Beyond Eradication

Top AIDS researcher Anthony Fauci sees the future in planned med breaks and immune boosters

March 1, 2000 By Lark Lands, PhD

Anthony Fauci, MD, director of the National Institute of Allergy and Infectious Diseases, has labored at ground zero of the epidemic since 1981, when his colleagues mocked his interest in the disease. As de facto head of federal AIDS research, Fauci has survived activist criticism and budget battles while remaining a scientific leader and a compassionate physician. As an immunologist, he has spearheaded research that has advanced our understanding of the immune system and its response to HIV. Here Fauci explains his recent controversial statement that he never believed that available antiretrovirals could eradicate HIV, and discusses his lab's most promising projects, especially research on ways to reduce the time HIVers must spend on drugs.

Lark Lands: Over a year ago, your lab announced that no virus could be found in two people who had long been on a combo of HAART and interleukin-2 (IL-2, an immune regulator)—leading those prone to conclusion-jumping to start buzzing about the "c" word. But back then you predicted that discontinuing HAART would cause the virus to come "roaring back." Bingo, it did. What was the basis for your prediction?

Anthony Fauci: The nature of the virus itself. With current therapies—and even those in the pipeline—the possibility of eradication is quite slim. We know that the virus replicates explosively as soon as a person is infected, and soon thereafter a latent reservoir of infected cells is established. The virus hides in the resting CD4 cells where it's protected from both the immune system and today's antiretrovirals. Furthermore, even when you treat people effectively and see viral loads in the blood drop below detectable levels, there's not a complete shutoff of viral replication. In 1997 we reported that in such people there were clear indications of recent viral infection in cells, strongly suggesting that some replication is always going on despite effective HAART. HIV's extraordinary ability to insert itself into resting CD4 cells and continue replicating and repopulating the resting-cell pool—despite therapy—is very efficient in propagating its survival. And that makes it very, very problematic to ever completely rid the body of HIV.

I never thought that we could truly eradicate the virus. That's why we're looking carefully at ways to boost the body's immune system to control the virus in a manner analogous to how most people control herpes. Virtually every American carries herpes viruses, but most have a potent immunological response that effectively contains them. That's probably the best way we can potentially contain HIV, and ultimately be able to take people off drugs. Not by eradicating the

virus, but by inducing the body to contain it.

There is considerable recent evidence that HAART actually works against this possibility. It appears that the longer people are on therapy, the less anti-HIV response they have. What treatment approaches can address this?
One possibility we're studying is structured therapy interruptions (STIs). These might provide two important things. First, they could give people less total time on therapy. In our upcoming study, after HAART gets people to undetectable viral loads, we'll keep one group on uninterrupted therapy and give the other group scheduled drug breaks.

After a year, we'll compare them. If the group on STIs is no different clinically from the group that stayed on HAART, we'll know it's possible to decrease some of the negative aspects of keeping people on these drugs every single day.

Second, we need to see if we can induce or enhance the immune response by allowing the virus to reemerge temporarily during these STIs. But unlike other researchers, we aren't going to wait for the virus to become detectable before putting people back on therapy. Instead, we will restart drugs at a predetermined time. Based on our previous results with taking people off therapy, we will probably start people on a two-months-on, one-month-off protocol. If after several such intervals we find that the virus isn't coming back, we will extend the time off drugs to perhaps two months, and if the virus again doesn't come back, to perhaps lengthier periods. The goal will be to lengthen the interval between the times on drugs.

When will you have the earliest results, and what do you expect to find?
We should have data by the fall. I think there will be a finite interval that we'll be able to keep people off therapy. I don't believe that this regimen will lead to eradication or the ability to take people off drugs permanently. But I hope it will allow us to give people progressively longer intervals off drugs. That way, instead of having to treat year-round, people might be able to do a truncated version of therapy. And that might be a third as much as they're having to do now, although it's never going to be zero.

Your lab has long studied the complex interplay of cytokines [cell-produced immune-system chemical messengers] in the immune response, and the possibility of boosting immunity by using one of them, IL-2, to expand HIV-specific CD4 cells. What have you learned from your recent results, and where will research go from here?
The proof of the pudding in immune-restoration research is whether immunity is enhanced enough to allow the body to contain the virus when the drugs are stopped. So far, of all the groups studying immune restoration approaches, we're the only ones who have actually taken people off drugs. And obviously, in our IL-2 research, despite big CD4 increases, the virus came exploding back. That tells me that we may need to treat people much earlier before the HIV-specific CD4 cells get deleted.

That's why we are currently studying people who are treated soon after infection either with HAART alone or with HAART plus IL-2. The hope is that by starting therapy very early, there may

still be HIV-specific cells that can be expanded sufficiently to control the virus. In people who've been infected longer, those cells may have already been deleted, which means we are just expanding irrelevant cells. We don't yet know how early to intervene, but the hope is that if you institute this approach in the first three or four months after infection, even if some of the HIV-specific cells have been lost, there may still be enough left to build on.

Of course, most people are not in the newly infected group that might benefit from this. The biggest concern for people in need of third-line therapy is that "newer and better" won't get here soon enough. Is there anything that holds out promise for them?
Unfortunately, salvage regimens don't have a high degree of success, although in some people, the virus is at least brought back down sufficiently to prevent further immunological damage. I don't think the best hope is just more drugs in the same old classes. Instead, we have to look at new targets.

Is there one that's particularly promising?
I mentioned HIV's ability to protect itself by hiding in resting CD4 cells. It gets there by using the enzyme integrase to insert itself into the genes of a cell. So if an integrase inhibitor could be developed to block that enzyme, you'd be preventing the virus from going down that path to hide itself. This could be an important new weapon to fight HIV.

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