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Paradox at the Heart of HAART

AIDS Drugs Lengthen Patients' Lives But Leave Them Vulnerable to Toxicity, Other Diseases

By Michael Gibbons

Money can do many things, literally move mountains. But it appears no amount of money nor all the king's horses and all his men can move a microbe, not if that microbe is famously named HIV and it infiltrates a human body.

Never say never, you protest; a wise saying, no doubt. But the virus that causes acquired immunodeficiency syndrome (AIDS) is so nimble, so adaptable, that the odds of scientists finding a way to rid the body of it in our lifetimes—of curing AIDS, in other words—seem remote indeed.

"It will be difficult to nearly impossible to eradicate HIV out of the body," said Brigitte E. F. Beer, DVM, PhD, an HIV/AIDS researcher since 1992. "The genome of the virus is stably integrated into the body cells and cannot easily be targeted with drugs or immunizations."

A cure for AIDS would only be possible, Beer added, if researchers found a way to eradicate HIV from the genome. "At the moment, this is highly unlikely and would require a gene therapy type of approach," she said.

Fortunately, money, time and talented scientists have produced the best possible result short of a cure: drugs that can duel the immunity-robbing virus to a standoff.

This "cocktail" of drugs, known collectively as highly active antiretroviral therapy or HAART, grants those living with HIV a relative degree of health and a reasonably lengthy lifespan (currently 16 years on average). The scourge's initial victims in the 1980s, mostly gay males, had neither.

But for most AIDS patients, it's rough sailing for those 16 years, given the toxicity of HAART drugs, the waning of drug potency over time and the disease's unrelenting dismantling of the immune system, which creates fertile fields for all manner of opportunistic pathogens.

Chronic Condition

An estimated one million Americans currently live with HIV. About 40,000 new infections occur each year in the U.S., 70 percent men, said Beer, a researcher in the Infectious Disease Research Department at Southern Research Institute, Frederick, Md.

"Since effective treatments are available, AIDS can be more and more viewed as a chronic condition," she said. "Currently, there are 29 FDA-approved medications available, many of them combination medications. These drugs target two enzymes of the HIV virus—reverse transcriptase and protease—and also the 'Envelope' protein."

However, the human body pays a stiff price by ingesting these life-sustaining but toxic drugs: lipodystrophy and liver toxicities to name two followed by abnormal lab values, abdominal pain, anorexia, depression, diarrhea, headache, nephrolithiasis, parasthesia, neuropathy, rash and vomiting, according to Beer.

"Newer drugs, such as co-receptor inhibitors that will be approved by the FDA this year, are a big hope for overcoming the toxicities of current therapies," she said.

Another problem occurs because most HIV drug regimens "fall off in potency over time because drug resistance develops," Beer added. "Drug resistance needs to be monitored closely, and the drug regimen needs to be changed as necessary. The administration of combinations of drugs has helped prolong the time till drug resistance develops."

Perils of Living Longer

There is an unavoidable paradox at the heart of HAART. By keeping AIDS patients alive longer, it ups their chances of contracting other diseases,

even diseases unrelated to a failing immune system.

For example, HIV-infected people appear to be at higher risk for two of the most devastating lung diseases, lung cancer and COPD, recent studies suggest.

A 2003 French retrospective analysis that compared the health records of 77,000 HIV-infected persons with records from the French general population through the 1990s found that lung cancer, classified as a non-AIDS defining cancer, was significantly higher in both sexes in the former group.¹

"Evidence is mounting that lung cancer incidence is increased in persons with HIV infection, especially now in the era of HAART," Mark Rosen, MD, chief of the Division of Pulmonary and Critical Care Medicine at Beth Israel Medical Center, New York, N.Y., told delegates at a recent American Thoracic Society meeting.

"Whether this trend is simply related to increased longevity (of HIV patients) leading to increased cancer rates, or a direct effect of HIV or HAART on oncogenesis or failure of immune surveillance, remains unknown." And a 2006 study of 1,014 HIV-positive and 713 HIV-negative male veterans found that after adjusting for age, race/ethnicity, pack-years of smoking, injection drug use and alcohol abuse HIV-infected subjects were approximately 50 percent to 60 percent more likely to have COPD than HIV-negative subjects.²

References:

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Michael Gibbons, senior associate editor, can be reached at mgibbons@merion.com.

HIV an Equal Opportunity Infection

In the United States, HIV infection still disproportionately strikes racial minorities.

"By race, 54 percent of the new infections in the United States occur among African Americans, and 64 percent of the new infections in women occur in African American women," AIDS researcher Brigitte E. F. Beer, DVM, PhD, said.

Among women in general, 75 percent of all new infections "are heterosexually transmitted," Beer pointed out.

