability to use the drugs. Other effects, such as *lipodystrophy*, may have unknown long-term consequences in addition to their visible impact. Many also develop psychological obstacles. Over time, it gets more difficult to adhere to the regimen. Whether the cause is physical or psychological, intolerance of the drugs will cripple their ability to aid in the fight against HIV. While these factors may affect only a portion of people on treatment at any moment, over time they are likely to effect everyone who hopes to live out a normal life span with HIV.

STIs in Scenario #1

Primary Infection: A Boston study followed 15 people with primary infection treated with HAART for over a year. Seven took an STI and their viral loads and CD4+ cell counts were measured weekly. Their immune response to HIV, or HIV-specific cytotoxic lymphocyte (CTL), was also measured. HIV-specific CTLs are cells that target and destroy HIV-infected cells.

At the start of their STIs, the seven participants had low level CTL responses and undetectable viral loads. During the STIs, all saw their HIV levels increase, as expected, so they restarted HAART. Everyone also experienced increases in HIV-specific CTL responses after the STI.

Three of the seven went on to a second and third cycle of STI, and with each cycle they had higher HIV-specific CTL responses. After each STI, the returning levels of viral load were lower than in the previous



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This Addenda Sheet represents information that is new and has not yet been incorporated into a Fact Sheet or Discussion Paper.

Structured Treatment Interruptions Addenda Sheet



STI and it often took longer for viral load to reappear. This suggests that the improved HIV-specific CTLs were at least partly effective in controlling HIV replication.

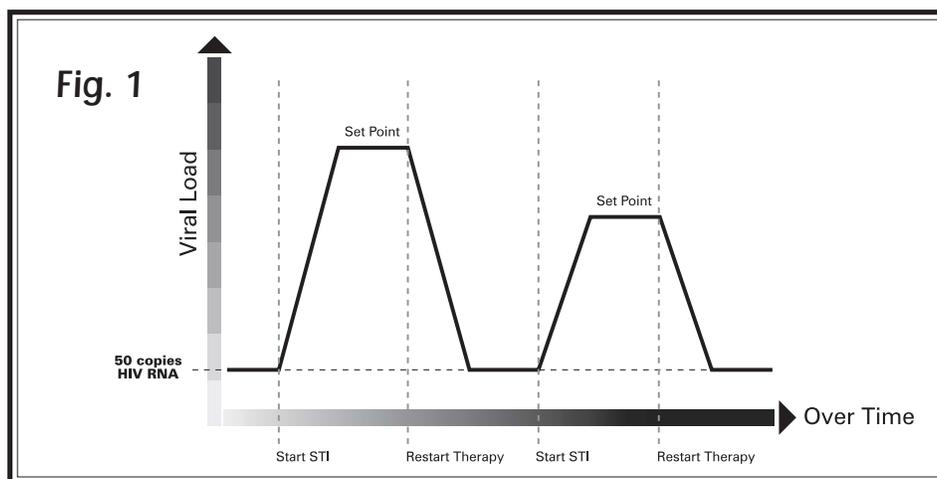
Chronic Infection: A Barcelona study followed 26 people with HIV levels below 50 copies for over two years. Fourteen continued on HAART while the other twelve took an STI. Among the twelve, five had two courses of interleukin-2 (IL-2, Proleukin) while on HAART; the other seven took their same HAART regimen as before their STIs. Those on STIs were closely checked for viral load (every two days to determine the rate of increase in HIV levels).

This study was designed for people to restart HAART either after 30 days of interruption or when their viral loads went above 3,000 copies HIV RNA. They then took their HAART regimens for three more months before taking another STI.

During the first STI, two had no detectable HIV levels during the 30-day period. However, on the second STI, only one person continued to have undetectable (below 50 copies HIV RNA) HIV levels during the 30 days off therapy. In most, HIV levels increased after 14 or 15 days off therapy during the first and second STI. The percentage of CD4+ and CD8+ cells did not change during the STIs. There was no difference between people who used IL-2 and those who did not.

Early results found little or no improvement in the immune response to HIV and all participants experienced significant increases in HIV levels during STIs. However, it is possible that more cycles of STIs are needed before the immune system can mount a stronger response against HIV.

