The Morning After

Even while some researchers prophesy complete eradication of HIV, protease combos often fail those who need them most

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The first hint of the coming treatment revolution was dropped in fall 1995. At a scientific meeting in San Francisco, a French researcher presenting data from his protease-inhibitor study claimed to have “drained the viral reservoirs” in a small number of patients. Then last May, news of the apparent eradication of HIV in perinatally infected infants broke at a Washington, DC summit. Right away an “eradication hotline” was set up encouraging journalists and researchers from around the world to call for a complete audio transcript. By the International AIDS Conference in July, the elation had reached such a frenzied pitch that longtime AZT investigator Dr. Paul Volberding was ambushed by a camera-and-microphone-wielding throng while checking into his Vancouver hotel. “Would you characterize the tone of this meeting as ’euphoric’?” one reporter asked -- even before the convention had officially started. Volberding demurred.

In the Oz-like aura of Vancouver, first-hand accounts of the powerful new anti-protease drugs transformed years of therapeutic nihilism into open speculation about a potential generation of “plague survivors.” At the center of the furor was ambitious, young Dr. David Ho of the Aaron Diamond AIDS Research Center in New York City. The lion’s share of the new research had come from his (and colleague Dr. Martin Markowitz’s) clinical and laboratory work. The diminutive Dr. Ho stood beneath two vast video screens in the convention center; the standing-room-only crowd of conference delegates was hanging on his every soft-spoken word. “All analyses to date suggest that we have completely shut off viral replication in our study patients,” Ho said, and then tantalized his audience with an eradication scenario arrived at with the use of sophisticated mathematical models: “Ninety-nine percent of all infectious HIV is found in the T-lymphocytes that, when treated with protease inhibitors, rapidly die and are replaced by new uninfected cells.” What of that last fugitive 1 percent of virus? “Over time, these [infected] cells, too, will ’turn over’ and die,” Ho said, “thus presenting the possibility that HIV will be completely eradicated from the body.” A hush fell over the hall. Was this the magic bullet? And, if so, was it too late to save already-ravaged immune systems with these dream drugs?

Just prior to the Aaron Diamond group’s stunning work, several research teams had shown that levels of HIV in the blood can predict who will develop AIDS and die over five years of observation. A low viral load (less than 10,000 copies of HIV per milliliter of plasma) was associated with a very low risk of progression. In fact, studies of long-term nonprogressors suggested that their survival

might be a direct result of their very low HIV levels. This advance, combined with the breathtaking antiviral effects of the protease inhibitors, inevitably led many to only one conclusion: “Hit the virus early, and hit it hard.”

In the Vancouver afterglow, two words -- *undetectable* and *eradication* -- took on totemic powers. The near-mystical allure of undetectable virus -- and eradication fantasies -- was so compelling that people at all stages of disease rushed to seek treatment (generally, triple combinations built on either indinavir or ritonavir). Friends who had started on anti-HIV therapy for the first time were told by their doctor just weeks later that their virus was now “undetectable.” “Does that mean I’m cured?” they demanded. Even patients with years of prior treatment with other anti-HIV drugs reported feeling dramatically better, gaining long-lost pounds and savoring the return of a “normal” daily life that had -- over years or overnight -- slipped through their fingers. While a few old-time researchers and treatment advocates urged caution in the interpretation of what was, after all, preliminary data, nothing had been so hot since the heady days of AZT. In a season of re-election posturing and record-breaking AIDS fundraising goals, high-profile opinion-makers fed the flames of new-found hope. A *New York Times Magazine* cover story mused wistfully on the “twilight of the epidemic.” A decade of activism and research had borne its fruits at last.

Geoff Wiley first got wind of the powerful new drugs last winter. A quick six-month study of the protease inhibitor ritonavir (Norvir) had drastically lessened illness and death in a large group of patients. Whether alone or in combination with other anti-HIV drugs, the foul-tasting capsules produced dramatic reductions of virus in the blood and increases in CD4 cell counts never before seen. For Geoff, this was a bright hope in a dark time. His lover had died last summer, and a friend or three. Geoff had once been a photographer who could take the most ordinary images -- his lover digging a garden, say -- and make them shimmer. But now all he felt was tired. Bone-tired. He had to get the drug.

