Good Morning, HAART Break

Flying the cocktail coop is every pill-weary HIVer's dream, but is a drug holiday right for you? With formal study results far from hatching, HIV docs are going on basic guidelines and gut sense to help patients weigh in what they have to gain-or lose-from kicking their combos for a time.

April 1, 2003 By Bob Lederer

Like countless other HIVers, Timm Dobbins joined the rush to triple-drug therapy during the protease revolution of 1996. His counts weren't too bad—349 CD4 cells and a viral load of 45,000—and he'd never had an HIV-related infection. But his doctor assumed that the prevailing "hit early, hit hard" strategy was a must to prevent immune-system deterioration. Dobbins got good results, but by June 2001, his arms and legs had shrunk from lipodystrophy and he was hit with bouts of depression. "I grew very tired of having my life run by medicine," he says flatly. "I wanted a break from all the drugs." And so, with CD4s at 895 and viral load at less than 50, he enrolled in a clinical trial at San Francisco General Hospital probing the effects of structured treatment interruptions (STIs) on the immune system. Over the next 18 months, Dobbins alternated between two (closely monitored!) months off meds and four back on. By 2003, he was, thanks to the breaks, a much happier HIVer. "Each time I restart the meds, they kick back in immediately," says the former FedEx dispatcher, 48, noting that his viral load becomes very low or even undetectable. "So I don't fear staying off them longer." But the benefits go way beyond good lab numbers (he currently has 725 CD4 cells and a viral load of 2,340). "I think breaks allow the body to repair some of the damage the HIV meds do," he says. "And they've done me good emotionally."

Timm dobbins is just one of the thousands of hiv pill-poppers kicking a regimen they may never have needed to start so soon. They're also prompting some pressing and complicated questions about treatment strategy: Are those who interrupt therapy courting drug resistance, treatment failure and disease progression? Or are they avoiding harmful side effects and wisely saving their drugs for a time they'll *really* need them? Are some people better candidates for med breaks than others? And what are the danger signals that it's time to restart?

BREAKING AWAY

Since *POZ* last tackled this topic ["Gimme A Break!" August 2001], a handful of formal STI studies have begun, including the huge, federally funded SMART, short for Strategies for Management of Anti-Retroviral Therapy (for enrollment info, see "We Interrupt This Program"). Launched in January 2002 and meant to enroll 6,000 HIVers in several countries, which would make it the largest-ever AIDS trial, SMART keeps half on standard continuous treatment. The other half stay off

meds until CD4 counts fall below 250—then they restart, and stop again after two readings above 350 (and so on). “The idea,” says principal investigator Calvin Cohen, MD, of Boston’s Community Research Initiative, “is to use antiretrovirals in the least amount so you’re protected against opportunistic infections [OIs]. We know you *can* stop therapy under certain conditions, but is this a good idea?”

SMART won’t have a final verdict for perhaps 10 years, but that’s a mere academic matter to many HIVers. The vast majority of treatment breaks are prescribed not in formal trials but in everyday clinical settings, where doctors are using a combination of basic CD4 parameters, grapevine wisdom and intuition. When federal guidelines for starting HAART dropped in 2001 from 500 CD4s to 350, many MDs let their patients know they may have started treatment too early. Now HIV docs nationwide are reporting that more and more patients—with long-term HAART-takers like Dobbins constituting the majority—are taking breaks averaging four to six months, with some as long as three years. Even patients with CD4 cells in or below the iffy 200-to-350 zone are telling docs they’d rather live with some risk of disease progression than go another day swallowing fistfuls of pills, panicking for public restrooms, watching their faces cave in or risking serious HAART-implicated complications such as mitochondrial toxicity, lactic acidosis and hyperlipidemia (see “Supercalifragilistic-lacticacidosis”).

Moreover, most HIV docs say patients on approved breaks are doing well—and most who return to meds resuppress the virus quickly. “In 1998, we were telling patients, ‘If you ever miss a dose, you’ll get drug-resistant and could die,’” says Los Angeles’ Gary Cohan, MD. “It’s fascinating how we’ve come full circle to ‘It’s not a big problem to stop the drugs if we watch you closely.’” Indeed, all doctors stress the importance of regular (and perhaps more frequent than usual) CD4 and viral-load monitoring during breaks.

