Happy Holidays?

December 1999's "poor adherence" is January 2000's "pulsed dosing." PWA pipe dream? No. Project Inform founder Martin Delaney explains why the first thing on your wish list should be Structured Treatment Interruptions.

December 1, 1999 By Martin Delaney

Let's start with a quick quiz:

1. What is a "drug holiday"?
A. a euphemism for forgetting to take your pills
B. a weeklong gay circuit party
C. a poor choice of words to describe a new AIDS-research experiment
D. the typical POZ reader's Saturday night

2. What is "STI"?
A. a revamped version of Reagan's Star Wars program
B. the Search for Terrestrial Intelligence
C. a carefully planned interruption in anti-HIV treatment
D. the epidemic of Sexually Transmitted Itching, a puzzling new STD

Answers: 1. (C); 2. (C) If you answered correctly, congrats -- you're in the zone when it comes to keeping up with treatment strategies. If you got it wrong, you may have a sense of humor, but you need to listen up. What you're about to read just might affect how long -- and how well -- you live.

HIVers have played fast and loose with medication schedules for as long as they've had medications to schedule, but the advent of protease inhibitors in 1996 set off alarms aplenty: Get with the program, or else drug resistance -- the Darth Vader of the HIV-treatment scene -- will get you. Repeatedly taking a night off to party or giving in to just plain sloppy adherence is nearly certain to decrease your HIV's vulnerability to the drugs (see "It's 10 O'Clock. Do You Know Where Your Meds Are?"). The harm from such practices is a simple equation of biology, evolution and math.

Yet it's equally clear that the demanding nature of the new drug combos, their sometimes severe side effects and the life sentence they impose make rigid adherence impossible for many. Eager for an escape-hatch from this Catch-22, bold researchers in the United States and Europe are launching new studies to find whether taking a break from therapy now and then is safe or even

beneficial. Since interest in the therapeutic potential of a planned, or "structured," "drug holiday" is by no means a retreat from earlier admonitions against missing doses willy-nilly, the consensus is that the experiments need a different name: ergo, Structured Treatment Interruption, or STI, the first snappy AIDS acronym of the new millennium.

To give credit where due, the impetus for much of this hotly debated research comes from observations of what HIVers have done themselves -- against the advice of the pros. A January 1999 POZ article by this writer advocating STI research set off a lot of Internet noise about a subject brewing in the background. Many HIVers were already concluding that no matter the lab-test benefits, taking so many drugs so many times a day and putting up with the roulette wheel of side effects was something they could not and would not do for the rest of their lives. Yet this was the only option offered to them. At the same time, intriguing anecdotal reports were surfacing that some had succeeded in maintaining nearly complete viral suppression after going off therapy altogether. And chat rooms were buzzing with reports of HIVers who had gone off therapy for years, based on how they "felt," with apparently beneficial results.

Of course, protests from the other side were deafening. Like schoolmarms who had caught the boys comparing the size of their dicks in the locker room, some researchers and physicians reacted with horror. "Go off therapy now," they warned their patients," and you'll throw away everything you've gained in the last three years. And you won't get it back." Terrified at the prospect of declining sales (and, they insist, worried about patient safety) Glaxo Wellcome rushed a new ad campaign into print, decrying "drug holidays" as destined to do harm no matter how they are done. AIDS service organizations scrambling to send a coherent adherence message to their minions felt that the community experimentation was pulling the rug out from under them. Since then, promising early study results have been publicized, and a small Strategic Treatment Interruption conference was hosted by activists last July. Today, more than a dozen STI studies are either underway or upcoming, all designed to answer the following three questions. (It can't be stated too strongly that, for now, these are primarily hypotheses for research, not recommendations for treatment strategy.)

Can STIs strengthen the immune response against HIV?

***Hypothesis 1** is that HIV itself can be made to function like a vaccine: Theoretically, by going off therapy, you let your suppressed virus come roaring back for a bit, forcing your immune system to react to HIV's full force. A few cycles of such on/off treatment, or "pulsed doses," could produce an immune response potent enough to control HIV replication without drugs. Where did researchers ever get such a subversive idea? Simple. A few HIVers, such as researcher Franco Lori's "Berlin Patient," followed this course on their own, and then lab studies showed that each pulsed dose boosted their anti-HIV immune response. After first achieving undetectable viral loads, these frisky folks stopped their drug regimens -- for a variety of reasons -- and their virus became measurable again in days or weeks. So they jumped back on their combos until their HIV once again withered below measurable levels, and then they stopped using again. This time it took longer for the virus to return. After a third on/off cycle, some lucky HIVers still have undetectable viral loads two years later sans drugs.*

Can STIs restore effectiveness to drugs that HIV has developed resistance to?

