The Eyes Have It?

The protease era brings PWAs less CMV retinitis ? and a shortsighted slowdown in research to fight it

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You can make one sure bet about CMV. After that, all bets are off.

Here's the sure bet: If you're old enough to have sex, you're probably infected with CMV – that's short for cytomegalovirus, which can cause blindness, brain infections and other evil things in people with derelict immune systems. If you're gay, HIV positive and sitting in a room with nine other gays with HIV, nine of you have CMV infection too. But you 10 HIV negative gay guys in the next room, don't get smug" Eight of you are CMV positive. And in that other room with 10 people who shoot up, seven or eight are a swim with CMV. How about the room with 10 folks who aren't HIV positive and never injected drugs or had gay sex? Six have CMV.

But HIV negative guys and gals, straight or gay, have an advantage: If they don't do something that wastes their immune system – like get cancer or have an organ transplant – their CMV will never cause disease. Meanwhile, people with AIDS, especially when their CD4 counts slide below 50, run a big risk that CMV will start burning up cells at the back of the eyeball – the retina – causing CMV retinitis. Or CMV may torch cells in the gut, lung, liver, esophagus or brain.

Now here are some things about CMV you can't bet on, unless you like long odds: That a whopping CD4 boost from protease inhibitor combinations protects you from CMV retinitis. That the recent plummet in new cases of CMV disease won't bounce back up in another year. That the one drug approved to prevent CMV disease will do that. That another anti-CMV drug doctors rave about, or blood test to help tell who's at risk, will be approved any time soon.

Protease inhibitors did much more than make lots of sick people feel better. They also changed the way everyone thinks about CD4 counts. Two years ago, if your CD4 count dipped under 100, you had to start worrying about CMV disease. If it skidded below 50, you worried more. Doctors routinely scheduled regular exams with an eye specialist for people whose CD4 counts fell below 100, because almost everyone who got retinitis got it with CD4 counts way down in the double digits.

Things are no longer so simple. Last year, AIDS docs began seeing scattered cases of full-fledged CMV disease in people whose CD4 counts had rocketed form 50 or lower into the 200s after taking

protease combinations called HAART – highly active antiretroviral therapy. How good can these protease combos be if people are getting retinitis despite plummeting viral loads and soaring CD4 counts? What's going on?

Eleven CMV savants interviewed for this article gave the same answer: They don't know. But they all have good ideas. These surprising cases don't mean protease inhibitors spark CMV disease, they all said – not exactly, anyway. You can look at it two ways.

First, maybe the CMV disease was already there when these people started taking protease inhibitors. Michael Polis, MD, of the National Institute of Health, notes that four of five people in one report hadn't had an eye exam before HAART started. So no one would know if retinitis was already smoldering, because signs of disease are subtle – or nonexistent – in its early stages.

Rich Pollard, MD, of Galveston, Texas, a co-author of the report on the five cases Polis mentioned, adds another reason that the "smoldering disease" scenario might make sense: Doctors detected retinitis in all five people in the first weeks after they started HAART. Eye experts figure that a few weeks pass between the time that CMV gets into the eye and when they can spot retinitis. So, if CMV had slithered into these people'' eyes just before protease combos began recharging their immune batteries, retinitis would have showed up exactly when it did – a few weeks into the new therapy. And once people have been taking protease combinations for more than two months, Pollard adds, new retinitis no longer appears – as long as CD4s stay high.

There's another way to explain CMV disease after HAART hikes low CD4 counts: The new CD4 cells don't work. Different crews of CD4 cells have different jobs. Some learn – and remember – how to grabble only with TB, while others can waylay a certain flu virus, a toenail fungus or CMV. When CD4 counts tumble, whole CD4 crews may be nearly, perhaps completely, wiped out. If HAART jacks up CD4 counts, it does so by multiplying the CD4 crews still left. And if HIV decimated the CMV crew, it could take moths for a person's new CD4 cells to relearn their anti-CMV stratagems. And it's possible they never would.

This explanation ticks off Larry Drew, MD, PhD, and a CMV ace in San Francisco. He calls the idea that new CD4 cells are wimps "a complete misinterpretation." Those cells may not be ready to take on CMV two minutes after people pop their first protease pills, says Drew. But given time, protease combos show a flair for anti-CMV bondage and discipline.

Drew's argument looks good for two reasons. First, the five people Pollard described all had remarkably well-controlled retinitis: Using anti-CMV drugs, they got no worse for up to a year, compared to the usual five months. Second, Polis and others published a report last year of four people whose retinitis cleared up and stayed controlled during HAART – even when three of them stopped taking their anti-CMV drugs. The fourth person never started anti-CMV therapy.