A break can have a number of benefits, too. “It helps patients detoxify from the drugs and differentiate what might be causing their symptoms,” says New York City’s Antonio Urbina, MD. “It’s also psychologically empowering.” And several studies have shown that within a year of stopping therapy, too-high levels of cholesterol and triglycerides often return to normal. But the disfigurement of lipodystrophy, which may be linked to high lipid levels, reverses only sometimes.

In short, a new consensus is fast emerging about treatment breaks, and the question increasingly is less “Should you?” than “When should you?” That’s because medical progress has presented HIVers with a paradox: They can now look forward to a long lifetime if they stay on their meds, but the meds are ultimately too toxic to stay on for a long lifetime. The solution may well be to build repeated drug interruptions into your long-term treatment plan. “My intent is to be proactive and get my patients off [meds],”says Michael Saag, MD, a veteran AIDS clinician and researcher at the University of Alabama, Birmingham, who has pioneered breaks for HIVers. “My mantra is, ‘[HIV treatment] is a marathon, not a sprint.’”

TOO EARLY, TOO HARD

The largest group of HIVers dropping their drugs are those whose CD4s have never been below 350. Last summer, an Argentinian study found that after three to four months off meds, viral load

for these relatively healthy folks always returned to near-starting (or "baseline") levels, even though breaks may have first sent their virus soaring. CD4s, meanwhile, generally stayed elevated. In North Carolina, David Wohl, MD, has noted corroborating results among his patients. "Their T cells have not dropped like a stone," he says. "Some have stayed off meds 18 months or more. I think, 'Wow! I've decreased their overall exposure to meds over their long antiretroviral career.'"

But not all docs are high on HAART-break. In Los Angeles, Mark Katz, MD, OKs them only for patients who complain bitterly of pill fatigue or side effects. "I wouldn't proactively recommend it," he says, given the lack of data on long-term consequences. Nor would New York's Howard Grossman, MD, who advises patients with 350 to 400 CD4s to remain on treatment, fearing a dangerous CD4 drop. "During a break, you're putting a big strain on the immune system, with a possible large burst of virus," he explains, "so it's possible that people can get sick."

LOAD OFF YOUR MIND

What about those whose CD4s, once below the magic 350, bounced back thanks to HAART? There are still too little data on the safety of breaks, but most doctors are highly cautious. Boston's Paul Sax, MD, says that in both the existing research and his own clinical experience, "the biggest and fastest CD4 drops and the highest viral-load spikes have been in those patients who started [HAART] with very low CD4s and had a tremendous increase [on the meds]." One large study found that 95 percent of HIVers in this category had to resume meds within a year (although the restart cue was a very conservative 5,000 viral load). Then again, to cocktail-weary HIVers, even a few months off meds can be a genuine holiday.

Some docs are in no rush to grant vacation time, though. "If someone's only been stable for six months, I don't think that's enough immune restoration" for them to take a break, says Karen Van der Veer, a Phoenix naturopath (natural-medicine physician licensed to prescribe drugs). "They're walking on thin ice. We often ask them to do adherence counseling and wait another six months or a year." Michael Saag disagrees: "I feel very strongly that 99 percent of patients who complain of being tired of taking meds will stop therapy on their own"—which, if done improperly, can lead to drug resistance. "If the patient says, 'I can't do it any more,' who am I to insist that he or she stay on? That's insane."

Many docs would use that same word—*insane*—to describe treatment breaks for anyone who's ever had an OI or wasting. Not Gary Cohan—as long as treatment has stabilized his patients. "I'd just monitor them more closely. When all else fails, listen to the patient. It's not about T cells and viral load, it's about quality of life and feeling really well." Cohan holds that patients will almost always suppress their virus again after resuming meds. What about the risk of developing drug resistance while on a break? "That's simply not true," he says.

Cal Cohen disagrees. "Resistance can, and does, happen with STIs,"he says, noting that stopping with detectable virus may increase such risk, as may stopping non-nukes (NNRTIs) at the same time as other drugs in a combo, because they linger longer in the body than other drugs, possibly leaving them vulnerable to HIV mutations that can lead to resistance. "So," Cohen says, "stopping

with detectable viral load on [the non-nuke] efavirenz is likely not such a good idea." (For tips on how to stop a non-nuke combo safely, see "We Interrupt This Program", this page). Still, the many doctors to whom POZ spoke confirmed that they'd seen little apparent break-related drug resistance in their patients.

