The Way We Die Now

AIDS is over, HIVers are living to ripe old ages, right? Not quite. POZ asked for autopsies of five who “died of AIDS” only to find that they top killers now aren’t always HIV.

September 1, 2001 By Tim Murphy

PCP. MAC. KS. CMV. These bite-size abbreviations of long, florid diagnoses and rare, grotesque diseases were once on the tip of every PWA’s tongue. But enter protease-based combos in 1996, and within two years, the HIV death rate in the U.S.had plummeted by 70 percent. Thanks to HAART and the array of antibiotics that KO opportunistic infections (OIs), these nasty acronyms are no longer among AIDS’s top killers. Now meet the new lethal lingo: HCV. HPV. HIVAN. NHL. Not to mention such HAART spoilers such as drug resistance and side effects.

What a difference a decade makes: In 1992, the top causes of death among PWAs were unspecified pneumonia, pneumocystis carinii pneumonia (PCP), bacterial infections and Kaposi’s sarcoma (KS). Unpublished data from the CDC shows that in 1998, unspecified pneumonia and bacterial infections still headed the list -- an early sign of the now-infamous difficulties of HAART regimens, which can bolster the immune system to avoid such OIs. But next are liver complications, kidney damage and heart disease. Now where the hell did they come from?

Confirming this pattern is a recent study conducted at Case Western Reserve University. Michael Lederman, MD, and colleagues examined the causes of death among 260 PWAs treated at a local hospital from January 1995 through December 1999. While those with a history on HAART avoided the big AIDS acronyms, they tended to die of “end-organ failure” -- surprise! -- damage to the liver, kidney and heart. This trend is reported across the U.S. and Europe.

Why this shift in the deathscape? In addition to HAART’s dramatic reduction in the old-guard OIs, a frustrating Catch-22 accounts for the rising incidence of organ failure: HAART can reboot the immune system, but it can also cause cholesterol levels to skyrocket, putting HIVers at risk for heart disease, and its often-high toxicity can take a vicious toll on essential organs. Also, HIVers have high rates of hepatitis B or C, and when these viruses join forces with HIV, they can increase each other’s virulence. Moreover, there’s a definite but dimly understood link between HIV, even when well controlled, and cancer.

POZ asked four top HIV docs this cheerless but pressing question: Why is the Grim Reaper blazing these new trails? Each physician singled out recent patient deaths and performed a kind of diagnostic autopsy, removing the “Died of AIDS” label to examine which specific complications were responsible, what -- if anything -- could have been done to prevent a fatality and what the

take-home message is for all of us HIVers who are dying to stay alive.

CASE NO. 1

Cause of Death
Non-Hodgkins' lymphoma, June 2000

Patient
Gay white man, mid-40s, Boston, tested positive in 1989

What Went Wrong
This man had a long history of serial monotherapy," says his doc, Calvin Cohen, MD, an HIV practitioner in Boston and medical director of Community Research Initiative of New England. Cohen's patient went on a protease combo in 1996 that cut his viral load from 80,000 to below 10,000 and boosted his CD4 count from 310 to 400. "He was doing well -- a little bit of a party boy, the occasional STD, but nothing that got in the way of his regimen." In 1998 his viral load rebounded, his CD4s started dropping, and he complained of neuropathy. After a complete cocktail switch, his viral load improved a bit, but then his CD4s fell below 200, and he went on Bactrim, an anti-PCP prophylactic. When hisCD4s continued to drop, he tried a Sustiva/ritonavir combo, but the first messed with his moods and the second caused lipoatrophy (the *loss*, rather than redistribution, of fat). At this point, off therapy with 150 CD4s, he hunkered down, waiting for new meds from the pipeline instead of recycling an old combo. "He had a sense we were losing ground, but he didn't want to know every dip of the roller coaster," Cohen recalls.

The PWA soon started having night sweats, occasional moments of disorientation (they laid it off to a recent Ecstasy jaunt), nausea, vomiting, abdominal pain and fevers. A biopsy of a few enlarged lymph nodes in his belly confirmed non-Hodgkin's lymphoma (NHL) that had already spread, and that Cohen says doctors had been unable to detect at an earlier, more easily treatable, stage. His doctors thought he would tolerate chemo better with a lower viral load and higher T-cell count, so Cohen put him on a combo with the then-experimental PI Kaletra (lopinavir and ritonavir). But he vomited up all his meds. "At this point, he lost ground very rapidly," Cohen says. "The cancer was running rampant, and nothing would keep him well."