Geoff acquired ritonavir through Abbott’s compassionate-use expanded-access program and added it to his current regimen of AZT/3TC. Although he’d had weeks of nausea and headaches when he began AZT long ago, he was not at all prepared for his body’s initial reaction to the powerful chemotherapy. Ritonavir made Geoff violently ill: Bouts of projectile vomiting, sudden colonic purges and painful sensitivity of his skin and scalp. After about a month, though, the worst side-effects abated; his body seemed to have adapted. For a few hours shortly after dosing he had to lie down -- making sure that a toilet was near if needed -- but overall the new medication was tolerable. Geoff joked of these daily muggings as his “ritonavir moments.”

Come spring, Geoff’s viral load had fallen from the mid-200,000 range to 2,000; his CD4 cell count surmounted the 300 mark (from just under 100) for the first time in years. And outside the ritonavir moments, he noticed an increase in energy. In another two or three months, if he was lucky, the virus in his blood would vanish. Because viral-load tests can only measure HIV levels of 400 to 500 (copies of HIV RNA per milliliter of blood) and above, it has become common to refer to viral load below this arbitrary cutoff as “undetectable,” the new holy grail of AIDS docs worldwide. Geoff hoped soon to refer to himself, in the strange way that others with such levels now do, as “undetectable.”

But in spite of all the furor over undetectable viral loads and the hope of eventual eradication, Geoff Wiley was seeing neither. After six months on treatment, his viral load never made it below 2,000, and his CD4 rise faltered. It was becoming apparent that a cruel hierarchy prevails among believers on the mass pilgrimage to eradication: Those newly infected have the greatest chance of successful containment of the virus; next in line are those who, although chronically infected, have not yet been treated with anti-HIV therapies -- some unknown element of being “drug naïve” renders them much more responsive to the new treatments; finally, there are the tens of thousands -- like Geoff himself -- who have been through one anti-HIV medicine after another -- often two at a time -- for years. So Geoff had only a small chance of reveling in the perks of the new paradigm. “If you’ve been making the most of AIDS research up to now,” he says in typical sardonic fashion, “you can just kiss your sweet ass good-bye.”

In fact, the best results with the protease combinations have been achieved in people very recently infected: Either adult “acute seroconvertors” or infants born to mothers with HIV. Targeting the virus before it has a chance to “seed” the various immune-system organs and the brain, researchers believe, may make the difference between actual viral eradication and merely long-term viral suppression. Over a 12-to-48-week period, several different three-drug regimens (most, but not all, protease-inhibitor-based) reduced viral replication to less than 500 copies in 80 percent to 90 percent of study participants. Four additional studies in chronically infected people -- two in previously untreated patients and two in AZT-pretreated patients -- also achieved very low HIV levels, but the degree of successful suppression ranged from 40 percent to 90 percent -- another example of the anti-protease pecking order.

Just as the shining reports issued from Vancouver, Geoff’s terrible nausea, vomiting and diarrhea inexplicably returned. Upon the advice of his physician, he stuck with -- “dosed through” -- the ritonavir while other possible causes of the gastrointestinal complaints were ruled out. Three weeks later, he and his doctor agreed to stop the drug. The vile potion had failed to work its magic.

There was still indinavir (Crixivan). He gave his body a two-week break -- hopefully not long enough for viral replication to run amok -- and then began again, keeping the same nukes (there were no new ones to try) but this time with ritonavir’s kinder, gentler sibling, the infinitely more palatable Merck protease. Suddenly, thrice-daily dosing-on-an-empty-stomach requirements, occasional nausea, rash and kidney stones paled in comparison to the miseries ritonavir had heaped upon Geoff. The daily meal-scheduling was difficult at first, but at least he could carry the two pills with him, not having to worry, as with the six ritonavir capsules, about refrigeration options in the August heat. After a month, Geoff was eager to confirm that his viral load had returned to the low levels initially induced by ritonavir. Another CD4-cell bump would be nice, too.

But Geoff was out of luck. Four weeks after he started on his second protease inhibitor, his viral load had risen to 30,000. Like so many well-intentioned but unthinking physicians who hurriedly add an anti-protease drug to a patient’s failing nukes, Geoff’s doctor was shocked to see breakthrough of resistant virus -- and treatment failure -- so soon. Incredulous, he repeated the PCR test; the results came back as 50,000. Something was terribly wrong. Ritonavir performed

reasonably well but was impossible to keep taking; indinavir, inconvenient to take but better tolerated, came nowhere near producing its famed 100-fold viral-load reduction.

