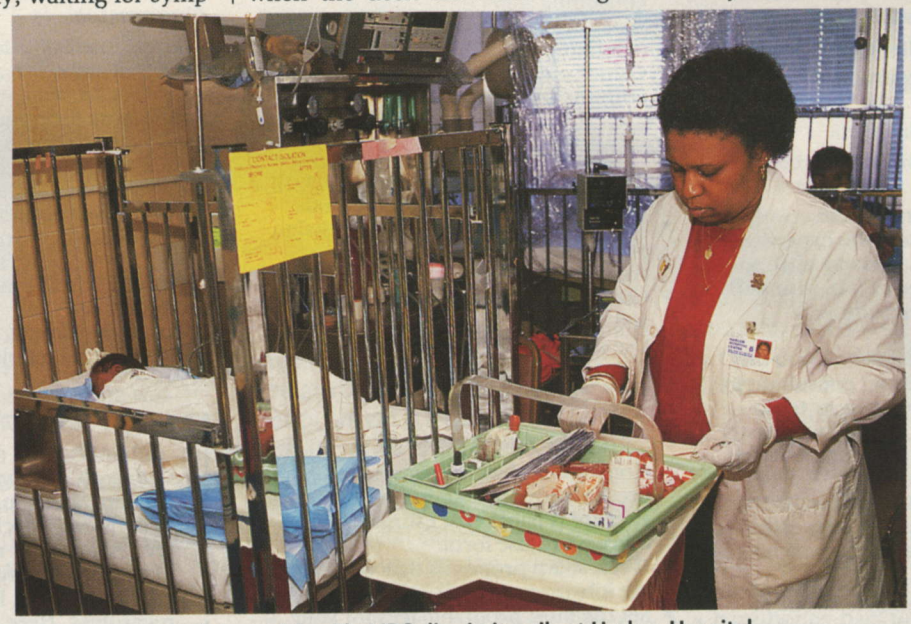
THE TREATMENT DILEMMA

Last year, two months before his forty-fourth birthday, Fred Ponder learned that he had tested positive for HIV, the virus that causes AIDS. Although the San Francisco marketing executive had felt well, he had seen too many friends suffer and die from the illness to resign himself to months or years of uncertainty, waiting for symptoms to appear.

Ponder took his test results to his internist, expecting to be treated. But when Ponder asked about the antiviral drug zidovudine (also known as AZT), his doctor replied that it was licensed for use only in those with full-blown AIDS or AIDS-related complex. Until Ponder became sick, his doctor said, he couldn't take care of him.



An infant, sick with AIDS, lies in its crib at Harlem Hospital.

The dilemma is one that growing numbers of people are going to face. One million to 1.5 million Americans are infected with the AIDS virus, and as time goes by, their prognosis looks increasingly bleak. Not so long ago it was widely believed that perhaps 30 percent of those who tested positive would go on to develop AIDS within five years. Now it appears that few will escape. A recent study, based on a group of homosexual men in San Francisco, suggests that nearly all those infected will develop the disease within a mean period of 7.8 years. This grim outlook for virus carriers, in light of the improvements seen in many AIDS patients taking zidovudine, has raised a whole slew of questions about who should be treated and when treatment should begin.

There's no longer any doubt that zidovudine, the mainstay of AIDS treatment so far, can slow the progress of the infection and prolong lives. The drug, which blocks viral replication (see diagram), is not a cure, but it does buy time. Could zidovudine and newer drugs such as dideoxycytidine (DDC), also buy time—perhaps a normal life span—for those who are infected but well?

"Any drug for any disease is likely to work better early on in infection, when the deck isn't stacked against you," says Samuel Broder, director of the National Cancer Institute's clinical oncology program. In this case, though, early intervention might have more than the usual impact. The hope is that it would limit the damage the AIDS virus inflicts on the immune system, especially on the T cells, white blood cells that are crucial to the body's defense against disease.

In a recent study in the Netherlands, when asymptomatic HIV-positive men were given small doses of zidovudine for three months, their T cell levels rose while levels of a protein that acts as a marker for the replicating virus went down. But whether these early encouraging signs will be borne out in long-term, large-scale studies still isn't known. "You can't assume you know the answers," says Broder, "and substitute hope and speculation for facts." Results from a large trial conducted by the National Institute of Allergy and Infectious Diseases aren't expected until 1990 at the earliest. Where does that leave people like Ponder?

"The only thing you can do wrong with HIV infection is not treat it," says Alan Levin, the San Francisco immunologist who is now Ponder's doctor. Levin's outpatient clinic specializes in treating the "healthy" infected, not only with zidovudine but also with the antiherpes drug acyclovir and various compounds thought to boost the immune system. (Once a drug like zidovudine has Food and Drug Administration approval, there is nothing to stop doctors from putting it to another, nonapproved use, if they wish.) Not treating infected patients until they develop AIDS, Levin believes, is like withholding insulin from diabetics until they go into a diabetic coma. "It's absolutely unethical," he says.

Broder, however, points out that no study has yet proved that AIDS can be forestalled. Moreover, about 40 percent of all adult AIDS patients who take zidovudine suffer side effects ranging from headaches and nausea to suppression of blood cell production in the bone marrow, with some patients becoming so anemic that they require repeated blood transfusions. The most severe problems are generally seen in patients in the advanced stages of the disease. Studies suggest that combining or alternating zidovudine with other drugs, such as DDC, may help avert some of the problems.

Less is known about long-term use in asymptomatic people, however. It's possible that they will be able to tolerate low doses of zidovudine quite well

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over time. But it's also possible that long-term use could lead to progressive bone marrow destruction or a loss in the drug's effectiveness. "There are a lot of unknowns," says Paul Volberding, director of the AIDS program at San Francisco General Hospital. "The real issue in people with no symptoms is not can they take zidovudine for a year, but can they take it for five, ten, or even fifteen years?"

