THE ETHICS OF HIV RESEARCH IN DEVELOPING NATIONS

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ABSTRACT

This paper discusses a dispute concerning the ethics of research on preventing the perinatal transmission of HIV in developing nations. Critics of this research argue that it is unethical because it denies a proven treatment to placebo-control groups. Since studies conducted in developed nations would not deny this treatment to subjects, the critics maintain that these experiments manifest a double standard for ethical research and that a single standard of ethics should apply to all research on human subjects. Proponents of the research, however, argue that these charges fail to understand the ethical complexities of research in developing nations, and that study designs can vary according to the social, economic, and scientific conditions of research. This essay explores some of the ethical issues raised by this controversial case in order to shed some light on the deeper, meta-ethical questions. The paper argues that standards of ethical research on human subjects are universal but not absolute: there are some general ethical principles that apply to all cases of human subjects research but the application of these principles must take into account factors inherent in particular situations.

INTRODUCTION

A controversy over the ethics of human subjects research in developing countries erupted in the United States when two representatives from the Public Citizen’s Health Research Group, Peter Lurie and Sidney Wolfe, attacked fifteen clinical trials designed to study the transmission of the Human Immunodeficiency Virus (HIV) from pregnant women to their babies in an essay in the New England Journal of Medicine (NEJM). Lurie and Wolfe, who had written a letter about the research to Secretary of Health and Human

Services, Donna Shalala, earlier in the year, argued in their essay that the research is unethical because it uses placebo-controls even though there is an effective treatment for preventing the perinatal transmission of HIV. Marcia Angell, executive editor of NEJM, wrote an editorial supporting the position taken by Lurie and Wolfe and compared the HIV research to the infamous Tuskegee syphilis study. Harold Varmus, Director of the National Institutes of Health (NIH), and David Satcher, Director of the Center for Disease Control and Prevention (CDC), defended the controversial research and argued that critics failed to understand the scientific, social, and economic complexities of the research.

Two members of the NEJM’s editorial board who are experts on HIV and Acquired Immunodeficiency Syndrome (AIDS), David Ho and Catherine Wilfert, resigned from the board to protest Angell’s editorial. The controversy also cast a shadow over Satcher’s nomination for Surgeon General of the United States (US), although his nomination was approved with little opposition. The New York Times gave front page coverage to the entire saga, which achieved global media exposure.

Researchers recently announced that the trials would stop using placebo-controls after several studies found that providing HIV-infected, pregnant women with $80 worth of zidovudine (also known as AZT) in the last four weeks of pregnancy can reduce the rate of perinatal transmission of HIV by 50%. Both sides are pleased with this outcome, though for different reasons.

This case highlights an important and profound question in the ethics of research, ‘are ethical standards absolute?’ In their essay, Lurie and Wolfe call for a single, international standard of research on human subjects. In her editorial, Angell claims that researchers should adhere to the ‘highest ethical standards, no matter where the

4 Daniel Hane, ‘AIDS researchers resign over editorial’, The Denver Post, 16 October 1997, p. 4A.
9 Stolberg, ‘Placebo use suspended’.

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research is conducted.¹⁰ The position taken by Varmus and Satcher, on the other hand, implies that ethical standards need to take into account the social, economic, and scientific conditions of research. In this essay, I will explore some of the ethical issues raised by this controversial case in order to shed some light on these deeper questions. I will defend Varmus and Satcher’s normative and meta-ethical claims. I will argue that the use of placebo-controls in these trials can be justified on scientific and moral grounds, and that standards of ethical research on human subjects are universal but not absolute: there are some general ethical principles that apply to all cases of human subjects research but the application and interpretation of these principles must take into account factors inherent in a given situation, such as social conventions, cultural norms, and economic conditions.

HIV RESEARCH IN DEVELOPING NATIONS

The clinical trials criticized by Lurie, Wolfe, and Angell involve over 12,000 HIV-infected pregnant women in nine countries, the Dominican Republic, South Africa, Thailand, Ethiopia, Uganda, Tanzania, Zimbabwe, Burkina Faso, and Côte d’Ivoire. Nine of the 15 studies are funded by the US through either the NIH or the CDC. The studies were designed in 1994 by officials from the World Health Organization (WHO), the NIH, the CDC, and UNAIDS, a United Nations agency that coordinates efforts to battle the AIDS epidemic. The studies also have the cooperation and support of local governments.¹¹,¹²

The perinatal transmission of HIV from pregnant women to infants is a major public health problem in many developing nations. It is estimated that over 1,000 infants outside the United States are born with HIV every day. In Uganda, it is estimated that 12% of pregnant women are infected with HIV and 100,000 children are orphaned by AIDS.¹³ According to Glenda Gray, a South African pediatrician, ‘in our wards, 30 percent of children admitted each day are HIV positive’.¹⁴

In 1994, researchers demonstrated that there is an effective way of preventing the transmission of HIV from pregnant mothers to their babies. This method, known as the AIDS Clinical Trial Group (ACTG) 076 protocol, requires women to be tested for HIV infection

