**Field Epidemiology Training Programs**
**Case Studies in Applied Epidemiology**
**No. 121-712**

# Short-course Zidovudine Compared to What?
## A Trial to Prevent Mother-to-Infant HIV Transmission

**Participant's Guide**

**Learning Objectives**

After completing this case study, the participant should be able to:

- Discuss the principle of equipoise and its relevance in designating an appropriate comparison group in a randomized controlled trial (RCT)
- Describe the role of an Institutional Review Board
- List the required elements of informed consent and discuss key considerations in using informed consent in developing countries
- Describe the ethical rationale for conducting an interim analysis of a clinical trial

*This case study is based on randomized controlled trials to determine the efficacy of short-course zidovudine in preventing mother-to-infant transmission of HIV in developing countries after the efficacy of a longer and more complex regimen of zidovudine had been established in the United States and France (see list of references at the end of the case study).*

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# Part I

AIDS was first recognized in 1981. Mother-to-child transmission was first identified as a mode of transmission in 1983. Zidovudine (also known as ZDV or AZT) was approved for use as treatment in 1987. The following year, research was begun to determine whether zidovudine could prevent mother-to-infant transmission of HIV and related viruses in mice and monkeys.

When the investigators reported that zidovudine was indeed effective in reducing mother-to-infant transmission in animals, human studies were designed. In particular, the Pediatric AIDS Clinical Trials Group (ACTG) Protocol 076 study was launched in the United States and France in 1991 to test the efficacy and safety of zidovudine in preventing mother-to-infant HIV transmission. This study was a multicenter randomized, double-blind, placebo-controlled trial.

**Question 1:** What does "multicenter randomized, double-blind, placebo-controlled" mean?

The design of the study called for enrollment of pregnant, HIV-infected women between 14 and 34 weeks' gestation, beginning in April 1991. Additional enrollment criteria are listed in Table 1. Women were randomly assigned to receive either zidovudine or placebo. The zidovudine regimen is described in Table 2.

Table 1. Eligibility criteria, ACTG 076 Study, United States and France, 1991

- Pregnant, between weeks 14 and 34 of gestation
- HIV-positive
- No indication for antiretroviral therapy in the judgment of their health care providers
- Had not received antiretroviral therapy during this pregnancy
- Had never received immunotherapy, anti-HIV vaccines, cytolytic chemotherapeutic agents, or radiaton therapy
- With following laboratory values:
  - CD4+ T-lymphocyte count above 200 cells per cubic millimeter
  - Hemoglobin concentration ≥ 8 g/dl
  - Absolute neutrophil count ≥ 1,000 cells / $mm^3$
  - Platelet count ≥ 100,000 cells / $mm^3$
  - Serum alanine aminotransferase concentration ≤ 2.5 times the upper limit of normal
  - Serum creatinine concentration ≤ 1.5 mg/dl or 8-hour urinary creatinine clearance ≥ 70 ml/minute
- No ultrasound evidence of
  - Life-threatening fetal anomaly
  - Anomaly that could increase fetal concentration of zidovudine or its metabolites
  - Oligohydramnios in second semester or unexplained oligohyrdramnios in third semester
  - Fetal hydrops, ascites, or other evidence of fetal anemia

Table 2. Zidovudine regimen, ACTG 076 Study, United States and France, 1991

- During pregnancy, beginning at 14–34 weeks: 100 mg ZVD orally 5 times daily
- During labor: 1-hour loading dose of intravenous ZVD 2 mg/kg body wt., followed by continuous infusion of 1 mg/kg/hr until delivery
- Newborn, beginning 8–12 hours after birth: 2 mg/kg orally every 6 hours for 6 weeks

**Question 2**: Review the treatment regimen described in Table 2. Would you consider this regimen relatively simple or relatively complicated?

Based on sample size calculations, the study plan called for enrollment of 636 assessable mother-child pairs. Three interim analyses were planned, the first one for data collected through December 1993.

**Question 3**: Why plan an interim analysis?

From April 1991 through December 1993, 477 pregnant women were enrolled, of whom 407 had given birth by the time of the first interim analysis. Among 363 infants with known HIV status, 13 infants in the zidovudine group (n=180) and 40 in the placebo group (n=183) were HIV-positive. Demographic and other characteristics of the women and infants in the treatment and placebo groups were similar.

