Attack of the Mutation Monster

AZT suppresses HIV. It also creates a virus that grows faster, is more deadly and may be more infectious.

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The advent of the protease inhibitors may have ushered in the era of resistance-based treatment choices, but drug resistance has been an important aspect of treating -- and failing to treat -- HIV infection from the outset. The reason that AZT, ddI, d4T and the like have failed to have a major impact on the course of HIV disease is that the virus mutates readily to resist the effects of these drugs. Combinations of two or more drugs are now used, on the theory that it is more difficult for the virus to mutate enough to resist multiple drugs, but the results of this approach so far have been mixed.

If the development of drug resistance is now widely acknowledged as a formidable hurdle to effective control of HIV, the entire ramifications of drug-resistant HIV are little understood. In a chronic infection such as HIV characterized by extremely rapid viral replication, the problem of drug resistance may lie not only in drug failure but also in the inadvertent creation of more-harmful strains of the virus. Although definitive data are just beginning to emerge, some researchers have been assembling the pieces of a puzzle that point to an alarming potential consequence of our treatment of HIV infection to date. Still somewhat unclear, it began to come together nearly three years ago, when the results of two large clinical trials were unveiled.

In the summer of 1993, the world's leading AIDS researchers assembled in the newly united city of Berlin for what was to prove the most devastating international AIDS summit in the history of the epidemic. That was the year that turned the paradigm of antiretroviral therapy and, in particular, early intervention, upside down. All this was accomplished in a mere word: Concorde. As is now well known, the huge Anglo-French long-term study of AZT showed that early AZT is no better -- and possibly worse -- than late AZT. While the drug appeared to extend the asymptomatic period of HIV infection, it also seemed to hasten clinical deterioration and death once AIDS developed. An AZT taker derived initial benefit from the drug, but then died faster once his or her CD4 cell count began to fall. All in all, survival expectations remained the same. Shattering the hopes of PWAs and the hype of manufacturer Burroughs Wellcome, the first drug licensed to treat the dreaded disease looked like a dud. Upon presentation of the data pandemonium erupted in the hall, and panic selling of Wellcome shares overtook New York and London stock exchanges.

The morning after British investigator Dr. Ian Weller dropped the Concorde bombshell, U.S.

virologist Dr. Victoria Johnson presented a small, apparently unremarkable study in an adjacent auditorium at the same Berlin meeting. In that study (labeled ACTG 116B/117), people who had taken AZT for an average of 14 months were randomly switched to ddI or continued on AZT. While everyone seemed to benefit from being taken off AZT, an analysis of the 900-patient study revealed that patients who entered the trial with virus that had developed resistance to AZT (specifically, with mutations in the reverse transcriptase gene at positions labeled 215 and 41) had a two-fold greater risk of illness and a more than five-fold greater risk of dying.

Nothing much was made of this worrisome resistance news at the time. The conference delegates were still in shock after having finally seen the Concorde data firsthand. Concorde was a beautifully conducted study, beyond scientific and statistical reproach; U.S. AZT investigators publicly congratulated the Anglo-French team on its work. The resistance presentation got buried beneath the bigger headlines. The data were, after all, preliminary.

As quickly as the Concorde shock waves could roll across the Atlantic, U.S. researchers, who had prematurely shut down their own large AZT trial at the first sign that early use of the drug might be beneficial, scrambled to explain this threat to their early-AZT orthodoxy. It was damage control in full force. Careers were on the line, and big money at stake. After a hastily assembled conference call, the AIDS Clinical Trials Group (ACTG) cabal came up with the suitable spin: A study of early treatment with AZT as a single therapy was irrelevant because, as was by then well documented, HIV develops resistance to the drug in as little as six months. HIV's trump card is its extraordinary mutability. Much as drug-resistant bacteria no longer respond to common antibiotics, rapidly mutating HIV grows "immune," or resistant, to the antiviral effects of AZT and all other antiretrovirals to date. As is the approach for treating tuberculosis, Mycobacterium avium complex (MAC) and many cancers, combinations of drugs are now thought necessary to combat the threat of resistance.

Commenting on the results of the early AZT findings, Johns Hopkins' AIDS program director Dr. Richard Chaisson ruffled the feathers of those wanting to believe in the early-intervention mythology with his own brand of highly vivid imagery. "You can take a long, slow walk down to the bottom of the Grand Canyon," he said in a National Public Radio interview. "Or you can wait at the top and then jump off the cliff." Both reach the bottom at the same time; the only difference is how you get there.

