RethinkingAIDS

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HIV DOCTORS CLAIM "HOME RUN" FOR mix of AZT plus "protease inhibitors"

Drug companies win approval in record time for toxic "cocktail" therapy based on unpublished studies, faulty assumptions, and misinterpreted data.

Same claims previously made for AZT-style drugs by Paul Philpott

Scientists at a major HIV/AIDS conference in January proclaimed a "home run" with a novel treatment based on a new "diagnostic tool" and a new class of pharmaceutical drugs. The diagnostic tool purportedly measures HIV blood concentrations using "DNA fingerprinting" technology, called PCR, and the drugs inhibit protease enzymes needed to construct HIV.

The first protease inhibitor, Hoffman La Roche's saquinavir, was approved by the FDA in December, just before the conference. By March, FDA commissioner David Kessler officially approved Abbott Laboratories' ritonavir following the fastest review process (72 days) ever conducted by federal drug regulators, and all but promised approval of Merck & Company's indinavir (to be marketed as Crexivan) within two weeks [New York Times, March 2]. As promised, Merck's drug won approval on March 14, following just 42 days of review, breaking the record just set by Abbott [NYT, March 15].

The Third Conference on Retroviruses and Opportunistic Infections in Washington, D.C. seemed to focus on the two protease inhibitors that at the time had not yet been approved. Scientists funded by Merck and Abbott presented over twenty apparently unpublished studies examining the effects of their respective protease inhibitors on about 2,000 HIV positive subjects, some with AIDS-defining illnesses, others with no symptoms.

These studies expanded upon two sensational reports published last January in the prestigious international science journal Nature. The Nature articles showed that when protease inhibitors were administered to AIDS-diagnosed patients, large PCR-measured HIV concentrations dropped by about 90% and "T4" immune cell counts approximately doubled. Although the results were only temporary, scientists who still think that AIDS is a contagious condition caused by HIV were buoyed by the studies. They interpreted the data as confirming their theory that HIV activity is the cause of low T4 counts in AIDS patients.

Furthermore, they proposed that the temporary results might be made lasting if protease inhibitors were combined with standard "anti-HIV" drugs such as AZT and other nucleoside analogs.

The corporate-sponsored studies presented at the conference compared standard two-drug treatments consisting of AZT plus one other nucleoside analog to three-drug "cocktail" treatments consisting additionally of one protease inhibitor (either Abbott's ritonavir or Merck's indinavir). Abbott and Merck reported the same results. Patients taking the protease inhibitors had half the likelihood of dying or developing new symptoms, their PCR-measured HIV blood concentrations fell below the zero, and their T4 counts doubled for as long as the studies lasted, which ranged from six months to two years.

Reports about these findings appeared in The New York Times, Newsday, The Washington Post, The San Francisco Chronicle and The Boston Globe. Coincident with the conference, Abbott and Merck submitted their unpublished studies to the FDA along with formal applications for licenses to market their drugs even to symptom-free people who test HIV-positive.

Home runs overshadow reservations

The New York Times [Jan. 30] noted that "leading scientists" (unidentified) "urged caution" about protease inhibitors, because "they had been wrong [before] about several other initially favorable AIDS findings."

A Feb. 2 front page article then reported on a seven-month study of Abbott's ritonavir. The study involved 1,100 AIDS patients taking standard treatments. Thirteen percent of those also taking ritanovir died or became more "unwell," compared with 27 percent of the patients receiving a placebo. A second New York Times article, published the same day, reported on a six-month study of 1,090 AIDS patients taking either ritonavir or a placebo in addition to standard treatments. These ritonavir patients also experienced half the death rate and 50 percent fewer new symptoms as compared to the placebo patients.

A Newsday article published three days earlier included these comments from Dr. Raymond Schinazi of Atlanta's Emory University: "The data is true, and it's unbelievable. There's no toxicity. It's a home run!" Newsday characterized the audience of physicians and researchers as "gasping" at the revelations of New York University's David Ho, who "pioneered" HIV-counting with PCR. Her next dispatch described "researchers" as having concluded that the effects of the three-drug cocktails are "startling and the side effects are minimal."