**Question 4**: Interpret these findings.

Using a life-table method of analysis, the investigators calculated a 67.5% (95% confidence interval 40.7% –82.1%) relative reduction in the risk of HIV transmission (Z = 4.03, *P*-value = 0.00006). Minimal short-term adverse side effects were observed — hemoglobin values at birth were lower in infants in the zidovudine group than in infants in the placebo group, but by 12 weeks of age hemoglobin values in the two groups were similar.

**Question 5**: Given these findings, what actions would you recommend?

# Part II

The study's Data and Safety Monitoring Board recommended that enrollment of additional patients into the study be discontinued, and that all patients enrolled in the study, whether in the treatment or the placebo group, be offered zidovudine treatment.

Within two months after the results had been announced, and even before the results of the study had been published, the U.S. Public Health Service Task Force on the Use of Zidovudine to Reduce Perinatal Transmission of Human Immunodeficiency Virus issued a recommendation that pregnant HIV-positive women who would meet (or come close to) the ACTG 076 study enrollment criteria should receive the protocol regimen, and other women should be evaluated on a case-by-case basis. Thus the ACTG 076 regimen quickly became the standard of care in the United States and other developed countries.

Unfortunately, the ACTG 076 regimen proved impractical in most developing countries because of the complexity of the treatment schedule, high cost and lack of availability of zidovudine, and lack of infrastructure for monitoring and record keeping.

The World Health Organization (WHO) convened a group in Geneva to discuss further research on preventing mother-to-infant transmission in light of the ACTG 076 study results. A key question that WHO wanted to address was whether a shorter and less complex regimen of zidovudine treatment — which presumably would be more practical for use in developing countries — would be effective in preventing HIV transmission from mother to newborn.

Because the standard of care in developing countries at that time was no antiretroviral treatment at all for pregnant women, some members of the WHO group asserted that clinical trials should compare short-course ZVD treatment with placebo. Others argued that because an effective intervention (the ACTG 076 regimen) was known, the trial should compare short course treatment with the ACTG 076 regimen. The second group claimed that use of a placebo-control group violated the principle of *equipoise,* an important but not universally accepted ethical concept in clinical trials meaning that the investigators genuinely do not know which of the treatments under study is more effective.

**Question 6**: What arguments could be used to support inclusion of a placebo group in studies conducted in low-resource countries? What arguments could be used against the inclusion of a placebo group in these studies?

**Question 7**: If you were a representative at the WHO meeting, which comparison group would you support?

## Part III

The WHO group concluded that "placebo-controlled trials offer the best option for a rapid and scientifically valid assessment of alternative antiretroviral drug regimens to prevent [perinatal] transmission of HIV."

The U.S. National Institutes of Health (NIH) and the U.S. Centers for Disease Control and Prevention (CDC) supported the WHO conclusion, and funded several studies that compared a short-course zidovudine regimen with placebo. Two companion studies were planned for Thailand and Côte d'Ivoire. Each of the studies sought to enroll HIV-positive women who were at least 18 years old and at less than 34 weeks' estimated gestation. Eligible women would be randomly assigned to a zidovudine or placebo group. In this regimen, each woman would receive 2 doses of either ZVD or placebo per day during the last 4 weeks of pregnancy and oral doses during labor, and the baby would receive no treatment. One notable difference between the two studies is that women in the Thai study would not breastfeed their infants, while women in Côte d'Ivoire would be allowed to do so.

***Question 8***: *What is the outcome of interest in these studies? What would the two-by-two table look like? What measure of effect would likely be used?*

| | |
|---|---|
| | |

A statistician determined that the target sample size for the Thailand study should be 392 women.

**Question 9**: What factors are used in the calculation of sample size?

You have been asked to serve as Principal Investigator of the study in Côte d'Ivoire. You need to develop the protocol, the informed consent form, and standard operating procedures. You also need to guide the protocol through the Institutional Review Board in Côte d'Ivoire and, because CDC is involved in the study, the IRB at CDC as well.

**Question 10**: What is the difference between a proposal, a protocol, and standard operating procedures?

**Question 11**: What is an Institutional Review Board?

**Question 12**: Are there epidemiologic investigations that do not need to be reviewed by an institutional review board?

**Question 13**: What elements need to be included in an Informed Consent form for participants?

One premise supporting the concept of Informed Consent is that an individual has a right to make a decision about his or her participation. However, in some cultures, a village leader tends to make decisions for the villagers, and individual informed consent could be viewed as usurping or challenging the leader's authority. Similarly, in some cultures a husband speaks for a wife.

