Old Drugs, New Tricks

Wanna give your meds more bite against HIV and less toxic bark? Three of yesterday's treatment no-no's may be just what the doctor orders

February 1, 2004 By Tim Murphy

What news electrified last fall's ever-important ICAAC (Interscience Conference on Antimicrobial Agents and Chemotherapy. Just say *ick-ack.*) conference in Chicago? Early data on that revolutionary new class of HIV meds called entry inhibitors, right? Bold strides toward a gene-therapy cure, right? Well—no. Actually, the news that livened up the Loop focused on new ways of using (or, uh, not using, or, uh, better using) the meds we already know and love-hate. Hey, don't knock it. "A little more information is a little more information than we already have," philosophizes longtime HIVer and activist Dawn Averitt. Here, *POZ* breaks down the latest research, so you can brush up on advances that may lead to kinder, gentler treatment—while we all hold our breath (ha!) for the cure.

Singular Sensation: *Kaletra Monotherapy*

When Ben, 50, a married Houston pharmacist, was hospitalized in 2002 with AIDS-related pneumonia, he didn't even know he was positive. With 47 CD4s and a viral load of 400,000, Ben needed powerful HAART pronto. His doctor sent him to Joseph C. Gathe Jr., MD, who treats 4,000 HIVers at his private practice/research unit/nonprofit clinic. "It's a one-stop shop," Gathe says.

Gathe started Ben on the protease inhibitor (PI) Kaletra, a.k.a. lopinavir "boosted" with a small dose of the older PI ritonavir. And that's all Gathe gave him. Ben was getting *monotherapy*, or treatment with only one drug (the booster dose of ritonavir in Kaletra doesn't count). Monotherapy made many HIVers resistant to the first wave of antiretrovirals—Retrovir (AZT) and Videx (ddI)—before PIs were added to create the multidrug dynamo known as HAART.

Fast-forward nearly a year: Ben has a hardy 358 CD4s and an undetectable viral load. "I feel perfectly normal," he says.

How It Works

Did Ben and his doc just get lucky? Hardly. Ben was one of 30 treatment newbies who enrolled in a Gathe study that became ICAAC's show-stopper—and may well produce the starter regimen that rocks the treatment world. Despite a wobbly average 169 CD4s, Gathe's HIVers started on nothing but Kaletra (the standard dose or slightly higher, depending on weight). He was betting Kaletra's

potency could justify prescribing the drug solo. It maintains robust levels in the body, putting up a uniquely high wall to HIV. Plus, to get around Kaletra, the virus needs *mucho* mutations. That's why Gathe calls Kaletra a "Porsche" compared to the "old Oldsmobile" of previous PIs.

So far, Gathe's gamble has paid off. Six months into their regimen, all but one of the 21 folks who hadn't dropped out had viral loads below 400—undetectable on the old-school test. Half of them were below 50, the new-school marker. On average, CD4s had jumped over 200 points, well into the safety zone. And last November, two months after Gathe's ICAAC stunner, his monotherapy mavericks were holding steady, he says, with no viral upcreep, resistance, fat loss, major fat gain or "humongous cholesterol and triglyceride changes."

Is monotherapy finally safe for humankind? The thought's inspiring. Kaletra-only treatment "would shave almost half the cost off" a combo regimen, Gathe says, rescuing not just the average middle-class HIVer (who'd pay only one co-pay instead of two or three) but also poor PWAs worldwide—including those in Gathe's own ADAP-strapped Texas. It would also nix all side effects from so-called nukes (the nucleoside analogue class of antiretrovirals) and perhaps prevent high cholesterol and triglycerides and even lipodystrophy, which has been linked, among other possible causes, to mixing protease inhibitors *and* nukes. Johns Hopkins' Joel Gallant, MD, adds that, were Abbott to reformulate Kaletra so it didn't require refrigeration, "we might really have something exciting" when it comes to treating HIV in the developing world.

Kaletra monotherapy may turn out to be an amazing starter regimen, but for HIVers with protease experience or resistance, going solo with Kaletra "may be too risky," says treatment activist Averitt. Even Gathe calls his scrappy pilot study "simply proof of concept." He's working with Abbott to launch a large trial to pit HIVers starting on Kaletra alone against those adding nukes. "In two years, I want to know if it works, who it does and doesn't work in, and what to do when it doesn't work," he says. But every doc *POZ* interviewed said that until Gathe's study and a European counterpart conclude, they won't get on what Gallant calls "the monotherapy bandwagon."

The Take-home

Be like Ben: Treatment naive HIVers interested in following Ben's example can inquire about a new monotherapy trial (expected to start in Houston in March 2004) at 800.522.2573 or www.josephgathe.com. Ben's coming to terms with his midlife diagnosis: "You have to accept it and move on," he says. He credits his supportive wife, a reminder that even if one drug may tackle HIV, one person can't.

Don't go solo, solo: If you're on a Kaletra combo and thinking of dropping your other meds to save the co-pay and side effects, *consult your doc first,* especially if you're beyond your first combo—you may have protease resistance, and we still don't know if Kaletra alone can lick that.

