

**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**

Instructor's Guide — Do not distribute to students

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).

This case study was developed by Richard Dicker and Dana Schneider in 2012 for the FETP Standard Curriculum. We acknowledge the valuable input from Stefan Wiktor and reviews by Aun Lor, Pam Valosen, and Fran Sanden.



How to use CDC case studies: CDC case studies in applied epidemiology allow students to practice applying epidemiologic skills in the classroom to address real-world public health problems. The case studies are used as a vital component of an applied epidemiology curriculum, rather than as stand-alone tools. They are ideally suited to reinforcing principles and skills already covered in a lecture or in background reading.

Ideally, one or two instructors facilitate the case study for 8 to 20 students in a classroom or conference room. Traditionally, the instructor directs a participant to read aloud a paragraph or two, going around the room and giving each participant a chance to read. When the participant reads a question, the instructor directs all participants to perform calculations, construct graphs, or engage in a discussion of the answer. Sometimes, the instructor can split the class to play different roles or take different sides in answering the question. As a result, participants learn from each other, not just from the instructors.

Prerequisites: For this case study, participants should have received lectures or other instruction in:

- Randomized Controlled Trials
- Research Ethics

Target audience: Residents in Field Epidemiology Training Programs (FETPs), Field Epidemiology and Laboratory Training Programs (FELTPs), Epidemic Intelligence Service (EIS) programs and others who will be engaged in conducting field studies involving humans, and others who are interested in this topic.

Level of case study: Intermediate, i.e., participants should have background in analyzing data from a two-by-two table and in interpreting data from tables.

Time required: approximately 3 hours

Language: English

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?

Answer 1

- *Multicenter = enrollment of participants occurs at several different medical centers. Multicenter enrollment provides a larger number of participants than a single center could enroll, and provides some diversity in the demographic characteristics of participants. However, multicenter enrollment creates challenges in terms of consistency of approaches, methods, decisions, etc.*
- *Randomized = study participants are assigned to a treatment group by a method based on chance. Randomization minimizes differences between groups (and hence confounding) by equally distributing people with particular characteristics between the two treatment groups (at least in theory).*
- *Double-blind = neither the participants nor the investigators (and the study staff) know which participants are getting which treatment. Double-blind trials are thought to reduce bias and produce more objective results.*
- *Placebo-controlled = a trial in which one group receives an intervention such as an experimental drug and the other group receives a similar but inactive intervention such as a pill with no active ingredients (“placebo”). The goal of a placebo-controlled trial is to determine whether the intervention works better than the placebo, i.e., better than no treatment.*

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 radiation therapy
- With following laboratory values:
 - CD4+ T-lymphocyte count above 200 cells per cubic millimeter
 - Hemoglobin concentration ≥ 8 g/dl
 - Absolute neutrophil count $\geq 1,000$ cells / mm^3
 - Platelet count $\geq 100,000$ 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 oligohydramnios 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?

Answer 2

Relatively complicated:

- *frequent doses (5 times per day) for pregnant woman*
- *intravenous infusion during labor*
- *frequent doses (4 times per day) x 6 weeks for newborn*

Also, expensive — about \$800 (U.S.) at that time

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?

Answer 3

An interim analysis is any assessment of data done during the patient enrollment or follow-up stages of a trial for the purpose of assessing center performance, quality of the data collected, or treatment effects [Meinert]. Interim analyses of experimental treatments are most often planned to identify as quickly as possible if (1) the treatment works, so it would be unethical to continue to enroll participants in a placebo group, or (2) the treatment causes unacceptable side effects, e.g., death, so it would be unethical to continue to enroll participants in the treatment group. The study protocol should specify in advance the levels required to stop the study for either reason.

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.

Answer 4

HIV positivity in treatment group: $13 / 180 = 0.072 = 7.2\%$

HIV positivity in placebo group: $40 / 183 = 0.219 = 21.9\%$

Risk ratio = $0.072 / 0.219 = 0.33$

Overall estimated effect = $(0.219 - 0.072) / 0.219 = 0.147 / 0.219 = 67.1\% \text{ reduction}^$*

** Same formula used for vaccine efficacy = $(Risk_{unvaccinated} - Risk_{vaccinated}) / Risk_{unvaccinated} = 1 - RR$*

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 ($Z = 4.03$, $P\text{-value} = 0.00006$). 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?