Across the Atlantic, British virologist Dr. Clive Loveday was also discovering the unsettling implications of mutant HIV. In one of his own resistance studies, Loveday included a provision that was elegant in its simplicity: Patients who had developed resistance to AZT he simply took off the drug. It was basic Darwinism, he thought. Remove the evolutionary pressure of the drug, and the dominant viral population would revert back to the original strains. The only problem was, that's not what happened in Loveday's experiment. Even after removing AZT, the five-times-more-deadly AZT mutants flourished. As Dr. Loveday would report in The Lancet, the proportion of AZT mutants continued to rise. "This observation," he wrote, "suggests that viruses that have genetic mutations at codons 215 and 41 might have a biological advantage over the wild [original] genotype."

This was a stunning amplification of the discovery that had horrified Dr. Johnson and her 116B/117 colleagues: Not only do AZT-resistant mutants increase the likelihood of illness and death, but they have an inherent ability to reproduce much faster than the wild-type strain of HIV. As was becoming increasingly evident, a peculiar interaction between AZT and HIV appeared, over time, to spawn a "Super HIV," as it were. The sort of sci-fi nightmare one would expect to see only in B-grade horror films now seemed to be taking place in flesh-and-blood humans.

In fact, this emergence of a kind of "Super HIV" was not completely unforeseeable. In the early 1980s it had became apparent that herpes viruses that developed resistance to acyclovir (another Wellcome blockbuster drug) caused much more severe disease than did the original acyclovir-sensitive strains. Now a similar phenomenon was being seen with HIV and AZT. Hadn't anyone thought of this? Did Wellcome not feel a responsibility to investigate this possibility before promoting wholesale use of AZT in hundreds of thousands of unwitting HIV positive humans?

The only true placebo-controlled study of AZT was a 1986 Wellcome-sponsored 19-week study, hardly an adequate vehicle for assessing the long-term usefulness -- or danger -- of the drug. But in a feverishly politicized research and regulatory environment where AIDS activists routinely staged massive die-ins and "zaps" of enemy scientists and bureaucrats, any more placebo-controlled studies of potential AIDS drugs seemed out of the question. Once AZT had steamrolled its way through the FDA in March of 1987, it not only became the first-line treatment for HIV disease but, perhaps more important, the yardstick against which all new anti-HIV drugs were to be measured; echoing the activist chant, there have in fact been "no more placebos." In all future studies, AZT was to be the control. By comparing every new drug to long-term use of AZT, no absolute assessment of new drugs would ever again be possible. Demoralizing as the Concorde news was, scientists and PWAs alike wondered if in their desperation to find treatments, they may have given bonafide clinical science short shrift. Could AZT have been licensed in error? If it didn't extend survival, what exactly did it do? Why, in the Concorde study, did more AZT takers turn up dead?

Stephen Gendin was infected with HIV 12 years ago, as a college freshman. He is now 30. Gendin was among the first to take AZT when it was licensed in 1987; through the "parallel track" expanded-access program pioneered by ACT UP in 1988, he began taking ddI. Since that time, he has taken every nucleoside reverse transcriptase inhibitor (RTI) available to him and is now working his way through the protease inhibitors. He started on saquinavir in 1993 -- more than two years before it was commercially available -- by volunteering to participate in a clinical trial.

Gendin is unimaginably well-informed about the drugs he puts into his body. He follows his bloodwork with a degree of attention bordering on obsession. He has often watched his CD4 cell count rise shortly after beginning a new antiretroviral regimen only to see it fall again a few months later. This CD4 cell (and, later, viral load) roller-coaster ride has continued for nine years, but over time the CD4 cell upswings have grown less and less dramatic and the overall direction of his immune-system blood cells has developed an increasingly downward trend. "I reached the point where I had used every drug in every conceivable combination," Gendin says, "but the virus always seemed to find a way around them." As fast as each new drug regimen begins to clear the

HIV from Gendin's blood, new HIV mutants emerge from deep within immune-system tissues that are relatively unaffected by the drug. When the drug-susceptible strains are killed off, the drug-resistant mutants take over. Survival of the fittest.

Except for the early days when AZT was the only drug available, Gendin has always used at least two drugs together, in hopes of slowing down the emergence of drug-resistant mutants. But in spite of the best intentions of those espousing the value of combination approaches, even when AZT is combined with ddI, ddC, nevirapine and, most likely, the other RTIs, resistance occurs after all. In fact, while combination therapy seems to hinder the emergence of resistance to the second part of the antiretroviral duos (ddI, ddC or nevirapine), the rate at which resistance to AZT develops remains unchanged. Even the much-hyped combo of AZT and 3TC delays or reverses AZT resistance in only a minority of individuals (perhaps as low as 40 percent). And since the 215 and 41 AZT mutants are reported to have a biological advantage over other HIV strains, as Dr. Loveday's experiment showed, simply stopping AZT is no guarantee of ridding the body of their lethal presence. With or without AZT, the mutants stake their claim.