The Washington Post [Jan. 30] described Anthony Fauci, the National Institute of Allergy and Infectious Disease director, as upbeat, but more reserved: "[The antiviral cocktails] are more potent than anything we've tried so far...the data looks impressive." But his comments were not all positive. Fauci, who manages the lion's share of the federal AIDS research budget, went on to "warn that the AIDS research community has gotten its hopes up many times in the

past about treatments that ultimately did not pan out."

Side effects: Symptoms of AIDS?

Fauci was referring to AZT, the immune-suppressing cancer chemotherapy that was approved in 1987 following enthusiastic preliminary reports sponsored by its manufacturer, Burroughs Wellcome (now GlaxoWellcome). Early reports praised AZT as an effective antiviral that temporarily boosts T4 counts while conferring minimal toxicity.

But by 1994, Wellcome's Physician's Desk Reference entry for AZT admitted that the "side effects" of its drug included many symptoms that matched official AIDS conditions: "It is often difficult to distinguish adverse effects possibly associated with AZT administration from underlying signs of [what is called by contagious-AIDS proponents] HIV disease."

On November 13, The London Times [1995] quoted a corporate biologist claiming that the new inhibitors do not block normal, healthy protease activity necessary for human life. "[The new protease inhibitors] ought to be incredibly selective, acting against HIV without any side effects against human enzymes," said Dr. David Clough, Director of Biology for Hoffman La Roche. Within a month his company's saquinavir became the first protease inhibitor approved by the FDA. But by January's conference a few side effects had already come to light.

The New York Times [Feb. 2] reported: "About 15 percent of patients taking ritonavir dropped out of the study because of side effects, chiefly nausea and other gastrointestinal problems. This was about double the 7 percent rate in the placebo group."

The first Newsday article revealed that two to three percent of those taking Merck's protease inhibitor passed kidney stones. "Such complex mixtures [of protease inhibitors and nucleoside analogs] are bound to produce varied side effects, all of which will require doctor visits and possibly additional medicines." The Washington Post listed two additional side effects for the Merck drug: bloody urine and "side pain."

By the time Abbott's ritonavir received its record-setting approval the first week of March, the list of acknowledged side effects had grown to include diarrhea, nausea, vomiting, kidney stones, weakness, tingling around the mouth, and liver inflammation [The New York Times Mar. 2, Newsday Mar. 5, the Boston Globe Feb. 1].

Claims of "No Toxicity" may change

There are two reasons to doubt the "no toxicity" claim made for the new cocktail therapies.

(1) Each proposed cocktail consists two-parts of the original "anti-HIV" class of drugs. These "nucleoside analogs," which include AZT, suppress indicators of "HIV replication" by blocking viral DNA construction. But these drugs also just as effectively block human DNA construction, of which there is much more. This means they kill the cells that compose the immune and digestive systems, which constantly reproduce, and destroy mitochondria, the constantly reproducing "mini-cells" that exist within all cells, including those comprising brain, nerve, and muscle tissue. This explains how these "nucleoside analogs" can cause perhaps all of the official AIDS conditions.

(2) The remaining third portion of the cocktails consist of the new class of "anti-HIV" drugs, the "protease inhibitors." They block the supposed HIV protease enzyme, which the HIV scientists claim is unique to HIV. They also claim that these drugs specifically block this particular enzyme, and no others, not even the many vital human proteases, such as those responsible for digestion. This forms the theoretical basis for claims by the HIV scientists that these drugs confer "no side effects" and "no toxicity."

But this seems unlikely. These same scientists originally claimed that the AZT-style drugs only blocked a particular, supposedly HIV-specific DNA-building enzyme, reverse transcriptase. Even then dissident scientists realized that these drugs just as effectively blocked the human DNA-building enzyme, polymerase [Deusberg, Inventing the AIDS Virus]. The HIV scientists now acknowledge the serious toxicities of the AZT-style drugs. And this accounts for one reason why they have sought to develop new "anti-HIV" drugs. (The other reason is that, as the dissident scientists predicted all along, the AZT-style drugs would not stop AIDS.)