During those months of on-again, off-again dosing and partially absorbed ritonavir, Geoff's body must not have been getting sufficient drug to pack the triple-combo wallop. Just enough drug, it seemed, had made it into his bloodstream and tissues to allow the virus to figure out how to propagate around it. And by merely tacking on a protease inhibitor to a nucleoside combination that had already lost its punch, he had been taking, in effect, protease monotherapy -- a regimen guaranteed to fail in record time. Whatever the reason, the devastating truth remained: In fewer than six months, he had become resistant to ritonavir. And since the two drugs are strikingly similar, high-level resistance to ritonavir rendered indinavir equally impotent. Worse still, resistance to indinavir raised the specter of cross-resistance to the whole class of protease inhibitors -- including those not yet commercially available. (Even among the research set, this fact was just beginning to be appreciated.) At the scientific meetings it had all looked so cut and dried.

Stories like Geoff's are not unusual. In fact, for every medical marvel touted in *The Wall Street Journal* or trotted out on *Good Morning America*, there are five to 10 lesser successes. According to Richard Jeffreys, executive director of AIDS Treatment Data Network in New York, physicians in Vancouver indicated that about 15 percent of patients do not respond to protease inhibitors, with some experts reporting the proportion to be as high as 40 percent. In the past, if someone "failed" on AZT, other reverse-transcriptase inhibitors (ddI, ddC, 3TC, d4T) could still be used with reasonable success; the protease inhibitors are revealing an unparalleled degree of cross-resistance. Although future anti-protease drugs (for example, the upcoming Agouron and Glaxo Wellcome agents) are expected to exhibit less cross-resistance, Merck's director of antiviral research, Emilio Emini, warns that "the similarities between patterns of resistance with the protease inhibitors greatly outweigh their differences." And once you develop resistance to indinavir, you can forget about the other anti-protease drugs. "The genetics of this virus," Emini says, "are incredibly unforgiving." For this reason, University of Alabama's Dr. Michael Saag is one of a growing chorus of front-line AIDS clinicians who argue that people with HIV should seek medical care only from highly trained specialists. Potent new drugs ideally capable of impressive, long-lasting benefit can be quickly squandered in the hands of inexperienced physicians and patients who don't take their doses exactly as prescribed.

Given these realities, the "hit it early, hit it hard" cheerleading begins to ring a little hollow. In a chronic but not immediately life-threatening disease such as HIV infection, where there is a greatly limited arsenal of effective treatments, even greater limits to our knowledge of those treatments and, by all accounts, a finite temporal benefit to even the best of these drugs, early intervention is not necessarily the best strategy. When to start treatment and what to start with are likely to remain in the realm of dogma and clinical prejudice rather than hard science, for in the maelstrom of eradication mythology there have not been -- and are not likely to be -- any clinical studies that can answer these fundamental questions. Deserving or not, for most physicians viral load has now become the be-all and end-all of treating this disease. And in the research realm as well, nearly all future studies will focus on this quick and dirty measure of a treatment's effectiveness, with investigators content to merely extrapolate from this any probable long-term clinical benefits. Last

year's research on viral dynamics in advanced patients, along with the retrospective analyses of viral load and disease progression, have swept under the rug (but not put to rest) public doubts about treating early.

In 1994, Treatment Action Group's Mark Harrington likened early intervention to using your last candle at noon: When night falls and you really need it, you'll be left in the dark. The therapeutic situation has admittedly improved since 1994, but there is still no reason to believe that even the best of the triple (or quadruple) combination regimens will not stop working over time. And although the "treat-early-to-prevent-wholesale-immune-system-damage" is an attractive argument, a convincing proof of the benefit of early intervention has yet to materialize.

Aaron Diamond's Markowitz says that once HIV in the blood is reduced to levels so low that current tests are unable to quantify them, there is essentially no viral replication -- and so, no viral mutation or resistance to develop. But we now know this to be untrue: Witness the scores of people who became "undetectable" on double-nuke combos, only later to see their viral loads soar. In the European Delta study, fully 40 percent of participants became "undetectable" on AZT/ddI; even 5 percent did so on AZT monotherapy. Apparently we have been reducing patients' viral load to undetectable levels for a decade -- but never knew it because the PCR technology has only recently been acquired and commercialized. If becoming "undetectable" on nucleoside combos hasn't prevented progression to disease and death, why is "undetectable" on the protease combinations impervious to failure -- except for the fact that we haven't followed patients long enough to see it?

