Tough Breaks

The SMART study stopped enlisting for its drug-holiday arm after too many people got sick. Is this the end of treatment interruptions?

April 1, 2006 By Tim Murphy

Sandra Benns, 47, is off her HIV meds—and lovin' it. Diagnosed in 1998, the Baltimore peer counselor and social-work student started taking a Crixivan/Combivir combo soon after. The pills knocked her virus down to undetectable, but she had issues: "Each time I took them, it was a reminder" of having HIV, she says—and they gave her lipo.

On a doctor-approved med break since 2002, she's maintained 300-ish CD4s and a 10,000-ish viral load—numbers traditionally considered safe for folks on break. She has planned to restart if her CD4s hit the 200 to 250 "hot zone."

Such thinking guided the massive, international drug-break study, Strategies for Management of Antiretroviral Therapy (SMART). Launched three years ago, SMART divided some 5,400 positive people into two groups. One stayed on HIV meds, the other went off until their CD4s hit 250, back on until CD4s climbed to 350, off again until 250 and so on.

The point? To determine over a decade which strategy is safer and more effective. Researchers expected AIDS-related illnesses in the on-off arm to be balanced by side effects (like heart attacks, diabetes and lipo) in the continuous arm.

But in January, SMART investigators abruptly closed the on-off arm because it had more than twice the risk of illness and death compared with the continuous arm. The rate was low—about 3% as compared to 1.5%—but participants (especially those who'd had meds fail them in the past) were urged to restart meds pronto. "We just weren't seeing the trade-off [AIDS-related complications in the off-meds arms balanced by side effects in those on meds] we'd expected," says Boston's Cal Cohen, MD, a SMART leader. At February's big retrovirus conference (CROI), investigators revealed that the study-stopping ills were more frequently heart and other organ problems than classic AIDS infections.

Was it the end of drug breaks? Two other recent studies help put things into context. One was a smaller version of SMART, with drug breakers resuming meds when CD4s hit 250—and it, too, found twice the complication rate for breakers as for constant med takers. But another medium-size study required drug breakers to resume at 350 CD4s—and found no higher complication rate

among breakers than takers.

What to make of it all? For starters, studies might look at restarting meds at 350 CD4s rather than 250 (as Cohen says, “the lower the CD4s, the more likely bad events”). And SMART shouldn’t speak for drug breaks overall: “None of these data suggest that people coasting steadily with [CD4s above 350] off treatment should change what they’re doing,” says Project Inform’s Martin Delaney. Moreover, some studies are testing breaks guided by set time frames (see below) rather than CD4 levels.

Will the new findings lead Benns to restart meds now, instead of waiting until her CD4s hit the 200s? “I’ll talk to my doctor,” she says. “We work in the same office.”

Now, that’s teamwork.

ONGOING MED-BREAK STUDIES: FOTO (Five days On meds, Two days Off) so far finds weekend-long breaks safe (likely because they’re too short to “allow viral rebound,” says Cal Cohen, MD—especially if combos contain long-lasting Sustiva). For FOTO info: shall@crine.org, 617.778.5454 x 238. For more start-and-stop trials: www.clinicaltrials.gov (search “HIV,” then “interruption”).
