Drug resistance vexes treatment of AIDS

Two reports in the April 22 NEW ENGLAND JOURNAL OF MEDICINE highlight the complexities and pitfalls of treating people with AIDS. One study finds that AIDS patients can become infected with a more lethal form of the tuberculosis bacterium while recovering from an earlier bout with TB. The second discusses the novel case of a patient who, before treatment, harbored a strain of AIDS virus resistant to zidovudine (AZT), one of the few effective AIDS drugs.

Conventional wisdom holds that a single infection confers immunity to the virulent *Mycobacterium tuberculosis*, which causes TB. But using a technique called DNA fingerprinting to identify different strains of the TB bacterium, researchers led by Peter M. Small, a Howard Hughes Medical Institute investigator at Stanford University, have now demonstrated that four TB patients became infected with a new, multidrug-resistant form of the disease while undergoing treatment for a previously diagnosed infection. All four men had AIDS, the advanced stage of HIV infection that cripples the immune system. All four died from the second TB infection after almost recovering from the first.

"I think that's very bad news," comments David E. Rogers of Cornell University Medical College in New York City. Until now, research had not clearly documented TB "superinfection" in people with AIDS, although "many of us have been concerned that it might happen," says Rogers, vice chair of the National Commission on AIDS.

Investigators have documented numerous outbreaks of multidrug-resistant tuberculosis in the past few years (SN: 2/6/93, p.90). Up to 90 percent of people with AIDS who get multidrug-resistant TB may die of TB, notes Small. In people treated for multidrug-resistant TB who do *not* have AIDS, the death rate falls to 40 to 50 percent.

Typically, drug-resistant strains of *M. tuberculosis* arise because of inadequate or incomplete drug therapy. This partial dosing kills the weakest bacteria first, allowing drug-resistant strains to proliferate. Public health officials should now consider reinfection a third possible explanation for the emergence of drug-resistant TB, says Small. But most instructive, the study "emphasizes the importance of conventional tuberculosis control, which is to identify sick patients and get them on therapy as soon as possible," he explains.

Moreover, because AIDS patients may die before they can be treated effectively for multidrug-resistant TB, public health officials should place "more emphasis on prevention of exposure," Small says. "As tuberculosis becomes multidrug-resistant, it essentially becomes untreatable," he warns. "And the only appropriate response to untreatable diseases is prevention."

In the second report, Alejo Erice of the University of Minnesota Medical School in Minneapolis and colleagues discuss the case of a 20-year-old man infected with a strain of HIV that proved resistant to AZT. Typically, the AIDS virus loses its sensitivity to the drug after six to 12 months of treatment, the researchers note.

In this case, however, the patient had sexual contact with an HIV-positive partner already on AZT, from whom he presumably contracted a drug-resistant strain of the virus, say the researchers. Physicians started the newly infected patient on AZT, but his health failed to improve and his HIV infection grew even *more* resistant to AZT. Eventually, physicians switched him to didanosine, another antiviral agent.

The researchers deem it "likely" that some of the estimated 40,000 new cases of HIV infection each year will prove resistant to AZT from the outset. Consequently, the researchers recommend that any future clinical trials to test the benefits of treatment with AZT and other antiviral drugs include tests for drug resistance.

– D. Pendick

Helium fusion and the fate of massive stars

The destiny of a massive star hangs on a number: the proportion of carbon and oxygen created in the final stages of the nuclear fusion reactions at the star's high-temperature core. This ratio determines how quickly and in what order various elements form within the star and, indirectly, the timing and outcome of its explosion as a supernova.

Now, two teams of physicists have for the first time found experimentally the rate at which alpha particles (helium nuclei) fuse with carbon-12 nuclei to produce oxygen-16. Previously, astrophysicists could do little more than roughly estimate what this rate might be, based on astronomical observations of the abundance of various elements in stars.

"The number one unknown in nuclear astrophysics [has been] the process of helium burning," says Moshe Gai of Yale University.

A star approximately 25 times more massive than the sun lasts about 7.5 million years before exploding as a supernova. For the first 7 million years, hydrogen nuclei fuse to produce helium and release energy. In the last 500,000 years, helium fusion takes over.

Stars initially create carbon-12 by fusing three alpha particles. A carbon-12 nucleus can then capture another alpha particle to make oxygen-16. The carbon-oxygen ratio at a massive star's core depends on the relative rate of these two fusion reactions. Nuclear physicists originally knew only the first rate.

Because of the extreme difficulty of duplicating on Earth the temperatures and pressures at which alpha particles fuse with carbon-12 and for a variety of technical reasons, researchers had to study the reverse reaction – the decay of oxygen-16 into carbon-12 and an alpha particle – to deduce the appropriate reaction rate. "That's a very difficult, but possible, task," Gai says.

In the Yale experiment, Gai and his coworkers aimed a deuterium beam at a titanium nitride target laced with nitrogen-15. Collisions between deuterium and nitrogen produce the radioactive isotope nitrogen-16, which then decays into oxygen-16 by emitting an electron (or beta particle). Oxygen-16 then decays via the emission of an alpha particle into carbon-12. The researchers monitored the emission of alpha and beta particles.

Sifting through these particles and removing extraneous background effects in order to identify the relevant interactions wasn't easy. "For every three alpha particles, there would be 1 billion electrons," Gai notes.

Lothar Buchmann of the TRIUMF high-energy accelerator in Vancouver, British Columbia, and his collaborators chose a somewhat different route. The researchers initially produced a beam of nitrogen-16 ions, then fired the beam into a carbon target. They used special detectors to look for coincidences between the emission of alpha particles and the recoil of carbon-12 nuclei from the breakup of oxygen-16 nuclei created in the target. The TRIUMF team eventually recorded 1 million such events.

Using these data, both groups then applied theory to derive the required reaction rate. The two experiments produced remarkably similar results. The findings – to be refined further – also approximately fit the estimates of nuclear reaction rates that astrophysicists have used for modeling the evolution of massive stars. Such studies suggest that a star a little heavier than 25 solar masses would contain sufficient oxygen near the end of its life to reach the supernova stage more quickly than a less massive, carbon-rich star.

Gai and Buchmann described their findings at an American Physical Society meeting held last week in Washington, D.C.

"We have done completely different experiments – with very different production mechanisms and very different detection [techniques]," Gai says. "But the two experiments are in perfect agreement."

– I. Peterson