# Detectable Rebels

HIVers who don't care about having an undetectable viral load are nuts, right? New research shows they may not be, igniting fresh—and even hostile—debate about undetectability and long-term health.

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Shane Theriot doesn't consider himself a risk-taker. The upbeat 28-year old flight attendant, diagnosed with HIV in 1993, lives with his best friend since grade school in the same small Texas town where he grew up—across the street from his mother and next door to his grandmother. His sister and two nephews are nearby. "My family and friends," he says, "are my life."

Nevertheless, Theriot is taking a major risk—according to most top HIV doctors. Since May 2003, he's been taking only Trizivir (the one-pill combo of AZT/3TC/abacavir), though it has never pushed his viral load to "undetectable" levels: fewer than 50 copies of HIV per milliliter of blood. His last labs, in August, showed that he had 220 CD4s (just above the 200 mark considered HIV's "danger alert") and a viral load of 24,900. The latter number is hardly a six-figure shocker, but it likely means that Theriot's virus has replicated fast enough to have developed resistance not only to the meds in Trizivir—but to future treatment options as well.

Why is this risk-averse small-town boy letting his HIV off the hook? If he added a pill from another med class—protease inhibitors (PIs) or NNRTIs (non-nukes)—he could probably crush his viral load. The answer is simple: side effects. Theriot fears the body-shape changes, or lipodystrophy, that PIs can bring. "Forty years from now, when I'm 68, I don't want to look like the hunchback of Notre Dame," he says. Indeed, Theriot calls PIs "a total last resort" that he would consider only if his CD4s stayed under 200 for a year—or if he developed an HIV-related illness, which he says he never has. As for non-nukes, Theriot says he once developed a bad rash after a few days on Viramune (nevirapine) and fears the risk of depression and nightmares linked to Sustiva (efavirenz). His doctor and others have urged him to do something now. But, Theriot says, "I'm not concerned about what makes them comfortable."

He's not alone. *POZ* spoke to HIVers all over the country who aren't living as close to the edge as Theriot (who says that skyrocketing viral load alone would not change his mind about his regimen) but are accepting low levels of virus over adding or changing meds. Among them is Brian Varner, 40, the director of treatment education for the Tennessee AIDS Support Service, who was diagnosed in 1993. His regimen of Sustiva and Combivir (AZT/3TC) has kept his viral load between 300 and 400—a few paces above undetectable—for two years. "The last time I talked to my

doctor, he started into a long, drawn-out explanation of resistance and switching regimens," Varner says. "I politely stopped him. If there was a big spike—say [up to] 20,000 copies—I'd consider switching."

Meanwhile, over in Phoenix, Chris Daley, 51, a computer consultant diagnosed with HIV in 1989, boasts stable CD4s and viral load between 1,000 and 3,000 on what many would call a sub-optimal regimen of Viracept (nelfinavir) and Zerit (d4T). "I'd rather have the side effects I know than those I don't," he says. "We've left well enough alone."

Theriot, Varner and Daley represent a subpopulation of American HIVers who get little play in the official research literature—not to mention big pharma's glossy ads featuring sunny types touting their undetectability—and until recently could be easily dismissed as detectable daredevils. But four studies published in recent months have challenged the presumed dangers of undetectability. As docs and people with HIV square off over the new research, it's time to ask whether Theriot, Varner and Daley are courting disaster—or whether they are pillars of sanity in a world gone cuckoo for undetectability.

## UNDETECTABILITY: THE DEFENSE

Without meds, HIV is constantly replicating inside your body, undergoing tiny changes in its makeup, called mutations. Now add meds: The more powerful, or suppressive, they are, the less HIV replicates—at least in the blood, where your viral load is measured. Research suggests that when your HIV replicates below the 50-copies mark (the lowest level that the most common viral-load test can detect), it isn't active enough to terrorize your immune system—or churn out the mutations that allow it to elude, or become resistant to, your current or future meds.

That's how meds are supposed to work. But as we all know, HIV drugs aren't always easy to tolerate, and even when they are, people, being human, miss doses. With a combo like Viramune or Sustiva paired with Truvada (FTC and tenofovir)—popular first regimens due to their relative lack of side effects and easy dosing—a few missed doses can spark enough replication to produce the dread K103N mutation, which, on those combos, may lead to permanent detectable virus. And detectability equals more mutations. Which means fewer treatment options and, in turn, AIDS, sickness and death—right?

That has been the thinking, more or less, since 1996, the watershed year when David Ho, MD, of the Aaron Diamond AIDS Research Center mesmerized audiences at the World AIDS conference in Vancouver with a new buzzword: *undetectable*. Citing patients whose new protease combos had squashed HIV to undetectable levels, Ho suggested that if the drugs were used to "hit early, hit hard," ultimately HIV might be "eradicated" from the body.