Happy Holiday: *Structured Treatment Interruptions*

Meet Yusef, 30, a lawyer, and Brandon, 25, a publicist. Both of these gay New Yorkers acquired HIV

during unsafe sex on crystal meth. Both, thanks to their seroconversion wake-up call, are in recovery. But that's where their stories diverge: At his spring 2003 diagnosis, Yusef had 350 CD4s—the point at which federal guidelines recommend starting treatment. "But I wasn't ready," recalls the Arab-American attorney. "With my emotional state, I felt that I'd miss doses." No problem, said doc—Yusef was on the upper end of the federal CD4 guidelines, and at 35,000, his viral load wasn't out of control. They'd watch and wait.

Brandon tested positive in early 2003 and began meds immediately. "The day I swallowed my first pills, I had three weeks clean from crystal and 453 CD4s," he says. Why did Brandon rush to join Club Meds? Because his doc encouraged him to join a study that's part of a research wave revisiting that outdated treatment strategy "hit early, hit hard." There's promising evidence that HIVers who do so have a better chance—but not a guarantee—of reaping a big reward: long-term drug holidays, or *structured treatment interruptions* (STIs).

How It Works

Data presented last summer from the Multi-Drug Resistance study suggested there was no benefit in taking an STI before switching from a badly failing regimen to a "salvage" combo. But shortly afterward, ICAAC revealed encouraging news that pertained to a much broader HIV population (at least in rich countries): chronically infected HIVers doing OK on treatment-as-usual. Many of them, it seemed, could break safely for months, even *years*, and go back on meds without incurring resistance. What did these patients have in common? *Their pre-treatment CD4s were high.*

Two Italian studies turned heads at ICAAC. They showed that HIVers who were doing swell on HAART (CD4s 500 and up, plus undetectable virus) and had CD4s that had never dropped below 500 could go off their cocktails without CD4s hitting the 350 to 400 range for a year and a half—and counting. And get this: Even folks with pre-treatment CD4s between 200 and 350 stayed above 350 to 400 CD4s for up to a year.

A recent study by Johns Hopkins' Joel Gallant, MD, has produced nearly identical findings. "For the most part, studies are all showing that it's the CD4 *nadir*—the lowest CD4 number you've had off therapy—that predicts how long you can stay off therapy," Gallant says. "That means, the lower the nadir, the shorter, and less advisable, the interruption." Since ICAAC, there's also been good news from the huge, ongoing international SMART trial, which compares HIVers who stay on treatment to those taking breaks: Monitors have found no reason to stop or redesign the study due to safety concerns, according to Cal Cohen, MD, a SMART principal investigator in Boston. Some of his SMART-alecks have been off meds for a year or more.

The Italian studies, the Hopkins research, SMART—they all raise a tantalizing question: If CD4 nadir is so important to the success of drug breaks, should we consider returning to the "hit early, hit hard" philosophy of the '90s so we can break long and lovely in years to come?

The Fine Print

For now, docs stand by the current federal treatment guidelines as they wait for the results of a definitive study like SMART, which won't conclude for several years. That's because going off meds

for long periods does have risks. “Some people in our STI group may, for example, have less lipo or heart attacks, but develop a case of thrush or anal dysplasia, a cancer precursor,” Cohen says. So SMART is comparing the rates of those and other HIV-associated disorders in its on-meds and off-meds volunteers.

The Take-home

Be like Brandon: If you think you or somebody you know has been exposed to HIV within the past 72 hours, ask a doctor about PEP (post-exposure prophylaxis), which may prevent infection. If it’s been longer than that—especially if you’ve got the flu-like symptoms that can signal seroconversion—ask your doctor for a PCR test (that detects actual virus, which shows up soon) rather than the traditional ELISA, which tests for slower-emerging HIV antibodies. If HIV appears, consider enrolling in the type of study that Brandon, who “hit early, hit hard,” joined. The info’s at www.aiedrp.org. AIEDRP (Acute HIV Infection and Early Disease Research Program) is a new consortium of research sites pursuing the question: Can early-infection HAART “lock in” the immune system’s natural ability to fight disease?

At press time, Brandon’s viral load was undetectable and his CD4s at 500. “I’ll come off meds around New Year’s,” he says, “and be holding my breath.” So will we, as we wait for data comparing high CD4 treatment starts like Brandon’s to Yusef’s low one. At press time, Yusef’s CD4 count was below 200. He’d been crystal-free for months and planned to begin a Viread (tenofovir)/Epivir (3TC)/Kaletra combo. “I’m not as afraid,” says the devout Muslim. “Everything will work out all right—*inshallah.”*

Want a meds break?: Talk to doc, whether you want to break solo or, preferably, in a study. (New Englanders should consider the “weekends off” study at www.crine.org.) Sustiva (efavirenz) and Viramune (nevirapine) last a long time in your system, so you may want to stop these drugs a few days before your other meds to avoid resistance.

Get SMART: On meds or not, you’re eligible for the SMART study if you have 350 or more CD4s and you’re willing to be randomly assigned to stop, start or stay on meds. Run the idea by your doc, and find a nearby site by searching “SMART” at www.smart-trial.org.

