CPR for HAART Failure

Best bets for antiretroviral vets

July 1, 1998 By David Stokes

After six years of taking all the available nukes (AZT, ddI, ddC, d4T, 3TC) in various combinations, I was relieved to hear Dr. David Ho's announcement two years ago in Vancouver that HIV eradication might be only 36 months of undetectable virus away. In July 1996, I switched from a failing regimen of AZT/3TC to a double **protease inhibitor (PI)** combo of ritonavir and saquinavir. Within two weeks, my viral load plummeted to an undetectable level (below 20 copies) and stayed there for 17 months.

So my HAART (highly active antiretroviral therapy) appeared to be working. But in early 1998—only, I hoped, 19 months away from realizing Ho's promise—my viral load jumped to 22,000; on retest it was 17,000. Was it HAART failure or had I just skipped a beat? Even more important, how could I restart a failing HAART?

The 1998 Retroviruses and Opportunistic Infections Conference in Chicago shed light on a few new options, but concerns over resistance and cross-resistance left no clear solutions. As Ho's eradication goal went from three years to as long as 20, I was left with lots of questions:

Should I intensify my regimen, and if so, with what?

Should I switch to an entirely new combo, and if so, how many new drugs are enough?

Will resistance block the new drugs' effectiveness?

Can I recycle already-used drugs?

Are there enough new drugs in the pipeline that I can just stick with my regimen and wait for at least three new drugs?

And the truly burning one: Will Susan Lucci finally win that Emmy?

Except for that last one, final answers on these aren't in yet. But a more informed therapy decision can come from considering all the latest on up-and-coming drugs—along with new tidbits on old ones. (The first batch of drugs to ponder are those FDA-approved or available now or soon through expanded access; the others are far from wide availability, in either Phase I—small safety trials—or Phase II/III—larger trials of safety and effectiveness.)

Efavirenz (Sustiva, DMP 266) from DuPont Merck joins nevirapine (Viramune) and delavirdine (Rescriptor) in the class of **non-nucleoside reverse transcriptase inhibitors (NNRTIs)**, also called non-nukes. The good news is that efavirenz is dosed once a day with no food restrictions, is

extremely potent and penetrates the central nervous system. The bad news is that cross-resistance to nevirapine or delavirdine will likely knock these off the list for anyone who used these drugs alone or in failing combinations. Side effects of efavirenz include lightheadedness, dizziness, nightmares and rash; serious birth defects were seen in the offspring of female monkeys given efavirenz. Currently available through expanded access, efavirenz is expected to be FDA-approved by mid-1998.

Abacavir (Ziagen, 1592U89) from Glaxo Wellcome is the latest in the class of **reverse transcriptase inhibitors (RTIs)** of the nucleoside-analogue variety (the nukes listed above). Abacavir is as powerful as AZT and 3TC combined, is well absorbed and has good penetration of the central nervous system. Resistance to AZT/3TC may create cross-resistance to abacavir, but probably not always. When you start abacavir, watch for noticeable side effects that could indicate an allergic reaction, including rash, nausea, vomiting, fever and malaise. If this occurs, stop the drug immediately, and *don't try it again*. Some patients who tried abacavir a second time after experiencing initial side effects had severe reactions, with one death in Europe. Abacavir is currently available through expanded access. FDA approval is expected in late 1998.

Fortovase (soft-gel cap saquinavir), a new PI from Hoffmann–La Roche, is an improved version of Invirase (hard-gel cap saquinavir), the first PI on the market. The company says Fortovase is 10 times better absorbed than the old saquinavir, but half that increase is due to a doubled dose-per-milligram. Results from several trials combining Fortovase with other antiretrovirals indicate that Fortovase is powerful, particularly when combined with ritonavir or nelfinavir. Cross-resistance, however, will make it a bust for many who tried saquinavir or failed earlier PIs.

Amprenavir (141W94) is Glaxo Wellcome's first PI. A long half-life (time it lasts in the blood) and high plasma trough levels (when least amount of drug is in blood) allow for twice-daily dosing, but cross-resistance to other PIs appears likely. Amprenavir in combination with other PIs looks good, achieving impressive viral load decreases. Side effects include headaches, intestinal distress and rash. Amprenavir is currently being studied in Phase II/III trials, and activists are pressing Glaxo to start expanded access.

Hydroxyurea (Hydrea), a 30-year-old cancer drug, is very hot right now. Dr. Franco Lori of the Research Institute for Genetic and Human Therapy in Gaithersburg, MD, suggests that HIV generates signals that activate resting CD4 cells, causing them to produce more viral copies, which infect and activate more CD4s. Hydroxyurea interrupts this process, blocking cellular factors used in viral replication.