Undetectability quickly became shorthand for all the hope and hype of the post-protease era. In doctors' offices, HIVers now on HAART prayed to pass a new test that could measure viral load as low as 400—and later even 50—copies. If they didn't, these HIVers were often branded a treatment "failure," even if they had robust CD4s. Many HIVers believed (wrongly) that undetectability was synonymous with uninfectious. There was even a 2001 documentary called

*Undetectable*, about HIVers both enjoying and missing out on the protease miracle.

Eradication, of course, turned out to be a fantasy. “Hit early, hit hard” is no longer a hard-and-fast rule. Icky side effects and reassuring research have led many to postpone starting meds—or take a treatment break—as long as CD4s exceed 200 to 350. And we now know that some HIVers have developed so much med resistance that aiming for undetectable is unrealistic.

But by and large, undetectability remains our treatment gold standard. Big-time HIV specialists such as Ho; the University of Alabama’s Michael Saag, MD; Boston’s Cal Cohen, MD; and Johns Hopkins’ Joel Gallant, MD, maintain that fully suppressing the virus should remain the primary goal for HIVers starting their first, second or even third regimen. Says Gallant, “Many studies show that people with detectable viral loads develop new mutations, and that’s true even when the viral load is as low as below 1,000. Those mutations will cause resistance that decreases future treatment options.” Even much-discussed research showing that drug-resistant virus is weaker than HIV that’s never been exposed to HIV meds hasn’t changed the detectability dogma. Steven Deeks, MD, of the University of California at San Francisco, who pioneered such research on “viral fitness,” considers his findings more of a consolation prize to HIVers with mulitdrug-resistant (MDR) virus. “There’s no reason to think it’s better to have MDR virus than suppressed or wild-type,” he says.

Ho and Gallant staunchly defend the undetectable benchmark. Ho calls it “the biological principle that should guide our therapy, even if it is inconvenient for the practicing doctor or the patient.” Gallant adds: “You can call it orthodoxy or a holy grail, but there’s a reason for it. I think it’s very unlikely that this will change. If anything, it’s changing toward a stricter view, not away from it.”

DETECTABILITY: THE REALITY

That hardcore message has been difficult to challenge without data on what happens to HIVers who maintain “failing” regimens with detectable virus. But now such information is emerging—and it looks surprisingly good for detectable HIVers. In a study published in the September 1 *Journal of AIDS*, researchers sorted 3,000 HIVers, most of whom were on HAART, into three groups: those with viral load below 400 copies (the old-school definition of undetectable); between 400-and-20,000 copies; and more than 20,000 copies. Following them on average for a little more than four years, scientists found that those in the 400-to-20,000 group were no more likely to die or get sick than the below-400 group. (The 400 to 20,000 group also had on average a slight CD4 increase.) Those in the 20,000-plus group were significantly likelier to get sick and die.

This “doesn’t mean that your target [of reaching undetectable] should be any less vigorous when you’re starting treatment,” cautions lead author Stephen Raffanti, MD, of Tennessee’s Comprehensive Care Center. But it does mean “that for people with resistance the outlook is not exceedingly grim,” he says. “Many of us have large numbers of patients on their second to their fifth regimen who are reaping the clinical benefits but are nowhere near undetectable. We have to look at each patient individually—you can’t apply this cookbook recipe on how to handle HIV.”

Other newly published research yields similar surprises. Investigators in Vancouver looked at

deaths in more than 600 HIVers from 1997 to 2001, finding that only six percent of those who had died had developed resistance to drugs in all three classes. “Treatment failure due to antiretroviral resistance was not a major factor influencing mortality in this cohort,” they concluded. In a similar study, Gallant and his Hopkins colleagues found that of nearly 600 HIVers, those with heavy resistance were no more likely over 15 months to experience disease progression or die than those with little or no resistance. And in the realm of slightly detectable virus—an area where many doctors are torn between tweaking treatment and taking a watch-and-wait approach—a recent University of Pennsylvania study found that among 79 HIVers who stuck with their regimens even though their viral loads had reached between 50 and 500, nearly 40 percent were undetectable again within a year. The same percent were still below 1,000 after three years. Vincent Lo Re III, MD, who led the study, says it suggests that sitting tight with slightly detectable virus “may be a reasonable approach”—though, he says, the study didn’t last long enough to firmly recommend it.

That, says Gallant, is the problem with all the new studies, including his own. “If we only cared about your progress in the next five years,” he says, detectability would be OK. “But we’re thinking 20 to 40 years”—during which he and others are certain that detectable virus will push CD4s below 200, a reliable predictor of illness and death. Ho agrees: “When your gas tank runs down from full to half, the car still runs fine. However, your reserve is now down to half. Sooner or later, you will have to pay the consequences.”

There may be other downsides to detectability. This year, a 125-person French study associated a viral load greater than 200 with a higher risk of anal cancer and found that the six HIVers with viral loads over 1,000 indeed progressed to the disease.

What does our rebel Texan Theriot have to say about such findings? Still not as scary as side effects. “I don’t want to fix what ain’t broken,” he says.