Most likely, at best, the new drugs simply demonstrate a *low affinity* for various known human proteases, and much greater affinity for blocking whatever protease species that scientists label as "HIV." But humans who demonstrate evidence officially indicating an "HIV infection" also possess only a very small fraction of eligible cells demonstrating what officially constitutes evidence of HIV infection, and even then, those cells contain very little possible HIV (despite high "viral load" counts) [Deusberg, Inventing the AIDS Virus]. Physicians must administer large amounts of any drug intended to target viruses present at such low quantities. This could mean "HIV-positive" patients who consume enough of these drugs to suppress the high-affinity HIV protease also consume enough to suppress the low-affinity normal proteases.

Dr. Clough's claims that protease inhibitors should not inhibit human proteases is undermined by the growing list of side effects cataloged for those drugs.

Another cause for alarm is that these protease inhibitors do not appear to have been tested alone (against true placebo arms), in human cell cultures, in otherwise healthy animals, or by independent investigators (rather than those receiving grants from the drug manufacturers).

Incomplete drug testing

The New York Times' carefully noted the following with regard to one of the studies: "The study was designed to allow all patients in both groups to continue receiving all the anti-AIDS virus drugs that they were taking before the ritonavir study began. Thus the participants were taking many combinations of the anti-HIV drugs."

In fact, there appears to have been no true placebo arm in any of the studies, as the following makes clear. "Participants had to meet several criteria before entering the study. One was to have been taking one or two marketed anti-HIV drugs for at least nine months at some time in the past."

In addition to the lack of single-drug testing and true placebo arms, none of the reports mentioned human cell cultures or animal studies, to say nothing of independent investigations. Yet only such studies can reveal the true effectiveness and toxicity of a given drug. One of the great and continuing scandals of AIDS research is the general lack of proper drug testing, even before FDA approval.

Unasked questions

Another continuing scandal is the determined refusal of researchers and reporters to subject HIV/AIDS studies to true scrutiny. Although a few establishment scientists, such as Anthony Fauci,

have asked about the ever-expanding list of side effects, none have asked fundamental questions about the scientific assumptions upon which the studies are founded.

For example, each study presented at the January conference and submitted to the FDA relied on PCR for measuring levels of HIV in patient blood. How accurate are these measurements? Do patients with "high viral loads" really have high viral levels? Nobody appears to have raised this question at the January conference or during the FDA reviewers that approved the new drugs. Only dissident scientists have asked this question, and the answer contradicts the assumptions of these studies [Duesberg, *Inventing the AIDS Virus.*]

Also, every study assumed that the elevated T4 counts, and reduced mortality and morbidity, resulted from suppressed HIV activity, as measured by PCR counting. Can other explanations account for these outcomes? Again, no funded researcher seems to have asked this question.

Misinterpreted data: Lots of HIV?

HIV-counting with PCR was introduced a year ago with the publication of two studies in the January 12, 1995 issue of Nature. Abbott Laboratories commissioned New York University researcher David Ho, who directs the Aaron Diamond AIDS Research Center, to study an unnamed, unapproved protease inhibitor. The second study, headed by University of Alabama professors Xiping Wei and George Shaw, examined the effects of the same drug, and was sponsored jointly by Merck & Co. and Abbott.

Both studies reported the same phenomena. First, using PCR, they showed that HIV-positive patients with low T4 counts have on average about 100,000 HIVs per ml of blood. This was news because previous reports showed HIV concentrations so low as to be inconsistent with disease causation. Second, the papers showed that upon administration of the protease inhibitor, HIV concentrations temporarily dropped close to zero, while T4 counts rose substantially, more than doubling in many cases, for as long as the HIV concentrations remained low.

Advocates of the HIV/AIDS theory made much of these studies. The editor of Nature, Sir John Maddox, devoted an entire page to the subject in the next issue. "The new developments are (or should be) an embarrassment for" scientists claiming that HIV blood concentrations are too low for disease-causation, he wrote. "The basis for the low CD4 T-cell count in AIDS patients is clear" from the studies. He presumed that the very high levels of HIV claimed for the subjects must explain the low T4 counts.

