Who’s Afraid of HU?

How—and why—the government and top docs have shelved a potentially lifesaving HIV med

October 1, 2004 By Austin Bunn

In the history of HIV treatment, certain drugs stop being just medicine and become social and political flashpoints. Bactrim, for instance, prevents PCP pneumonia in organ-transplant patients, but pioneering ’80s AIDS docs, challenging the medical establishment’s conservatism, used it to treat HIVers (the Food and Drug Administration wouldn’t approve the usage until 1994). After AZT arrived in 1987 at the staggering cost of $10,000 per year, ACT UP and other activists hounded Burroughs Wellcome into lowering the price and would later force the FDA to radically alter the design and pace of the drug-approval process.

No one would have predicted that the 40-year-old, generic chemotherapy drug hydroxyurea (HU) would be a candidate for such historical distinction. Used to “cool down” leukemia patients’ immune systems, which battle fatal amounts of white blood cells, HU seemed promising for HIVers dealing with immune systems run amok. But after HAART’s success—and the 1998 deaths of two HIVers taking HU—the drug became as outmoded as ACT UP die-ins. The final blow came in July 2003, when the Department of Health and Human Services’ (DHHS) HIV guidelines panel recommended to HIV docs that HU “not be used at any time” to treat HIVers.

A year later, however, HU is back from the dead. New research, as well as ongoing studies by those who never doubted the drug’s potential, suggest it could have a place in the evolving science of HIV care. What’s more, Paul Bellman, MD, a top New York City HIV specialist who has successfully prescribed HU for years, is leading a bold one-man crusade to reverse the DHHS recommendation, publicly accusing those responsible of making a “serious error,” pandering to big pharma and “potentially jeopardizing” his patients’ health. Indeed, says Bellman, there’s more at stake than the fate of HU and the patients who take it. HU, Bellman contends, symbolizes HIV treatments outside the “HAART paradigm” of combination therapy, which, he points out, dooms HIVers to “a lifetime of antiviral therapy with brand-name drugs”—and the side effects they bring with them. The brawling inside story of the controversial DHHS decision—and the skepticism a variety of top docs shared with *POZ* about HU—capture a pill’s twisted course from promising treatment to dangerous drug and, possibly, back to promising treatment. But first, a brief science lesson.

What HU could do for you

HAART is the undisputed standard of HIV care, but its limits, especially for HIVers who have

developed drug resistance, are all too familiar: a lifetime of pills that must be taken like clockwork and the hovering threat not only of lipodystrophy, neuropathy and other side effects, but of running out of treatment options. Such limits are why some docs believe that a drug like HU could play an important role in long-term HIV survival: It doesn't cause resistance—and could lessen HAART toxicity.

Antivirals hinder HIV replication, but HU works differently, targeting the body's own infection-fighting CD4 cells. To proliferate, HIV needs active and dividing CD4 cells to attack and infect, so HU slows down CD4-cell division, reducing the number of cells HIV can infect and replicate in. Think of it, says leading HU researcher Franco Lori, as "predator" and "prey." If HIV is a predator and CD4 cells are its prey, when you "decrease the number of prey, the virus has fewer chances to replicate," he says.

That's HU's "immunological" effect. When taken with the antiviral Videx (ddI), it also has a "virological" effect. As it replicates, HIV needs a chemical it finds in CD4s called nucleosides, which HU reduces. If the virus enters an HU-assisted cell and doesn't find nucleosides, it takes up ddI, which *resembles* nucleosides. Lori calls ddI "the poison food" that stops viral replication.

Even if you don't get the subtleties of the science, it's easy to grasp HU's biggest advantage. It works on the cell's machinery, not on the virus—avoiding the problem of drug resistance. That gives HU exciting potential uses: It could serve as another line of defense for HIVers who've run out of HAART treatment options, sidestep lipodystrophy (by reducing the antivirals HIVers need to take) and steady the immune system during structured treatment interruptions (STIs).

Bellman has 20 patients who have taken HU from four to six years. Most are on salvage therapy. Diagnosed in 1988, Mark once had almost no CD4s and a viral load over 100,000; over the years, he has become resistant to every class of HIV medication, including the "nukes" (NRTIs) that make up his current regimen of Viread (tenofovir), Epivir (3TC) and Ziagen (abacavir). But with HU added to that trio, his CD4s last numbered 424 and his viral load 283. "Bellman said something about HU being used [as chemotherapy] to treat leukemia and that was a red flag for me," Mark says. "But I've never had an opportunistic infection. My health has been very good, and I've been lucky: My meds are working." And he's not experiencing any side effects.