Douglas Jabs, MD, an eye specialist in Baltimore, isn't surprised. He's found that even fairly feeble anti-HIV therapy like solo AZT sometimes bucks up the immune system enough to corral CMV. But Jab's isn't convinced that HAART solves the CMV problem. He points to another part of the Pollard

report that catalogued CD4 counts of people with new retinitis before and after widespread use of protease drugs. Almost everyone in the “before” group got retinitis with a CD4 count below 50. But seven of the 49 in the “after” group had CD4 counts over 100 when their retinitis surfaced. And the CMV Hotline of the National Association of People With AIDS (NAPWA) reports plenty of calls from people whose CMV got worse despite HAART and anti-CMV drugs.

But to get a better fix on whether CMV disease is coming or going in the protease era, you have to look at the big picture. Sizing up CMV from sea to sea, do you count more or fewer cases since Crixivan made Merck investors richer?

Fewer – by a lot. Only a year ago, CMV experts routinely wrote 25 percent to 40 percent of people with AIDS get retinitis. No more. Comparing notes with CMV colleagues across the country, Atlanta’s Dan Martin, MD, figures the number of new cases has dropped at least 50 percent, maybe 70 percent. In New York City, the picture may be even rosier. Early last year Murk Heinemann, MD, began trooping to local clinics and AIDS residences, peering into the eyes of a hundred people with low CD4s. His goal is to find candidates for CMV drug trials. So far he’s found just one.

But Martin, Heinemann and the others aren’t celebrating yet. Everyone worries about what Martin calls “a CMV honeymoon.” Indeed, Judith Currier, MD, in San Diego sees signs of what could be “a beginning of a resurgence” in CMV disease, though she doesn’t have hard numbers. Douglas Jabs does. His numbers don’t show CMV on the rebound, but they do show the decrease may have bottomed out. In the Baltimore area, new CMV cases plunged 55 percent from their peak. But in the first half of 1997, jabs counted the same number of new cases as in the first half of 1996.

Besides what they may say about how long HAART works, these CMV ups and downs directly influence the development of new anti-CMV drugs. If Heinemann and Jabs can’t find enough people for trials, new therapies won’t get studied. And if drug makers see a dwindling market, they’ll slow down – or stop – testing new products.

We’re not talking hypotheticals here. Hoffman-La Roche, which makes intravenous (IV) ganciclovir and ganciclovir capsules (also called Cytovene) for CMV, has what most CMV wonks rate as a potentially potent new drug: Progan (or valganciclovir) is similar to ganciclovir, but could work better than oral ganciclovir. Why? When you drip ganciclovir straight into a vein, you get high drug levels in blood – but you need a permanent hole in your chest. Even if you take 12 ganciclovir capsules a day, the standard dose, you don’t get as much into your blood. Four Progan caps a day equals a day’s worth of IV ganciclovir.

Sound promising? Want to find out about Progan trails? Not so fast. Roche was planning three Progan trials – two for people who already have CMV disease, and one to prevent disease in people at high risk. Michael Marco of the Treatment Action Group, who studies these things, says the trials looked well designed. Then, after reports circulated about plummeting rates of CMV disease, word came from Roche headquarters in Basel, Switzerland: Kill two of the studies, including the prevention trial.

“Dumbfounded” is the word Dan Martin uses to describe the reaction of most CMV experts. He, Marco and others pleaded with Roche to push ahead with all three trials. Numbers of new cases may be falling, they concede. But that’s now. Like Currier, martin fully expects to see a CMV rebound in 1998 as HAART fails in more people. Even if the market stays smaller than it was, Martin thinks Roche has a “moral obligation” to develop Progan – not just for PWAs, but for everyone who gets CMV disease.

Roche’s U.S, point man, Dan O’Day, MD, vows the company is “absolutely committed” to getting Progan licensed. Trial planners are redesigning the scrapped studies, which O’Day predicts will begin again “most likely in early 1998.” But according to Roche, the prevention trial, which needs 600 participants to show valid results, may be too big. Currier disagrees: “They can get 600.”