Hypothesis 2 *is every bit as radical as the first. Since scientists have long sworn that HIV drug resistance lasts forever, it was a shock when German researchers, motivated by their own curiosity and their patients' preferences, reported that some HIVers who took a holiday from all antiretroviral therapy for a month or more saw their drug-vulnerable virus make a comeback. The docs, led by Veronica Miller, MD, launched a trial: One group of multidrug-resistant HIVers were immediately given a new Godzilla five-to-nine-drug regimen; the other group took a break for an average of two-plus months before facing the big lizard. Old theory predicts a similar outcome for both -- mostly abysmal failure -- or that the HIVers who delay the drugs would do even worse. But surprisingly those who went on holiday proved more likely to have their viral levels fall below the level of detection once they were back on treatment -- and the HIV remained suppressed for eight months or longer. Perhaps the most surprising finding was that two-thirds of the holiday group showed evidence of a reversal from drug-resistant to drug-sensitive virus. Can everyone be induced to overcome resistance in this fashion? Or is this effect only temporary? are questions that current studies seek to answer.*

Can STIs offer a reasonably safe haven from treatment fatigue and nasty side effects?

As more people are overwhelmed by toxicities, incapable of adherence or just plain weary of the endless use of drugs, they need to know as much as possible about how the risks and benefits -- both physical and psychological -- of going off treatment for a while compare to those of staying on. ***Hypothesis 3*** *focuses on safety, not benefits: There is no assumption that HIV will act like a vaccine or that time off will restore drug sensitivity. Such results would be pure gravy. All researchers and patients want to know is if an STI does more harm than good. Will viral load go up while off therapy? Almost certainly. Will it go back down when therapy is restarted? Unknown. Will CD4 cell levels drop? Probably, but not necessarily. Will the risk of opportunistic infections reappear? Maybe. But we need hard data.*

Too Little Information

Are STIs anything more than just a PWA pipe dream?

Anecdotal evidence from the case of the Berlin Patient and other HIVers studied by David Ho's team in New York City and Bruce Walker's in Boston seem to support ***Hypothesis 1*** *-- that pulsed therapy results in longer intervals between the return of viral load. But beware -- these are outcomes of a few, self-selected HIVers. We don't know how many others may have tried the same thing without getting the same results. More important, these HIVers all started therapy very soon after initial infection and are far more likely than the average HIVer to still have the capacity to mount a strong immune response against HIV. Further, they may just happen to be among the lucky few "long-term nonprogressors" who can thank their genetic makeup or other unique characteristics -- not their STIs -- for their drug-free viral suppression. Clinical trials are up and running in the U.S. and Europe to determine whether STIs can cause this outcome in a controlled, predictable way. Researchers worried about low recruitment due to fears about going off therapy report that people are lining up to enroll. Despite the fact that such studies fly in the face of years of conventional wisdom, neither the FDA nor institutional review boards have posed obstacles to*

the research. Except for the aforementioned Glaxo ad, drug companies have remained largely silent, perhaps because anything they say will be viewed as self-interested.

The evidence for ***Hypothesis 2*** *-- that STIs might restore sensitivity to drugs that had previously succumbed to resistance -- seems more compelling, though still not conclusive. Die-hard virologists question whether the return to drug-vulnerable "wild type" virus seen in the German patients is true for all the virus in their bodies (it's unlikely that mutated forms of HIV disappear completely). If not, resistant virus will likely recur. However, many HIVers don't give a damn about such microbiological esoterica. What they care about is whether a treatment break improves their chances of responding a second time to the old drugs or increases the durability of this response. So far, the German observations suggest they do, though these are less than reliable predictors of what will happen when others try the same thing. New studies should provide clear answers within a year.*

