# Reboot Your System

Eradication ’96 crashed. This year’s hope is called remission. If it works, you may be able to quit the cocktail and keep HIV in check.

December 1, 1998 By Richard Jefferys

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The scientific quest to unravel the mysteries of HIV has always had a certain yin and yang. This takes the form of two research specialties: virology, or the study of viruses and how they invade and conquer cells, and immunology, research into the immune system and how it disarms attackers. Virologists have long been gung-ho about the potential of drugs to blast the virus out of the body, while immunologists often demurred, declaring that the immune system has always been the key to long-term control of viral infections.

Many observers with allegiance to neither camp suspect that, as is often the case in life, the truth must lie somewhere in the middle -- if only we could find it. Now, a gaggle of giddy researchers, some yining and others yanging, believe that they’re on the trail of that truth. In fact, a renowned immunologist or two have even been overheard whispering the “c” word. The more cautious have coined another phrase to describe what may be on the horizon: *remission*.

So what’s the big idea? It’s pretty straightforward. If anti-HIV cocktails can’t completely rid the body of the virus -- the “eradication” that virologist Dr. David Ho & Co. had aimed for -- why not see if the immune system can contain what HIV is left? The theory strikes skeptics as a long shot, but there’s already rampant gossip about a handful of individuals -- mainly in early stages of infection -- who may have managed this miracle. Best of all, remission boosters are quick to point out that the theory, if it works at all, should benefit people with advanced disease, too.

Serendipity is science’s wild card. Ironically, the three discoveries that have conspired to steal research’s flash and sparkle this year are all decidedly unglamorous: a 30-year-old cancer chemotherapy, a decade-old vaccine dreamt up by the late Jonas Salk, and that battle-scarred stalwart of the immune system, the CD4 cell. From this chance intersection, a new immune-system star was born: the HIV-specific CD4 cell.

This shy and often-even-absent cell has captivated Harvard University researcher Dr. Bruce Walker. What piqued his interest were studies of long-term nonprogressors, those lucky HIVers who have been infected for as long as 18 years but maintain a normal immune system and a low or undetectable viral load. It turns out that such people have what Dr. Walker has described as “vigorous HIV-1-specific CD4 T cell responses.” In other words, this tiny 1 or 2 percent of all people with HIV have immune cells that recognize the HIV destroyer and launch a counterattack by

making many copies of themselves (the technical term is lymphoproliferative response, or LPR). LPR is absent or extremely weak in those with progressive disease.

In tandem with Walker's findings, New York University's Dr. Fred Valentine has been collecting data on a product called Remune. First studied in 1987, Remune is one of the hardy perennials of HIV therapeutics, formerly referred to as the Salk Vaccine or Salk Immunogen. It's basically a dead HIV virus from Zaire, tweaked by its inventor, polio pioneer Jonas Salk. (He stripped the virus of its sugary outer coat so that the proteins in its core could be detected by -- and then kickstart -- an effective immune response.) Salk's intent was to stimulate a response to HIV, in the hope of extending the period prior to the development of symptoms, when the virus (scientists then believed falsely) is dormant.

The first Remune-vs.-placebo study was presented to a standing-room-only crowd at the 1993 International AIDS Conference in Berlin. Results were a mixed bag at best, and attendees scoffed at what they perceived as researchers' blatant attempts at a positive spin of meager data. A front row packed with buzzing investment analysts didn't improve the atmosphere. Salk's company, the Immune Response Corporation, is still viewed with suspicion. But with the advent of HAART and the search for Walker's HIV-specific CD4 cell responses, interest in the aging agent has revived. In fact, Remune was snapped up last May by Agouron Pharmaceuticals, a small California Biotech company that has had its own share of run-ins with activists over its single drug, Viracept. This background of suspicion has converted healthy skepticism into a profound leeriness about Remune's promising but unproved results.

The third investigative strand woven into this intriguing tale involves hydroxyurea (HU), which popped into the limelight in 1994, when test-tube studies showed that combined with ddI (Videx), it could put the brakes on HIV's replication. This anti-HIV potency was seen even when the virus had mutations that would otherwise stop ddI from working. More important is the recent -- and timely -- evidence that HU may have a unique effect on the immune system itself, allowing HIV-specific CD4-cell responses to flourish in a way not seen with any standard antiretroviral drugs.