**Question 14**: How might you handle informed consent in these cultures?

**Question 15**: What other considerations affect development of an informed consent process appropriate for the target audience?

**Question 16a**: Review the draft Informed Consent form on the next page. Is anything missing?

**Question 16b**: Comment on the "Nature of the Study" section of the Informed Consent form.

## Intervention Study to Reduce Mother-to-Child Transmission of HIV-1 Through the Administration of Zidovudine to Pregnant Women, Abidjan Côte d'Ivoire

## Consent Form for Study Participation (Draft)

In a blood test that we did earlier in this clinic we found that you were infected with the HIV-1 virus. This is the virus that causes AIDS. HIV can be passed from you to your baby during pregnancy, during birth, or after birth through breast milk. One out of three babies born to women who have the virus will become infected. You and your baby are asked to take part in a study to see if a drug called zidovudine (ZDV) can keep your baby from becoming infected with the HIV virus.

It is important that you understand the following: a) you can choose to take part in this study or you can choose not to take part; b) if you do take part in this study, you can change your mind about taking part at any time; c) if you do not take part in this study or if you change your mind about taking part, you will still be able to come to this clinic to see the doctors and nurses and you will be able to deliver your baby here and bring him or her to the clinic for care. Thus, your choice to participate or not participate will not in any way affect the care that you will receive.

We are also interested in the baby's father's permission to permit you and your baby to participate in this study. If the father of your baby agrees to your participation, that will be easier for you and your baby to continue to come to see us for the regular clinic visits. If he refuses to let you take part in this study, we will ask that you not participate, although we will be happy to provide you with the usual care in the clinic.

Nature of the study:
Previous studies have documented that zidovudine (ZDV), a drug that inhibits replication of the Human Immunodeficiency Virus (HIV), is efficacious in reducing maternal-neonatal transmission of HIV when administered during the third trimester of pregnancy and parturition, and to the neonate. The current study is a randomized, placebo-controlled trial designed to assess the efficacy of a truncated regimen of ZDV in preventing such transmission. This study will compare the risk of HIV transmission among women who receive the truncated regimen of ZDV to the risk of transmission among women who receive placebo therapy.

Study procedures:
Before you enter this study, you will be checked by a doctor and a blood sample will be taken. If these tests show that taking part in the study is safe for you and your baby and you agree, you will randomly (by chance) be given either ZDV or placebo. This means that you have an equal chance of either receiving ZDV pills which may prevent the HIV virus from infecting your baby or placebo pills which has no effect on HIV. Once you start taking the pills you will keep taking it for the rest of your pregnancy. Neither you nor your doctor will know which pills you are receiving.

You will swallow one pill two times a day every day. When labor begins you will take one extra dose of 1 tablet before coming to the clinic to have your baby. While you are taking the medicine, you will be checked every two weeks in this clinic to make sure that the medicine is safe for you and your baby. When you come to the clinic a doctor will check you and blood will be drawn from your arm. The total amount of blood drawn at each visit will not be more than 3 teaspoons.

After delivery, your baby will be checked and one teaspoon of blood will be taken. You and your baby will then come to the clinic 6 weeks after you give birth and then every three months until your baby is 2 years old. At each visit a doctor or nurse will ask you some questions, examine your baby, and draw about a teaspoon of blood from your child. Sometimes a doctor or nurse will draw some blood from you.

## Consent Form for Study Participation (Draft) - Continued

Risks to you
The major side effect seen in patients taking ZDV is anemia (a decrease in the number of red blood cells in the blood) that may cause you to start labor early. This side effect could also diminish your body's ability to fight infections. You may also experience nausea, vomiting, and dizziness. The blood drawing may hurt a little. Sometimes a bruise or blood clot, or swelling of the arm might happen where the blood is taken.

Risks to the fetus
Your baby may also get anemia from the ZDV, however this does not happen often, goes away without treatment, and does not seem to hurt the baby. The long-term effect of ZDV on your fetus is not known.

Risks to your baby
Blood drawing may cause some pain to your baby. Blood drawing may also cause some bleeding and bruising. Rarely, a small blood clot or swelling of the skin can happen.