¹¹ Stolberg, ‘Placebo use suspended’.
¹³ Bloom, ‘The highest sustainable standard’.
early in pregnancy, to receive oral and intravenous doses of the antiretroviral drug zidovudine, and to forego breast feeding.\textsuperscript{15} It also requires infants to receive zidovudine for six weeks after birth. Approximately 25\% of all HIV positive pregnant mothers who do not receive this treatment transmit the virus to their infants, but that number falls to less than 8\% when HIV positive pregnant women and their infants participate in the 076 protocol.\textsuperscript{16}

In the US and other developed nations, the 076 protocol has become the standard of care for pregnant women who are HIV positive, but very few women in developing nations have access to this therapy. Expense is a prohibitive factor in administering the 076 protocol in developing nations: it costs more than $800 to administer zidovudine to mother and infant, a sum that is several hundred times the per capita health care allocation in many developing nations.\textsuperscript{17} Another factor making it difficult to implement the 076 protocol in developing nations is that it is a complex regimen. The 076 protocol must be started early in pregnancy, it must be continued after birth, and it requires the administration of intravenous and oral AZT. In order to accomplish these tasks, patients must know that they are pregnant, they must enroll in trials early in pregnancy, and they must continue with the regimen after birth. These tasks require considerable cooperation between subjects and researchers to make sure that the subjects take all the doses of AZT (or the placebo). The tasks also require a great deal of labor, and health care professionals and medical researchers are in short supply in most developing nations.

There is clearly an urgent social and medical need to develop a method for preventing the perinatal transmission of HIV that would be a realistic and workable option in developing countries. The 076 protocol is safe and effective, but it is not a realistic option in many developing nations due to its cost and administrative complexity. The discovery of cheaper and simpler regimens that are just as safe and effective as the 076 protocol can help prevent thousands of infants from becoming infected with the AIDS virus.

In order to meet this urgent need, researchers and public health officials developed a study design that would determine whether there is a simpler and cheaper alternative to the 076 protocol. In this research protocol, subjects are randomly divided into an experimental group of HIV-infected women that receive AZT during the last four weeks of pregnancy, and a control group that receives a placebo. This alternative treatment regimen uses $80 worth of AZT.

\textsuperscript{15} Varmus and Satcher, ‘Ethical complexities’.
\textsuperscript{16} Varmus and Satcher, ‘Ethical complexities’.
\textsuperscript{17} Bloom, ‘The highest sustainable standard’.
as compared to $800 worth of AZT in the 076 protocol. The alternative regimen is also much simpler than the 076 protocol. The studies were designed to obtain the informed consent of subjects; subjects were informed that they may receive a drug or a placebo. All subjects, including those who receive placebos, received medical care.\(^{18}\) As noted earlier, preliminary data indicate that researchers have been successful in developing simpler and cheaper regimens. A study in Thailand demonstrated that the rate of perinatal transmission of HIV can be cut in half by giving AZT to pregnant women for less than a month. In the study, only 9% of pregnant women who received the treatment transmitted HIV to their babies, as compared to 19% in a placebo-control group.\(^{19}\)

According to proponents of the disputed research, placebo-control studies are (or were) necessary to provide faster and clearer answers to questions that cannot be answered effectively through studies that compare different treatments without using a control group. In countries that cannot afford the 076 protocol, it is important to determine whether any treatment regimens are better than no treatment at all. These countries need to be able to decide whether to invest their scarce health care resources in interventions designed to prevent the perinatal transmission of HIV.\(^{20}\) These concerns point to a common theme cited by proponents: the research is ethical because it uses scientific rigor to address urgent social needs.\(^{21}\)

ETHICAL QUESTIONS ABOUT THE RESEARCH

Lurie, Wolfe, and Angell attack these studies on the grounds that they deny a proven HIV treatment, zidovudine, to pregnant women and their babies. Women and their babies in the placebo-control groups receive no HIV treatment at all. According to critics, placebo studies are justified only when researchers are in a state of clinical equipoise at the outset of the study; that is, the research community must lack sound scientific evidence for believing a particular treatment is better than a placebo.\(^{22}\) As soon as the research community has good evidence that a treatment is more effective than a placebo, researchers have an obligation to discontinue the use of placebos, according to


\(^{19}\) Meyer, ‘Cheaper perinatal’.

\(^{20}\) Varmus and Satcher, ‘Ethical complexities’.


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many ethicists. Studies that use placebos even when effective treatments exist subordinate the welfare of research subjects for social or scientific goals. According to the critics, the use of placebos under these circumstances violates one of the principles of the Declaration of Helsinki, which holds that all research subjects, including those in control groups, should receive the best proven treatments and medical care. Other documents relating to the protection of human subjects in research, such as the Belmont Report and the CIOMS’ International Ethical Guidelines for Biomedical Research Involving Human Subjects, also support the principle of providing the best proven treatments to all subjects.