Why all the commotion about HIV-specific CD4s? Well, CD4 cells are the leading protagonist in the drama of the immune system vs. "intracellular pathogens" -- infectious agents such as viruses that invade cells. CD4 cells help coordinate the immune-system response (which is why they are also referred to "helper" cells). The other major players are a subset of CD8 cells known as cytotoxic T-lymphocytes, or CTLs. CTLs are responsible for killing infected cells and -- according to Dr. Walker's data -- rely on HIV specific-CD4 help to do their work against HIV.

Since the body can't know in advance what virus it might have to do battle with, it makes billions of CD4 cells, each with a unique "T-cell receptor" on its surface. If a CD4 cell encounters an "antigen" (virus or other pathogen) that matches its receptor, it becomes activated and kicks off the immune response to that antigen. A CD4 that has yet to meet its antigen match is called a "naive" CD4 cell. If a naive CD4 cell encounters, say, the chickenpox-causing herpes-zoster virus that matches its receptor, it reproduces like crazy, spawning an army of similar CD4s to get the herpes zoster under control. (Recovery from chickenpox is evidence of mission accomplished.)

Then, in a stroke of genius, the immune system saves some of these herpes zoster-specific CD4s from disposal, preserving them as “memory” cells primed to respond to any future herpes-zoster antigens. The only chance the chronic, low-level infection gets to cause illness again is if cell-mediated immunity is impaired, as a result of immune damage from aging or disease, which is why shingles breaks out in people with HIV.

For long-term nonprogressors, luck lies in the HIV-specific CD4s that first check the virus during primary infection and then become memory cells producing Walker’s “vigorous HIV-1-specific CD4 T-cell responses.” The $64,000 question is, why do most HIVers lack these responses, even after HAART quells viral load?

It may be that their HIV-specific CD4 cells are wiped out in the viral onslaught that occurs during the first few weeks of infection. Previous studies have indicated that activated CD4 cells are the most susceptible to infection by HIV. Walker investigated this possibility by treating three people with HAART during primary infection -- even before they had seroconverted on the antibody test. After six months of treatment, all three showed strong HIV-specific CD4s, suggesting that treatment has saved the cells -- in the nick of time, as it were -- from obliteration. How? One hypothesis is that the anti-HIV drugs intervened after the virus has already activated an HIV-specific CD4-cell response but before the cells are overrun and lost; then, once viral replication is reduced and HIV no longer an apparent threat, the HIV-specific memory cells persist, policing the remaining virus.

The $64 million question then becomes, what (if anything) will bring back these responses in the 98 or 99 percent of all HIVers -- those who have already lost their HIV-specific CD4s? At a World AIDS Conference late-breaker session in Geneva last July, Fred Valentine unveiled his Remune data showing that a few people treated with HAART had “absolutely huge” HIV-specific CD4 cell responses after just 20 weeks and two vaccine injections; those treated solely with HAART had none. “Remune can induce HIV-specific immune responses comparable to, and in fact often exceeding, those seen in long-term nonprogressors,” Valentine enthused. Similarly, Italian researcher Dr. Franco Lori has been following 12 people on ddI/HU for two years, and -- to the surprise of many -- six have evidence of new HIV-specific CD4-cell responses.

So far, so good. But for remission to work, these cells must eventually allow the immune system to control the virus without drugs. The hope is that once people go off HAART, their HIV-specific memory CD4s will be ready to take over and contain any remaining virus, turning them into virtual long-term nonprogressors. News that this may already have occurred in a handful of cases recently morphed from the medical media into the mainstream.

The first report appeared in the British medical journal The Lancet in September 1997. A relatively obscure French doctor named Jorge Vila wrote a letter describing two patients who had taken a ddI/hydroxyurea combination for a year and then stopped, with no reappearance of viral load. However, critics made haste to note that since both had started treatment not only within a year of infection but with very low viral loads (under 1,000 copies), they may have been “natural” nonprogressors.

Then came “The Berlin Patient” -- not a John LeCarré character, but a young gay German described in detail by POZ contributing writer Mark Schoofs in a New York Times Magazine story last June. The German, the native of a small town who asked not to be identified by name, had started a ddI/HU/Crixivan combination soon after infection, and had a substantial viral load. Three weeks into treatment, with his viral load already successfully suppressed, a testicular infection forced a short drug holiday. Virus briefly rebounded, followed by a return to undetectability when he restarted the drugs. Another four months, and another complication: hepatitis A. Once again, drugs were stopped, but this time viral load remained undetectable. When the hep A resolved, treatment was restarted. A few months later, right before Christmas 1996, the Berliner decided he’d had enough of the drugs and gave them up for good. The result? His viral load remains undetectable nearly two years later.