PATH OF LEAST RESISTANCE

Other HIVers part with HAART in hopes of returning better prepared: heavily treated types who have developed drug-resistant HIV but have few or no combo options left. They're banking on the widely held theory that taking a break may allow pockets of nonresistant, or wild-type, virus to outgrow the resistant strain once the drugs' pressure is removed.

There's little research on this. A small French study did find that people with resistant virus, high viral loads and very low CD4s who took an eight-week break before starting a mega-drug combo fared better than those who didn't. Then again, a small study by San Francisco's Steven Deeks, MD, found that the virus increased sharply—and CD4s plummeted—when drug-resistant HAART-takers with viral loads above 2,500 stopped their meds. Deeks says the results persuaded him that "a lot of people with highly resistant HIV who stop the drugs do very poorly." That's likely why most docs who talked to POZ feel that HIVers with low CD4s and high risk for OIs should not stop their meds.

What about low-CD4 types who want to stop meds because of side effects? "During the break, focus on prophylaxis [OI-preventing meds] and nutrition until the toxicities have washed out," Paul Sax says. "The goal is to find a regimen that's tolerable—even recycling old drugs." Most MDs recommend that *before* you stop your meds, you take a resistance test to suggest which untried meds may work best when you restart. During a break, of course, test results are meaningless.

WHEN STOPPIN MAKES SENSE

Perhaps the most promising foray into med breaks comes from Harvard's Bruce Walker, MD, and his research team, which coined the term "STI" in 1998. Their pilot study of people in the first six months of infection found that after a few months of treatment followed by an indefinite break, most maintained low or undetectable viral loads without drugs. Thus was born the "auto-immunization" theory, which goes like this: In order to boost levels of HIV-specific T cells—specialized immune cells often lost early in infection, which are believed to attack the virus' inner proteins—the immune system must periodi-cally "see" the virus. That's where med breaks enter, causing viral-load surges. The result, the theory holds, is that during each break, the CD4 count will settle a little higher than it did after the last one, and those CD4s will more effectively control HIV—*without* meds.

Since then, Walker and others have conducted several small, similar studies and found comparable results: Some lucky HIVers were able to stay off meds for up to three years with no viral rebound. Sax, who collaborates with Walker, says, "What's not known is whether they would have done as well with no interruption or even no treatment at all." What's more, less than half of his patients in the ongoing studies have maintained viral loads under 5,000 after stopping

medication. Some have resumed meds; others are waiting until their CD4s drop into the 200-to-350 range.

Meanwhile, earlier hopes that Walker's modestly promising results could be extended to non-newbie HIVers have faded, after several studies showed that such patients' CD4s settled no higher during breaks than they did before treatment. Says Sax: "There is no good evidence that auto-immunization happens anywhere except in acute [early] infection."

THE RESTARTING LINE

Most docs agree: Before you go off meds, determine with your doctor the marker at which you'll go back on them. "Some people with high CD4s may not want to go [off meds] below 500," Wohl says, "whereas others have been through the wringer with drugs and are willing to tolerate low counts."

So how low can you go? Most docs say 200 CD4s (though some, playing it safe, set a higher bar for those who are multi-drug-resistant). For HIVers with CD4s below 200, several STI studies have found that the risk of OIs shoots up. Does viral load factor in? "I go more with CD4 counts," says Antonio Urbina. "Viral load is affected by new infections, immunizations or even stress, so it's a less reliable test for immune function." But, Urbina adds, when finding a viral load above 750,000 after two consecutive readings, he considers a med restart. Van der Veer would do likewise, she says, "if CD4s drop from 800 to 400 over a six-month period. But if it's been a slow progression"—say, from 500 to 400 in the same period—"don't panic, just keep monitoring. The level may be plateauing." Still others rely on the CD4 *percentage* (the ratio of CD4 to CD8 cells) as a more reliable marker of immune strength.