Benefits to you and your baby
It is not known whether ZDV given in the dose you might receive will lower the chance of your baby getting HIV. Taking part in this study may not benefit you or your baby, but the information gained from this study may help to find a treatment to prevent the transmission of HIV from mother to baby.

Confidentiality of Records
Information about you and your baby will be identified by a study number and not your name. Information about you and your baby including your blood test results and those of your baby will not be given to anyone without your permission. Blood drawn from you will be tested in different laboratories to learn more about ZDV and HIV. In these laboratories your blood will only be identified by a number. You will not be identified in any papers or talks that come from this study.

Costs to you for participation
There is no cost to you or your baby for the study clinic visits, study drug, or laboratory tests with this study. For each visit we will give you [about US$ 2] to help pay for your transportation. In addition, you will not have to pay for the cost of delivery. If you or your baby become sick, you can come to the study clinic. You will be seen by a study doctor and when possible the doctor will give you medicine at no cost.

Circumstances for withdrawal from the study without your consent
You may be asked to no longer take part in this study for several reasons. a) if you become too sick; b) if you miss appointments or stop taking the study drug; c) if you have a serious reaction to the drug; or d) if the father of the baby decides that you can no longer take part in the study.

Voluntary withdrawal
You may choose at any time to withdraw from the study and you can continue to attend the clinic and delivery unit as other women do for their usual care during pregnancy, delivery and for the baby after delivery.

Statement of Consent
The purpose of the study, the steps to be followed and the risks and benefits have been explained to me. I understand that I may withdraw my participation at any time and my baby and I can still receive medical care at this clinic.

[Signature block not reproduced, but included name, signature, and date for participant, witness of participant's signature, father, and witness of father's signature.]

The analysis plan within the protocol called for analysis of results by "intention to treat."

**Question 17**: What is "intention to treat"? Describe the rationale for analyzing these data by intention to treat rather than by actual treatment received.

The Thai study showed the following results.

Table 3. HIV Mother-to-infant transmission risk, Bangkok Collaborative Perinatal HIV Transmission Study, Thailand, 1996–1997

| Treatment Group | HIV-positive | HIV-negative | Total | Transmission Risk* | |
|---|---|---|---|---|---|
| Zidovudine | 18 | 176 | 194 | 9.4% | |
| Placebo | 37 | 161 | 198 | 18.9% | p = 0.006 |
| Total | 55 | 337 | 392 | | |

* Using Kaplan-Meier method

**Question 17**: Interpret these results.

The Côte d'Ivoire study had enrolled fewer participants per month than the Thai study did, so enrollment in Côte d'Ivoire was ongoing when the results of the Thai study became known.

**Question 18**: Should the Côte d'Ivoire study be allowed to continue enrollment until the required sample size is reached? Why or why not?

Three fundamental principles of ethical health research practice using human participants are now widely accepted:

- Respect for persons
- Beneficence
- Justice

These principles have been enumerated in three landmark declarations related to the treatment of human research study subjects—the Belmont Report, the Declaration of Helsinki, and the *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. These principles also remain the basis for U.S. Government human subject protection regulations.

**Question 19a**: In this context, what does *"respect for persons"* mean? How does it relate to the zidovudine studies?

**Question 19b**: In this context, what does *beneficence* mean? How does it relate to the zidovudine studies?

**Question 19c**: In this context, what does *justice* mean? How does it relate to the zidovudine studies?

Once the results of the Thai study became known, the Côte d'Ivoire and a similar study, the French-sponsored DITRAME study conducted in both Côte d'Ivoire and Burkino Faso, were stopped prematurely. Table 3 summarizes the features and results of the four ZVD studies.

Table 3. Studies of zidovudine to prevent perinatal HIV transmission

| Study | Ante partum | Intra partum | Post partum mother | Post partum infant | Relative efficacy | Breast-feeding |
|---|---|---|---|---|---|---|
| ACTG 076 | 100 mg orally 5x/d starting at 14–34 weeks gestation | 2.0 mg/kg IV over 1 hr, then continuous infusion of 1.0 mg/kg/hr | No | 2 mg/kg oral every 6 hr for 6 weeks | 68% (for infection status at age 18 months) | No |
| Thailand | 300 mg orally 2x/d starting at 36 weeks gestation | 300 mg orally every 3 hrs | No | No | 50% (for infection status at age 6 months) | No |
| Côte d'Ivoire | 300 mg orally 2x/d starting at 36 weeks gestation | 300 mg orally every 3 hrs | No | No | 37% (for infection status at age 3 months) | Yes |
| DITRAME (Côte d'Ivoire, Burkino Faso) | 300 mg orally 2x/d starting at 36–38 weeks gestation | 600 mg orally at onset of labor | 300 mg orally twice daily for 1 week | No | 38% (for infection status at age 6 months) | Yes |