The largest study to date involving STI is the Swiss-Spanish Intermittent Treatment Trial, currently enrolling 120 people with CD4+ cell counts above 300 with viral loads under 50 copies HIV RNA for at least six months. The study design involves alternating between two weeks off HAART and eight weeks on, for a total of four cycles. After 40 weeks, anti-HIV therapy will be stopped indefinitely until a person's viral load increases to 5,000 copies HIV RNA, when therapy is then restarted.



Early results from this study involve 96 people who had one STI, 54 people a second and 23 a third STI. All had viral load increases during the STI. So far, there's no indication that the viral load set point is lower or that there are any significant changes in CD4+ cell counts with each STI.

All of these studies have found that when people restart HAART, viral loads decrease and, in almost all cases, go back to under 50 copies HIV RNA. This suggests that participants are not developing anti-HIV drug resistance. However, people should be cautious with efavirenz (Sustiva) and nevirapine (Viramune) when undertaking an STI since these drugs remain in the bloodstream far longer than other anti-HIV drugs. Researchers recommend that they be stopped two to three days before stopping other drugs when initiating an STI.

STIs in Scenario #2

A Frankfurt study of people who had developed resistance to most or all currently approved anti-HIV drugs reported that three-quarters of them shifted from multi-drug resistant virus to wild type virus during the STI. Groups in London and San Francisco have duplicated this observation.

The San Francisco study followed 18 people who had developed resistance to protease inhibitors and nucleoside analogue drugs. During the STI, all experienced decreases in CD4+ cell counts (an average of about 100 cells) and increases in HIV levels (about a ten-fold increase). Sixteen of the eighteen shifted from protease inhibitor-resistant virus to protease inhibitor-sensitive virus during the STI, although seven retained some degree of resistance to the nucleoside analogue drugs.

However, when using extremely sensitive techniques, researchers found that about half the participants had very low levels of drug-resistant HIV. In other words, they did not find protease inhibitor-resistant virus in blood when using standard tests but did find it when using extremely sensitive tests. Since no participant had restarted therapy when these results were presented, the significance of these findings is unknown.



Structured Treatment Interruptions

STIs in Scenario #3

Little research has yet been conducted on the use of STIs for combating physical or psychological intolerance of drug regimens. However, this scenario probably reflects the most common form of “unstructured” interruption in which people simply stop treatment to recover from side effects and give themselves a rest. There is some work underway to create observational databases of the experiences of such people.

Commentary

These early studies primarily looked at the potential risks rather than the benefits of STIs. They suggest that, at least in the short-term, there's a low risk for developing drug-resistant HIV. However, decreases in CD4+ cell counts to pre-treatment levels and increases in HIV levels in some people suggest the need for frequent and careful monitoring, particularly if the resulting CD4+ count falls into the

ranges with increased risk of opportunistic infections (under 200 for some OIs, under 100 for others). When this occurs, people should resort to earlier strategies of treatment, such as Bactrim for preventing pneumocystis pneumonia.

Numerous STI studies are planned for the near future. They will explore different lengths of STIs and different lengths of time on therapy as well as possibly using therapies, like IL-2 and therapeutic vaccines, that affect the immune system.

More results will be available soon that will help determine the role of this strategy in treating people with HIV. Project Inform, the Foundation for AIDS and Immune Research (FAIR) and the Treatment Action Group (TAG) will convene a second workshop on STIs in the fall of 2000. At this meeting, new results, ideas and observations will be discussed and incorporated into future studies.

New Developments in STIs and SIT

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As more and more researchers have come to acknowledge that current treatments are incapable of eradicating HIV, growing attention has been focused on structured treatment interruptions (STIs) and structured intermittent therapy (SIT). New strategies will apparently be required to deal with issues around long-term use of anti-HIV therapies, including side effects, adherence, treatment fatigue and the lifetime costs of the anti-HIV drugs. If ways can be found to make treatment a temporary or intermittent requirement, many of these problems might be resolved.

Most of the STI studies so far have been small and exploratory in nature, primarily seeking to determine the safety of such a strategy. Results are emerging from one larger European STI study, which is looking at the safety as well as the effectiveness of this kind of approach to treatment.

A slight variation on previous studies, called SIT (Structured Intermittent Therapy), seeks to determine whether carefully planned bursts of intermittent therapy might sustain viral control while reducing the cost of treatment. Early results of two such studies have been reported by the National Institutes of Health (NIH). The first study enrolled eight people who started on cycles of seven days on anti-HIV therapy [d4T+3TC+ indinavir (Crixivan) + low dose ritonavir (Norvir)] and seven days off therapy. The seven-day cycle was selected because previous studies have shown that—among people receiving optimal anti-HIV therapy—it generally takes at least seven days before viral loads climb back up to detectable levels over 500 copies HIV RNA after therapy is discontinued. “Failure” in this study is defined as having a viral load above 500 copies HIV RNA on two consecutive

tests or more than a 25% drop in CD4+ cell counts on two consecutive measurements.