While awaiting for new drugs for CMV-disease prophylaxis (prevention), people with low CD4 counts face tough decisions about the one such drug already approved, oral ganciclovir. Let’s say protease inhibitors didn’t work for you and your CD4 count’s under 100. Or maybe HAART did work – for a while – but you’re losing CD4s again. If you’ve never had CMV disease, should you try to prevent it with oral ganciclovir? Or should you just get eye checkups every three or four months and watch for early signs of retinitis – fuzzy vision, blind spots, bright flashes, “floaters”? (See “When Irish Eyes Are Smiling”.)

Last summer, a government panel said adults with CMV in their blood and CD4s under 50 “may” consider oral ganciclovir to prevent disease. They gave four reasons why people may not want to take it: Serious side effects, like drops in red or white blood cells, “limited efficacy,” no evidence that it prolongs life, stratospheric cost ($18,000 a year wholesale). This is like Dad giving you the keys to the Firebird on prom night and saying, “By the way, kid, it’s missing four wheels.”

The panel didn’t even mention a possible fifth flaw: Resistance. Based on preliminary data, CMV expert Larry Drew expects to find resistant virus in about five percent of people who’ve taken the drug for 18 to 24 months. Others worry this could be a wild underestimate, because resistance can only be measured in urine or blood, not where it matters most – in the eye. If CMV is resistant to oral ganciclovir, it’s also resistant to IV ganciclovir – making the latter worthless. Worse, there’s good evidence that two other CMV therapies – foscarnet and cidofovir – don’t work as well in people with ganciclovir-resistant CMV.

Kevin Frost, director of clinical research at the American Foundation for AIDS Research, who knows CMV inside-out, scoffs at the new guidelines for offering oral ganciclovir with one hand, then taking it back with the other. He calls the blanket recommendation to use ganciclovir as prophylaxis “a mistake” because of the drug’s many disadvantages. Even Michael Polis, who sat on the panel, says he feels “lukewarm” about the guidelines and adds: “There was a lot of disagreement about how strongly to recommend oral ganciclovir.” Debate ended, though when one panelist asked the 80 or so AIDS specialists in attendance how many routinely use the drug to prevent CMV disease. Only two raised their hands. And no one interviewed for this article touts ganciclovir as prophylaxis, although most say they’ll consider it for people at highest risk of CMV disease – those with CMV in blood, CD4 counts under 50 and no response to HAART (especially if they’ve had MAC,

indicating seriously compromised immune function).

One Roche-sponsored study showed that oral ganciclovir cut CMV disease rates by half – although by current estimates of annual incidence, for every 100 PWAs with CD4s below 50 who take Cytovene, only ten would be protected. And 31 percent of those at highest risk (shown by measurable CMV in the blood) developed the disease despite taking the drug. Meanwhile, a federally funded community study found that the drug provided no protection at all.

The federal panel's clearest finding was that "the most important method for preventing severe CMV disease" is early detection and treatment. To learn more about early signs, you cam call NAPWA's Roche-funded CMV Hotline (800.838.9990) or Roche itself (800.624.CHECK), which will send you a "screening kit" with a video and a self-testing grid.

But buyer beware: These "educational" campaigns are riddled with blunt reminders that (expensive) ganciclovir capsules can save your sight. Roche's striking posters widespread in some urban neighborhoods (blaring "Don't let CMV leave you in the dark" on a window shade half-covering an eye), like its Cytovene and in POZ and elsewhere, use very old data to scare you about the rate of CMV disease – the references are from pre-HAART 1983, 1987 and 1993. And – surprise – nether the ads nor the posters mention the conflicting study results, the federal panel's reservations or even its guideline to consider the drug only after dipping below 50 CD4 cells.

There's another early-warning system for CMV disease. For years, researchers have been fine-tuning tests that count CMV copies in blood – viral load assays. Early data suggest that doctors will be able to use such tests, just as they use now HIV viral load assays, to predict a person's risk of worsening disease and chart responses to therapy. Such CMV assays could help in deciding whether to start CMV prophylaxis.

But development of CMV assays is creeping along. Roche Diagnostics says its test will be ready for research use in 1998 but can't say when, or if, they'll have a test your doctor can use. Researchers already use Chiron's CMV assays, but the company has no immediate plans for an office kit. In fact, Chiron's David Chernoff, MD, points to the scuttled Progan studies as evidence of an evaporating market.

Some might call this development sluggish. A less patient Michael Marco calls it dicking around. The Progan and CMV-assay stories offer chilly reminders of how much market forces – not altruism – drive AIDS industry. Are drug boardroom captains being penny-wise and pound-foolish? Some CMV experts think so. Three interviewed for this article, with no coy intent, used the same adjective to describe Roche's Progan procrastination: Shortsighted.

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