The critics agree that it is important to develop safer and simpler methods for preventing the perinatal transmission of HIV, but they argue that experimental designs should compare different therapies instead of using a placebo group. This strategy enables all subjects to get proven treatments while allowing researchers to determine whether simpler and cheaper regimens are still effective. Lurie and Wolfe discuss a study in which Marc Lallemant compared shorter zidovudine regimens to the 076 protocol to determine whether these regimens are still effective but less toxic and expensive. Lallemant sought to determine whether it is possible to reduce the amount of zidovudine used in treatment while still achieving the efficacy obtained by the 076 protocol. Lallemant refused to include a placebo group in his research because he believed that using placebos would be unethical. Lurie, Wolfe, and Angell all argue that medical researchers and health officials overestimate the importance of placebo-controls in clinical research, and that it is often possible to obtain scientifically rigorous results without using placebo-controls.

Lurie, Wolfe, and Angell accuse researchers of retreating from ethical principles and of exploiting research subjects for scientific or social ends. All subjects, whether they live in the US or in Uganda, should receive AZT, since AZT has been proven to be effective in

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28 Lurie and Wolfe, ‘Unethical trials’.
29 Lurie and Wolfe, ‘Unethical trials’.
30 Angell, ‘The ethics of clinical research’.
preventing the perinatal transmission of HIV. AZT is the best proven therapeutic method and the standard of care. There should be a single standard of care, not a double standard; and there should be a single, international standard of ethics in human subjects research. If a research design is unethical in the US, then it should also be unethical anywhere else in the world.

In their reply to these attacks, Varmus and Satcher argue that placebo-controls are required for the reasons discussed above, viz. placebo-controls allow researchers to get a quicker and clearer response to questions about toxicity, effectiveness, and the costs of alternative treatments. They also argue that the ethics of human subjects research should be judged according to several different principles mentioned by the Declaration of Helsinki, the Belmont Report, and other documents. All of these principles have prima facie validity although they may conflict in practice. Hence, ethical study designs must balance these different principles. In their view, the decision to employ placebo studies can be justified on the grounds that it emphasizes justice and utility in health care research: the studies are designed to meet the needs of people in developing countries who do not currently have access to effective ways of preventing the perinatal transmission of HIV.  

One provision of the CIOMS guidelines requires that researchers should be responsive to the health needs of host countries and that the products of research should be made available to the people in host countries.

ANALYSIS OF THE DISPUTE

One can see from this summary that these two sides agree on some important points and disagree on others. It appears that Lurie, Wolfe, Angell, Varmus and Satcher all agree that it is important to develop simpler, cheaper alternatives to the 076 protocol, that medical experiments should meet standards of scientific rigor, and that some basic ethical principles apply to research on human subjects. However, they also disagree on questions that encompass ethical and scientific, as well as meta-ethical issues. The main point of this paper is to determine whether this case sheds some light on an important metaethical issue, viz. ‘are standards of research ethics absolute?’ (By an ‘absolute standard’ I mean a ‘universal rule that cannot be overridden by other rules.’ A universal standard that can sometimes be overridden is not an absolute standard.) As we have seen, the two

31 Varmus and Satcher, ‘Ethical complexities’.
32 CIOMS, International Ethical Guidelines.
sides give different answers to this question. In order to understand their positions and shed some light on the meta-ethical issue, it will be useful to analyze and evaluate their views.

Since both sides agree that it is important to develop simpler and cheaper alternatives to the 076 protocol, the main sources of disagreement concern the most ethical means of achieving the goal. Varmus and Satcher believe that placebo-control studies are an ethical means of achieving this goal; Wolfe, Lurie, and Angell do not agree with this position. So what can be meant by ‘ethical means’ in this dispute? The ‘means’ are, of course, scientific experiments on human subjects, which can be evaluated according to the following widely accepted concepts of human subjects research:\(^{34,35}\)

1. Informed consent  
2. Beneficence to subjects (or an acceptable benefit/risk ratio)  
3. Privacy/confidentiality  
4. Social utility  
5. Justice/fairness  
6. Scientific rigor  
7. Monitoring of studies and subjects

(Each of these different concepts imply principles of research, e.g. privacy/confidentiality implies the principle ‘researchers should protect the privacy and confidentiality of test subjects’. For the sake of brevity, I will not state all the principles implied by these concepts.)

We can understand this dispute in terms of these different concepts and principles. Lurie, Wolfe, and Angell emphasize (2) while Varmus and Satcher stress (4) and (5). Both sides agree that (1) and (7) must be satisfied, but they do not agree about how to best satisfy (6). Varmus and Satcher believe that placebo-control studies are required to meet the demands of scientific rigor; Lurie, Wolfe, and Angell do not accept this position.