Yet this man is not completely HIV free, as eradication-buster Dr. Bob Silicano has shown. Silicano, a researcher at Johns Hopkins University, went fishing for virus in a vast sea of CD4 cells taken from the German’s blood. About 1 in 44 million cells harbor HIV that happily reproduces in the lab -- just as he had found in Ho’s eradication cohort. On closer inspection, these turned out to be a particular type of CD4 cell: ironically, memory cells. There’s no way of determining which antigen they “remember” -- it could be chickenpox, measles, TB or any other infection to which he has been exposed. The important point is this: Once HIV has infected -- incorporated its genetic material into -- the memory cell, the virus lies dormant; if the cell encounters the infectious foe it’s programmed to remember, it becomes activated. That’s when the HIV inside gets the opportunity to complete its life cycle, releasing an estimated 100 to 200 new copies, a new generation to continue its dirty work.

With nothing to stop it, this multiplying HIV could easily restart the all-too-familiar battle with the immune system. Why isn’t this happening in the Berlin Patient? In what could be a key new discovery, Walker announced at September’s ICAAC conference in San Diego that he has tested the Berlin patient and found a robust HIV-specific CD4 cell response. Naysayers claiming this case is a fluke or arguing that he’s a natural nonprogressor must account for the fact that nonprogressors tend to have a small amount of active virus (under 5,000 copies), while this guy has zilch (on the standard test).

Even more startling, Dr. Franco Lori and Dr. Jorge Vila are said to know of (at last count) a total of 13 patients who have stopped HU-based combinations without experiencing viral-load rebounds. These findings suggest that maybe, just maybe, a vigilant immune system -- equipped with the HIV-specific CD4 cells it needs to help run things -- can deal with the HIV that HAART can’t reach. “Complete eradication is not required,” Dr. Bruce Walker says. “The immune system can control HIV.”

A dose of healthy skepticism about remission couldn’t hurt. All too often in the epidemic, today’s “dramatic new data” dissolves into tomorrow’s dud. Much about this research is up in the air, to be sure. If any Remune-treated person does succeed in evading viral rebound after going off therapy, intensive study will be needed to work out the ideal protocol for achieving these result in others. When is a rebuilt immune system strong enough for you to risk quitting therapy? Will you have to

take Remune boosters for the rest of your life? What to do if your virus breaks through? Above all, the approach may be fatally flawed: The presence of HIV-specific CD4 cells may be a marker for some other immune response yet to be identified. As savvy Brit Dr. John Moore from New York's Aaron Diamond AIDS Research Center points out, "The reactivation of this immune response does not necessarily mean this is beneficial -- it could simply be irrelevant."

Or not. Only time will tell. It's good to bear in mind that not everyone stands to gain should remission pan out -- pharmaceutical companies can't bill you for your own CD4 cells! And while Agouron would certainly be tempted to price Remune as if it was designed by Jean-Paul Gaultier rather than Jonas Salk, what if cheap ol' generic hydroxyurea could pull off the same feat? Whatever the outcome, right now this is research worth watching.

**A REMUNE-VS.-WONK TRIPLE-HEADER**

**Mike Barr, August/September TAGLine:**
"At face value, one would have thought Valentine and the Immune Response folks had stumbled onto a quick and easy cure. But cries of 'Eureka!' are few and far between... What if the these bozos could show Remune capable of inducing or augmenting HIV-specific immune responses to the strain of HIV that the individual is actually infected with? Now that would be something! But stimulating a response to a recombinant immunogen we've seen for years. Come on, Fred, you can do better than that."

**Martin Delaney, Project Inform:**
"We don't know the significance of the HIV-specific response. No idea whether it correlates to any kind of clinical outcome. No data yet on whether it adds to further reduction in viral load. No information on what size CD4 changes are meaningful or on the durability of the response. No information on how it compares to the original HIV-specific response, which almost always fails over time. In short, all this proves is that there's a measurable response to Remune. Almost any vaccine candidate can produce the same."

**John James, Aug. 10 AIDS Treatment News:**
"What surprises us is how well this very important study worked... It takes [a person on HAART] months or years for naive CD4 cells to recover after immunosuppression. If the cells able to recognize HIV had indeed been wiped out, how could the HIV-specific response have come back so strongly in only 16 weeks? If, however, the cells had not been destroyed but turned off in some way, it would be important to learn how HAART plus Remune reversed this effect. Perhaps a more specific treatment could produce the same result."

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