To Bellman, Mark and patients like him are a compelling argument against the government's HU prohibition. "With HU as part of their regimen, they have stabilized, despite extensive drug resistance, multiple treatment failures, very high baseline viral loads and low T cells," he says. "I challenge people to tell me if it's not HU contributing to Mark's regimen's success, what is it?"

Another compelling argument is recent research on HU and lipodystrophy. A forthcoming study in the journal *AIDS* followed 187 Spanish HAART patients with undetectable viral loads who switched to HU and ddI. "My patients were tired of so many drugs, lipodystrophy and the psychological problems that came with it," says Dr. Pablo Barreiro, the lead researcher. "I said, 'I can offer you another way.'" After 48 weeks, 58 percent of the patients had viral loads below 5,000 and 41 percent had loads below 500. CD4 counts dropped—HU is immune- suppressive—but 77 percent

kept CD4 counts above 350. Most important, the majority saw improvements in lipohypertrophy (fat buildup), lipoatrophy and lowered cholesterol.

Franco Lori has also quantified HU's viral-load suppression during STIs. In a 60-subject study, he showed that patients on ddI, Zerit (d4T), and HU had lower viral-load rebounds and were faster to return to undetectable levels than patients taking a ddI, d4T and Crixivan (indinavir) combo during a three-week on, three-week off STI. In another Spanish study, 20 patients took HU during their STI—and after nine months, 80 to 90 percent saw no viral-load rebound.

Even if they don't justify HU's widespread use, these and a handful of other studies are encouraging. Some recent research has been less so, and even HU proponents say more studies are needed. In high doses—higher than typically used in an HIV setting—over a long time, HU can deplete red blood cells (causing anemia) and white blood cells (neutropenia). But, says Bellman, "the fact that [antiretroviral] medications are developing severe, life-threatening illness makes us look for alternative therapies. I think it's clear that we've learned enough about HU to say that we should be learning more."

The HU controversy begins

If HU has such promise, why do the DHHS guidelines, the de facto manifesto on proper HIV treatment, stipulate that HU is "an antiretroviral component that should not be offered at any time" with "no exceptions"? That pronouncement "placed HU in a category that is almost like thalidomide [which causes birth defects] for pregnant women," says Bellman. HU's bad rep springs from the two HIVers who died while taking it in 1998.

After Lori published a groundbreaking HU paper in *Science* in 1994, a host of HU trials began, including two by the AIDS Clinical Trials Group (ACTG), a network of physicians created in 1987 to streamline drug testing. According to Lori, one of the ACTG studies—the only one referenced in the DHHS guidelines—was deeply flawed because it added HU to "completely suppressive" HAART regimens. In ACTG 5025, HU was added to Crixivan, ddI and d4T in patients with undetectable viral loads. "If you are adding a fourth drug to a regimen that is [already] completely suppressive, there's no way you can see increased efficacy," says Lori. "But will you see increased toxicity? You bet." HU's promise rapidly diminished when two patients in the 5025 study, all in its HU/ddI/d4T/Crixivan arm, died from pancreatitis. The study was stopped short.

When the research was eventually published in *AIDS* in 2001, Lori "found something peculiar": Dosages for HU and ddI were much higher than in most previous HU studies. ACTG 5025 gave patients 1,200 mg of HU and 400 mg of ddI once a day, whereas previous studies had used 1,000 mg of HU and 200 mg of ddI twice a day—a small shift, but enough to damage blood chemistry, says Lori. What's more, ddI at the time was not "enteric-coated," or formulated for slow absorption by the body, as it is now. Lori says that a high dose of HU with a spiked dose of ddI—in the non-enteric-coated formulation that Bristol-Myers Squibb (BMS) gave to ACTG 5025—can cause the toxicity that leads to pancreatitis.

Lori's nonprofit Research Institute for Genetic and Human Therapy, located in Washington, DC, and

Pavia, Italy, recently studied 120 patients on HU and ddI to find the optimal dosage. He found that the lowest dose of HU (around 600 mg once a day) was the most effective. One patient taking 1,200 mg of HU and 400 mg ddI (identical to ACTG 5025) developed a fatal case of pancreatitis. "So the only cases of fatal pancreatitis are when ddI is used at a certain formulation and HU is at 1,200," says Lori. Refining the new drugs' dosage, he adds, is part of the legacy of HIV treatment. "If you look back at AZT, the initial dosages were too high and too toxic but got experimented down," he says. "Same with ddI. We now have an optimal dose of HU—half of what was used in ACTG 5025—and I think it's time that we try that new formulation."