PLACEBO CONTROLS AND SCIENTIFIC RIGOR

Let us first examine the scientific dispute in this case. Neither side in this dispute denies the importance of scientific rigor in human subjects research. If studies do not meet standards of scientific rigor, then there is a good chance that they will not provide us with reliable data. Since researchers place the welfare and dignity of subjects at risk, they need to have good reasons for believing that their studies will yield reliable


data; human subjects should not be used in spurious or poorly designed studies. Moreover, conducting research that is not likely to provide us with reliable data is also a waste of time, money, and human resources.

Do research protocols need to include placebo-controls in order to meet the demands of scientific rigor? To answer this question we need to discuss some issues in experimental design in more depth. (My apologies to readers familiar with these topics, but it will be useful to review them here.) The randomized clinical trial (RCT) is currently the ‘gold standard’ of medical research because it offers scientists the best way of discovering whether new treatments are beneficial. RCTs follow widely accepted procedures for controlled, intervention experiments. In a controlled experiment, researchers divide a population into two groups, the experimental group and the control group. If researchers obtain statistically significant data, then they use statistical reasoning to draw causal conclusions from the data. If the presence of a given factor in the experimental group increases or decreases the occurrence of an effect, then that factor can be said to be causally relevant to that effect.

RCTs divide human subjects into experimental and control groups but they also take measures to counteract bias and control the placebo effect. To counteract bias, subjects are randomly selected for participation in different groups. This helps to prevent researchers from biasing their results, such as placing more healthy subjects in the experimental group or giving the more compliant participants the experimental treatment. In order to control the placebo effect, researchers and subjects are prevented from knowing who will be placed in the control group and who will be placed in the experimental group. Both groups receive some form of ‘treatment’ but the control group receives a placebo. (The placebo effect, a well-documented phenomena, occurs when a person who believes that he is receiving treatment is likely to do better than one who believes he is not receiving a treatment.) Thus, randomization and placebo-controls play a key role in drawing causal inferences from the data by helping researchers eliminate bias and spurious causes (e.g. the placebo effect).

Since causal conclusions should be based on statistically significant results, it is also important for researchers to take steps to increase the odds that the data obtained from an experiment will have statistical significance.

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36 Levine, *Ethics and the Regulation*.
38 Levine, *Ethics and the Regulation*.
39 Elwood, *Causal Relationships*.
significance. When results lack statistical significance, then we have no way of knowing whether the relationships we observe are no more than statistically normal variations in the data. As John Gardenier is fond of saying ‘may your results have statistical significance’. The procedures that researchers follow in RCTs are not required in order to obtain statistically significant results nor do they guarantee statistical significance, but they do play an important role in increasing the odds of obtaining statistically significant data.

To make a long story short, RCTs are the best way of answering questions about the safety and efficacy of a new treatment in a given population. Once scientists answer questions about safety and efficacy, then they may use other kinds of clinical trials, such as comparative studies. (A comparative study is a clinical trial that compares different treatments that have some known beneficial effect.) Thus, once a treatment has been proven safe and effective for a population, research protocols do not need to include placebo-controls. Moreover, many ethicists would argue that it is unethical to use placebo-controls once the scientific community has reliable data on safety and efficacy, since the continued use of placebo-controls subordinates the welfare of research subjects for social or scientific goals. In the US, AZT has been proven to have a beneficial effect in preventing the perinatal transmission of HIV. Hence, one might conclude that there is no need to use placebo-controls in subsequent research on the perinatal transmission of HIV. Placebo-controls were needed to meet the demands of scientific rigor when the 076 protocol was first being tested, but they are no longer necessary and should no longer be used. Thus, it appears that Lurie, Wolfe, and Angell are correct in their contention that placebo-controls are no longer appropriate in research on the perinatal transmission of HIV.

However, this is a hasty and simplistic conclusion. The reason that this conclusion is mistaken is that researchers are no longer asking the same research question that they were asking in developing the 076 protocol. The 076 protocol asked the question ‘is a specific treatment regimen (the 076 protocol) a safe and effective way of preventing the perinatal transmission of HIV in subjects in developed nations?’ The disputed studies ask a different question, i.e. ‘is a specific treatment regimen (e.g. 4 weeks of AZT) a safe and effective way of preventing the perinatal transmission of HIV in subjects in developing nations?’ There are two ways that this is a different question. First, the question is testing a new regimen, not the 076 protocol. Though we have

41 Levine, ‘The use of placebos’.
evidence concerning the 076 protocol’s safety and efficacy, researchers did not know when these disputed studies were done whether the new regimens were safe and effective. In particular, researchers did not know whether the simpler and cheaper treatment would be as effective as no treatment at all.

Second, the disputed studies use a different population of research subjects. AZT has been proven to be safe and effective for use in populations from developed countries but we have not yet proven safety and efficacy in populations from developing nations. Medical research questions and answers must be understood with some reference to a specific population. For instance, if a drug is proven to be safe and effective in adults, this does not mean that the drug is safe and effective in children, since children are not like adults: they have less body mass, they metabolize drugs differently, they have different nutritional needs, and so on. Thus, a placebo-control is still required when a drug is being tested on children even if the drug has been proven safe and effective for adults.