Source: Mofenson

**Question 20**: Interpret these data.

**Question 21**: What conditions must be in place to implement the short-course ZVD regimen throughout a country?

# Conclusion

Following the announcement of results of the ZVD studies in Thailand and West Africa, additional international trials were conducted to test other short-course drug regimens. The Joint United Nations Programme on HIV/AIDS (UNAIDS) and the United Nations Children's Fund (UNICEF) launched pilot projects using short-course zidovudine and infant formula in a number of east and west African countries. Shortly thereafter, international donor groups such as the Gates Foundation, and U.S. and European governments provided funding for implementing and scaling up these short-course interventions in resource-limited settings. The U.S. Presidential Emergency Funding for AIDS Relief (PEPFAR), established in 2003, included substantial funds for prevention of mother to child transmission (PMTCT) in 15 countries. However, while substantial strides have been made, in 2012, numerous challenges remain in providing short-course PMTCT regimens to all pregnant women who need them.

## History of Research Ethics Guidelines

Concern about research ethics and protecting human subjects dates back to the Nuremberg Trials for Nazi war criminals, especially Nazi physicians. These physicians were accused of conducting torturous and often fatal experiments on concentration camp inmates. The **Nuremberg Code**, a list of ten ethical principles or guidelines for human subjects research, was developed as a benchmark against which these physicians could be prosecuted. These ten principles are:

1. Research participants must voluntarily consent to participate in the research
2. The intent of the research should be for the good of society, and not available by alternative means
3. The research should be based on sound theory and knowledge, including animal studies
4. The research must avoid unnecessary physical and mental suffering and injury
5. The research should not result in death or disabling injury
6. The degree of risk taken by the participants should not exceed the potential benefits of the study's results
7. Investigators should have appropriate protections and facilities to protect participants from injury, disability, and death
8. The experiment should be conducted only by scientifically qualified persons, who use the highest degree of skill and care
9. Study participants should be free to discontinue their participation in the experiment
10. The principal investigator must be prepared to terminate the experiment if he/she has reason to believe that continuation is likely to result in injury, disability, or death to study participants.

Thus the Nuremberg Code codifies informed consent (principles 1 and 9) and the researcher's responsibility to protect participants (principles 2–8, 10).

**Declaration of Helsinki**

In 1964, the World Medical Association adopted the Declaration of Helsinki, providing the first global guidelines to physicians for conducting biomedical research involving human subjects. The Declaration reinforced the ethical principles included in the Nuremberg Code. The Declaration has undergone six revisions and two clarifications, growing from 11 paragraphs in 1964 to 35 paragraphs in 2008. The first revision (1975) supported the primacy of the individual over society and introduced the concepts of independent review boards and publication ethics. The last two revisions (2000 and 2008) have been influenced by the contentious debates over the use of placebo controls, including the zidovudine trials.

**Belmont Report**

In 1978, the (U.S.) National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research published its landmark report, "Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research," commonly known as the Belmont Report. The Belmont Report established three basic principles for ethical conduct of research

involving human subjects— respect for persons, beneficence, and justice.

**45 CFR Part 46 and The Common Rule**
Based on the Belmont Report, in 1981 the Department of Health and Human Services (DHHS) issued regulations based on the Belmont Report. These regulations were published in the Code of Federal Regulations (CFR) Title 45 (Public Welfare), Part 46 (Protection of Human Subjects).

In 1991, the regulations in 45 CFR Part 46 Subpart A were adopted by numerous other Federal Departments and Agencies as the Federal Policy for the Protection of Human Subjects, or "Common Rule." The main elements of the Common Rule address:

- Requirements for assuring compliance by research institutions,
- Requirements for researchers obtaining and documenting informed consent,
- Requirements for Institutional Review Board (IRB) membership, function, operations, review of research, and record keeping, and
- Additional protections for certain vulnerable research subjects — pregnant women, prisoners, and children.

