# Here Comes the Cure

It’s due out this decade. It’s no magic bullet. It’s going to make HIV eradication look as quaint as a chinese cucumber. But first you gotta believe.

January 1, 2001 By Martin Delaney

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It’s time once again to make “Cure AIDS now!” the primary goal of treatment activism. Ever since 1996’s mass hysteria, when the “eradication” of HIV was confused with a “cure” for AIDS, we have had to face this brutal fact: Even maximum viral suppression does not lead to a complete recovery of the immune system. Stopping viral replication, however, does lead to a condition that most HIVers can live with -- not a perfect immune system, but a perfectly adequate one. And this, I propose, is how we must start thinking: Instead of equating cure with an unobtainable state of HIV-free perfection, we should redefine it as a state that allows you to live out a normal lifespan without day-in, day-out drugs. Such a functional cure may fall short of the fantasy of exorcising the virus from your body’s every cell, but it has the distinct benefit of being achievable. How soon? By 2010, at the very latest.

In the long-ago ’80s, there was a trembling, if naïve, faith that the cure was out there somewhere and it was only a matter of time before someone overturned the rock it was hiding under.Hopes ran high when the first drug, “compound S” (later renamed AZT), achieved a Lazarus effect in HIVers in clinical trials. It wasn’t long, of course, before we learned this wonder drug only worked for about six months, and then only if used at the right time, and accompanied by a high price paid in side effects. But follow-up nukes like ddI and ddC further demonstrated that the strategy of suppressing HIV was both possible and useful. From there, we hoped the only question was finding drugs that were more potent, less toxic and could be used earlier.

The 1992 International Conference on AIDS in Berlin all but shattered that dream. Disappointing results of the much-hyped Concorde Trial -- that early treatment was a bust -- lead many to despair. But a few of us saw the gloom and doom as an unfortunate underestimation of the true state of the AIDS art. Proof of the benefit of combination therapy’s one-two punch was just around the corner, and the promise of immune-based therapies on the horizon. There were also new designer drugs coming out of the labs that made the therapy of the day look wimpy indeed.

Behold 1996’s protease revolution, triple-combo therapy and the media’s misguided trumpeting of HIV “eradication” after the Vancouver International AIDS Conference, including musings in The New York Times by openly positive Andrew Sullivan about “When Plagues End” and Newsweek’s “A Cure for AIDS?” cover. Now the public seems to think that Sullivan was right. But ask anyone else who’s spent the past five years on the drugs, and the cure is clearly as elusive as ever.

So should we just give up? Should we tell people to settle for a lifetime of pill-induced misery? To quit 'yer bitchin and be grateful you aren't dying of scrambled brains and PCP-clogged lungs before you turn 30? This old-timer doesn't think so. I not only still believe in the cure but think the AIDS community should get out in the streets and demand it. It's far too convenient for the pharmaceutical industry, which increasingly directs AIDS research, to just keep giving us refinements of current anti-HIV approaches. Such products will keep their cash register ringing for a long time, but will never cure AIDS. And as for what's possible and what's not, the only thing I'm sure of in life is that we create our own possibilities, just as surely as we can kill our dreams with disbelief.

Purists define a cure as the complete elimination of an illness, with no after-effects or need for follow-up. In fact, few treatments ever meet such a standard. Sure, drugs for acute infections like mumps do, but we also count cancer as "cured" if the patient is alive five years after diagnosis -- even if she dies in year six. And when people are "cured" of, say, chronic hepatitis, they are not guaranteed a normal life span: The infectious agent, such as hep B or C, may be gone, but vital organs may have already suffered irreparable damage.

In most people, the first years of HIV infection are clinically no big deal; the immune system functions reasonably well as long as CD4-cell counts remain well above 200. Often the greatest damage is done not by the virus but by inappropriate early use of anti-HIV drugs. At worst, HIV causes a decline in immunity, a process that is very slow for some, gradual for most and rapid for few. If the viral proliferation driving that destruction can be sufficiently tamed, the immune system can coast along in neutral, still handling most challenges. Even in people who wait until quite late to start therapy, the immune system mounts a heroic recovery once HIV levels are lowered, from improved cell numbers and function to the restoration of affected tissues, such as the lymph nodes. This phoenix-from-the-ashes immune act is one of the amazements of the HAART era. Additionally, there is increasing data that suppressing viral load results in reduced rates of transmission. Thus, from both a personal and a public health perspective, this situation -- the peaceful co-existence between a low level HIV infection and a reasonably healthy immune system, together with drastically lowered transmission rates -- would represent a functional cure if it can be sustained without day-in, day-out drugs.