According to Varmus and Satcher, there are some important differences between pregnant women with HIV in developed nations and pregnant women with HIV in developing nations. Pregnant women with HIV in developing nations have a higher incidence of anemia, malnutrition, and various diseases, such as tuberculosis and malaria. AZT is not a benign medication; it has toxic side-effects. Although we have reliable data about AZT’s safety and efficacy in populations of pregnant women from developed countries, we do not have reliable data about safety and efficacy in populations from developing countries. Researchers cannot obtain clear information about zidovudine’s safety and efficacy in developing nations unless experimental designs include a placebo-control group.

There are several objections to this line of argument. First, one might object that we do not need placebo-controls in order to answer questions about safety and efficacy because these questions have already been answered. AZT has a proven therapeutic effect in preventing the perinatal transmission of HIV. The problem with this objection is that researchers did not know (when these studies were initiated) whether AZT has a therapeutic effect at the comparatively low doses that were administered in the studies. These studies used about 10% of the AZT used in the 076 protocol, and researchers had reasons to believe that this dosage of AZT might not have a therapeutic effect. Suppose the experimenters conducted a comparative trial instead of an RCT and obtained the following (hypothetical) results:

\[42\] Elwood, *Causal Relationships*.
\[43\] Varmus and Satcher, ‘Ethical complexities’.

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Experiment 1

<table>
<thead>
<tr>
<th>Group</th>
<th>AZT*</th>
<th>Transmission rate</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.30</td>
<td>14%</td>
<td>1000</td>
</tr>
<tr>
<td>B</td>
<td>0.20</td>
<td>17%</td>
<td>1000</td>
</tr>
<tr>
<td>C</td>
<td>0.10</td>
<td>20%</td>
<td>1000</td>
</tr>
</tbody>
</table>

*AZT dose for the 076 protocol = 1.0

If researchers had obtained these results, they would have some reasons for believing that lower doses of AZT have a therapeutic effect, but they would not know whether giving only 10% of the dose given in the 076 protocol would have a therapeutic effect. They would not be able to make this determination because they would not have the information needed to understand whether the rate of HIV transmission is significantly lower (in a statistical sense) in Group C than the rate of transmission among members of the population that receive some form of treatment but no AZT.

But suppose the protocol had including a placebo group. Consider the following two hypothetical experiments:

Experiment 2

<table>
<thead>
<tr>
<th>Group</th>
<th>AZT*</th>
<th>Transmission rate</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.10</td>
<td>8%</td>
<td>1000</td>
</tr>
<tr>
<td>B</td>
<td>0.00</td>
<td>20%</td>
<td>1000</td>
</tr>
</tbody>
</table>

Experiment 3

<table>
<thead>
<tr>
<th>Group</th>
<th>AZT*</th>
<th>Transmission rate</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.10</td>
<td>18%</td>
<td>1000</td>
</tr>
<tr>
<td>B</td>
<td>0.00</td>
<td>20%</td>
<td>1000</td>
</tr>
</tbody>
</table>

In experiment 2, researchers have good reasons for believing that giving a 10% dose of AZT has a therapeutic effect because the results that are obtained indicate differences beyond a statistically normal variation for this sample size (+/- 3%). In experiment 3, researchers have reasons to believe that a 10% dosage of AZT does not have a therapeutic effect because the transmission rate (18%) falls within a statistically normal range of variation in the data for this sample size.

These reflections do not prove that it would be impossible to obtain statistically significant results or make causal inferences without...
placebo-controls nor do they prove that placebo-controls always lead to statistically significant results or good causal reasoning. Placebo-controls are a useful strategy for making causal inferences and for acquiring statistically significant data. Although placebo-controls are often inappropriate in medical research, placebo-controls allow researchers to get quicker, more reliable answers to scientific questions. (I refer the reader to some other writings for further discussion of these complex statistical issues and alternative perspectives on this subject.\textsuperscript{44,45})

Concerning the argument that researchers required placebo-controls because they were studying a different population, one might object that there are not significant differences between HIV-infected women in developed nations and HIV-infected women in developing nations. This is an empirical issue that I will not explore in detail here. However, since there clearly are some epidemiological differences between these two populations, a policy of ‘better safe than sorry’ requires us to assume that these differences are significant enough that they could affect experimental outcomes. If we have some reasons to believe that the toxic side-effects of AZT may affect its therapeutic value in preventing the perinatal transmission of HIV in a specific population, then we should propose study designs that can determine whether these side-effects have statistically significant effects in that population. For comparison, one might argue that teenagers (age 12–17) and adults (ages over 21) are medically similar enough that we do not need to include placebo-controls in research on the effects of a new anti-depressant in treating depression if we have demonstrated that it has therapeutic effects in adults. The new anti-depressant may affect teenagers and adults in the same way, but can we afford to take that risk?