## FIGHTING WORDS

Risk-takers like Theriot have their defenders. Dr. Raffanti, who believes that detectability may not be as important as we think, wonders whether there’s a virologic thought police: “We’re heavily influenced by this barrage of talking heads, the providers closely associated with drug companies who go around doing talks telling other people how to manage their patients,” he says. “There’s enormous pressure by the industry to make us accept technology and different treatment options more readily than we should.”

Consider an ad that debuted in early 2004 for the entry inhibitor Fuzeon, declaring “Detectable is unacceptable.” In early 2004, activists accused Roche, the drug’s maker, of trying to shore up Fuzeon’s disappointing sales by scaring drug-resistant HIVers into submitting to Fuzeon’s twice-daily self-injections in order to achieve undetectable viral load, which has not proved possible in all HIVers on the drug. The company toned down the ad slogan to “Refuse to settle.” Maureen Byrne, a Roche rep, says it “was never our intention to put fear in anybody” over being detectable but that “if the patient does have the ability to become undetectable it should still be the primary goal.”

But some veteran activists and HIV docs reject that prescription, whether it comes from drug companies or star researchers like Ho. “When doctors say it has to be this way, they’re not talking about [having to take the meds] themselves,” says longtime treatment activist Martin Delaney, founder of Project Inform. He adds that “doctors say, ‘We go by the data,’ but they control what data exist. They affect the dominant point of view, and that affects the independent review boards [that OK studies at individual sites], so that’s a closed loop.” New York City’s Paul Bellman, MD, believes that “more viral suppression is not necessarily better” when you balance it against med side effects. He accuses honchos like Ho of ignoring research showing that generally nonsuppressive regimens like Videx (ddI) and the experimental drug hydroxyurea can help “significant numbers of patients clinically and immunologically stabilize despite low levels of viral replication” (see “Who’s Afraid of HU?”, *POZ*, October 2004).

Even angrier is longtime HIVer-treating New York City physician Joseph Sonnabend, MD, who has repeatedly—and publicly—denounced HIV orthodoxy. “On principle, I refuse to use the 50-or-below [test],” he scoffs. “If your viral load is 75, then 300, then 3,000, then 10,000, even I get a little scared—then we know you’ve got to change. But the decision should not be made on a snapshot. I have had detectable patients whose viral load has not gone up.” He calls his conservative approach “traditional infectious-disease medicine, not this cowboy bullshit marketing that has replaced it”—and blames the cult of undetectability on a small group of marquee doctors for whom AIDS medicine is “almost Hollywood,” he says. “David Ho is the leader of the pack.”

Ho takes offense, wondering “why people are trying to demonize us for putting forward our true scientific beliefs based on solid evidence. Some of us may actually know something about HIV that a doctor like Sonnabend does not. The real enemy is HIV.”

LAST WORDS

The two sides may not be as polarized as they seem. Viral vanquisher Ho concedes that we can “relax” about viral load—if, he says, relaxing means the “need to strike the right balance between tolerability and undetectability.” And contrarian Sonnabend admits that “we’re better off” now that we have a yardstick for viral load as well as CD4 count. The official government stance straddles this middle ground, too: The federal HIV-treatment guidelines says that viral suppression is a “critical goal” but should be “balanced against the need to preserve options.”

In the end, one thing is clear: While most HIVers remain committed to staying undetectable, all the data in the world, explained by the most earnestly antiviralist doctor, can’t make some people do what doesn’t feel right. There is a personal, semi-intuitive place where HIVers make their final decisions—the same place where many decided to avoid AZT when it was the only med available or take a drug holiday before research endorsed it. “Patients do indeed decide not to take your advice,” says the University of Cincinnati’s Judith Feinberg, MD, “and you have to accept their decision.” Though it may horrify antiviral purists, or titillate lab-weary HIVers, for Theriot, that decision remains a simple one. “If I feel perfectly healthy,” he says, “I don’t care about the numbers.”

**DETECTABLE DOs AND DON'Ts**

On meds but detectable? Try this six-point plan:

**Relax** The sky isn't falling.

**Get honest** Are you missing doses? (That could account for detectable virus.) If yes, talk to Doc about why and what to do about it. Maybe you need another combo—or a drug holiday.

**Avoid "snapshot" decisions** If you're newly detectable, test again in a month or two—especially if your viral load is low (50 to 500). It may just be a "blip," which, research suggests, is nothing to sweat.

**Look for a pattern** Is your viral load stable—or steadily rising? The latter is more worrisome.

**Consider a resistance test** Once your viral load tops 500 to 1,000, a genotype/phenotype test can show whether your virus has mutated against your meds. Doc may suggest adding or switching meds.

**Assert yourself** If you don't want to switch, Sonnabend says to ask Doc: Am I at risk of something—and if so, what? Could we monitor my viral load and CD4s for another six weeks to two months? You have the right to a second opinion—and Doc should make your records available for it

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