Check, Please: *Therapeutic Drug Monitoring*

Rick Roberts knew something was wrong. The 40-year-old San Francisco communications professor, diagnosed with HIV in 1988, was a month into a “salvage” regimen that included a slightly-higher-than-usual dose of Invirase (saquinavir, the PI to which he had the least resistance) boosted with a low dose of ritonavir—and was suffering excruciating nausea and belly pain. “I’ve been on lots of cocktails,” he says, “and usually my body adjusts after a couple of weeks.”

“I can’t take this,” he told his doctor, Mary Romeyn, MD. A gastrointestinal work-up revealed nothing. So Romeyn did something HIV doctors seldom do: She tested Roberts’ blood levels of saquinavir—the first step in what’s called *therapeutic* drug monitoring (TDM), or measuring drug levels in your system and adjusting doses if levels are too high or low. Sure enough, even at its

lowest point (or trough), the saquinavir was twice as high as expected. She cut Roberts' twice-daily pill gulp from six to four. Follow-up tests revealed he was still getting the saquinavir he needed—*without* big-time tummy travails.

How It Works

Seven years into combination therapy, HIVers still get a one-size-fits-all dose, even though a drug's *bio-availability*—how much of it ends up fighting the virus—can vary greatly by gender, weight, age, genetics, food intake, interactions with other drugs, and liver and kidney health. What little research has been done through TDM suggests that when it comes to med doses, HIVers are on a very unlevel playing field, especially with regard to side effects: One small Dutch study found that significantly more women than men had toxic levels of Sustiva and Viramune, while a University of Colorado group found that women had higher concentrations of AZT and 3TC. These drugs can sustain *and* savage our lives: Shouldn't we know how much we're actually getting?

Another Dutch study presented at last fall's ICAAC emphatically answers yes. It found that HIVers who had their protease-inhibitor concentrations measured and adjusted had better disease control and fewer side effects. University of Colorado researchers had similar findings with HIVers on a combo of Crixivan (indinavir), AZT and 3TC. Especially for women, TDM "is a way to get the answers we didn't get in clinical trials," Dawn Averitt says. "We often treat women like men"—who have dominated dosing studies for most HIV meds—"and hope that it's satisfactory. It's not." Hawaii's Drew Kovachs, MD, admits that "most of my women patients will say, 'This is enough [dose] for a man, but I weigh 108 pounds,' and we'll adjust down the dose [of a drug like Zerit (d4T)] if their neuropathy is terrible. The women have been smarter about all of this."

The Fine Print

Despite the new research, federal guidelines discourage routine TDM, and several top docs told *POZ* they agree, saying that current TDM tests give at best a muddy read of PI and NNRTI (non-nuke) levels and how to adjust doses. Results often vary with each test, even when accounting for tricky factors like time of testing (right before you've taken the drug? right after?). Measuring nuke levels remains complex because available tests read drug levels in the blood, which may not accurately reflect how much nuke is in cells, where the meds do their work. Plus, docs claim, treatment failure can almost always be traced to resistance or poor adherence, not insufficient levels, while side effects can be treated with other remedies or eliminated through switching meds, especially with today's broad HAART palette.

Everyone would like to see larger studies demonstrating TDM's utility, as well as how to optimize its use. Gal Mayer, MD, of New York's Callen-Lorde Community Health Center, calls TDM "an unpolished gem." But of the two major HIV studies groups, AIDS Clinical Trials Group (ACTG) has only one TDM study, to test its use on HIVers failing PI regimens (A5146), and Community Programs for Clinical Research on AIDS (CPCRA) has none planned, though it may go back and analyze drug levels in blood samples from multidrug-resistant HIVers. TDM expert David Back, PhD, of the University of Liverpool in England—where TDM for HIV treatment is somewhat further along—says a TDM confab will take place February 12, the day after the Conference on

Retroviruses and Opportunistic Infections (CROI) in San Francisco. As Cal Cohen, MD, of Boston's Community Research Initiative puts it, "Can we figure out an intelligent use of this test?"

The Take-Home

Be like Rick: Despite TDM's flaws, docs relate cases where a clear reading of a patient's drug levels could be vital—Rick Roberts, whom Romeyn calls an "AIDS warrior," won't soon forget TDM's intervention. He's holding steady with detectable but low-flying virus and CD4s in the more-than-respectable 400s. "Don't just accept feeling bad," he urges. "It's worth checking the things you can check." If a new regimen with a PI in it is making you miserably sick more than a few weeks in, get your PI levels checked—they may be too high. Ditto, if your doc is frustrated that your protease regimen's not kicking butt and you *know* you're not missing doses—your levels may be too low.

Dosing down: If you're suffering bad nuke-related side effects like neuropathy and you don't have the option of switching meds, talk to doc about cutting your dose—especially for Zerit. Recent research suggests it can still do the trick at as low as half the standard 40 mg dose.

Contact high: E-mail the ACTG (at aactg.s-3.com) and the CPCRA (at www.cpcra.org) and clamor for studies into HIVer drug levels. And if you've failed a protease regimen and your viral load exceeds 1,000, you're eligible for a TDM study. Search "A5146" at www.clinicaltrials.gov for sites near you.

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