Backstory
This man's misfortune had partly to do with the dimly understood link between HIV-battered immune systems and cancer, particularly NHL and Kaposi's Sarcoma (KS) -- both thought to be caused by viral infections (Epstein-Barr and human herpes virus 8, respectively). Most clinicians agree that these were more common in HIVers prior to HAART, though some data suggest that NHL has remained constant and may even be rising. For his part, Cohen has seen few patients with well-controlled HIV develop NHL or KS. "It's not clear yet what it would take to make the rate of these cancers in HIVers closer to zero. But," he adds, "that's mostly because we don't understand cancer."

Cohen says that he thinks this man is one of those HIVers whose recent deaths are rooted in what he calls, with grim humor, "old AIDS" -- a syndrome in which they have developed not only viral

resistance to many HIV meds but also irreparable immune-system damage. As Cohen notes, doctors increasingly think this might happen when CD4 cells fall below 200, even if they rebound later with effective therapy.

Take-home
“Minimizing the virus’ resistance to therapies in any way we can is crucial,” Cohen says. “We have more meds than before, but we don’t have an unlimited number. If you’re having adherence troubles on a med, take it seriously and talk to your doctor -- don’t just take it half the time and risk developing resistance.”

CASE NO. 2

Cause of Death
Staphylococcus pneumonia, February 2001

Patient
African-American woman, 18, New York City, infected at birth

What Went Wrong
A bright,successful high school senior with a loving, supportive family, this young woman came, at age 15, to Montefiore Hospital. She was doing well on a four-drug combo, but soon her hoarse voice led to the discovery of nodules on her vocal chords. “The first biopsy didn’t answer what it was, so we treated it symptomatically,” says Adolescent AIDS Program head Neal Hoffman, MD. It ended up being MAC (mycobacterium avium complex), a common but dreaded OI, yet “no one had ever reported such a symptom for MAC before -- we called all around the country.”

At this point, the young woman had a 50,000 viral load and fewer than 50 CD4s. “You don’t see MAC except inpatients with low T cells who were never on treatment or who are failing it. It turned out she wasn’t adherent on her regimen,” Hoffman says. “We worked with her on that and pushed her viral load down to below 10,000.”

Still, her MAC was progressing, and her health declining. New treatment included a mobile central IV that enabled her to go to her prom and graduation, and then take a summer vacation. “We decreased her hospitalizations, which had included several ER visits when her airway would close up,” Hoffman says. “We put her on Kaletra, changed her NRTIs.” Her CD4s rose above 50, but in fall 2000, she had a blood clot and was put on an anticoagulant. Then her IV line had to be pulled when she developed a staph infection in it, which led to anti-staph therapy. She nonetheless developed chronic pneumonia that, Hoffman says, was likely from the original staph infection. “With all her complications, she ended up stopping her antiretrovirals -- it was too much.” She died last February from staph pneumonia with bleeding abnormalities. “Ultimately she made a decision to limit how much intervention she was willing to accept,” Hoffman says of her last wishes to have no intubation or ventilation, and no resuscitation when her heart and breathing stopped.

Backstory

Hoffman says that because neither his team nor any HIV specialists around the country recognized vocal-chord nodules as a MAC symptom, its treatment was delayed. He is currently “writing the case up” because it hasn’t been previously documented. “AIDS patients are not only susceptible to infections,” he says, “but to unusual manifestations,and all treatments carry complications.” What *really* happened here, says Hoffman, is “we spent a year taking care of problems that are hard to treat without a stable immune system. The one question I’ll always have is: Could this have been prevented if there were more work done to help her to adhere to her regimen? We put her on triple therapy, but I think she was missing a dose a day.” Still the fact that this young woman -- born 15 years before effective HAART --lived 18 years is itself remarkable. Most mid-’80s HIV positive newborns lived an average of five years.