Is this too much to ask for? Too much to demand? I think not, because the tools are all within reach. No miracles are needed. For the most part, it's less a matter of finding an exotic club with which to beat the virus -- patients be damned! -- than of figuring out how to reprogram the immune system. In this new context, let's consider these three necessary goals:

**Goal no. 1:** To create a robust, well-targeted HIV-specific immune response. The current scientific consensus is that this is the trick to achieving low or no HIV levels without drugs. How do we know? Because there are long-term nonprogressors in whom this happens already, quite naturally. The challenge is to extend it to others. The immune system usually fails to maintain a strong specific response against HIV. There are many theories as to why, but little debate that it does. Can the immune system be reprogrammed to get around this problem? It increasingly looks like vaccine research may well provide the necessary clues. Today's best vaccines are finally

producing vigorous HIV-specific immune responses in two ways: They are spurring production of a broad spectrum of antibodies that target free-floating copies of HIV in the blood -- the humoral immune response. But only a small amount of HIV floats freely in the blood or body fluids; most gets integrated into your own cells. There are also signs that the second part of the system -- the cellular immune response -- will learn to recognize cells with HIV, and target them for destruction.

These two arms of the immune system, working together, are theoretically capable of handling HIV or any other infectious agent. For many years, we knew only that this poor cellular response against HIV gets worse over time, probably because HIV directly infects the cells responsible for creating this response. But in recent months, we have seen early results of a vaccine that seems able to program the immune system to improve at this critical task -- apparently because the vaccine does a better job than the virus itself at presenting HIV's key proteins and markers to the immune cells without harming them. At any given moment, the vast majority of immune cells in an HIVer are not infected, and can be trained to help in the fight.

So the fog begins to clear. Imagine a period -- say, a year or so -- of profound HIV suppression with antiretrovirals, a period long enough to permit a robust immune-system recovery of cells and tissue. Follow or combine this with a high-potency vaccine that will stimulate production of new anti-HIV immune cells. Add a cycle or two of our old friend IL-2 (Interleukin 2, a T cell growth regulator) to speed the production of these newly charged cells, awakening and strengthening HIV-specific immune responses. Increasingly, let the newly invigorated and retrained immune system take over responsibility for crushing HIV-infected cells, perhaps over a drug holiday. Go shopping, get a makeover. But repeat this cycle only when necessary.

Yes, the harpies will scream that this isn't completely proven yet. But remember, each aspect of this sequence has already shown promise: Antiretroviral drugs already cause profound suppression of HIV; long-term nonprogressors already keep HIV under control -- as do most HIVers for up to 10 years, naturally. We're invested in creating the future here, not preventing it. All those who prefer to exhaust their energies instead on the next lifelong antiretroviral can stop reading now.

**Goal no. 2:** To sustain the immune responses once HAART is stopped. For the most part, a reasonably healthy immune system is a done deal; the treatment responses either preserved or rebuilt by HAART are already doing that job. People with 200-plus CD4-cell counts rarely get serious opportunistic infections; often it's drug side effects rather than compromised immunity that endangers them. A further hint of long-term success is taking shape in several IL-2 studies, where the immune modulator's substantial CD4-cell gains seem to be at least as functional as those from HAART. Additionally, the immune system is riddled with redundancies and multiple ways of achieving its goals. Our genetic codes contain the remnants of primitive, nonspecific types of immunity that are often sufficient to handle many diseases, and these are not crippled by HIV in the first place. With a little help, these other functions may well sustain relatively normal immunity. All we have to do is prevent HIV from causing catastrophic failure -- and we've already achieved that, for now, in hundreds of thousands of people. In a way, it may turn out to be as simple as we believed in 1996 -- "It's the virus, stupid" -- with this added twist: The goal is to

preserve the immune system. Studies show that if you knock down viral levels to the low side of measurable the risk of disease progression drops to near zero -- as does damage to the immune system. The only exception is in HIVers who have already reached a stage of severe immune dysfunction, something we don't yet know how to fix. The immune system can function as long as the virus is kept bottled up. Now do it without a lifetime of drugs and we're home -- **Goal no. 3**.

