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In the Line for AIDS Drugs, Children Are Last

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The revolutionary drug therapies helping many adult AIDS patients are unavailable to most infected children.

None of the three protease inhibitors prescribed for adults — Roche Holding

MEDICINE

Ltd.'s Invirase, Abbott Laboratories' Norvir and Merck & Co.'s Crixivan — has been tested widely in children. Lacking pediatric data, the Food and Drug Administration hasn't cleared the drugs for use in children. While doctors can legally prescribe a drug for a child without such clearance if it has been approved for use by adults, many won't do so in the case of the protease inhibitors because of a paucity of information. They worry that incorrect use of the drugs could be harmful or make it difficult for a child to use a better, yet-to-be-developed medication.

"I'm frustrated," says Ann Petru, director of the pediatric AIDS program at Children's Hospital Oakland in California. "I don't have any dosing information. I have no idea what is a safe dose or a toxic one."

One of her patients is nine-year-old Samuel Fox of Newark, Calif. While Samuel appears healthy — playing soccer, scrapping with his older brother — tests show that the amount of virus in his blood is six times higher than it was in March. His mother, Marilyn, wants Samuel, who

Mostly Out of Reach		
BRAND NAME	MANUFACTURER	APPROVAL DATE
Retrovir	Glaxo Wellcome	Adults, 1987; infants and children, 1989
Videx	Bristol-Myers Squibb	Adults and children, Oct. 1991
Hivid	Roche Holding	Adults only, June 1992
Zerit	Bristol-Myers Squibb	Adults only, June 1994
Epivir	Glaxo Wellcome	Adults, children and infants, Nov. 1995
Invirase*	Roche Holding	Adults only, Dec. 1995
Norvir*	Abbott Laboratories	Adults only, March 1996
Crixivan*	Merck & Co.	Adults only, March 1996
Viramune	Boehringer Ingelheim	Adults only, June 1996

*Protease inhibitors Sources: Pediatric AIDS Foundation; Food and Drug Administration

is adopted, to start taking a protease inhibitor. "It just scares the hell out of me that I'm going to lose him," she says. But Dr. Petru wants more information about the drugs before she considers putting him on one of the new drugs.

Of the three protease inhibitors, Roche Holding's Invirase was approved for adults last December; Abbott Laboratories' Norvir and Merck's Crixivan were cleared early this year. Studies in adults showed that the protease inhibitors, when combined with existing AIDS drugs, were the most potent anti-AIDS weapons yet devised.

Teenagers with AIDS are routinely treated with the new drugs, but only the sickest of the younger children or those in

small-scale clinical trials are getting them. Newborns aren't getting the drugs at all. Heightening the frustration of pediatricians and parents is the fact that some of these trials suggest that the protease inhibitors may be of great benefit to infected children. Just last week, for example, the National Cancer Institute reported that, in a small study of children aged six months to 14 years, Abbott's drug is safe and appears to have "a significant antiviral effect."

"There is such a feeling of optimism and hope among adults, but it hasn't yet been translated into hope for children," says Michael Kaiser, a New Orleans doctor who works with people with AIDS.

How did this happen?

The fact is that the protease inhibitors are part of a larger picture: Only about 80% of all drugs approved for use in the U.S. have been tested in children and have had labeling information about their pediatric use approved by the FDA, says Susan DeLaurentis, co-founder and chief executive officer of the Pediatric AIDS Foundation, which is based in Santa Monica, Calif. Of the nine AIDS drugs that have been approved for adults over the last decade, only three have also been approved for pediatric use: AZT, ddI and 3TC.

In the case of the protease inhibitors, critics contend that drug companies have been slow to develop pediatric data because children make up only a small proportion of infected individuals. Since 1981, more than 7,200 children aged 12 and under have been diagnosed with AIDS in the U.S., compared with more than 548,000 adults, according to the Centers for Disease Control and Prevention. "The attitude of the drug companies is that it's not economically feasible or profitable because there is a limited number of infected children," asserts Dianne Donovan, a resident of Queensbury, N.Y., who adopted two children who are HIV-positive.

Abbott, in particular, comes in for tough criticism. Because Norvir was initially developed as a liquid, making it readily ingestible by infants and small children, it "was the one that could have been pushed into pediatric studies at a much earlier stage," says Philip Pizzo, a

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In Line for Medicines Used to Treat AIDS, Children Come Last

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leading AIDS researcher who is physician in chief and chairman of the department of medicine at Children's Hospital in Boston. "But the company simply didn't push hard to put pediatric studies in place."

Abbott officials vehemently deny that they acted too slowly or that the small size of the pediatric market has influenced their priorities. They say they have followed the prudent course of testing the drug extensively on adults first. "We go through a careful process where adults, who can give their consent, can participate; and once we have the information from adults, we can take it to the children," says John Leonard, the head of Abbott's antiviral venture. Abbott has begun having preliminary talks with the FDA about adding recommended doses for children on Norvir's label, and the company hopes it will get the go-ahead before long.

Merck and Roche are further behind. Merck officials say they are moving as quickly as they can to develop a liquid that young children can take, but have encountered frustrating obstacles involving taste and the way the drug is absorbed in the body. Roche is working on a powder-like pediatric version of Invirase that can be sprinkled into a child's milk or formula bottle. All three protease makers say they are proceeding quickly by historical standards; in any case, various studies involving larger numbers of children are likely to begin later this year or early next year.

Two other drug companies that are

working on new protease inhibitors, Agouron Pharmaceuticals Inc. and Glaxo Wellcome PLC, plan to seek FDA approval for use by children at the same time they seek approval for use by adults. On another front, researchers at the University of Massachusetts Medical Center have gotten encouraging results in tests involving infants given a new mixture of drugs not including any protease inhibitor.

FDA Commissioner David Kessler, who already has eased the rules on pediatric drug approvals once, says more needs to be done to prod companies to develop pediatric data. The Pediatric AIDS Foundation backs legislation that would give companies an extra period of market exclusivity if they develop the needed information on the use of their pediatric drugs.

As for Samuel Fox, he has begun speaking out about kids' access to the drugs. "He wants to do something," his mother says. "He's angry right now. We're all angry."

Says Samuel: "I want to live to be an adult."