Answer 5

- *Stop the study. The results are so compelling that it is unethical to continue to enroll women in the placebo group.*
- *Recommend that all HIV-positive pregnant women who are similar to the study participants be given the study regimen*
- *Recommend that HIV-positive pregnant women who are not similar to the study participants be considered for the study regimen*

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?

Answer 6

Instructor's Note 1: Split class into two groups and assign one side to each group. Allow them about 5 minutes to develop an argument and name a spokesperson. Then let each group present their arguments.

Instructor's Note 2: The purpose of this question is simply to present the arguments for each side. For the next question the class can decide which argument is more persuasive.

Arguments in favor of using a placebo group

1. *Zidovudine safety: Investigators were concerned about the safety of zidovudine, a powerful drug, given to women in developing countries who are more likely to have malnutrition, anemia, and other diseases. Without a non-zidovudine group, any adverse maternal, delivery-related, or neonatal outcome could be attributed to zidovudine. [Simonds, et al. NEJM 1998]*
2. *Zidovudine efficacy: Although the 076 protocol was shown to be effective for women in developed countries, its effect cannot be assumed to be equal in women in developing countries who are more likely to have malnutrition, anemia, and other diseases*
3. *Comparing a treatment of unknown efficacy (the short-course treatment) to the proven 076 treatment would be of little value if the short-course (affordable) treatment was not found to be as*

effective, because the 076 treatment would never realistically be available in developing countries

4. Furthermore, it would not answer the question of whether the more affordable treatment was better than nothing, which was the current standard of care
5. Equivalency studies have their own challenges (larger sample size needed, sloppy methodology biases toward the null, which supports equivalency, etc.)

For these reasons, CDC and NIH argued that a placebo-controlled trial was the best way to obtain conclusive answers about the safety and feasibility of the intervention in the populations and settings in which the studies took place.

**Arguments in favor of comparing short course to longer course ZVD regimen
(Arguments against using a placebo group)**

1. It violates the principle of equipoise. An effective treatment (076 protocol) was known to investigators. Therefore, participants in the placebo groups in the short-course trials would knowingly be given an inferior treatment. Research ethics dictate that control-group participants must receive the best known treatment. [Angell, NEJM 1997]
2. Local standard of care cannot be used as an argument if that standard of care is known to be inadequate. Ethicists worry that adopting the lower "local" research standard in resource-poor settings would act as an incentive to enroll research participants in settings where standards are less stringent than in developed countries [Lurie & Wolfe, NEJM 1997]. Because of this concern, U.S. health agencies and the World Health Organization require that participants of research studies conducted by scientists of another nation must receive protections at least equivalent to those required by the sponsoring country
3. There is no reason to assume that persons from different populations would respond differently to the same treatment. It is safer and more responsible to assume they would respond similarly
4. Instead of conducting a placebo-controlled study, the researchers could have conducted an equivalency study (conducted when a certain treatment has already been proven to be effective, but one would like to know if a different regimen of that treatment would be approximately as effective, but with less cost and/or toxicity). An equivalency study, some argued, would not have required a substantially larger sample size (small sample size was given as a reason for conducting a placebo-controlled trial), as the statistical test used would be one-sided (because the goal was to prove simply that it met some pre-established level of efficacy instead of that it was superior to another treatment) [L&W editorial]
5. Some subgroup analyses of the original ACTG 076 study had already suggested that a shorter-course treatment might have been as effective as the longer-course treatment. L&W argue that these findings should have been more thoroughly explored by CDC and NIH researchers by conducting short-course vs. long-course trials, as there was already evidence that a shorter course could be effective. [L&W editorial]

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

Answer 7

Instructor's Note: Opinion question. No right answer, and no need to achieve consensus.