"Eradication" may be another chimera. As Roche's Dr. Mickey says, "We need to distinguish between eradication as a goal of research and eradication in terms of the reality of treatments as they exist today." The fact remains that HIV insinuates itself into the DNA of the body's cells. Immune-system organs are ridden with virus; there's virus in the brain, the lymph nodes, the bone marrow and throughout the gut. In time, the Aaron Diamond players wager, these cells will all turn over and die. And yet Vancouver brought word of at least one person who had been "undetectable" -- lymph nodes and all -- for a full 20 months. When his doctor stopped his protease-based triple-combination therapy, the HIV surged back without so much as a pause. Similarly, HIV-infected infants who, after early aggressive therapy, cleared all traces of HIV from their blood and lymph nodes were later shown to harbor infectious pro-virus "sleeping" within their cells. If 20 months is not long enough for these cells to die, why will 24 or 36 months be? And if eradication is, as Tufts University's celebrated retrovirologist John Coffin suggests, a fantasy rather than a realistic outcome of aggressive treatment, should people with HIV and relatively normal immune functioning be rushing to the new treatments?

Ten years ago, when reports about AZT's curative powers made headlines, people with HIV flocked to the drug; only years later did we come to understand the severe limitations of its elixir. San Francisco's Don Abrams, who has been at the dead center of this epidemic since the early 1980s as clinician, researcher and thirtysomething gay man, urges publicly that the mistakes of the early AZT euphoria be avoided with the protease inhibitors. "I have a large population of patients who have not taken any antiretrovirals since the very beginning," he says. "They've watched all of their

friends go on the antiretroviral bandwagon and die, so they've chosen to remain naïve to drug therapy. More and more, however, are succumbing to the pressure that protease inhibitors are 'it.' We're in the middle of the honeymoon period with these drugs, and whether this is going to be an enduring marriage is unclear. I'm advising my patients if they still have time, to wait."

Even the "hit it early, hit it hard" conjurer himself concedes that when faced with the specter of problematic compliance, he "would advocate waiting" over early intervention. Asked to calculate the possibility of the current eradication strategies succeeding -- whether in acute seroconverters or those chronically infected -- Ho says, "The possibility is low, probably about 10 percent. But we need to see."

Robert Schooley, an immunologist and AIDS Clinical Trials Group chair, ventures even further out. "Is HIV eradication possible with the drugs we have now?" he asked at a November meeting in Birmingham, England. "No. Even a plasma viral load less than 20 is unlikely to shut down viral replication in every [anatomical] site or in every cell type. Many of these things we simply cannot yet measure." Such statements rarely see print.

The protease inhibitors have unquestionably infused with new life many people desperately in need of powerful anti-HIV treatment. In the absence of a cure, though, the finite benefits of these new drugs should be employed strategically -- with the aim of conserving as many therapeutic options as possible, as first choices fail and lead to second choices, and second choices fail and lead to third. Look at Geoff Wiley's experience. Bruised by ritonavir and burned by indinavir, Geoff now likens these combination therapies to "swatting down a nest of hornets." "You'd better get them all," he jokes, "because if you don't, they come back madder than hell." And Geoff knows. Less than two months after going off the dream drugs, his viral load had rebounded to 320,000 -- well above pretreatment levels. Perhaps we need not even-more-powerful drugs, but longer-lasting ones. For Geoff, he is pinning his hopes on the chance that the next protease inhibitor to come along (Agouron's nelfinavir) -- perhaps in combination with nevirapine (Viramune) and 1592U89 (Glaxo's) -- will beat back the hornets. At least for a while.

Whether 1996 marked a revolution in AIDS treatment, it is too early to tell. The most that can be said right now is that significant advances in monitoring and treating HIV infection were made during an unexpectedly fruitful year of fortuitous biological breakthroughs. But like any powerful new technology, the recent advances are a double-edged sword. Studies based on viral load threaten to eclipse more-long-term studies of well-being and survival, which are more expensive and more difficult to execute. But what does a 24-week change in viral load really tell us about long-term control of a chronic disease? The protease inhibitors too can harm as well as help people with HIV who wish to be alive for the next round of advances. The time of treatment despair may deservedly be behind us; for the vast majority of HIV positive people, however, the lasting benefit of antiretroviral therapy remains as elusive as ever. Rather than the twilight, we may simply be getting our first glimpse of a new morning in the struggle against this disease.