As the evidence against AZT and its potential to select for a "Super HIV" steadily accumulated, it was hotshot young Dutch virologist Dr. Jaap Goudsmit who first dared to broach the touchy subject in a public forum. At an AIDS meeting in Copenhagen last autumn, he bravely challenged the early-interventionist orthodoxy before an international audience. "If we only partially treat people," he cautioned, "viral load could be greatly reduced, but millions of viral particles are still left circulating." Even worse, this "bottleneck" created by therapy could be holding back less-fit, less-troublesome HIV species and letting more-transmissible virus through its narrow aperture. "We might get more-infectious virus with lower viral load. In other words, reduction in viral load might make the virus more infectious," he said. "So drug therapy might actually increase the more-infectious virus population and increase the potential of asymptomatic patients to infect others."

While AZT-resistant HIV is clearly transmissible (especially, it seems, from HIV-infected pregnant women to their newborns), there is no evidence to date that these mutants are more infectious than the original virus. And as for the infectivity of HIV that has mutated to evade other antiretroviral drugs (ddI, ddC, d4T, 3TC and the protease inhibitors), there are no data at all. Only time will tell.

If Goudsmit's worst fears about the consequences of incomplete suppression of HIV have so far failed to be realized, a corollary concern has been borne out: While not (yet) selecting for more-infectious virus, drug therapy with AZT appears to select for more-virulent virus. At an AIDS meeting last winter in Washington, D.C., two research papers (one by Dr. Tony Japour, the other by Dr. Richard D'Aquila) reported that AZT-resistant virus with mutations at 215 and 41 shows a five-fold greater capacity for reproduction in the test tube than nonmutated HIV. These lab results are uncanny in their similarity to what has been observed with AZT therapy in humans, although Dr. D'Aquila cautions that "we don't really know how relevant the lab conditions are." Still, he concedes that "it seems reasonable to speculate that better replication of such mutants might explain the...Concorde observations. Patients with highly AZT-resistant, multiple mutant viruses

might do less well than patients with wild-type viruses" -- even when they are switched to another RT inhibitor. Dr. Robert Coombs, a virologist who worked on the 116B/117 study, argues that "the 215 mutation and resistance susceptibility are clearly associated with a replicatively more 'fit' virus."

A related observation at the D.C. meeting reported that out of eight HIV-infected babies (born to HIV positive women), the two with AZT-resistant virus died in less than two years. One died in only six months. Of the six HIV-infected babies born with wild-type HIV, all but one are still living. Clearly, the issue of AZT resistance will have to be strongly considered in the timing of AZT-based strategies designed to reduce the risk of mother-neonate transmission of HIV. In cases where the intervention fails, AZT initiated before the second trimester can be expected to markedly increase the risk of transmitting a more virulent strain of HIV to the newborn.

When Stephen Gendin realized that the emergence of drug-resistant mutants would greatly limit the effectiveness of all anti-HIV treatment regimens, he began looking for a lab that could test his virus for resistance. "I was ready to switch to a second protease inhibitor and felt it would be best to combine it with another drug that still had antiviral activity against my virus," Gendin says, "so I decided to have my virus analyzed." Right now there are five AIDS physicians in New York City who routinely send off samples of their patients' blood for resistance analysis. Gendin went to Dr. Jeffrey Wallach. Although costly (and not reimbursed by his insurance), the procedure was relatively straightforward (see page 108). After shipping off double-vialed samples of his blood, Gendin received the virology results two weeks later. While there was not yet commercially a test for d4T and 3TC resistance, Gendin's suspicions about the other drugs he has taken were confirmed; his virus is resistant to all three: AZT, ddI, ddC.

What Gendin's virology results did not tell him, though, is where exactly the virus has mutated to evade the activity of the medications. AZT resistance can be accomplished by any number of molecular changes within the reverse transcriptase gene. U.S. researchers have reported that mutations 215 and 41 are the first to appear; British and Dutch researchers argue that a mutation at codon 70 is more likely to appear first, and is then followed by the 215 and 41 mutations. While Dr. Japour and Dr. Coombs reported that 215 and 41 alone are sufficient to create a more lethal HIV, Dr. D'Aquila's experiments suggested that three or more mutations were required (at 219 or 67, in addition to 215 or 41). Does Gendin have the dreaded 215 or 41? Or the possibly more benign 70 mutation? Only additional genotypic tests can answer these questions. For Gendin, it was bad enough to discover that his virus is no longer inhibited by the drugs available to him. The idea that he and his doctors might have, through the incomplete suppression of HIV, created a "Super HIV" that multiplies five times faster than the original virus, though, was truly frightening. "All I can do at this point," Gendin says, "is switch to a new, non-AZT-based combination and hope that the new mutations to those drugs will lessen the harm from the AZT-resistant mutants."