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?*

Answer 8

The outcome is HIV positivity of the infant.

The two-by-two table would look like:

	<i>HIV-positive infant</i>	<i>HIV-negative infant</i>	<u>Total</u>	<u>% Positive (Risk)</u>
<i>Zidovudine</i>	<i>a</i>	<i>b</i>	<i>a + b</i>	<i>a / a + b</i>
<i>Placebo</i>	<i>c</i>	<i>d</i>	<i>c + d</i>	<i>c / c + d</i>
<u>Total</u>	<i>a + c</i>	<i>b + d</i>	<i>T</i>	

Efficacy of treatment = percent decrease in risk

$$= (Risk_{\text{placebo}} - Risk_{\text{zidovudine}}) / Risk_{\text{placebo}}$$

$$= 1 - RR$$

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?

Answer 9

- Confidence level, usually 95%
- Power, usually 80%
- Estimated risk in the unexposed group, e.g., "usual" HIV transmission rate in Thailand (24% in a previous study at the same hospitals)
- Difference in risk worth detecting in the exposed group, expressed either as risk ratio or as the risk in the exposed group (investigators wanted to be able to detect a 50% reduction, i.e., $RR = 0.5$, i.e., 12% transmission rate in ZVD group)
- Ratio of exposed to unexposed participants (1:1 in RCTs)
- Estimated loss to follow-up (estimated as 10% for Thai enrollees)

Instructor's Note: Epi Info has an easy-to-use utility that provides recommended sample sizes based on the first 5 elements. The result must then be adjusted to account for possible loss to follow-up.

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?

Answer 10

- Proposal = statement of work for research or non-research study, needs to meet requirements of sponsoring and funding agencies; reviewed and approved by funding agency; can be relatively brief (often 1-3 pages)
- Protocol = systematic description of procedures to be used in research or non-research study; needs to meet regulatory requirements to justify research and protect participants; reviewed and approved by appropriate regulatory body, i.e., IRB; usually relatively long (10-30+ pages, with attachments such as copy of the questionnaire, informed consent form, etc.)
- Standard operating procedures = actually two types
 - Institution's SOPs independent of study, e.g., how blood is drawn, how samples are sent to and processed in the laboratory, etc.
 - Study's Manual of Procedures = procedures specific to the study (can simply reference Institution's SOPs for procedures done in the "routine" way)

Question 11: What is an Institutional Review Board?

Answer 11

An Institutional Review Board (IRB) is a committee formally established to protect the rights and welfare of human participants recruited to participate in biomedical or behavioral research, usually by reviewing, approving, and monitoring planned research. In the United States, an IRB must have at least five members, must include both men and women, must include at least one scientist and one non-scientist, and must include at least one person not affiliated with the institution (a "Community Member").

A Federalwide Assurance of compliance (FWA) is an agreement between an institution and the U.S. Department of Health and Human Services that the institution will comply with HHS regulations for the protection of human participants. An FWA is required if an institution (anywhere in the world) is proposing or planning to participate in human subjects research supported by an agency of the U.S. Government.

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

Answer 12

At CDC, the basic consideration for what is research and what is non-research public health practice is whether the purpose of the activity is to benefit the persons or community in the study or to generate "generalizable knowledge." For example, a church-picnic-type investigation to determine, for example, the cause of gastroenteritis is usually considered to be public health practice (goal is to limit spread of disease in that community) rather than public health research, and would not need IRB review.

The determination of what is or is not research is usually made by the IRB or a designated representative, not by the investigator. In some organizations (including CDC), the investigator must submit a description of the activity if not a full protocol and a form requesting that the study be designated non-research. This application is then reviewed by the appropriate authorities who decide whether the activity is or is not research. If the study is determined to be research, the IRB will review the protocol and other study documents to assess whether or not the participants will be adequately protected from harm.