Not everyone has climbed aboard this ship just yet. The classic virologists -- many all too intertwined with the manufacturers of antiretroviral drugs -- will whine to the last that what we need is a test-tube-perfect antiretroviral. That's OK -- the world will no doubt continue to benefit from the advances they've brought us. But the tide is irrevocably turning now from virology to immunology. Even the notoriously "viral" AIDS Clinical Trials Group (ACTG) is conducting studies of IL-2 and immune functions. But as we make the transition from poisoning the virus to reprogramming the immune system, we must be careful not to fall into the same wishful thinking that permeated virology. Already some activists and researchers are looking for magic bullets under immunologic labels, trying to resurrect deadbeat "therapies" of decades past, pet rocks like ampligen (see "Care for a Cure" below). But we're not going to go there this time. No simple pill or potion -- not even IL-2 -- will magically fix the immune system. A shift of the programming here, a better presentation of antigen there -- in other words, a strategic process, not a single product -- is how we will move from viral suppression to a functional cure.

Who will give us one? Bruce Walker, Eric Rosenberg, Mario Clerici, Alan Landay, Mike Lederer and Cliff Lane are just a few of the scientists who are today breaking ranks with the total-viral-suppression-or-nothing crowd. We should throw our weight behind those who are advancing our knowledge of immune response, sorting out the immune correlates of vaccines, doggedly working on modulating the immune system in a rational fashion. It would be nice to see Big Pharma take some risks for a change by throwing some money in this direction. And we need new people at the FDA who have a vision about how to evaluate and license immunologic approaches -- a daunting challenge for those schooled on the rapid development of antiretrovirals. But the FDA came through for us once and can do so again.

Treatment activists need to leave antiretroviral pursuits behind and dedicate themselves, wisely and strategically, to nagging or dragging the FDA and researchers toward a functional cure. Groups like the ACTG need new leadership. Fortunately, the staff at the National Institute of Allergy and Infectious Diseases, where many big-bucks decisions are made, have long been involved in immunologic approaches, so we can expect a helping hand from them.

As I said at the start, I, for one, am deeply optimistic. The convergence of modestly better antiretrovirals, vaccine progress and immunologic intervention, will deliver a functional cure before the decade is out. But the tools will be available to those who want them even sooner, just as the benefits of combination therapy were available long before the protease era was formally ordained. This doesn't mean that no one will ever again die from AIDS, but that we will be able to guide HIVers to a long and full life, using tools that may be applicable even in the poorest settings. And to all those who have abandoned hope of a cure, who have yelled, "No, it won't work, this hasn't been proved" while reading this article, I say: If you have a better solution, let's hear it. If

not, get out of the way. We have work to do.

**CARE FOR A CURE?**

It may be hard to believe, but the AIDS epidemic has actually had more “cures” than benefit concerts by Betty Buckley. Consider these colorful classics:

**1985** HPA-23
**Rock Hudson** secretly flew to Paris for a five-day regimen of this **toxic, ineffective experimental chemical**. Back in Hollywood for a Dynasty cameo and a controversial kiss with Linda Evans, the ailing heartthrob was said to be cured. He died in July.

**1985** Ribavirin & Isoprinosine
**These meds weren’t available in the U.S**., but you could pick them up over-the-counter at just about any south-of-the-border farmacia. The Tooth Fairies of Berkeley, California, helped gringo HIVers smuggle them in from Tijuana. But once here in el norte, the drugs didn’t stop el SIDA.

**1986** AL-721
PWAs whipped out the whisks to concoct this **egg-lipid batter** in the comfort of their own home. “Mixone part raw egg yolk with lecithin and stir into three parts fruit juice. Chill. Serves...your purpose.” It could have been sold as a nutritional supplement, but the patent-holder was waiting (in vain) for FDA approval to market the goop as a drug. In the end, cholesterol levels rose, not CD4s.

**1986** DNCB
“Guerrilla clinics” nationwide ladled out this lotion -- a **blend of Vaseline Intensive Care and aphotographic sensitizing chemical** -- for free. HIVers dabbed a patch on their forearms and counted on higher T cells. Instead, DNCB produced a nasty rash -- and had a deservedly not-so-glossy finish.

**1986** Lentinan
This extract of the **shiitake mushroom** waited years to make its maiden voyage in clinical trials -- only to find it don’t do diddly when flying solo. But one study says recruiting an anti-HIV co-pilot might give the famous fungus a lift-off. Still no word from the control tower.

**1987** Ampligen
With such a power name, how could this **antiretroviral and immunemodulator** fail to become the great HIVer hope? But after more than 10years of clinical research, it’s still craving regulatory approval. Devotees swear it seeks and destroys HAART-resistant virus inside infiltrated inner sancta such as the brain and lymph nodes. Check back in 2010.