Despite Lori's detective work, HU's economic prospects had already suffered. In the fall of 1999, the FDA castigated Bristol-Myers Squibb, which makes ddI, d4t and two brand-name versions of HU called Hydrea and Droxia, for promoting a ddI, d4T and HU combination without mentioning ACTG 5025's side effects. After the study's lead researcher, Diane Havlir, MD, had presented her findings, but before the results of ACTG 5025 had been published in AIDS, the FDA sent BMS a letter saying it had promoted drugs for unapproved uses. BMS was forced to write a "Dear Doctor" letter warning physicians about pancreatitis and other potential toxicities.

In July 2003, the DHHS guidelines panel, which uses published papers in peer-reviewed journals to evaluate treatment regimens, caught up to the 2001 HU data published in *AIDS*. They designated HU as "not recommended" because of a lowered CD4 count, ddI-associated side effects (such as pancreatitis) and "inconsistent evidence of improved viral suppression."

No wonder a variety of doctors queried by *POZ* responded with skepticism about HU. "I didn't know anybody was still using [HU/ddI]," wrote Charles van der Horst, MD, at the AIDS Research and Treatment Unit at the University of North Carolina/Chapel Hill. Top HIV doc Michael Saag, MD, says he stopped using HU in the late '90s "due to fears about toxicity," adding, "I found it could lead to cases of advanced neuropathy and pancreatitis." Dr. Marie-Josèphe Commoy of France's Agence National Recherches sur le Sida, which oversees that country's AIDS research, says "there are no plans to treat patients with HU in trials." Martin Markowitz, MD, of the Aaron Diamond Research Center says the "data…would not support its routine use," and veteran HIV doc Donald Abrams, MD, says doctors who use it "may be doing harm."

Oncologist Paul Volberding, MD, a professor at the University of California/Los Angeles and a member of the guidelines panel, says "so many things have come along that are so much more potent without the questions of toxicity that we've moved on [from HU]." He uses HU in his cancer practice but not for HIV. To combat lipodystrophy, Volberding says that docs can simply juggle nukes. As for HU and ddI combined, he asks, "Why would a drug that is fairly toxic be preferable to just using more ddI?" Bellman says that "you can't just juggle drugs and expect significant results" and argues that Volberding "lacks appreciation for the toxicity of ddI." Bellman, however, rarely prescribes HU with ddI because of its "small band" between efficacy and toxicity.

HU's fundamental problem, says Lori, is that it lacks a strategic "development plan." In an era of big pharma chess-like maneuvers, it was crafted chaotically. "People threw it into all kinds of experiments, and the result of that is disaster," he says. Now that HU is generic, "it's very difficult

to put together a development plan for it because there is no interest in its use by big pharma." And since the July 2003 guidelines, "there are no NIH-funded trials and doctors will be reluctant to participate," Lori adds. "There's a definite chill on HU research."

Bellman on a mission

Bellman heard about the guidelines changes only coincidentally. One of his patients is *POZ* publisher Brad Peebles, who discussed taking HU and the guidelines in his January *POZ* publisher's letter. Bellman was livid when he discovered that HU had been "taken out of his tool kit."

In April, Bellman decided to fight the panel's decision. In a strongly worded letter to the guidelines panel, Bellman wrote that "a serious error that could potentially jeopardize the health of my patients as well as others" had been made. Because the decision was based on ACTG 5025, Bellman presented the trial's flaws. But he went well beyond that, claiming that panel members are caught up in "the current paradigm of HIV treatment…that contains a bias towards treatment with brand-name drugs that are highly lucrative for big pharma." That bias, he says, undermines research into generics like HU or structured treatment interruptions, which, if properly studied, could dramatically improve HIVers' lives. Although Bellman calls this bias "unconscious," his letter names names. Havlir, he says, is "a paid consultant to BMS." Her coauthor on ACTG 5025, Martin Hirsch, MD, serves on the guidelines panel. Referring to Hirsch in his letter, Bellman writes, "Sometimes academic conflicts of interest can prove more compromising than financial ones." Hirsch refused comment for this article; Havlir did not return *POZ*'s calls or e-mails.

