AP: U.S. Officials Knew of AIDS Drug Risks

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_go_pr_wh/bush_aids_drug

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By JOHN SOLOMON, Associated Press Writer

ghw WASHINGTON - The government's research on using an AIDS (news - web sites) drug to protect African babies was so flawed that health officials had to use blood tests after the fact to confirm patients got the medicine. Ultimately, they had to acknowledge the study broke federal patient protection rules.

But the National Institutes of Health (news - web sites) never told the White House about problems it found in 2002 with its research on the drug nevirapine before President Bush (news - web sites) unveiled a $500 million plan to distribute the medicine across Africa, documents obtained by The Associated Press show.

Instead, officials inside the government's premier health research agency scrambled to keep its safety experts' concerns from scuttling the use of nevirapine in Africa as a cheap solution to stopping babies from getting AIDS from infected mothers, the memos show.

"Everyone recognized the enormity that this decision could have on the worldwide use of nevirapine to interrupt mother-baby transmission," NIH's AIDS research chief, Dr. Edmund C. Tramont, reported March 14, 2002, to his boss, Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases (news - web sites).

Since then, hundreds of thousand of doses of the drug have been

administered to African mothers and babies under the Bush plan.

Up to half those babies may have been stopped from getting AIDS, officials said. But now concerns are emerging about whether patients who received those single doses have developed resistance to further AIDS treatment.

The documents show Tramont and other NIH officials dismissed the problems with the nevirapine research in Uganda as overblown and were slow to report safety concerns to the Food and Drug Administration (news - web sites).

A professional auditor hired by NIH who first helped disclose the problems said in an interview that most of the problems were fixable but NIH officials were in a rush to declare that things were OK.

"It seemed to me we were drawing conclusions too quickly across the board, especially the implementation of nevirapine in South Africa," auditor Michael Hensley told AP.

Ultimately, NIH did stop the Uganda research for 15 months - from the spring of 2002 to the summer of 2003 - to review the science and take corrective actions.

NIH officials told AP they remain confident after re-reviewing the Uganda study and other research that nevirapine can be used safely in single doses by African mothers and children to prevent HIV (news - web sites) transmission during birth.

But they acknowledged their Uganda research failed to meet required U.S. standards and have asked the National Academy of Sciences (news - web sites) to investigate.

"I would say there are many lessons that we have learned from this review that will help us do our clinical research, both domestically and internationally, much better," said Dr. H. Clifford Lane, NIH's

No. 2 infectious disease official.

The White House said it remains confident in Bush's $500 million plan in 2002 to send nevirapine to Africa, a continent that accounts for more than two-thirds of the world's AIDS cases, with 27 million people infected. The United States approved $2.9 billion to fight global AIDS in 2005.

"The president's mission is to try to stop the spread of AIDS in Africa and to come at it from a new angle, and that is what this is all about," spokesman Trent Duffy said.

Though the White House was never told of the problems, they were serious enough that the U.S. Health and Human Services (news - web sites) Department sent a nine-page letter to Ugandan officials identifying violations of federal patient protection rules by NIH's research.

The NIH research "may have represented a failure to minimize risk to the subjects," the Office of Human Research Protections told Ugandan authorities in summer 2002, a month after Bush's announcement of the nevirapine announcement.

NIH officials said a recent closer review of the Uganda research has identified a new concern - that even single doses of nevirapine can create instant resistance. That means patients may not be able to use the drug or others in its class again when their AIDS worsens, Lane said.

"It was unexpected, and what it means is nevirapine probably shouldn't be a drug of first choice if other options are available," Lane said.

Lane said NIH officials were aware in spring 2002 of the impending White House announcement on nevirapine but did not tell presidential aides of the problems because they were confident, even before

reviewing the Uganda research, that the underlying science was solid.

In order to reconstruct the research to make sure the science held up, NIH officials in summer 2002 found they couldn't use patient records because of sloppy record keeping and missing files. Instead, they had to review blood samples to determine which patients got the medicines.

Nevirapine is an antiretroviral drug marketed in the United States as Viramune. It has been used since the 1990s to treat adult AIDS patients and is known to have potentially lethal side effects like liver damage and severe rashes when taken over time.

In 1997, NIH began studying in Uganda whether it could be given safely in single doses to stop mother-to-baby HIV transmission. That research showed it could reduce transmission in as many as half the births.

But by early 2002, an NIH auditor, the agency's medical safety experts and the drug's maker all disclosed widespread problems about the U.S.-funded research in Uganda.

Boehringer Ingelheim, the Connecticut-based company that makes nevirapine, told NIH it identified at least one "critical compliance issue" that compromised the integrity of the study and more than four dozen issues it described as serious and major.

Boehringer and NIH auditors cited concerns such as failing to get patients' consent about changes in the experiment, administering wrong doses and delays and underreporting of "fatal and life threatening" problems.