When the controversial studies were initiated, researchers had evidence about AZT’s therapeutic effects in preventing the perinatal transmission of HIV in populations from developed nations, but they lacked evidence from populations from developing nations. Researchers needed to know, for example, whether AZT would have an adverse impact on pregnant women (and their unborn children) who are likely to be suffering from anemia, malnutrition and various diseases. In particular, they needed to know whether these women would be better off without even the low levels of AZT that were under test. Once again, the best way to answer these questions is to


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include a placebo-control group in the study. (For further discussion of medical research and the methodology of HIV studies, I refer the reader to some relevant texts.46,47)

Finally, one might object to the research question that the studies addressed. One might argue that the need to protect the dignity and welfare of human subjects outweighs the need to develop a cheaper, simpler alternative to the 076 protocol. If scientific rigor requires us to use placebo-controls to solve this research problem, then we should not attempt to solve the problem. This objection concerns the selection of problems deemed worthy of scientific inquiry, not scientific methodology per se. Various moral, political, economic, religious, and cultural assumptions and conditions can affect the scientific community’s choice of research problems. Indeed, this is one area where most scholars agree that ‘values’ cannot be avoided in scientific decision-making.48 As noted earlier, the decision to seek a cheaper and simpler way of preventing the perinatal transmission of HIV is based on the need to find a treatment that addresses the social and economic conditions in developing nations. Even critics of these controversial studies recognize this need. Once scientists chose to tackle this research problem, empirical and methodological considerations support the case for using placebo-controls to meet the demands of scientific rigor.

To summarize this section, I side with Varmus and Satcher in their view that placebo-controls are (or were) required to meet the demands of scientific rigor in these disputed studies.

**ECONOMICS OF SCIENCE**

There are some economic reasons for using placebo-controls that have little to do with scientific rigor. First, there is some evidence that a lack of funds to purchase zidovudine and other items needed in research has been a key concern in these clinical trials. In a letter to the NIH, Edward Mbidde, a Ugandan researcher, wrote: ‘These are Ugandan studies conducted by Ugandan investigators on Ugandans. Due to lack of resources, we have been sponsored by organizations like yours. We are grateful that you have been able to do so.’49 When medical researchers lack funding for experiments, they may not be able to

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afford to include enough subjects in their studies. If researchers do not include enough subjects, it can take more time to obtain statistically significant data, due to an insufficient sample size. Second, one might argue that pharmaceutical companies might offer to sponsor placebo-control studies but not alternative studies. An offer to sponsor research, assuming that other sponsors do not make offers, could benefit those subjects that are fortunate enough to receive the medications that are being tested. Thus, placebo-control studies might be employed to promote beneficence and social utility even if they are not needed to satisfy the principle of rigor.

I do not find these arguments to be very decisive by themselves although they can provide some additional reasons for using placebo-controls. However, economic considerations should not dictate experimental designs. If placebo-controls are not required to meet the demands of scientific rigor, then they should not be used. If placebo-controls are used only as a means of funding research, then researchers would be using some research subjects, i.e. those receiving placebos, for the sole reason of benefiting other subjects. These subjects would not be needed in order to insure that the studies obtain reliable data; they would only be needed to insure that the studies are funded. But this is not a good reason to use placebo-controls. Since placebo-controls deny treatments to some research subjects, they should not be used unless we have good reasons to think they are required to satisfy scientific rigor.

SOCIAL UTILITY AND JUSTICE

Let us assume, then, that Varmus and Satcher are correct in maintaining that the research needs to include placebo-controls in order to meet the demands of scientific rigor. Even if we grant this point, it would not follow that the studies are ethical, since ethical research must satisfy other principles, such as informed consent, beneficence, utility, and so on. To support their case, proponents of the HIV studies need to appeal to other principles of research ethics. Proponents argue that HIV studies that use placebo-controls also do a better job of promoting justice and utility by enabling researchers to develop safe, cheap, and effective treatments. The studies promote justice by providing a fair distribution of the benefits and burdens of research and they promote social utility by meeting urgent social and medical needs. The studies provide physicians and public health administrators in developing nations with practical answers about preventing the perinatal transmission of HIV. Another way of putting this point is that the research satisfies the Declaration of Helsinki’s requirement of reasonable availability.
**ANALOGY WITH TUSKEGEE?**

However, even social utility, justice, and scientific rigor are not sufficient reasons for conducting a clinical trial, since an experiment could be unethical by failing to meet other demands, such as informed consent or beneficence. Critics of HIV trials argue that they are unethical because they subordinate the good of individual patients for the good of society, and these critics invoke the Tuskegee study as instructive analogy. Critics argue that the research violates the principle of beneficence since it does not provide a proven treatment to all subjects. Just as the Tuskegee study denied penicillin to its subjects even after the drug had been proven effective, this HIV research denies zidovudine to its subjects. Like the Tuskegee study, it violates informed consent and takes advantage of poor, uneducated populations to meet scientific or social goals, or so the critics argue.  