But the high levels of HIV that so impressed Maddox were detected only with PCR, a tool that does not detect viruses. It detects genetic material (DNA and RNA), including that associated with viruses. It can't tell if the DNA or RNA is tucked into the core of a whole, functional virus, or if it is associated with a virus rendered non-functional (and thus clinically irrelevant) by one of the many immune responses. Furthermore, the inherent purpose of PCR makes it inappropriate for counting, as opposed to detecting, DNA/RNA molecules.

PCR essentially takes a minute quantity of DNA or RNA and turns it into a haystack's worth of it. PCR is used to detect (not count) DNA/RNA that is present at uncountably low concentrations--on a crime scene where only a speck of blood is left, for example. This raises the question: if there is, as Ho, *et al.* claim, such a large quantity of HIV, why must PCR be used to find it?

The answer lies in other papers published by these same scientists, in which they compared HIV-counting using PCR to the standard technique, which counts only whole, "live" virus. The result: 100,000 HIVs measured by PCR correspond to only about ten actual HIVs [Duesberg, Nature 375, May 18, 1995, p197].

The other 999,900 HIVs are probably debris left over from HIV destroyed by immune mechanisms, defective (and thus inactive) virus produced by dysfunctional HIV, or artifacts of PCR technology. Ho, Wei, and Shaw assumed that all HIV RNA left over from their PCR "cycling" corresponded to actual HIV. Perhaps these scientists prefer PCR-counting because only it produces data that can be used to support their view that HIV causes AIDS.

Low T4 Counts From HIV Activity?

The discoverer of HIV, Luc Montagnier of the Pasteur Institute in Paris, established in 1984 that HIV "expression depends on cell growth" [Annals of NY Academy of Science, 1984, p228-37]. HIV can be active only if its host cell is growing, whereas disease-causing, or pathogenic, viruses kill their hosts when active. Duesberg was criticized for publicizing this point, which most infectious-AIDS advocates disputed. Today, however, even Duesberg's harshest critics, including Ho, et al. concede that "an intrinsic cytopathic effect of the virus is no longer credible [Nature 373, Jan. 12, 1995, p102]."

But instead of dismissing HIV as a pathogen, as Duesberg does, funded AIDS researchers insist on various indirect "new" mechanisms to explain why the activity (or even inactivity) of a benign virus should cause deadly disease.

Ho et al., and supporters at Nature, for example attribute T4 cell decline in AIDS to host T8 cells, the so-called "killer-T" cells which destroy host cells harboring active viral infections. Since these researchers thought they found high concentrations of HIV using PCR, they assumed that there were lots of actively HIV-infected T4 cells to be killed by T8 cells in an internal "civil war."

But since the large concentrations of HIV are PCR-created phantoms, or otherwise uninfectious entities, this assumption cannot be incorrect.

Alternative Explanations

If HIV activity is not the cause of suppressed T4 counts in AIDS, why did suppressed HIV levels correspond with increased T4 counts, reduced mortality, and fewer AIDS symptoms?

In a letter to Nature (Vol. 375, May 18, 1995, p193), Donald Mosier of The Scripps Research Institute disputed the conclusions of Ho *et al.* that low T4 counts in AIDS results from HIV-infected T4 cells being killed by T8 cells. "An alternative possibility," he wrote, "is that higher viral load is correlated with more trapping of [T4] cells in lymphoid tissues, and that effective antiviral therapy liberates these cells into the peripheral circulation." In other words, high loads of any virus can cause T4 cell levels to drop not because infected T4 cells are being killed, but because during times of high viral load, T4 cells cluster in the lymph nodes where they perform their job of directing the immune system's anti-viral activity.

Antiviral drugs, including protease inhibitors or cancer chemotherapies like AZT, suppress viral infections and thus may permit hidden T4 cells to reappear in the general circulation where they can be counted. This view was explicitly supported in the same issue of Nature in three other letters, one by Mosier's colleagues at Scripps, a second by two scientists at the National Institutes of Health, and a third by three scientists at London's Royal Free

Hospital School of Medicine.