"It appeared likely, in fact, that many adverse events and perhaps a significant number of serious adverse events for both mother and infant may not have been collected or reported in a timely manner," Westat Corp. found in March 2002. Westat is a medical auditing firm

hired by NIH to visit and audit the Uganda site.

Westat reported there were 14 deaths not reported in the study database as of early 2002 and that the top two researchers in Uganda acknowledged thousands of bad reactions that weren't disclosed.

NIH said the subsequent review whittled that list down significantly, all deaths were eventually recorded and the majority of bad reactions are believed to have been caused by the poor health of patients, not the single dose of nevirapine. But they conceded it was incumbent on a U.S. research project to disclose them fully and quickly.

Officials said the problems began when NIH converted the research from determining the drug's usefulness to supporting FDA (news - web sites) approval for the drug. Paperwork in Uganda wasn't kept to FDA standards, they said.

"We may not have reported exhaustively, but we reported all serious side effects," said Professor Francis Mmiro, a lead doctor in the Uganda study. "What you may call a serious side effect in the U.S. is not a serious side effect in Kampala."

NIH officials reviewed the bad news in early March 2002.

Meeting minutes, written in shorthand, raised broad concerns: Half the babies in the study were also enrolled in a vitamin A study that could have affected the outcome, and medical staff running the trials didn't follow procedures for divulging serious adverse events (SAEs).

"No mtg minutes, no training doc(umentation), site used their own criteria for grading SAEs. No lab normal values & serious underreporting of SAEs," the minutes stated.

They also quote an NIH official who visited Uganda as saying, "The site staff doesn't know what they don't know."

But Tramont, the AIDS research chief, and other top NIH officials repeatedly dismissed the concerns as preliminary or overblown, and sought to salvage the flawed research's underlying conclusions rather than start over.

"There is presently no evidence that the study's scientific results are invalid," said a report Tramont sent to his staff less than two weeks after getting the March 2002 Westat audit.

In January 2002, Boehringer had sent NIH an early copy of its report. But the drug maker, fearing publicity about the report might destroy its chance to get FDA approval of the drug for domestic use, asked NIH to destroy it before FDA regulators could learn about it.

"Sensitive information. Asked for it to be destroyed when audit is upon us," NIH official Mary Anne Luzar wrote on the cover page of Boehringer's report.

But Boehringer says it never requested the document be destroyed, saying "our actions throughout the study evaluation were proactive and forthcoming."

Lane said the request to destroy the report was inappropriate and NIH never complied. But he conceded his agency inappropriately kept the audit from FDA for weeks, saying, "It shouldn't have happened that way."

NIH at first sought to postpone the FDA review of nevirapine, then top NIH and FDA officials arranged for the drug maker to pull its U.S. application rather than risk a public rejection that might scare African countries looking for U.S. guidance on the drug.

Unaware of the internal NIH concerns, Bush announced in June 2002 the $500 million effort to fight the spread of AIDS in Africa and the Caribbean. The plan's centerpiece was nevirapine.

"This major commitment of my government to prevent mother-to-child HIV transmission is the first of this scale by any government, anywhere," Bush said in a Rose Garden announcement.

African health officials are having second thoughts. South African officials in July recommended ending the single-use treatment because of the new concerns about drug resistance.

African doctors said they weren't aware of the full extent of NIH's concerns but feel comfortable - at least until better options emerge - administering it in single doses to AIDS-sickened mothers who have few other choices to protect newborns.

"It's not ideal, but it works," said Dr. Ashraf Coovadia of Coronation Mother and Child Hospital in Johannesburg, South Africa. Without it, "many, many more babies would be born with HIV."

Boehringer Ingelheim said it has donated enough doses to treat more than 411,000 mothers and infants in Africa, and self disclosed the problems it found with the Uganda research. But it says it has research from other locations, like Thailand and South Africa, showing single dose usage at birth is safe and effective.

"The bottom line is there were these procedural issues, such as the speed of reporting adverse events, and the like. But the important scientific data was intact, and found to be valid," said Dr. Patrick Robinson, a top Boehringer AIDS specialist.

Still, the German-owned company is no longer seeking FDA permission in 2004 to use nevirapine for protecting U.S. infants because better treatments have emerged, he said.

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AP reporter Alexandra Zavis in Johannesburg, South Africa, contributed to this story.

On the Net:

Documents gathered by AP for this story are available at:
http://wid.ap.org/nevirapine1.html

National Institutes of Health: http://www.nih.gov

Boehringer Ingelheim: http://www.boehringer-ingelheim.com

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"Just look at us. Everything is backwards; everything is upside down. Doctors destroy health, lawyers destroy justice, universities destroy knowledge, governments destroy freedom, the major media destroy information and religions destroy spirituality" ....Michael Ellner