Hypothesis 3 *-- that STI offers much-needed R and R from drug fatigue and side effects without unrecoverable advances by HIV -- has little evidence to support it. Yet it is likely to be tested "at home" much more often than the other hypotheses because so many people feel that continued constant therapy isn't a realistic choice. Such HIVers eyeing STIs simply want a break: to let their livers heal, their tummies shrink, their diarrhea stop. Wanting it, though, is no proof that it will. No one yet knows how long a treatment break must be in order to reverse drug-related harm. In theory, almost any side effect can be expected to lessen, but until serious data is collected, this remains in the category of "hope." And this hypothesis will be the hardest to test. Truly meaningful studies are bound to take a long time because "clinical events" -- disease progression, death, improvement in damaged organs -- happen slowly. Both HIVers and their docs will have to resist the impulse to panic the moment viral load goes up or CD4 cell counts go down. For now, though, there are no controlled trials on the drawing board. Yet it may be possible to tease answers out of data from large numbers of people sharing their medical histories. To this end, the July STI conference called for the creation of a large observational database of people self-administering STIs. Stay tuned.*

STI is Risky Business

In addition to the dozen or so clinical studies in the works, word has it that many HIVers are conducting their own private STI tests of hypotheses 2 and 3. Six important issues have already emerged and, once out of the bottle, cannot be stuffed back in.

1. *There is no contest when it comes to the $64,000 "How do you feel?" question:* ***A vast majority of HIVers say they feel much better while taking an STI****, at least initially.*

2. Viral load tends to go up during a treatment break. *Well, duh. But often after it shoots up, it peaks and finally falls back to a less alarming, lower "set point," just as in early HIV disease. The high-peak viral load is likely due to the lack of an initial anti-HIV immune response. The return to a lower, stable viral load, conversely, possibly reflects a renewed response once the immune system "realizes" the drugs are no longer taking care of business. So far, people taking STIs rarely*

report having any physical symptoms accompanying the rise of viral load -- it's just a change in the lab numbers. And, of course, many seeking STIs don't have full control of their virus in the first place.

3. STIs also often result in a sudden drop in CD4 cells, and this can cause panic. *Interestingly, the German team reports that this occurs mainly in people who had a large CD4 cell increase when they first went on HAART; those with a small initial increase or none at all seem less likely to have an STI-related CD4 loss. Some scientists at the STI conference theorized that the drop signals not the sudden mass death of CD4s -- as in the "sink and drain" immune-system analogy -- but merely a turnaround in the trafficking pattern of CD4s, with many cells hightailing it to the lymph tissues as in untreated HIV infection. If so, the abrupt fall might not warrant panic. The more important, and as yet unanswered, question is whether after treatment is restarted the CD4 levels will return to where they were.*

4. STIs can result in a short-term improvement in quality of life, but this may be followed by a return of serious AIDS-related complications.

5. *Although time off therapy is unlikely to induce drug resistance,* ***withdrawing all drugs in a combo all at once might pose a risk if each has a different half-life*** *(the amount of time they stay in the blood). Precise formulas are being worked out.*

6. *Scientists who hold out hope for eradicating HIV through long-term HAART worry that* ***STIs may allow the virus to "reseed" the hidden reservoirs of infection*** *-- though others note that a single day of nonadherence could have the same effect.*

These issues raise some red flags. Above all, researchers and activists alike urge everyone to take planned holidays only in a clinical trial, not "at home." And no taking STIs on a lark. Given our ignorance about long-term effects, you need a damn good reason for an STI. Mere convenience? Do not apply. But multi-drug resistance, intolerable side effects and/or severe treatment fatigue and inability to stick with regimens still qualify.

The biggest STI fear among HIVers is that they may be unable to recover any ground lost while off therapy, whether in terms of viral load or CD4 cell counts. There's an equal amount of anecdotal evidence to confirm and dismiss this fear. But harm measured on lab tests must be compared to that of organ damage and other side effects due to continued drug use. In the final analysis, length and quality of life count more than lab tests.

Those using STIs would do well to hearken back to how HIVers coped with the risks of opportunistic infections in pre-HAART times. If STI results in a CD4 cell count below 200, protect yourself by taking drugs to prevent PCP. Similarly, a CD4 drop below 50 should trigger preventive treatment for CMV and MAC. The lost art of management by prophylaxis must be renewed as a tool to keep people safe in their STI ventures.

STI is a concept that must be tested. It is painfully clear that lifetime therapy is not an option for all, even with the better drugs that are "just around the corner." HAART is daily chemotherapy,

and rough on those who use it. If pulsed therapy or periodic interruptions offer even a slim chance of a less demanding alternative, HIVers deserve to see that it gets tested. Science's job is to quantify the risks and benefits so that well-informed people can make their own choices. The exciting aspect in the field of STI is that, spurred by the decisions of HIVers, researchers are racing one another for the answers people need. Too bad such alacrity isn't driving the rest of AIDS research.

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