Furthermore, half of all new infections in the United States occur in people 25 years of age or younger. HIV/AIDS is now the third leading cause of death among women ages 25 to 44, according to the National Institutes of Health, and the leading cause of death among African American women in this age group.

That said, the risk of AIDS remains high for careless and/or reckless individuals of all races, age groups and sexual leaning, a fact of life often underappreciated by primary care providers, AIDS experts say.

A lot of health care providers "often don't even think of their patients being at risk for HIV," noted Robert Ramien, PhD, a research scientist and associate professor at the HIV Center for Clinical and Behavioral Studies at the New York State Psychiatric Institute and Columbia University.

"I often see people newly infected: older people, married people," Ramien told *ADVANCE*. "Their physicians didn't have a clue or ask them about their sex behavior or even consider giving them an HIV test, even though they run every other test in the book. I don't think physicians, for the most part, are well-trained in talking with patients about their sex behavior.

"HIV is a hidden epidemic among older people, among middle-age hetero people, people who don't think it can happen to them. A nicely dressed white woman isn't perceived of being at risk by a physician."

By Michael Gibbons

HIV Infection May Adversely Affect TB Regimen

Payam Nahid, MD, MPH, didn't set out to rebel against the prevailing medical wisdom. And he hasn't yet.

"I continue to use the current regimen recommended by the American Thoracic Society and the CDC," Nahid told *ADVANCE*. "We should follow the guidelines. They are our best source of information."

He is referring to the currently accepted regimen for treating tuberculosis: a rifamycine-based regimen coupled with pyrazinamide during the first two months. This is the officially recommended treatment for all TB patients regardless of their HIV status.

Readers should sense a "but" coming on.

"But," Nahid added, "as shorter TB regimens are pursued, it is important that we consider HIV status."

Why? The reason can be found in June's *American Journal of Respiratory and Critical Care Medicine*, the pulmonary field's famed "blue" journal.

That issue contains an exhaustive retrospective study by Nahid and eight associates of 700 patients with culture-positive TB treated between 1990 and 2001. Its principal finding jumps off the page: HIV-positive patients given the recommended 6-month rifamycin-based regimen had four times the relapse rate of TB patients given medicine daily or treated for longer periods.

"I think, overall, it's a surprising finding," Nahid said. "It was unanticipated to find that a short-course regimen would be associated with a higher rate of relapse among HIV-infected patients with TB."

Counterintuitive Idea

Truth be told, Nahid et al. did undertake their study with a certain suspicion that something was amiss with the accepted regimen.

"It seemed to us counterintuitive that, physiologically, HIV-infected and HIV-uninfected patients were identical to the point where you could use the same TB regimen in both groups," said Nahid, an assistant professor of medicine in pulmonary and critical care at the University of California, San Francisco.

He and his research team poured over the medical records of one TB control program in San Francisco. They discovered that HIV-infected TB patients given standard 6-month therapy had significantly higher relapse rates: 6.6 percent versus 0.8 percent in uninfected/unknown patients.

Non-compliance with TB's elaborate drug regimen often accounts for relapses but Nahid's study took that factor into account. "It's worth emphasizing that the cohort of patients receiving six months of treatment had associated characteristics that identified them as ideal candidates for the short-course regimen," the scientist noted. "They were the most adherent. But it was this group that, paradoxically, had four times the relapse rate. That's the major take-home from this paper."

HIV infection could increase TB relapse rates for numerous reasons, Nahid speculated. For one thing, HIV infection compromises the immune system. For another, factors such as HIV's own drug regimen (highly active antiretroviral therapy or HAART) may cause malabsorption of some TB medications.

New TB Drug Research

As pharmaceutical firms pursue newer, more powerful TB drugs, they should consider the implications of this finding, Nahid stressed.

"The duration of treatment of HIV-infected individuals is almost off the radar. It has largely been believed to have been settled," he said. "But are we comfortable designing our future trials assuming that HIV-positive and HIV-negative TB patients respond in the same way? Or should this be re-evaluated?"

"(Our study) suggests that the duration of treatment needs to be revisited, especially as we design and launch new studies to evaluate potentially safer, faster-acting and thus shorter regimens for TB," he said.

One study is inadequate to determine the ideal TB drug regimen, "but it points to questions out there," Nahid added. "Have we truly identified the ideal regimen and the ideal duration of treatment or is there room for improvement?"

"This perhaps serves as a word of caution that as we aggressively try to identify a shorter regimen for active TB, the complexity of HIV infection as well as the benefits and impediments of HAART all need to be taken into account as we move forward."

Will the scientific community heed his advice? Nahid eagerly awaits a trip he'll take in November to Cape Town, South Africa, site of the 2007 meeting of the International Union against Tuberculosis and Lung Disease, a conference essentially devoted to TB and HIV.

"I'll be curious to see if the paper has a splash there," he said.

Reference:

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