Mosier and the others assumed that the high viral loads of HIV obtained by PCR manipulation accurately reflected actual HIV concentrations, and therefore did not dispute the view that HIV is the root cause of low T4 counts in AIDS. But we know now that there is no high HIV concentration, so HIV can not possibly account for low T4 counts by any proposed mechanism. Other microbes, however, can.

In 1985, Anthony Fauci demonstrated that several viruses, such as those that cause herpes, hepatitis, and mononucleosis (CMV and EBV), were more prevalent than HIV among the original AIDS patients [JAMA 257:19, May 15, 1987, p2617-21]. HIV critic Robert Root-Bernstein has compiled an exhaustive list of non-HIV infections common to AIDS patients, several of which are as common as, or more common than, HIV [*Rethinking AIDS*, 1993, p165-70]. The medical literature contains no documentation of an HIV-positive AIDS patient who is not also positive for a variety of other viruses (except, perhaps, patients who developed AIDS only after being prophylactically treated with AIDS-causing pharmaceuticals such as AZT).

Thus clinical benefits of administering antiviral drugs such as protease inhibitors, or even nucleoside analogs, may result from the suppression non-HIV viruses. None of the protease inhibitor studies presented any data refuting this possibility because non-HIV viral loads were not measured. The non-HIV microbe theory is more plausible than any involving HIV because those germs, unlike HIV, have inherent pathological properties and reach large concentrations measurable by conventional methods.

This is not to suggest that non-HIV viruses "cause" AIDS. In healthy people, even these viruses are suppressed to latency. But nearly all AIDS patients have been subjected to such health-destroying factors as recreational drug drug use, heavy medication, or abject poverty in developing nations. In such compromised patients, otherwise latent viral infections may reassert themselves, drawing T4 cells out of the general circulation (where they can be counted) and into the lymph nodes (where they can direct antiviral activity). New antiviral drugs (like protease inhibitors) thrown into the mix may offer some benefits, at least in some patients, by blocking those viruses (and freeing sequestered T4 cells), even if such benefits eventually give way to effects that are toxic to the patient.

Another possible explanation for why protease inhibitors may reduce mortality and morbidity in HIV positive people: they block the assimilation of many other drugs, including some that may ironically be causing AIDS symptoms.

The March 5 Newsday reported on a "dramatic effect" that protease inhibitors have on the liver. "When it reaches the liver, dozens of enzymes...bind to ritonavir. The metabolism of the drug thereafter is slow, and during that time other drugs that may be in a person's body can not be properly metabolized."

Many AIDS dissidents have proposed that one of the major causes of AIDS is the array of side effects and unpredictable interactions of the many medications prescribed to healthy people who test HIV positive. Could it be that protease inhibitors sometimes benefit patients by blocking some of the other drugs (such as AZT) they are taking?

Of course this possibility was not addressed by the studies or anybody considering the studies, though this explanation is more plausible than any invoking HIV.

Cocktails on the House

Some HIV advocates, including David Ho, now urge all patients to take the newly approved cocktails as soon as they test positive, even if they have no symptoms [Newsday, March 5]. He and the other HIV doctors intend these treatments to last a lifetime. The symptoms that subsequently result, if they match the "AIDS" likely to be blamed on the benign, inactive HIV, not the potent drugs consumed in large quantities several times a day.

According that article: "Scientists strongly believe that the most dramatic effects on patients will result from taking three or four protease inhibitors and more traditional anti-HIV drugs [AZT and other nucleoside analogs] at the same time. But that could well cost more than $40,000 a year for drugs and another $20-40,000 a year for labs tests and doctor visits."

Although questions important to science have not even been asked, one question important to the drug manufacturers has already been answered. "President Clinton said he would ask congress for $52 million more in money to pay for prescriptions for the new drugs," reported Philip Hilts of The New York Times [Mar. 2]. This is good news for the drug companies, but perhaps not for their customers.

Rethinking AIDS

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