Bellman's letter, published in the newsletter of the influential Treatment Action Group, wound its way upward. By mid-June, during the guidelines' monthly conference call, the panel addressed Bellman's letter, agreed to look at the most recent data and "will be reviewing" its position on HU at a future meeting, said panel chair John G. Bartlett, MD.

The panel's 33 members are a mix of academics, pharmacists, researchers and community activists; many are members of the ACTG (or as it is now called, AACTG). Bartlett and another guidelines panel member, Cornelius Baker, executive director of DC's Whitman-Walker Clinic, deny that big pharma influences them and their colleagues. "The panel clearly has no bias for brand-name drugs," says Bartlett. "In fact, there have been occasions when we have said some drugs were limited due to expense." Pharmaceutical companies can lobby the panel, but Baker says it "doesn't influence the outcome," adding that which researchers conduct which trials is "not an important factor" in the panel review process. "That would really change our partiality," he says. When ACTG 5025 was presented, Hirsch publicly acknowledged his involvement. Indeed, the expertise of physicians with specific drugs is vital to making recommendations, says Baker: "To deny that expertise would undermine the recommendation's whole value."

Not everyone, however, believes the panel works impartially. One member who requested anonymity believes that the panel's many AACTG members means it is "somewhat dominated by their point of view" and that the two largely negative ACTG studies on HU shaped the guidelines position. (Currently, no AACTG trials explore HU.)

Bartlett acknowledges that the guidelines are “primarily driven by viral load” and that the panel looks for treatments that bring it “down to 50 [copies].” That disadvantages HU, which is less virally suppressive than HAART. But Baker stands by the panel decision. “HU is an artifact,” he says. “It first came into discussion in 1998, and since then, we’ve had 10 additional drugs approved. Instead of 10 to 24 weeks of data for some regimens, our standard is having 48 weeks of data on everything we consider.” But if it’s a matter of data, ACTG 5025, upon which the panel based its conclusions, “represents just one-quarter or one-fifth of patients tested on HU,” says Lori. “It represents the minority of patients.”

AACTG vice-chair Daniel Kuritzkes, MD, also defends the panel decision. “There was a lot of interest in HU because of preliminary data from Franco Lori, but the fatalities quashed any other interest,” he says. However, the panel member who declined to be identified called the overemphasis on ACTG 5025 “bullshit,” adding: “You had two other drugs in there with a history of pancreatitis. It was a little disingenuous to rule against HU. I wasn’t alone in thinking that HU warranted a more even handling. But we all vote, and it’s majority rule.”

The guidelines also ignored a handful of positive published reports on HU. In an upcoming issue of *Drug Safety*, Lori highlights three such studies, including one AACTG trial, that claimed “encouraging results” for hydroxyurea-based combinations that challenge the conclusions of the other two ACTG studies. The guidelines panel, says one member, will reexamine these studies, as well as Barreiro’s forthcoming piece in AIDS. Baker says the panel has also instituted a new 60-day “comment period” when the guidelines are changed. Bellman says he has “never seen anything in the guidelines that referred to such a period, nor is there any particular e-mail address that invites comments.”

But the guidelines process isn’t the only problem—to some docs, it’s the guidelines themselves. “I’ve never been an advocate for the guidelines,” says Robert Redfield, MD, at Baltimore’s Institute of Human Virology, run by Robert Gallo, codiscoverer of HIV. “I never bought into AZT mono-therapy or dual therapy [both recommendations at one time].” Redfield, who was skeptical of ACTG 5025 as far back as 1998, says,“It’s clear to me that somebody is driving this nail down” against HU.

When the guidelines were created in 1997, pioneering AIDS doc Joseph Sonnabend, MD, wrote a letter declaring them a step backward. “I said we don’t need guidelines—we need evidence,” he says. Sonnabend founded the Community Research Initiative on AIDS (CRIA), a community-based trial system held in doctor’s offices. (Sonnabend eventually left; the organization is now ACRIA). CRIA and similar efforts lessened the influence of big pharma by offering alternative systems to try out drugs. But HAART’s success diminished their importance, and many of these alternative channels for drug testing—for HU or even aspirin—closed.

It’s easy for a drug like HU, with medical potential but little profit potential, to get lost in the waves of pharmaceutical HAART hype. But as long-term treatment leads to serious side effects, clinicians—often spurred on by desperate patients—will reexamine their treatment options, says Bellman, and wonder what’s missing and why. As Lori says, “HU is an experimental drug. If they

banned every experimental drug, nobody would experiment with anything.”