Recent trial results suggest that hydroxyurea with ddI and/or d4T makes for a potent combination, which can even work in PWAs who have developed resistance to those nukes. This is good news for folks like me who used the "d" drugs previously—hydroxyurea may allow them to be recycled effectively. On the downside, this chemotherapy can suppress white blood cell and CD4-cell production, but in several studies this has not been a serious problem. The drug is available by prescription.

There are also several new classes of drugs on the horizon, giving the heavily pretreated among us new hope:

Nucleotide (not nucleoside) analogue RTIs include Gilead Sciences' **adefovir** (Preveon, **bis-POM-PMEA**) and bis-POC-PMPA, both of which can be taken orally (earlier forms were injection-only). Currently in Phase II/III trials and available through an expanded access program, adefovir appears active against both HIV and herpes viruses, including CMV and herpes simplex. Side effects include nausea, diarrhea and a reduction in carnitine levels (a key nutrient that must be supplemented). Bis-POC-PMPA appears to be more potent than PMEA in Phase I trials. So far, there is little evidence of cross-resistance between these drugs and currently approved antiretrovirals, and they may be as good as any RTI. But there is a possibility of cross-resistance with the nucleoside analogue RTIs, particularly ddC.

Fusion inhibitors (FIs) are—after a long wait—in sight. They're designed to block fusion between HIV and CD4 cells, a critical early step in viral reproduction. Without fusion, HIV's genetic material cannot enter the cell, and the virus cannot replicate. FIs target HIV in the step before RTIs and PIs. All currently available antiretroviral drugs inhibit the reproduction process after the cell is infected. **T-20**, an intravenous drug from Trimeris, is the first FI on the block. Recent Phase I/II trials with T-20 provided the first clinical evidence that FIs can produce anti-HIV activity. Yay!

Zinc finger inhibitors (ZFIs) are exciting new agents for a number of reasons. HIV uses a "zinc finger" structure to process a tiny protein that enables HIV to mature and infect a host cell. Because these zinc fingers are almost identical across all retroviruses, any drug that destroys this structure may stop HIV replication and keep the virus from developing resistance. Fortunately, there are potentially hundreds of cheap, relatively nontoxic agents out there that could target HIV's zinc fingers, and two are already being studied in early human trials.

Tat, rev and integrase inhibitors are other potential anti-HIV drug classes now being studied, but lie farther back in the pipeline.

And a gaggle of second-generation old-class drugs are just beginning their long journey through the testing process. Some appear to be active against virus resistant to current drugs of the same class, but who knows how they'll pan out? The next round of **PIs** includes Pharmacia & Upjohn's **PNU-140690** and Parke Davis' **PD-178390PI.** New **RTIs** include **F-ddA, FTC, dOTC (BCH-10652)** and **MKC-442**.

Based on all this knowledge, I decided to stick with the ritonavir/saquinavir combo but strengthen it by recycling ddI and d4T, giving them a turbocharge—and hopefully restored effectiveness—by adding hydroxyurea. This enables me to get a bit more mileage out of my regimen. Other contributing factors to my decision: Recent evidence that CD4s do not necessarily plummet despite viral load rebounds; concerns over the possibility of cross-resistance to abacavir and amprenavir; and my desire to save efavirenz (and the entire non-nuke class) for future salvage therapy.

Within the next two years, I hope to be able to combine efavirenz with PMPA, F-ddA, FTC, PNU-140690 and, what the heck, maybe even a zinc finger or two for good luck. Now if I could just get David Ho to lower that eradication estimate again…

Where to find it

p. 27, Gazette

To catch air with Board AID, contact www.boardaid.com or 760.722.0653.

p. 43, POZ Picks

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p. 68, "Dream Team '98"

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Get a house call from Doctors Without Borders at www.dwb.org, or page them at 212.679.6800.

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p. 92, "Ashok to the System"

Write to the man known as India's Larry Kramer, Ashok Row Kavi, at The Humsafar Trust, P.O. Box 6913, Santacruz (West), Mumbai, 400, 054 India, or email him directly at ADMIN@humsafar.ilbom.ernet.in.

p. 98, "Bank on Disaster"

For more info on the World Bank and IMF policies, contact the 50 Years Is Enough Network at 202.463.2265, or the Development Gap at 202.898.1566. Contact the African Women's Economic Policy Network at the Church of Uganda, Box 14123, Kampala, Uganda.

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