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

Answer 13

- **Purpose and procedures:** *tell a prospective participant that the study involves research, explain the purpose of the study and the length of time you expect the person to participate, describe the procedures to be followed, and identify any experimental procedures*
- **Risks or discomforts:** *describe any foreseeable risks or discomforts*
- **Benefits:** *describe any benefits to the participant or to others that may reasonably be expected from the research. For example, "You may not benefit directly from being in this study, but your participation will help us learn more about HIV, which may benefit others in the future." Or "You may benefit directly from being in this study by.....Also, your participation will help us learn more about HIV, which may benefit others in the future"*
- **Alternatives:** *disclose any appropriate alternative procedures or courses of treatment that might benefit the prospective participant*
- **Confidentiality:** *tell prospective participants whether their records will be kept confidential, and, if so, explain the level of confidentiality*
- **When there is greater than minimal risk:** *tell whether they will receive any compensation and/or medical treatments if injury occurs and, if so, what compensation or treatment will consist of, or where to obtain further information*
- **Persons to contact:** *Whom to contact if they have questions about the research and their rights as a study participant, and whom to contact if they have an injury that may be related to the study*
- **Voluntary Participation, Refusal, and Withdrawal:** *state that participation is voluntary, that refusal to participate involves no penalty or loss of benefits to which the person is otherwise entitled, and that the person may discontinue participation at any time without penalty*

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?

Answer 14

Approach the traditional decision-maker in the community (leader, husband, etc) first and obtain their permission. If they refuse to give consent, no one for whom they make decisions may be approached to participate. If they provide consent, the individual who would be enrolled must also provide their informed consent. The primary decision-maker should agree that if the individual concerned does not want to participate, they do not have to.

(Reference?)

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

Answer 15

- *Literacy and level of language used in either written or oral consent*
- *Need for translation?*
- *Special or vulnerable populations, including*
 - *Pregnant women*
 - *Children*
 - *Prisoners*
 - *Marginalized populations*
 - *Economically disadvantaged populations*

Knowledge of the disease or health issue under study?

Being approached by people from their community vs someone they do not know? (and/or level of trust w/ outsiders and/or gov't officials)

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

Answer 16a

The form includes all of the required sections except for contact information, i.e., whom to contact if the participant has questions about the study or her rights as a study participant, and whom to contact if she has an injury that may be related to the study.

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

Answer 16b

The content is accurate but the language is much too technical.

MS Word Flesch Reading Ease = 8.3, compared with 70-80% for rest of Informed Consent form

MS Word Flesch-Kincaid Grade Level = 19.7, compared with 7-8 for rest of Informed Consent form

The reading level must be appropriate for the audience. The actual informed consent form used the following language:

Zidovudine (ZDV) is a drug that slows the growth of the HIV virus. This drug when given to an HIV infected woman during most of pregnancy, during delivery and to her newborn baby has resulted in preventing some babies from becoming infected with HIV. We are doing this study to see if giving this drug in late pregnancy only will also lower the chance of a mother passing the virus to her baby. To do this some women will be given ZDV and some will be given placebo. Placebo is like a "sugar pill" which has no benefit or risk to your health or your baby's health.

MS Word Flesch Reading Ease = 62.5

MS Word Flesch-Kincaid Grade Level = 9.8

**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.

Answer 17

Intention-to-treat analysis = analysis of clinical trial results according to the group to which participants were randomized, not on what they actually did (or did not) receive, and regardless of whether they completed the study or not. (“Once randomized, all analyzed!”)

The rationale for using intention-to-treat analysis is to reduce the potential effects of drop outs (i.e., loss to follow-up) and crossover, both of which can result in bias.

As a result, intention-to-treat analysis addresses treatment as policy. In a way, the analysis addresses whether the treatment, if made available to the target population, would be superior to the alternative.

Instructor’s Note: The alternative to intention-to-treat analysis is per-protocol analysis. **Per-protocol analysis** includes only patients who complete the entire treatment. Per-protocol analysis represents the best treatment results that could be achieved if everyone was 100% compliant. In general, intention-to-treat is the preferred analysis for clinical trials. Per-protocol analysis is sometimes conducted and presented as a secondary analysis.

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.