**1988** Dextran sulfate
Dexie delivered an **AZT-like antiretroviral** punch in the lab, sans the nuke’s potential to poison. The good news was it was available over-the-counter for arteriosclerosis -- in Japan. The bad: HIVers who dashed off to Tokyo to get it got to learn what pharma knows so well:What works in

the lab rarely does in the body. And that jet-lag can be a killer.

**1988** Carrisyn
PWAs sipped **carrisyn-containing aloe vera juice** along with other treatments and waited for their T cells to blast off. Months later, if they squinted hard enough, they just might see a blip -- but who could tell what caused it? Alas, there's still no evidence that aloe's carrisyn confers AIDS-fighting ability. But when it comes to sunburn relief, it is the wonder drug.

**1988** Hypericin
Immediately after hypericin, a compound found in **St. John's Wort**, showed the first signs of putting the brakes on HIV motion in the test tube, PWAs' kettles whistled, ready to brew up a cup of tea from this herb. Oops, the New Age pepper-upper -- St. John's Wort is also said to counter SAD (Seasonal Affective Disorder) -- contains a measly 1 percent of the active antiretroviral ingredient. Pass the sherry.

**1989** Compound Q
This extract of a **Chinese wildcucumber** -- or is that a wild Chinese cucumber? -- was the great green hope of 1989. Even cynic Larry Kramer crowned it the cure from the floor of ACT UP. The initial sub rosa trials -- the ol' FDA was dragging her heels again -- revealed dramatic decreases in HIV replication, and a network of brave community docs opened queues for (illegal) Q shots. But then two very ill patients died sudden, well-publicized deaths. These, coupled with seizures and such, meant the cucumber's salad days were over.

**1989** M-HAD
Japanese dairy company Meiji Milk bellowed they'd made a medicine out of two blood substances -- hemin and albumin -- that killed HIV better than AZT. Who moo? Only Bessie knows for sure.

**1989** Psychic Healing Network
It was the (Louise) heyday of "positives who don't stay positive die"when every meal was a course in miracles. For five minutes at precisely 7 p.m., virally challenged participants (and those who love them) would visualize good health and a cure for AIDS. There were no reported side effects. But is anyone still alive to report them?

**1989** Mandatory Gay Law
The statement on official New York City letterhead read: "**Homosexuality must be outlawed**, or else death will spread like wildfire." Then-mayor Edward Koch extinguished the hoax. Homosexuality is not only legal but

flourishes in New York. Thanks, Ed! How ya doin'?

**1990** Hyperthermia
Fever is the body's way to fight infection, right? So PWAs cashed in their viaticals to finance pricey stays in foreign clinics where the **blood was taken from their bodies, heated and returned,** presumably HIV free. Apparently, the heat got to some, as several patients died. Take-home message: Getting HIV can make your blood boil, but boiling your blood doesn't get rid of it.

**1990** Kemron
A Kenyan study reported “HIV-seroreversions” using a low-dose oral form of interferon. A decade--and more than a dozen (non-U.S.) studies showing its uselessness --later, Kemron still has fans in the African American community. Charging $1,500 for a six month supply, the Nation of Islam hopes Kemron’s run never ends. Ca-ching!

**1993** “Cure!”
Francis Ford Coppola, of major movie fame, hit the AIDS conference circuit. He was developing a script for a movie dubbed Cure! designed to chronicle the science, industry, egos, corruption and triumph in the development of an AIDS cure. Coppola hoped that “the cure” would be found in time to write a happy ending. But when Columbia decided America wasn’t ready for an AIDS movie, Coppola shifted his attention to Dracula. Whatever.

**1993** Nevirapine
At Harvard, test-tube samples of HIV were stopped in their tracks by a triple nevirapine-containing cocktail. Always easily intoxicated, the press went cure-crazy. Unfortunately, the virus developed resistance to all three drugs. Nevirapine is now taken in combination with nukes. Safe to say she’s no cure.

**1994** Sex with a virgin
An Indian police constable accused of raping and murdering a young girl claimed he’d heard that sex with a virgin would cure him of AIDS. The practice remains rampant in Asia and Africa.

**1995** Kombucha tea
A miracle mulch of yeast and bacteria “guaranteed” to cure AIDS,cancer, baldness, flatulence and other ailments. Yeah, right...a blowout.

**1996** Three-herb miracle cure dot-com
This one sprouted on the World Wide Web. A court order swiftly nipped it in the bud.

**2000** Bone tea
Grave robbers in South Africa disinterred a former deputy minister of the apartheid regime after being told that the crushed bones of well-known white people, brewed into a calcium-rich but rather chalky tea, would cure AIDS. Will that be one lump or two? Strain well.

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