After 14 weeks, seven out of the eight participants continued to maintain viral loads below 500 copies; the one person who did not had forgotten to take his medications with him on vacation. While these results are very preliminary, they are encouraging and warrant further exploration.

The second SIT study only enrolled three people on a cycle of two days on therapy (same regimen as above) and five days off. All participants had maintained viral loads below 500 copies for at least six months before starting the new treatment cycles. Results from this study have not been as encouraging with only one person maintaining viral loads below 500 copies HIV RNA after 14 weeks. The other two participants both had detectable viral loads at some point during the off therapy period. However, once anti-HIV therapy was restarted both had viral loads return to undetectable levels. Based on the disappointing results, this study will not be continued.

Structured Treatment Interruptions Addenda Sheet



Further preliminary results have been presented from the Swiss Spanish Intermittent Treatment Trial (SSITT). We previously reported on this ongoing study in *PI Perspective* 30. The study includes 122 people with viral loads below 50 copies HIV RNA and CD4+ cell counts above 300. It is evaluating cycles of eight weeks of anti-HIV therapy followed by two weeks off therapy, for a total of four cycles. At the end of the four cycles (week 40) everyone stops anti-HIV therapy, which is then only restarted if viral loads rise above 5,000 copies at week 52.

During the first two-week interruption, 28 people had no detectable viral load, in other words all had less than 50 copies HIV RNA during the two weeks off anti-HIV therapy. However, fifteen people had a high rebound in viral load (reaching over 100,000 copies HIV RNA) during the interruption. A preliminary analysis of the first 56 people who completed all four cycles showed no general trends in patterns of response. Almost equal numbers of people had widely differing responses during each interruption (some had roughly the same viral load levels during each interruption, others had viral loads that increased with each interruption, still others had viral loads that decreased with each interruption). Of note, there were eight people with no viral load rebounds, whatsoever, during the four interruptions. There is no known reason why these eight people responded

differently than the rest of the group. The final results from this study are expected by the end of this year.

Another ongoing STI study is being conducted at the NIH. Seventy people are participating with half taking an STI and the other half taking continuous anti-HIV therapy. The STI cycle for this study is two months on and one month off therapy. Early results suggest that there is a trend towards a lower rebound of viral load with each interruption. These results are, at least for now, different than what has been seen in the SSITT study.

Commentary

The results from NIH's small SIT study are certainly encouraging but it must be stressed that the study is too small to draw any firm conclusions. If these results are confirmed in larger studies, they suggest that it may be possible to only have to take anti-HIV therapies every other week, which might help with adherence, may reduce the likelihood of developing side effects and will cut the cost of treatment in half.

Further analysis of the results from the SSITT study and the STI study from the NIH is needed to try to understand whether there is a reason some people seem more likely to benefit from this kind of treatment strategy or whether their success is merely a coincidence.

Highlights from IAS 2001

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Structured Intermittent Therapy

More data were presented from the National Institutes of Health structured intermittent therapy study. Early data were reported in *PI Perspective* #31. Ten people were started on seven days of anti-HIV therapies [d4T+3TC+indinavir (Crixivan) + low dose ritonavir (Norvir)] followed by seven days off. The seven-day cycle was chosen because in previous studies, including people who received optimal anti-HIV therapy, it generally took at least seven days before viral loads climbed back up to detectable levels (over 500 copies/ml HIV RNA) after a therapy interruption. All ten people who participated in this study had taken and responded

well to therapy before. As a result, at the start of the study, they had an average CD4+ cell count of about 800. Five volunteers have been in the study for more than six months and an additional three for more than a year. All have undetectable viral loads (below 500 copies/ml) although some have had intermittent blips. An interesting observation was that people who stopped therapy for ten days or longer were more likely to have a blip in viral load. Everyone experienced a significant decrease in triglyceride and cholesterol levels, commonly increased due to the protease inhibitors, especially ritonavir. Further, there have been no indications of resistance developing to any anti-HIV drugs nor are there signs that HIV is replenishing the sites where it likes to hide, such as the lymph nodes.