Behind the Eight Ball

CD8 cells take center stage as research aims for remission

February 1, 1999 By Lark Lands, PhD

Jay A. Levy, MD, a longtime AIDS and cancer researcher and full professor at the University of California at San Francisco (UCSF) School of Medicine, has many firsts tagged to his name. He was one of the first to isolate HIV. He pioneered the use of heat treatment to kill the virus in clotting factors, protecting many with hemophilia from the virus. He was the first to report HIV in the brain. And his UCSF team blazed a trail by demonstrating the ability of CD8 cells—the understudied virus-suppressing arm of the immune system—to control HIV replication. Now he's on the front line of work to translate this into a potential treatment advance with therapeutic vaccines. *POZ* Science Editor Lark Lands recently spoke with Levy about the current state of his cutting-edge research, and about the controversy he sparked last year with a Viewpoint article in *The Lancet* advocating a more conservative approach to antiretroviral therapy than the current standard.

Lark Lands: In your *Lancet* piece, you suggested that instead of following the federal guidelines to treat people whose CD4 counts are consistently below 500 and whose viral loads are consistently above 10,000, therapy should be started when the CD4 count is below 400 and the viral load above 30,000. What was your reasoning for this approach?

Jay Levy: While my recommendations were not too far from the federal guidelines, they were sufficiently different to warrant physicians thinking twice about immediately putting some patients on therapy. I believe that if one just waited until the CD4 cell counts dropped below 400 and the viral load was above 30,000 (on two occasions), many people—perhaps 30 percent of those now on combination therapy—would not be treated. For the academic physicians and those covering people with HIV regularly, this type of advice might not be new. But for the general physician following the clinical formula advanced initially, treatment of a patient often begins with any evidence at all of a viral load. I would point out that we have learned that the immune system is resilient, and that even with treatment delay, a return of immune responses to other pathogens [disease-causing organisms] can still occur.

In support of your treatment conservatism, you mention several concerns that most would consider reasonable: drug side effects, development of drug resistance and the daily difficulty of taking the drugs as instructed. But your concern that long-term treatment may erode the body's natural ability to fight the virus has generated

controversy.

In essence, over time on therapy, the CD8 cell antiviral response decreases. While CD4 cells are helpers to other immune-system players, it is the CD8 cells that mount the crucial response to the virus. I worry that the reduction of CD8 cell antiviral function in people on long-term therapy may not be reversed when drugs are stopped, allowing a large rebound in viral load to take place. It's possible that the immune system won't know how to make these HIV-specific CD8 cells any more, and the patient will have lost this important natural source of viral control.

You were a pioneer in proposing the existence of the so-called CD8 cell Antiviral Factor (CAF), the cell-produced chemical that you have long proposed may be the body's most protective response to HIV. What is the current state of your research?

Our research has established that activity of a CAF exists, and that it is a major correlate of long-term survival. Although we have not yet specifically identified CAF, we certainly expect to. We do not believe that it will be given directly as a drug. Instead, we would likely either use small molecules that mimic it or find a way of inducing it within the CD8 cell population of individuals with HIV.

There is now much support from researchers that HAART therapy eventually provides at least partial immune restoration. Based on this, some have raised the idea of structured drug holidays—to allow the body to recover from drug toxicity—interspersed with periods on HAART. What is your position on this?

Regardless of when a person begins therapy, at some point the drugs are likely to become useless or too toxic. Therefore, we need to structure therapy to address these problems. Obviously, the best solution would be better drugs. In the meantime, a drug holiday might be the right idea. It could allow the immune system to recognize—and respond to—the virus again. But emergence of resistance could be a problem depending on the schedule. Alternatively, I suggest studying the possible use of vaccines or immune modulators. The hope is that the drugs could eventually be stopped, and the immune system, so boosted, might prevent a
viral rebound.

I think the most effective way to prolong life is to try to bring a person with HIV to the status of a long-term survivor who has a normal CD4 cell count, is not on therapy and has an immune system that can keep the virus in check. That's our laboratory's direction, and I think it's achievable. But it requires attention to the immune system—not just the virus.

In the past you've suggested doing studies of HAART plus therapeutic immunizations, one goal being to enhance CD8 cell suppression of HIV—given its apparent correlation with long-term nonprogression. Recently, a lot of attention has been paid to the "vigorous HIV-1-specific CD4 T-cell responses" found by Dr. Bruce Walker in long-term nonprogressors—and to the possibility of the Remune vaccine and/or hydroxyurea helping to restore these responses. What are your views?

We will soon begin a study of Remune in individuals after one year of HAART. We will be looking at this vaccine's ability to induce immune responses to HIV after such therapy. Walker's work shows that long-term nonprogressors maintain the ability of their CD4 cells to respond to viruses. Nevertheless, it appears that some healthy people with HIV may not have CD4 cell anti-HIV responses, but retain CD8 cell antiviral responses. Given that CD4 cell proliferation is necessary for CD8s to function, this finding suggests that soon after infection, HIV-specific CD4 cells survived long enough—before their destruction by HIV—to help trigger the CD8 cells' anti-HIV activity. Perhaps by using vaccines such as Remune, we can bring back that important immune response.

I think hydroxyurea, or a new drug (MPA) that we will be evaluating, may also help by quieting down the immune system while permitting anti-HIV immune responses. Essentially, exchanging some of the toxic antiretroviral drugs for treatments that have less toxicity and lead less easily to resistance is the most promising direction.

Based on both your research and long-term observations of people living with HIV, what do you think the characteristics of long-term nonprogressors suggest about approaches to therapy?

As a virologist and immunologist, I am impressed with how long-term survivors can contain this virus because of an active immune system. I have emphasized before that this virus can reside inside infected cells, and is destined to remain within the body, probably forever, unless the immune system can eventually get rid of it. Certainly there is not going to be rapid eradication.

Instead, we should be looking at enhancing the immune response so we can keep the virus in check, just as the immune system does for many other viruses that we carry throughout our lifetime, and just as is being done with HIV in long-term survivors.
