November 27, 2010

An AIDS Advance, Hiding in the Open

By DONALD G. McNEIL Jr.

In the war against AIDS, a new weapon has emerged.

It wasn't a secret weapon. It was a well-established treatment pill that has only now been shown to be effective as a prevention pill too. Which raises a question: What took so long?

Last week, a clinical trial showed that taking Truvada, a pill combining two drugs, once a day would greatly reduce a gay man's chances of getting infected with the dangerous virus. Although confirmatory studies are still needed, the practice — called "pre-exposure prophylaxis," or "prep" — will, in theory, also protect sex workers, needle sharers, wives of infected men, prison inmates and anyone else at risk.

But Truvada has been sold since 2004. And the world has known since 1995 that antiretroviral drugs, used in combination, can rescue people with AIDS. As far back as at least 1990, it also knew that "post-exposure prophylaxis" ("pep") often works in humans — that is, that a victim of a needle stick or rape or unprotected sex who begins taking a short course of antiretrovirals within 72 hours can probably avoid infection.

A few scientists even knew by 1995 that a drug in Truvada can protect

monkeys from infection with the simian version of the AIDS virus.

So couldn't "prep" have been "discovered" earlier? Why did it take until 2010?

The delay turns out to be a combination of scientific caution and the fiery politics of AIDS. While a medical advance can be made by a momentary flash of inspiration or luck — as legendarily happened with penicillin — proving that it works can take forever. And that is particularly true with AIDS, a disease surrounded by visceral fears, longstanding prejudices and the potential for huge profits.

The chief reason this advance took so long, said Dr. Robert M. Grant, a virologist at the Gladstone Institutes in San Francisco and the study's chief author, is that the two drugs in Truvada, tenofovir and emtricitabine, were not approved for use in humans until 2001 and 2002, respectively. Older drugs, like AZT, the first AIDS drug, adopted in 1987, were too toxic.

Doctors once debated using nevirapine, approved in 1996. In poor countries, single doses for mother and baby are given at birth to prevent mother-child transmission. But taking nevirapine for even a few weeks can bring on brutal side effects. Over 10 percent of users get rashes. In rare cases, the drug can kill if not stopped in time.

Giving powerful drugs to healthy people is different from giving them to the desperately ill. No doctor would give cancer drugs to a healthy person. Prophylaxis is common with, for example, malaria drugs for travelers making brief sojourns in the tropics. But a drug to be taken all one's life — or at least for all of one's sex life — must be very safe.

Also, the drug must not prompt drug-resistance mutations in the virus. Tenofovir is unique that way, said Dr. Howard S. Jaffe, president of the Gilead Foundation, the philanthropic arm of Gilead Sciences, which makes Truvada. Structurally, it is so nearly identical to the bit of DNA it blocks that "the virus can't easily outsmart it," he said. Resistance to nevirapine, by contrast, can

develop after a single dose.

Another factor is that not every drug company wants to see its best treatment drugs, on which it earns billions of dollars, tested for prevention. Dying patients accept unpleasant side effects; healthy ones might sue. And any patient who gets infected, even if taking the drug improperly, could sue. Gilead Sciences was willing to let Truvada be tested, although it has not yet decided, Dr. Jaffe said, whether to apply for F.D.A. permission to sell it as prophylaxis.

Also, several AIDS experts said, lab scientists were focused for years on the dream of an AIDS vaccine, while behaviorists assumed everyone would adopt condoms or abstinence. None of those hopes has been realized.

The final delay was caused by political battling. Plans to test Truvada began in 2003, and sites were chosen not just in American cities with gay populations like San Francisco and Boston, but in countries where the virus was also killing prostitutes and clients: Nigeria, Cameroon, Ghana and Cambodia.

Then, at the 2004 International AIDS Conference in Bangkok, the Paris chapter of the AIDS activist group Act-Up unexpectedly attacked Gilead Sciences' booth, spraying it with fake blood and accusing the company of experimenting on poor people.

As Dr. Jaffe tells it, French activists "played the anti-U.S. card in Francophone countries" and stirred up sex workers' unions in Cambodia, eventually leading the Cameroonian and Cambodian governments to stop their trials. Nigeria's stopped for other reasons, though many Nigerians were hostile to drug companies because of rumors that polio vaccine was an anti-Muslim plot and because Pfizer had tested a new antibiotic on children with meningitis. "If not for this misplaced activism, we might have had an answer five years earlier," Dr. Jaffe said.

Dr. Grant saw the same struggle differently. The activists were disruptive, he said, but also "raised significant questions" about whether participants would

be protected from side effects and about who, if anyone, would pay for lifelong treatment if participants did eventually get AIDS. One result, he said, was that protocols were improved and more countries added: South Africa, Brazil, Peru, Ecuador, Thailand.

But more important, he said, was the emergence of the two agencies that now pay for treatment in poor countries, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and the President's Emergency Plan for AIDS Relief. It took until about 2005 for most poor countries to take advantage of that aid.

Enrollment finally began in 2007. While monkey trials are quick and vicious — give the drug, zap the caged animals with virus, wait a bit, and dissect a few — ethical human trials are complex. At a cost of $44 million, this one screened nearly 5,000 people to find 2,500 participants to follow for up to three years.

Any approval process takes time and hits unexpected roadblocks, Dr. Grant said. "But," he insisted, "we started working on prep the minute the right drugs became available."