What about the fabled flulike illness that sometimes hits when viral load zooms shortly after starting a break? Docs say such "acute retroviral syndrome" is more common among those whose CD4s have in the past fallen below 200. Because of it, Cohan says, "I've had to put a few back on meds, but most plow through and get better after about two weeks."

Next up on the med-break horizon? Pulse therapy, which the NIH's Mark Dybul, MD, is exploring in three STI trials: one with five days on meds, two days off; one with four on, three off; and one with seven on, seven off. "The goal is to give people much less drug but still have effective treatment," Dybul says, adding that all three schedules were derived from STI studies in which no major viral rebound occurred for at least one week. (One found that after two years of a week-on, week-off cycle, viral control and CD4 levels resembled those of patients on continuous therapy.) Mark Katz says, "Some of my patients who have done best are on pulsing regimens, almost all done to minimize lipodystrophy." But few other doctors appear to be following Katz's lead, and Dybul cautions that "we just don't have enough data" to try this outside of a clinical trial.

TREATMENT BREAKOUT

Indeed, we still lack the formal data to make all sorts of conclusions about treatment breaks—which, despite the launch of the giant SMART trial, may be tough to collect, notes SMART researcher Cal Cohen: "The pharmaceutical industry has been reluctant to support anything that

involves stopping meds, for obvious reasons."

Not true, says Mark Shaefer, group director for HIVclinical development and medical affairs at GlaxoSmithKline (GSK), which makes best-selling NRTI-combo pills Combivir and Trizivir. "If it were, I don't think companies would continue vaccine research and other ways to help stop this pandemic." He says not only is GSK doing its own studies using STIs to test a vaccine, it is also funding STI research by independent investigators. "Even with an STI approach, people are going to require drug therapy at some point," he says, explayning why meds breaks are no big threat to Pharma.

Plus, as Richard Jefferys of the Treatment Action Group points out, "Illness requires treatment' is still the paradigm."But Jefferys is hopeful about the emerging treatment-break consensus. "A lot of doctors who didn't support SMART initially are now looking for it to answer the question their patients are asking," he says. And many practitioners are not waiting for studies before starting their own "experiments." Gary Cohan epitomizes doctors' new flexibility: "In HIV medicine, we've always operated by the seat of our pants," he says. "Things we used to believe in are compleately wrong. The key is willingness not to hold to dogma."

Meanwhile, Tim Dobbins, the HIVer who just finished his third STI in a clinical trial, says he can't wait for the next break. "My gut says that being off the poisonous drugs has done some good for my body," he says, adding, "I get a bump up in positive feelings. Plus I know that I'd go back on if something goes wrong." He encourages his fellow HIVers to follow his lead. "I wouldn't recommed a treatment interruption to those who are vervous or fixated about their CD4 count and viral load," he says. "But I have learned that the quality of my life is not toed to my blood numbers."

WISH YOU WERE HERE

Postcards from three HIVers' treatment holiday:

Monica Johnson, 37
Columbia, Louisiana
Volunteer CEO, HEROES
Currently ON meds

VITAL STATS
Diagnosed: 1989
Before HAART: 700 CD4s, viral load unknown
Before break: Combivir and Crixivan; 650 CD4s, undetectable viral load
Length of break: 1 year
Before restarting meds: 650 CD4s; 80,000 viral load

Current combo and stats: Combivir and Sustiva; 902 CD4s, undetectable viral load

Took a break because: I was tired of being on the drugs. Plus, I found out that I probably shouldn't have started at all, given my high CD4 count.

How she spent vacation: I did nothing special, other than getting blood work every two months.

Back on meds because: Neither I nor my doctor were aware of the latest facts about STIs, and my doctor started freaking out when my viral load hit 10,000.

How she's doing: Fine. I've switched drugs due to kidney problems. I'm glad to be on a twice-daily regimen now.

P.S.: Before my break, I thought I could probably take one, but no one would listen. Then I met a doctor who told me to try it. Finally finding someone with initials after her name who agreed gave me the courage.