Take-home
Hoffman says that, for HIV docs, “the lesson here is to be vigilant about a change in symptoms. Look for a cause, and then always pursue a diagnosis -- weighing that against the risks that might accompany any subsequent procedure.” But again, the backstory here is one of a host of complications arising in the wake of a bottomed-out immune system, due in part to checkered adherence. That’s why Hoffman stresses the critical importance of counseling, mental health services and support groups in HIV-care settings, particularly for adolescents. “They don’t want to disappoint their parents or providers, so they often don’t disclose their adherence problem,” he says. “Fortunately simpler regimens are coming out, but still we find youth motivating one another is more effective than just us working with them one on one.”

CASE NO. 3

Cause of Death
Cardio-respiratory failure due to liver failure, December 2000

Patient
African-American male, 53, Baltimore, tested positive in 1990

What Went Wrong
Triply infected with HIV and both hepatitis B and C (HCV), he was on several antiretroviral combos over the years, including protease inhibitors. “Eventually he became intolerant of retrovirals because they all gave him high liver enzymes,” says his physician, David Butcher, MD, an HIV practitioner in Baltimore. “He started showing rapidly worsening signs of chronic liver failure” -- including ascites, a massive accumulation of fluid in the abdomen that needs to be regularly drained with a long needle. Unfortunately, necessary nutrition and protein gets drained out with it. The man lived for another year with these complications before dying of hep-related cardio-respiratory failure, caused by the stress that his liver disease put on the heart and lungs.

Backstory
Butcher says that this man is emblematic of his predominantly African-American AIDS patients and their high incidence of IV drug use and hepatitis C, which Butcher calls his practice’s “biggest issue.” He says the No. 1 cause of death among his HIV positive patients is liver failure related to chronic viral hepatitis. With their livers shutting down, they often suffer from malnutrition and

other life-threatening crises, though their CD4s may be high and their HIV prognosis hopeful.“ Together, HIV and hep C are a double-whammy, ”Butcher says. “They accelerate each other’s progression rate, so those who are co-infected have a worse prognosis overall.”

Take-home
The importance of spotting and treating both hep B and C earliest istotal. “Advanced liver disease doesn’t leave many options,” Butcher warns, before stressing that hep C treatment, still far from widely effective, “has improved a lot in a year.” He cites the “new gold-standard” combo of interferon and ribaviran. “Interferon has always had heavy side effects like depression, but a far-easier-to-take once-weekly injection is coming out soon.” Response rates for the new combo are up to a dramatic 50 percent, so if caught early, hep C can be eradicated in six to 18 months. Researchers are increasingly recommending that doctors treat co-infected patients for hep B or C while their immune systems are still hearty, to rein in the hep and keep the liver in shape for a future onslaught of HIV meds.

CASE NO. 4

Cause of Death
Pneumonia, congestive heart failure, kidney failure, April 2001

Patient
African-American man, 48, Los Angeles, tested positive in 1985

What Went Wrong
This man was a long-term survivor with low T cells, says his doc, HIV specialist Gary Cohan, MD, managing director of Pacific Oaks Medical Group, in LA. About 18 months before he died, he developed HIV-related nethropathy (HIVAN), a form of kidney failure most commonly seen in African-American HIVers with CD4s below 200. “Soon we had him on dialysis three times a week,” Cohan recalls, "but because he developed intolerance to his HIV meds -- we’re not exactly sure why -- he started dialyzing them out, too -- and he was on his fifth combination already.So his HIV was definitely *not* well controlled. We put him on OI prophylaxis, but he dialyzed these, too, and got pneumonia. His kidneys were now under full attack by the HIV, and that was the beginning of a long downward spiral.“ Ultimately he suffered heart failure from end-stage kidney disease and fluid overload in a patient with wasting syndrome and a very weakened heart muscle, or cardiomyopathy.”

Backstory
“We tried everything to save this man,” Cohan says. “Dialysis, diuretics, antibiotics, heart medication -- but ultimately his entire body was far too weak to fight anymore. We call this multi-organ system failure.” Cohan attributes this man’s kidney disease and death to --you guessed it -- the “old AIDS” dilemma of resistant virus. Such patients are left with a shrinking arsenal of med options to suppress a virus that has likely exacted an irreparable toll on their immune system. “We caught him very early, started him on a low-protein diet, stopped meds we thought might be contributing to [HIVAN] and put him on dialysis,” Cohan says, but once the unchecked HIV unleashed its full wrath on this man’s kidneys, “there was nothing more we could do.”