**PROBLEMS WITH INFORMED CONSENT**

 Critics of the HIV research are correct in pointing out problems with obtaining adequate informed consent in these study populations. A *New York Times* story casts doubt on the effectiveness of informed consent in this controversial research. In interviews, it appears that the subjects did not know what they were consenting to or why the research was being conducted; they only seemed to understand that they were consenting to some form of treatment. One might also ask whether the research constitutes a ‘coercive’ offer under these socio-economic conditions, since subjects are given the choice between a 50% chance at a proven therapy or no therapy at all. In response to these concerns, UNAIDS has taken some steps to safeguard informed consent in HIV clinical trials. One method that researchers have used to improve informed consent in HIV research in the third world is to employ trusted community leaders to convey information to people in local populations. Researchers work with the community leader to explain the research to the people and obtain informed consent. To address concerns about coercion, eligible subjects are also told that they are free to not participate in the study. This method deviates from the highly individualistic notion of informed consent that one finds in Western nations, but many scholars have argued that that Western interpretations of informed  

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50 Angell, ‘The ethics of clinical research’.
51 French, ‘U.S. AIDS research’.
consent may not be appropriate in non-Western countries. Indeed, problems with informed consent are not unique to the disputed HIV clinical trials. Due to cultural and linguistic differences, it is often difficult to obtain adequate consent in non-Western and developing nations. The proper response to these difficulties is not to abandon the principle of informed consent, but to develop an interpretation of the principle that can be applied to research in non-Western and developing countries.

However, none of these problems with informed consent prove that the disputed research is analogous to the Tuskegee study, since the HIV studies have been designed to employ ethically sound notions of informed consent; the Tuskegee study was not designed to employ ethically sound notions of informed consent. In the Tuskegee study, subjects were not told that they were participating in an experiment, and they were told that they would receive treatment when they received no treatment. While the subjects received some information, they were deceived and they were not adequately informed; ethically sound informed consent was simply not a key part of the Tuskegee study design or its implementation.

BENEFICENCE

Second, these studies do not constitute unacceptable violations of the principle of beneficence. In the Tuskegee study, subjects were denied an effective treatment for syphilis, i.e. penicillin, even after it became widely available to the general population in the US. An effective treatment for preventing the perinatal transmission of HIV is available to the general population in developed nations but is not available to the general population in developing countries. Given their economic circumstances, populations in these countries are not likely to have access to an effective treatment until one is developed that meets their needs. To clarify this discussion, we should therefore distinguish between two different ways of failing to act with beneficence:

(VB1) Denying treatment when treatment is not available to the general population (but may be available in some populations);

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56 Pence, *Classic Cases*. 

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(VB2) Denying treatment when treatment is available to the general population.

I contend that VB2, which is exemplified by the Tuskegee study, is morally unacceptable, while VB1, which is exemplified by the HIV research, is morally acceptable.

The reason why it is acceptable to deny treatment that is not available to the general population is that there should be some reasonable limits on beneficence in research or in therapy. If there were no limits on the demands of beneficence, then it would follow that physicians and physician/researchers would be required to provide all medical care that could benefit patients or research subjects. This excessive demand would have absurd consequences: a physician who did not order a CAT scan for a patient with a concussion would be acting unethically even if there are no CAT scanners within three hundred miles; a physician who tests the efficacy of aspirin in preventing heart disease in developing nations would be acting unethically if she does not offer subjects the latest and best cardiological procedures, such as triple bypass surgery.

A more philosophical way of stating this point is that there is a difference between doing what is ethically required and doing what is ethically supererogatory. Supererogatory actions go above and beyond the call of duty. One might argue that researchers should strive to exceed their ethical duties, but that they are not required to do so. The demands of beneficence in medicine require physicians and researchers to benefit patients and subjects up to a certain point, but they do not require physicians and researchers to do more than they can be reasonably expected to do, given their circumstances.\textsuperscript{57,58}

So how do we determine the reasonable limits on the demands of beneficence in medical research? It should be clear that the limitations on these requirements depend on what researchers can reasonably be expected to do, which is a function of our current medical knowledge and techniques as well as social, economic, and political conditions. Since different nations have different social, economic and political conditions, the demands of beneficence may vary from one nation to another. (Since medical knowledge and techniques change over time, these requirements may also change from one era to another.) If we apply this point to the dispute concerning the HIV trials, it implies that beneficence may require researchers in the US to provide subjects with AZT even if they are


under no obligation to provide this treatment in nations where this treatment is not available. Whether researchers have an ethical obligation to provide zidovudine to subjects depends, in part, on the social and economic conditions of research.

CONCLUSION: ASSESSING FACTS AND BALANCING PRINCIPLES

After analyzing the disputed trials in terms of scientific rigor, utility and justice, informed consent, and beneficence, one should conclude that the controversial trials were ethical. Varmus and Satcher were correct in their contention that the trials were a scientifically rigorous way of addressing some urgent social needs while conforming to widely accepted standards of research ethics. This analysis also provides us with some insight into the meta-ethical question addressed by Lurie, Wolfe, Angell, Varmus, and Satcher. Although there are some basic ethical principles that pertain to all cases of research on human subjects, the application and interpretation of these principles depends, in part, on scientific, social, cultural, economic, and political conditions. Local conditions play a key role in determining how to apply the principles of beneficence, scientific rigor, justice, and utility in research on the perinatal transmission of HIV.

