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HEALTH

A Failed Trial in Africa Raises Questions About How to Test H.I.V. Drugs

By DONALD G. McNEIL Jr. FEB. 4, 2015

The surprising failure of a large clinical trial of H.I.V.-prevention methods in Africa — and the elaborate deceptions employed by the women in it — have opened an ethical debate about how to run such studies in poor countries and have already changed the design of some that are now underway.

Scientists who conduct clinical trials are now testing participants' blood more often and holding group discussions to quell rumors and urge participants to take their medications diligently.

As a result of the failed trial, scientists are arguing vigorously about the extent to which it is ethical to pay participants for their time, and whether results of trials that do so can be trusted.

The trial — known by the acronym Voice, for Vaginal and Oral Interventions to Control the Epidemic — was abruptly halted by independent safety monitors because it was not working: Women who were given pills or vaginal gels containing anti-H.I.V. drugs were becoming infected at roughly the same rate as women who were given placebos.

The study, paid for by the National Institutes of Health, was supposed to definitively establish whether pre-exposure prophylaxis — the use of small amounts of anti-AIDS drugs to prevent infection — would work for African women. It enrolled 5,029 women at 15 clinics in South Africa, Zimbabwe and Uganda, and cost $94 million.

In Africa, where there are 1.6 million new infections each year, women are at particularly high risk: About 60 percent of Africans living with H.I.V. are women, and teenage girls are far more likely to be infected than teenage boys.

The strategy has worked well for gay American men and Thai drug users who took their pills daily, but worked for African women only when they were in stable relationships with partners who admitted to being infected.

When parts of the trial had to be stopped prematurely in 2011, scientists suspected it was failing because some women were not using their gel or pills, even though they claimed they were and produced empty bottles and applicators to prove it.

But all blood samples had been stored for later testing, so the researchers had no idea how pervasive the problem was. The final analysis, published on Wednesday by The New England Journal of Medicine, said that about 70 percent of the women actually had no tenofovir, the main study drug, in their blood, even though about 90 percent had claimed they were taking their pills or using the gel, and counts of empty pill bottles and used gel applicators suggested that 86 percent had been taken or used.

Dr. Michael S. Saag, an AIDS researcher at the University of Alabama at Birmingham, wrote in an editorial accompanying the study that "a large number of participants actively removed unused medications from their allotment before returning to their study site in order to create the appearance of compliance with the protocol."

Ariane van der Straten, a researcher who led follow-up interviews with over 300 participants, found that many admitted to discarding pills or pouring gel down the toilet. One gave hers to a friend working as a prostitute. Another stockpiled them for later, to take if they were found to work, "but her sister-in-law threw everything out," Dr. van der Straten said.

"No one expected they would go to such contortions to appear being adherent when they were not," she said.

Clinic waiting rooms, she said, were often abuzz with rumors — that the drugs would "rot the uterus" or cause liver cancer or infertility, that the blood samples were sold or used for Satanism, that the foreign scientists conducting the study were secretly spreading H.I.V., that a woman could tell from nausea or tingling whether she was getting the placebo.

"A lot of them got really scared," she said, and the least adherent were those

most at risk: young, single women.

They lied for many reasons, she said. Some feared being scolded by the clinic nurses. Many wanted to stay in the trial because it offered free monthly gynecological exams at a clean clinic where the staff members were polite, appointments were kept and the pharmacy was well stocked — a far cry from conditions at many public hospitals.

Some cited the free contraception.

Also, they were paid $10 to $15 per visit, depending on the country and how far they had to travel.

For some women, Dr. van der Straten said, $10 "meant having food on the table to feed their kids." For others, she added, "it was a loss — they made more at their jobs."

The size of the stipends raised the eyebrows of some scientists.

Dr. Saag — who was not connected to the study and had not known the size of the payments when he wrote his editorial, said: "Wow — that explains most of this. That's a meaningful amount of money. Where I do trials in Zambia, wages are less than $5 a day."

Dr. Jeanne M. Marrazzo, an H.I.V. specialist at the University of Washington and Voice's lead investigator, defended the payments, noting that the South African Medical Research Council requires that all clinical trials pay 150 rand, or about $13. Poor African women are chosen because they are the high-risk group.

In the interviews, she said, women cited free tests and contraceptives more often than the stipends.

Dr. Jared Baeten, a global health specialist at the University of Washington, noted that the payment of stipends was common even in clinical trials at American universities and "discussed in tremendous detail" by ethics oversight panels.

He oversees a trial of a vaginal ring that it is hoped will protect a woman against H.I.V. for a month.

Women in the trial are paid varying amounts. In Malawi, he said, they are reimbursed only for bus fares. But even the $10 to $15 payments, he argued, "are within reasonable amounts."

Women join trials for many reasons, including wanting to protect themselves,

their children and women in general from H.I.V.

"I've never been concerned that money is the factor driving participation or is corrupting the results," he said.

The Voice revelations, several scientists said, have profoundly changed how similar trials are run.

Investigators now test blood immediately, but doing so is tricky because trials must remain "double-blind," meaning neither the patient nor the doctor can know who is getting the drug or the placebo.

Gita Ramjee, director of H.I.V. prevention at the South African Medical Research Council and a site leader for the vaginal ring trial, said the lab was not allowed to tell her any individual's results, but it could say which sites had lower overall drug levels in participants' blood.

If that happened, her nurses would hold group sessions gently telling the women that they were doing worse than women at other sites and reminding them that success would help women all over the world.

Also, she said, her trial was trying to get local men to be more sympathetic by sponsoring movie nights and soccer matches with free food, and pamphlets explaining the trial.

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