Three’s Company

...but is a triple-nuke combination enough crowd to stop HIV? Tim Murphy probes Trizivir, the trendy three-in-one pill that...might

January 1, 2003 By Tim Murphy

Jeremy Tjhung’s first meds marriage was unhappy. Right after seroconverting and testing HIV positive in 1999, the 38-year-old Manhattan designer started a study at the Aaron Diamond AIDS Research Center (ADARC) that put newly infected HIVers on a brawny protease inhibitor (PI)-based cocktail to try to stop HIV from taking off. Within weeks, his spiking viral load was undetectable -- and he’s had over 450 CD4s ever since. But he quickly ran into a gamut of side effects and adherence problems. An initial combo, including the PIs Agenerase (amprenavir) and Crixivan (indinavir), gave Tjhung an itchy rash he recalls as “no trip to Paris.” ADARC’s Martin Markowitz, MD, replaced Crix with PI Norvir (ritonavir), but he still had gas -- a major social bummer.

So last June, when Markowitz offered him a switch to Trizivir (AZT, 3TC and abacavir) -- and nothing *but* Trizivir, mind you, for a treatment total of one little pill twice a day -- he jumped at the chance. Five months after Tjhung’s second trip down the aisle, he’s still a happy honeymooner. His viral load has remained undetectable and his CD4s have stayed strong. But best of all, Tjhung says, “My adherence is up. I miss maybe one dose a week. It’s heaven.”

That’s just the kind of love story GlaxoSmithKline (GSK) hoped to hear many times over when, in November 2000, the FDA approved Trizivir, a one-pill combo of GSK’s old-line NRTIs (nukes) AZT, 3TC and the newer “power nuke” abacavir. The FDA nod was based on 24-week studies showing that the first triple-nuke-in-one-pill held its own in safety and efficacy against a combo of Combivir (GSK’s popular pairing of AZT and 3TC) and Crixivan. Soon after, GSK launched an aggressive campaign marketing Trizivir *alone* as a cheaper, simpler alternative to PI-based regimens for healthy HIVers just starting therapy. “You simply can’t argue with one pill twice a day,” says Markowitz. “It’s easy to take, easy to take and easy to take.”

For HIVers faced with fistfuls of horse pills, such a pitch is, well, easy to take. But wait a minute, you might say. Wasn’t it just yesterday that the experts were warning us that a nukes-only regimen wasn’t enough? Isn’t that how pre-protease HIVers developed the kind of resistance to nukes that has left them with limited treatment options today? And isn’t the success of today’s combination therapy built on taking a *combination* of classes of HIV drugs...often still including at least one PI?

To a great extent, that’s still true. But, lucky for GSK, Trizivir comes along just as we can

confidently say you don't *always* need a PI to effectively suppress HIV (Sustiva combo, anyone?). We also now know that PIs are linked to a staggering array of side effects -- from killer diarrhea to skyrocketing cholesterol to body-warping lipodystrophy. Yet despite their downsides, PIs remain the most potent meds in our current arsenal, often packing a lifesaving punch against HIV when nukes (and non-nukes, which can poop out fast) have lost their bite. For all these reasons, more and more HIV docs are postponing PIs when their patients first start on meds, saving them for the rainy day when drug resistance rears its all-too-common head.

Add to that the common sense assumption that if we're going to have a virgin's chance in hell of sticking with a lifelong HIV meds program, it's best to be on as gentle and pill-paltry a regimen as possible. *Voila!* The stage is set for the 3-in-1 Trizivir as an irresistible option for treatment-naïve HIVers. What gives Trizivir the leg up over the wimpy nukes-only combos of the early 1990s is its inclusion of the relative newcomer nuke abacavir (marketed alone as Ziagen), which in trials has generally proven itself to be a more potent, longer-lasting drug than either AZT and 3TC. That means whereas those earlier nuke combos allowed resistance faster than you could say "Holy mutating virus, Batman!" Trizivir has the fighting power to hold resistance at bay and thus keep HIV suppressed.

The $64,000 Question, though, is for how *long*? The answer may depend on just how much HIV -- and how many other nukes -- have circulated in any one person first. When GSK looked at the study's two arms after a *second* 24 weeks, among the HIVers who started treatment with viral loads over 100,000, the percentage of those in the Crixivan arm who were still undetectable was about 15 percent higher than those in the Trizivir-only group -- suggesting that for HIVers starting therapy with a viral load over 100,000, Trizivir alone just might not pack enough of a wallop. And Markowitz notes that, even given the study's 100,000-plus contingent, it was done overall with "patients far less advanced (in their HIV disease) than some patients being prescribed [Trizivir] now." For his own patients with advanced disease or high viral load, he says, he would definitely add a fourth non-PI drug, like Viread (tenofovir) or Sustiva (efavirenz).

But if Trizivir alone is an iffy choice for treatment-*naifs* with advanced disease or high-flying viral loads, it's likely even *less* of an option for those needing "salvage therapy" to make up for treatment failure with other HIV meds -- especially those who have developed resistance to older nukes. You might be able to pull it off if you're only resistant to 3TC -- but add heavy AZT resistance to that, and even Trizivir's studly abacavir may not save the day. San Francisco HIV doc Stephen Deeks, MD, predicts that, all told, "the rate at which resistance will occur with a triple-nuke regimen is dramatically lower than occurred in…the early '90s," when two-nuke combos were the norm. "But clearly over time a significant proportion will develop resistance variants, and then how do you handle that if other options are not available?"

Such a question begs the question: Just what *are* the other triple-nuke alternatives to Trizivir? After you rule out adverse nuke combos, you could theoretically add abacavir to ddI+3TC or to AZT+ddC, but until these pills' separate makers partner up to pour 'em together, they'll lack Trizivir's tidy one-pill allure (though about a half-dozen second-generation nukes coming down the pike, like potential 3TC rival FTC, may broaden the palette in years ahead).

Still, Trizivir's current reign over the Land of Triple-Nukes-Only is not without its side-effect side story. Trizivir is already out of the question for anyone who's ever had the infamous hypersensitivity reaction that Ziagen (abacavir) causes in 3 to 5 percent of takers, who must stop the drug immediately and risk a fatal second attack if they take it again. In addition, Trizivir possesses the potential side effects of three drugs combined, from the merely miserable (headaches, nausea, fatigue) to the more serious but treatable (anemia, neutropenia) to very scary, not fully understood or easily treated conditions linked to long-term nuke use, particularly lactic acidosis (elevated lactate levels), which can damage the liver (way-bad news for HIVers with hep B and/or C), and mitochondrial toxicity (damage to cellular DNA), which can cause muscle weakness and that dreaded fat loss in the face and limbs.

So, two years after its FDA go-ahead, is Trizivir on its way to earning GSK's pride as The Little Pill That Will...hold back HIV all by its wee self? That's not a good bet for nuke-weary HIVers, or even treatment-newbies with raging viral load -- and precisely why shiny, happy numbers from a 24-week study weren't enough to keep U.S. federal experts from "strongly recommending" that Trizivir be paired up with a drug from another class for starter therapy. Right now, though, Trizivir looks like a good bet for treatment-naïve types with docile viral load -- or even treatment toddlers like Jeremy Tjhung, who can now afford to gear down from a power PI-combo to a nukes-only regimen. With not even a year of Trizivir success under his belt, Tjhung knows that resistance could eventually foil this match made in heaven. Meanwhile, "I'm keeping my fingers crossed," he reports, then adds -- in the spirit of nervously happy newlyweds far and yon -- "I hope this lasts."