It is interesting to note that both sides in this controversy claim that the Declaration of Helsinki supports their position. Lurie, Wolfe, and Angell argue that the disputed research is unethical because it violates the Declaration’s provisions concerning beneficence; Varmus and Satcher argue that the research is ethical because it addresses some of the other key provisions of the Declaration, such as justice and scientific rigor. On the interpretation I am suggesting here, one needs to consider the Declaration as a whole in order to understand how it applies to research designs. The document, taken as a whole, mentions several different principles of ethical research, and we have already seen that these principles may conflict. Since these principles may conflict, it will always be possible for someone to claim that research is ‘retreating from ethical principles’ if the research happens to satisfy all but one of the principles. Varmus and Satcher recognize the need to look at the whole document in interpreting its recommendations; their opponents appear to have singled-out some parts of the document as key points of contention.

We can also see why we should not expect a single standard of research to govern all study designs. There are a variety of ethical principles that apply to research on human subjects, and they sometimes conflict.59 (In the disputed research, the conflict can be

59 Levine, Ethics and Regulation.
viewed as beneficence and informed consent versus scientific rigor, justice and social utility.) We must balance these different principles in designing studies and in evaluating research. In order to achieve an optimal balance of these different ethical standards, we need to take into account various social, cultural, economic, political, as well as scientific factors. Thus, although there are some general principles of research on human subjects, ethical study designs depend, in part, on the facts we encounter in particular situations. Norman Fost, Director of the Medical Ethics program at the University of Wisconsin, offered a defense of the controversial research in a *New York Times* story by putting the matter this way: ‘The facts are different in different places.’

EPILOGUE: ETHICAL IMPERIALISM OR EXPLOITATION?

One might even argue that it is unjust, unfair, and insensitive to demand that the exact same standards of research that govern study designs in developed nations should also be implemented in developing countries. As we saw earlier, it may be inappropriate to maintain that Western interpretations of informed consent should also be applied to non-Western nations. Suppose, for the sake of argument, that a researcher from a developing nation had solicited the NIH for funds to conduct research on preventing the perinatal transmission of HIV and that her proposal included placebo-controls in the study design. If the NIH had refused this request on the grounds that the proposed studies are unethical, this funding organization could be condemned for unfairly imposing its standards of ethics on that developing nation and ignoring that nation’s special needs and conditions. Although a nation should be able to require that sponsored research proposals from abroad meet some globally accepted ethical standards, insisting that all nations meet those standards in exactly the same way amounts to ethical imperialism.

Yet the need to avoid ethical imperialism should not be used as an excuse for accepting unethical study designs. Since there is not a single standard of ethical research, we must be on guard against study designs that take advantage of the social, cultural, economic, and political conditions of research. Recognizing the importance of these factors in study designs does not grant researchers license to exploit study populations in order to achieve social or scientific objectives. One can easily imagine how pharmaceutical companies might be tempted to save money on drug research costs by conducting studies.

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in the third world. Just as US industries now conduct manufacturing operations in the third world in order to take advantage of lower production costs, i.e. a cheap labor force, pharmaceutical companies could take advantage of lower research and development costs in third world clinical trials. The potential connection between ethics and economics is very disturbing: clinical trials cost less where ethical standards are ‘lower’.

Thus, while it is important to avoid ethical imperialism, we must also avoid exploitation. (Exploitation occurs when an individual or group use unethical means to obtain a benefit from another individual or group.) What is the difference between exploiting the social, economic, cultural and political conditions of developing nations and recognizing that study designs must take account of these factors? One might argue that only retrospection can answer this question. Hindsight allows us to see that the Tuskegee study exploited its subjects, but foresight will not allow us to see whether the controversial HIV studies will exploit their subjects. I agree with this argument, to a certain extent: hindsight is, as they say, ‘20–20’.

However, acknowledging this point does not imply that researchers cannot take specific steps to avert exploitation, such as subjecting study designs to careful ethical and scientific scrutiny and working with local institutions, governments, and communities in implementing research protocols. International conferences, symposia, workshops, and other forums can also help the research community to deal with these concerns. Hindsight allows us to see that some of the more infamous examples of exploitative research, such as the Tuskegee study and the Department of Energy’s human radiation experiments, have failed to take these preventative measures, but we have good reasons to believe that researchers who are involved in the controversial HIV studies have taken appropriate steps to avoid repeating the mistakes of Tuskegee. Indeed, UNAIDS has taken specific measures to address these concerns and the organization plans to continue examining ethical issues in HIV research while it works with researchers and public health officials from around the world. Let us hope that researchers around the world, including those funded by private industry, follow this example.

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