Whether AZT-based combinations with protease inhibitors will prove capable of suppressing or delaying the 215 and 41 variants is a subject of debate. Soon after the initial protease-induced mutations develop, a whole series of "compensatory" mutations are added on to the earlier ones. The virus continues to mutate, developing multiple changes over time. As ACTG virologist Dr.

Douglas Richman observes, “Anyone who knows anything about chemotherapy knows that when sequentially chasing a highly replicating biologic population -- be it tumors, tuberculosis or anything else -- you don’t treat with one drug after another. You try to take care of the population up front. The best strategy is to inhibit [viral] replication [in the first place].”

Dramatically reducing viral activity -- as is now at least temporarily possible with the protease inhibitors -- admittedly reduces the rate at which new mutants are produced, but, as Dr. Goudsmit observed, there are still hundreds of thousands of viral particles unchecked. Whether protease-resistant mutant HIV will prove more or less virulent, more or less infectious than the original virus looms as an ineffable unknown in the minds of the most conscientious AIDS virologists. Information to date suggests that ddI- and possibly 3TC-resistant HIV are less capable of reproduction than is the original HIV, which might argue for combinations based on these drugs, but there is not yet any clinical data. All in all, very little is known about the clinical consequences of mutations spawned in the face of therapy with any of the current anti-HIV drugs, and what new effects they might have on the course of the disease or, for that matter, the epidemic.

Has Gendin used up his time atop the cliff over Dr. Chaisson’s metaphoric Grand Canyon? Is the earth loosening beneath his feet?

In March of 1997, AZT will celebrate its 10-year birthday as an anti-HIV therapeutic. The celebration may resemble more a wake than an anniversary, though, for AZT’s days are unquestionably numbered. After the ACTG’s second-most-high-profile nucleoside study, ACTG 175, reported last autumn that AZT was inferior both to combination regimens and to ddI, AZT’s fate as a single agent was forever sealed. Even before the 175 results were in, a pediatric study of AZT against ddI (ACTG 152) made headlines when it became apparent that the AZT takers were doing worse than those on ddI. With these studies added to the likes of Concorde, 116B/117 and others, there are more studies refuting the clinical effectiveness of AZT as there are studies that support it. Moreover, if long-term use of AZT -- whether alone or in combination -- is in reality the equivalent of a negative placebo, then the results of all clinical studies that include or have included AZT pre-treated patients, an AZT treatment arm or an AZT combination arm may need to be reconsidered.

But if ACTG 175 and 152 served as the final nails in the coffin for AZT monotherapy, the wisdom of using AZT in combination with other antiretrovirals remains unchallenged, even though the vast majority of regimens are incapable of slowing -- let alone reversing -- the emergence of AZT-resistant mutants. Equally unsettling is the fact that AZT, in combination with Glaxo Wellcome’s second-best seller, 3TC, has been wholly embraced by the medical community as the de facto standard of care -- in the absence of any clinical data. On the rare occasion that a physician might choose an alternative to AZT+3TC, another AZT-based combination is routinely employed. Through an almost unimaginable succession of disingenuousness and misjudgments, AZT has emerged as the faltering foundation upon which all new antiretroviral combinations are constructed and against which they are compared. As such, every subsequent three-, four- or five-drug combination approach is being piled atop this veritable house of cards.

Like the parricidal Menendez brothers and subway vigilante Bernhard Goetz, AZT will go on trial yet again. The most recent arraignment followed fast on the heels of the 1993 Berlin meeting. An NIH-sponsored State of the Art (SOTA) conference was convened to establish new guidelines for the treatment of people with HIV. The panel of AIDS experts, headed by San Francisco General's Dr. Merle Sande, found themselves without sufficient evidence to recommend across-the-board treatment of HIV infection with AZT, except for those who had begun to develop overt symptoms of the disease. Beyond that, they were in a quandary. At one point during the three-day-long meeting, Dr. Sande threw his hands up in despair and cried out, "We need better drugs."

A final hearing is set to take place this summer at a second NIH-sponsored SOTA meeting chaired by Dr. Richard Whitley of the University of Alabama. A day of closed-door deliberations among the panel's hand-picked clinicians, scientists and AIDS advocates is expected to follow two days (July 24 and 25) of scientific presentations and public testimony. The question with which the SOTA panelists and their clinician colleagues will have to grapple is: Given what we now know about the heightened virulence of AZT-resistant mutants and the limited ability of combination regimens to slow their emergence, should AZT be a component of any of these antiretroviral regimens at all?

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