Short-term treatment is another matter. Volberding has openly advocated zidovudine for health-care workers who have stuck themselves with needles contaminated by infected blood. A month's course of the drug right after the accident, it's speculated, might stop any transmitted virus dead in its tracks. "This is the one setting in which it's theoretically possible to achieve a cure," agrees Broder.

Perhaps the most painful choices, though, confront those who take care of very young patients. More than 1,000 children in this country have AIDS, and many more test HIV-positive. Yet so far zidovudine is only in the test stages with children. It is not even approved for use in those with full-blown AIDS.

"If the data don't come out soon on zidovudine's use in children, the pressure to treat children with the drug is going to become intolerable," says Larry Bernstein, a pediatric AIDS researcher at Albert Einstein College of Medicine in New York. Physicians talk with dismay of the early toll the disease takes on their young patients' development. "A baby who's starting to sit no longer sits, a child who takes a few steps or says a few words loses that ability," says pediatrician Wade Parks of the University of Miami School of Medicine. In fact, some pediatricians are refusing to wait for the FDA's sanction to prescribe zidovudine for their patients. Parks, one of the earliest investigators of the drug in children, says he can't wholeheartedly approve of their actions but adds, "I don't approve of babies dying."

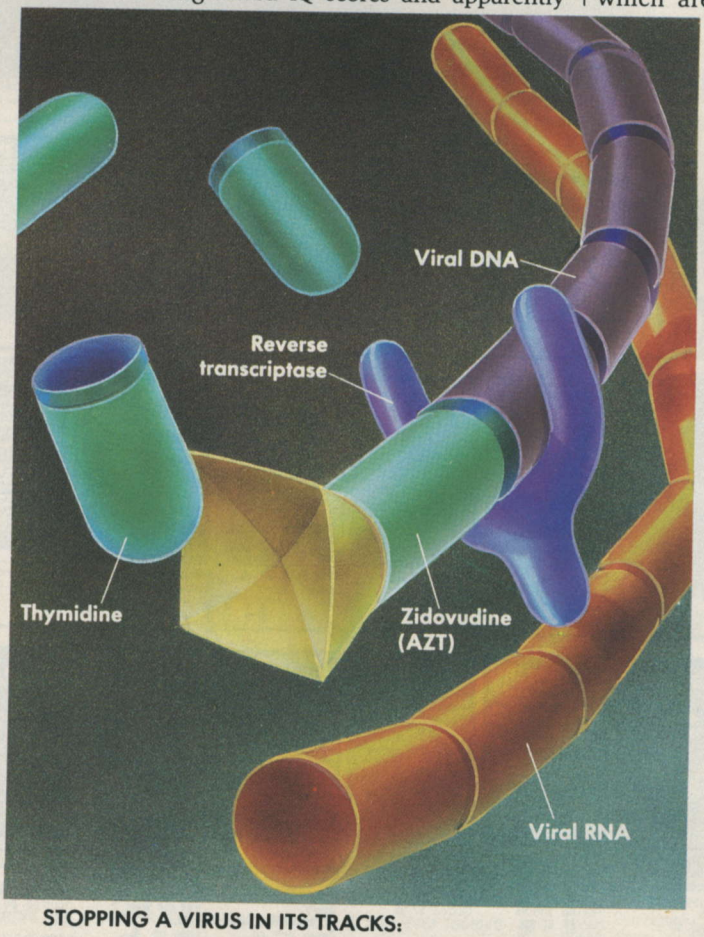
Promising results in early tests of zidovudine in children are only increasing the pressure. In one study, children aged 14 months to 12 years who were given the drug regained their appetite, put on weight, and had higher T cell counts. Most dramatic of all, the drug raised IQ scores and apparently reversed brain damage in some children. Children taking zidovudine also seem to experience fewer side effects than adults, notes Parks. The less-sick children, moreover, appear to improve the most, suggesting that HIV-infected children with no symptoms might do the best of all. But that only raises a further dilemma.

The vast majority of children with the AIDS virus are born with it—if a mother is infected, her baby has a 30 to 50 percent chance of acquiring the virus from her. But it is difficult to diagnose which newborns are infected and which are not. The problem is the limitations of the current antibody screening tests. These tests can't tell if a baby is making its own antibodies because it's infected or just carrying antibodies temporarily inherited from its mother. Pediatricians may have to wait until a baby is 15 months old to make the diagnosis. In the future a test that can detect minute amounts of the virus's genetic material should make it possible for doctors to diagnose the infection more quickly.

Meanwhile pediatricians are forced to wrestle with their ethics. Should all babies born to HIV-infected mothers be treated in the hope of helping the 30 to 50 percent who inherit the virus, as some doctors suggest? "Is it ethical," asks Parks, "to treat children who may not be infected? Every time you think you're on top of the problems, another one comes along."

The next problem is already in the making. As Bernstein points out, if drugs are shown to help infected people who are symptom-free, the question of who to *treat* and when will shift to who to *test* and when.

—Margie Patlak



STOPPING A VIRUS IN ITS TRACKS:
To reproduce, the AIDS virus must copy its genetic message from a strand of RNA to a chain of DNA. With RNA as the template, a viral enzyme called reverse transcriptase assembles the building blocks for the DNA chain. The drug zidovudine (AZT) wrecks the assembly job: because the drug looks like the building block thymidine, it tricks the enzyme into incorporating it into the chain. But the drug lacks the attachment point for the next building block in the sequence, so the chain is stunted.

ILLUSTRATION BY IAN WORPOLE