Answer 17

$RR = 9.4 / 18.9 = 0.5$

Efficacy of treatment = $1 - RR = 1 - 0.5 = 0.5 = 50\%$ reduction in mother-to-infant transmission of HIV in the treatment group

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?

Answer 18

Arguments in favor of allowing completion of the Côte d'Ivoire study

- *Thai study is only one study. Two studies allowed to go to completion would be more convincing than a single study*
- *Thai study did not allow breastfeeding; Côte d'Ivoire study does, and most women in Africa will breastfeed*
- *Thai study may not be generalizable to Africa — different populations, different cultures, possibly different genetic predispositions*

Arguments against completion of the Côte d'Ivoire study

- *Thai study demonstrated that short-course ZVD regimen works. It is unethical to continue enrolling women in a study in which half will not receive treatment that has now been shown to be effective and practical in the developing country setting*

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.

Instructor's Note: Note that equipoise is not one of the universally accepted principles of ethical health research. It is not mentioned in the Belmont Report. One criticism of equipoise is that it does not balance individual autonomy with social good.

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

Answer 19a

Respect for persons = protecting the autonomy (freedom of choice, self-determination without coercion or constraint) of all people and treating them with courtesy and respect and allowing for informed consent. Researchers must be truthful and conduct no deception. Further, a person should understand the subject matter of the research sufficiently to make an enlightened decision, e.g., nature, duration, and purpose of an experiment, methods of experimentation, possible effects on health, and any inconveniences entailed by the experiment.

In the zidovudine studies, autonomy was addressed through the informed consent process, in which women were told about the nature, purpose, and methods of the study. They were also told that they were under no obligation to participate and could refuse or leave the study at any time if they chose to do so, and all of this information was presented in easily understood language without pressure from the investigators.

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

Answer 19b

Beneficence = do no harm and minimizing risks for the research participants while maximizing benefits for the participants and project. The interest of science and society should never take precedence over considerations of a participant's well-being.

In the ZVD studies, the studies were conducted in developing countries to identify interventions that were both efficacious and practical in those countries. Furthermore, side effects of the ZVD regimen to both mother and infant had been shown to be minimal and tolerable.

Instructor's Note: Participants may raise the argument about withholding the ACTG 076 regimen and enrolling a placebo group, but this issue has been addressed previously in this case study.

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

Answer 19c

Justice = benefits and burdens of research should be reasonable, non-exploitative, and distributed fairly. Resources should be allocated in the way that best benefits the society being studied. Research protocols should undergo independent ethical review by both the sponsoring country or agency and the local country or countries in which the study is to be conducted. The sponsoring country's review must use the same ethical standards as those used for research conducted in the sponsoring country. The local review board should review the protocol independently and without undue influence by the sponsoring country, and the local review board should be composed of both medical professionals and laymen qualified to represent local community, cultural, and ethical values. [Barry]

In the ZVD studies, the protocols were reviewed and approved by the ethics committees of the respective Ministries of Health (Thailand and Côte d'Ivoire) and by the U.S. CDC. The Thai study was monitored by a U.S. National Institutes of Health data safety monitoring board which included a senior Thai health official not involved in the design or conduct of the study.

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.

Answer 20

- *First, short-course ZVD regimen reduces the risk of HIV transmission by 37–50%. This is less than the 68% reduction achieved by the ACTG 076 regimen, but better than no treatment*
- *Second, efficacy appears to be lower among breastfed than among non-breastfed babies*
- *Third, a week of ZVD treatment of the mother after delivery appears to provide no additional protection*

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

Answer 21

- *Antenatal care must be available and accessible*
- *Woman must know her HIV status, so HIV-1 counseling and testing services must be available, woman must accept testing and return for result (in era prior to rapid testing)*
- *Zidovudine must be available and affordable*
- *Woman must adhere to the regimen*
- *To ensure intrapartum ZVD administration, obstetric services must be available, woman must get to a health facility for delivery, and facility must administer the ZVD*
- *Ideally, safe and effective alternative to breastfeeding should be available (might not be realistic)*

Ref: Mofenson

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.

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).

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

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.

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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