## Two Unfortunate but Illustrative Studies

In addition to the Nazi experiments conducted by German physicians during World War II, two studies conducted by U.S. researchers before publication of the Declaration of Helsinki, Belmont Report, and the Common Rule highlight the need for ethical conduct of human subjects research.

### Tuskegee Study

By the 1920s, syphilis had been recognized as a serious public health problem in the United States, with the burden seeming to be disproportionately high in the African American population. However, little was known about the disease and no effective treatment existed. In 1932, the U.S. Public Health Service, in collaboration with the Tuskegee Institute and others, began enrolling African American sharecroppers from Macon County, Alabama — a rural and impoverished area in the Southeastern United States — in a study to better understand the natural progression of untreated syphilis. A recently-conducted syphilis control survey had revealed an infection rate of 36% in Macon County [1]. The "Tuskegee Study," as it became known, enrolled 399 African American men with syphilis and 201 without the disease. Study participants were not made aware of the purpose of the study, nor of their disease status; however, as an incentive to participate, they received free medical care — something that most would have been unable to afford otherwise — as well as free meals and burial benefits.

The study was originally planned to last less than a year; however, interest continued and, by 1936, a decision was made to follow the men until death [2]. Over the course of the next four decades, in spite of the introduction in 1947 of penicillin as the standard treatment for syphilis, as well as the establishment of the Nuremberg Code in 1948 and the Declaration of Helsinki in 1964 — both of which were designed to protect the interests of human subject research participants — the Tuskegee Study continued. At no time were participants offered treatment or informed that treatment was available. In fact, the researchers actively tried to prevent enrollees from receiving treatment when it was offered to men drafted into military service or to other Macon County citizens via venereal disease eradication campaigns [2, 1].

In 1972, journalists learned of the study from scientists who knew of it and who were concerned about the study's treatment of the enrollees. Following the publication of several high-profile newspaper articles, the U.S. government convened a panel to examine the conduct of the study. The panel found that the research had been conducted not only without the informed consent of the participants, but with deliberate deception and denial of treatment. The advisory panel concluded that the study had been unethical and that the risks to the participants far outweighed the limited new knowledge that had been gained [3].

Although a number of participants and their families were lost to the researchers over the course of the study, by 1969, records indicate that at least 28 of the original study participants had died of syphilis and possibly 100 more had died from complications of infection [1].

In 1974, as part of an out-of-court settlement, participants, or surviving members of their families, were awarded a share of a $10 million dollar payment by the U.S. government as well as lifetime health benefits and burial services to all surviving participants. The same year, the National Research Act was signed into law, mandating the establishment of IRBs to review all federally funded studies conducted on human subjects. Other regulations requiring voluntary informed consent to be given by all participants in studies conducted by the U.S. Department of Health, Education and Welfare (predecessor of Dept. of Health and Human Services) followed.

In 1997, President Clinton issued a formal apology to the study's participants and their families.

**Guatemala Study**

Taking the Tuskegee Study a step further, the U.S. Public Health Service, together with the U.S. National Institute of Health, the Pan American Sanitary Bureau and several Guatemalan government agencies, began a series of studies in 1946 in which they actively infected approximately 1,300 Guatemalans — soldiers, prostitutes, mental patients, and prisoners — with syphilis and other sexually transmitted diseases, including gonorrhea and chancroid [4]. Subjects were then treated with penicillin in order to test its efficacy on these diseases. However, it is not clear if all study subjects received treatment, or if sufficient treatment was given to all subjects. Study subjects were not made aware of the purpose of the studies, nor did they provide consent [5].

The studies apparently ended in 1948, with the findings never published or made public. Records from the time indicate that the head of the U.S. Public Health Service (who had also been involved with the Tuskegee Study) had admitted that studies such as these could not have been conducted in the United States and that the investigators and their supervisors were aware of their unethical nature [4]. Similar to Tuskegee, the ethical violations of the Guatemala studies included deliberate deception of participants, recruitment of vulnerable populations, and not enabling participants to provide their informed consent. Unlike the Tuskegee study, however, subjects were deliberately exposed to pathogenic agents of known danger to their health.

In 2010, President Barack Obama issued a formal apology for the study to Guatemalan President Álvaro Colom. U.S. Secretary of State Hilary Clinton and Health and Human Services Secretary Kathleen Sebelius also issued a joint statement of apology.

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These studies highlight the need for investigators to maintain the highest standards in both human subjects protections and scientific inquiry, without sacrificing one for the other.

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