Take-home
There is much to learn about the relationship between HIV and HIVAN (as well as other kinds of kidney failure in HIVers), although we do know that its disproportionate prevalence in blacks is thought to be of genetic origin. Most research suggests that HIV is active in the kidney, and that HAART lowers one's risk of HIVAN or slows its progression to end-stage liver disease. In recent years AIDS docs have pushed to conduct kidney biopsies on at-risk patients because signs of kidney complications might be a cue to start combo therapy earlier than usual -- say, when the CD4 count hits 350. Echoing many physicians, Cohan urges stepped-up research in this area: "When the kidneys go, everything goes."

CASE NO. 5

Cause of Death
Heart attack, February 2001

Patient
White male, early 50s, Los Angeles, tested positive in 1985

What Went Wrong
A medical professional retired because of AIDS, this patient had "had his ups and downs," according to Cohan, but "by the time the year 2000 rolled around, he was doing better than ever." A protease combo had suppressed his viral load, and his hep C was under control. For 10 years he had what Cohan calls "unrelated heart problems" -- a too-thick heart wall and arrhythmia -- "but he was on treatment to keep his heart pumping properly and doing fine." Until...

Backstory
"There was nothing here that made me think HIV was related to this death," Cohan says, adding that the only HIV link may be that protease therapy further deprived oxygen to his clogged, weak-walled heart. "As for an interaction between his HIV meds and his heart meds, we were always very careful about that." Cohan also says that this man's case was likely an exception to the growing trend of protease-related elevated cholesterol, which can precipitate a heart attack. "We're very worried about that -- how long would it take for us to gum up our arteries for a heart attack if our cholesterol levels suddenly shoot from normal to way high, and stay that way?" Of course, there are meds like Lipitor to treat high cholesterol, "but few interact OK with HIV meds," Cohan says.

Take-home
Very often, meds that squash HIV can create other problems. "You can't ignore this incidence of high cholesterol, diabetes and hypertension in HIVers on combo therapy," Gary Cohan says. "You have to address them aggressively." Like other cutting-edge docs, Cohan makes a point of putting eligible patients on protease-sparing combos that seem to be "as or more effective than the protease, and less toxic," he says. "One combo with Sustiva beats PI combos hands down."

But this patient's case may illustrate a more general and important point: As HAART ushers more and more HIVers into a once-unthinkable middle-age, they have no choice but to protect

themselves against the same old humdrum health problems that plague the general population -- heart disease, high blood pressure, cancer. “In the early ’90s I used to joke with my patients when they came in with a pack of Marlboros in their pocket,” Cohan recalls. “Now I’m their worst nightmare of a Jewish mother.” Still, HAART complicates these humdrum canards of aging so that it’s often hard for HIVers to determine where their “normal” problems end and their HIV- or HAART-related ones begin.

Are there common lessons to be learned from these disparate profiles to keep us HIVers stayin’ alive well into the 21st century? You bet.

Ya gotta be irresistible. Most HIVers die these days from complications (old OIs or new organ failure) that occur when their CD4 cells fall below 200 and their immune system collapses -- a result of viral resistance leading to HAART failure. Everyone has a responsibility here: Researchers must keep concocting new meds to take HIV by surprise, doctors must tune into the latest treatment thinking, and HIVers must enlist all possible support to avoid the adherence flubs that enfeeble an effective cocktail. (And don’t forget that bareback sex, needle sharing and other forms of “strain swapping” among HIVers are viewed by many as a sure fire recipe for mass-scale viral resistance and treatment failure -- a spoiler of all HAART’s good work so far.)

Every new solution presents a new problem. While HAART has saved many a life, it can also trigger new, life-threatening health crises such as high cholesterol, high blood pressure and diabetes. Even as you and your doctor work to minimize these effects, pharma must not minimize the nasty side effects of their drugs: Once more, we need better research on the drugs we have as well as better drugs.

So, as usual, it’s the best of times and the worst of times. The sunny (though oversimplified) message that “HIV no longer means a death sentence” is, for the most HIVers in the developed world, resoundingly, blessedly true. For longtime virus-carriers, though, there remains the urgent need for brand-new drugs to squelch the virus preying on their long-battered immune system. As for the newly infected, their burden is to care for themselves as though good health in the age of undectectability were not a right but a privilege—one as fragile as the difference between life and death.