Scott Williams, 34
New York City
Associate editor in chief, Academic Physician and Scientist
Currently OFF meds

VITAL STATS

Diagnosed: 1995
Before HAART: 400 CD4s, 3,000 viral load
Before break: Viracept, d4T, ddI and hydroxyurea; 400 CD4s, 3,000 viral load
Length of break: three years and counting
Current stats: 520 CD4s, 10,000 viral load

Took a break because: I was feeling shitty between liver toxicity, neuropathy, Viracept runs and lipoatrophy in my face and legs. But even before these symptoms, I was contemplating giving my body a rest, and my doctor agreed.

How he spent vacation: I've taken some workshops in Reiki, a form of hands-on healing. A year ago, I quit my Madison Avenue job, which was too stressful. Now I have a saner 9-to-5 job.

Not back on meds because: 9/11 said to me there's so much in life that we have no control over. I'm not in denial— I'm just not willing to live by my lab numbers anymore.

How he's doing: Soon after quitting the drugs, all the side effects resolved—except that my lipoatrophy has not reversed.

P.S.: It's incredibly liberating not to be on the drugs—your life isn't constantly run by a pill-taking schedule, and it's wonderful not to have the eating restrictions. I'd encourage people not to hop on the drugs too soon—they're just too toxic.

Fred B., 41
New York City
Acupuncturist
Currently ON meds

VITAL STATS

Diagnosed: 1985
Before HAART: 0 CD4s, 3 million viral load
Before break: Kaletra, Ziagen, 3TC and d4T; 280 CD4s, 4,000 viral load
Length of break: Three months
Before restarting meds: 70 CD4s; 100,000 viral load
Current combo and stats: Kaletra, Ziagen, 3TC and d4T; 260 CD4s, 86 viral load

Took a break because: I get a toxic feeling on meds. And tests showed I had developed drug resistance, so I thought stopping might allow wild-type virus to proliferate. (It was actually the latest of five breaks I've taken over the past seven years.)

How he spent vacation: I kept taking the Chinese-medicine supplements and herbs I usually take, but I added milk thistle, alpha-lipoic acid and more of my usual mix of lemon juice and water to help detoxify my liver. I also boosted my vitamins and antioxidants, and did more acupuncture and yoga.

Back on meds because: A while into each break, my viral load bumps up again and I get pooped and unmotivated. That's my signal to go back on.

How he's doing: After I went back on my combo (the third time on the same one!), my viral load immediately went down to almost undetectable.

P.S.: These drugs do amazing things, but at a great price in side effects. That's why it's important for me to nurture my body both on and off meds**.**

WE INTERRUPT THIS PROGRAM

Dish with doc. Your MD can help you weigh the pros and cons of a break—and plan its length, restart markers and post-break combo.

Nip the non-nukes first? If you're on Sustiva, Viramune or Rescriptor, ask if you should ditch 'em a few days before your other drugs. NNRTIs, or "non-nukes" (especially Sustiva), tend to stay in the body longer; if you drop them with the rest of your cocktail, you could be on NNRTI therapy alone for a short while. There's no proof yet, but some researchers think this could induce resistance.

Go down for the count more. Most docs suggest getting yourCD4s and viral load done no later than a month after you've dropped meds, every month thereafter until your numbers stabilize, then every other month and finally every third. Got drug resistance or a history of low CD4s? Do your numbers two weeks after stopping and every two thereafter.

Clean up your act. Enhance the drug detox process by reducing stress, exercising more and minimizing sugar and all that yummy fried stuff.

Take a "study break"! Joining an STI trial will ensure you expert monitoring and help improve breaks for future HIVers! Click "treatment interruptions" at www.aidsinfo.nih.gov, or call 800.TRIALS.A (Spanish available) to connect to these trials:

CPCRA "SMART" (www.smart-trial.org) Continuous vs. on/off treatment

AACTG 5068 STIs with vs. without ALVAC experimental vaccine

AACTG 5086 and **CPCRA 064** Immediate vs. deferred (four-month STI) treatment for salvage therapy

AACTG 5170 Effects of stopping HAART

VA Cooperative Studies Program 512 "OPTIMA" standard HAART vs. "mega-HAART" with and without STI in salvage situation; veterans only, call local VA hospital

AMP 720 STI with vs. without experimental drug Ampligen; call 215.988.0080

AACTG 371 5-drug combo followed by 24-week STI; newly positive only

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