

The Ethics of Placebo-Controlled Studies on Perinatal HIV Transmission and Its Treatment in the Developing World

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Abstract

Perinatal HIV transmission in the United States has been greatly reduced since the 1993 discovery of zidovudine, known as protocol 076. However, a feasible treatment in developing countries has not yet been found due to the high cost and medical standards needed to implement protocol 076. This presents an ethical question: whether placebo or active control should be used in testing new treatments. Proponents of a placebo control argue that a placebo control is the only method that provides definitive evidence of efficacy and side-effects, especially important given the scarce financial resources present in developing countries. Critics, however, argue that the use of a placebo controlled study when an effective treatment exists would be jeopardizing the health of individuals in developing countries. The key to resolving this debate is realizing that protocol 076 would not necessarily be effective when transplanted to developing countries due to the lack of adequate medical infrastructure, malnutrition, prevalence of disease, and low standard of living—it is not certain that protocol 076 would be better than placebo at all. Following this line of reasoning, quite a few placebo-controlled studies on perinatal HIV treatment have already been performed. Upon examination of this accumulated evidence, one finds that protocol 076, and shortened courses of it, are indeed effective in non-breastfeeding participants in developing countries; however, no treatment has been proven effective for breastfeeding populations. Therefore, it would be ethical to conduct placebo-controlled studies on breastfeeding populations, but not on non-breastfeeding populations.

In 1993, an effective treatment, protocol PACTG 076, was discovered to significantly reduce perinatal transmission of HIV (Connor et al, 1993). This protocol was a breakthrough in stemming the transmission of HIV; however, it was both costly and difficult to implement in areas without established medical facilities. A more cost-effective and practical treatment is still necessary to treat

the bulk of HIV infections, which take place in developing countries. Unfortunately, an ethical dilemma presents itself: should new treatment options be tested against a placebo or against active controls such as protocol PACTG 076, the current standard of treatment? The answer to this question hinges primarily on whether the current standard of treatment would be effective when transplanted to developing countries. If it is not proven to be effective, then placebo-controlled studies are warranted to find effective treatments. Once definitive proof of the efficacy of the treatments in developing countries is obtained, however, the use of placebo as a control would put the health of the individual taking the placebo at unnecessary risk. This would be unacceptable because it would be unethical to sacrifice the individual for societal gain—especially when the sacrifice is unnecessary.

The original study that is the focus of this ethical debate was conducted in 1993 by Conner, et al. This study, known as the Pediatric AIDS Clinical Trials Group (PACTG) Protocol 076, used zidovudine to try to prevent the perinatal transmission of HIV. The results were unprecedented: zidovudine, otherwise known as AZT and ZDV, was shown to be 67.5% more effective than placebo at preventing the transmission of HIV from mother to newborn. Moreover, this study was a double-blinded, placebo-controlled trial and was therefore considered definitive proof of the effectiveness of zidovudine—at least in the developed world. Subsequent “epidemiologic data have [...] extended this efficacy to children of women with advanced disease, low CD4+ T-lymphocyte counts, and prior ZDV therapy” (“PHS Taskforce,” 2005, p. 2). Therefore, with slight modifications, the current treatment against perinatal transmission of HIV remains nearly identical to the protocol 076 treatment used in the 1993 study, at least in developed countries.

In developing countries, however, there has been a significant amount of research due to the fact that PACTG protocol 076 is unfeasible in these countries. Although PACTG protocol 076 was recommended by the US Public Health Service for widespread use in 1994 (“PHS Taskforce,” 2005, p. 3), it remains out of reach and unfeasible for implementation in the most AIDS-devastated regions of the world due to the medical infrastructure and financial commitment needed for such large-scale implementation of the program. In particular, protocol 076 stipulates that the mothers take 100mg of zidovudine orally, five times

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a day, from 14 to 34 weeks before the expected due date. During birth, zidovudine is injected intravenously, which may be inconvenient in locations lacking adequate medical facilities. Finally, the infant is given oral zidovudine every 6 hours for 6 weeks. The total cost of this full regimen is “estimated to be in excess of \$800 per mother and infant, an amount far greater than most developing countries can afford to pay for standard care” (Varmus, 1997, para 8).

The goal, therefore, is to find a treatment that is both effective and feasible in developing countries. In the process of achieving this goal, one is faced with the question of whether placebo-controlled or active-controlled studies should be used to affirm the effectiveness of alternative treatments. Proponents of using placebo-controlled tests have several reasons for supporting placebo controlled trials, even when proven treatment exists.

First, they argue that the standard of care in a developing country is so minimal that giving placebo doesn't jeopardize the health of a subject beyond the type of care that they would have received otherwise. Second, they argue that the support of the host country for studies on their own people is what matters, not the ethicality of the study from the sponsoring countries' viewpoint. Third, they argue that using an active-control presents the risk that the new treatment will be less effective than the control and thus render the study irrelevant since the active control is too difficult to implement. The fourth, and most solid reason, is the fact that the placebo-controlled tests can provide definitive proof of whether a treatment is effective in a particular population and can definitively provide evidence of side-effects. In the case of PACTG 076, they claim that just because PACTG 076 has been shown to be effective and feasible in industrialized nations doesn't mean that it has the same effect in developing countries. In particular, they speculate that the lower standard of living in developing countries may affect the safety and effectiveness of zidovudine:

Zidovudine is a powerful drug, and its safety in the populations of developing countries, where the incidences of other diseases, anemia, and malnutrition are higher than in developed countries, is unknown. Therefore, even though the 076 protocol has been shown to be effective in some countries, it is unlikely that it can be successfully exported to many others. (Varmus, 1997, para. 7)

The first three arguments are easily shown to be invalid. The first reason, which argues that subjects would not be treated anyway and therefore are available for use as placebo controls, has disastrous implications. It would be akin to a doctor refusing a patient treatment on the grounds that the patient wouldn't have received treatment anyway. Incidents of this type of reasoning have occurred in the past, most

notably in the Tuskegee Syphilis Study where several hundred syphilitics were not given treatment because “these African-American men probably would not have been treated anyway, so the investigators were merely observing what would have happened if they were not in the study” (Angell, 1997, para. 4). Thus, it would be unethical for placebo-controlled studies to be conducted when proven treatments exist on the grounds that the subjects were not going to be treated anyway.

The second argument that proponents make in support of placebo-controlled trials in developing countries is that there is local support. Yet, the studies are conducted with the participation of US agencies and funded by US money. Thus, the ethicality of the studies is important to the US because the US is the country sponsoring the studies. If a study is unethical in the United States, then any study conducted or supported by the US should also be unethical. Otherwise, one could exploit study participants by simply moving the study outside of the US. It is critical to note, however, that keeping the same ethical guidelines does not necessitate the same treatment or procedure in and outside of the US. The standard of treatment in the US may be different from the standard elsewhere, depending on factors such as medical facilities and living conditions, yet the determination of these standards of treatment should be made based on the same ethical guidelines. Overall, studies supported by the United States must follow the same ethical guidelines regardless of where they are conducted.

The third argument, made by Varmus (1997) is that “if the affordable intervention is less effective than the 076 regimen—not an unlikely outcome—this information will be of little use in a country where the more effective regimen is unavailable” (para 13). This argument is flawed. In testing new treatments in developing countries, the intention is not to find treatments that are more effective than protocol 076, although it would be great if researchers happened on one. Rather, the intention is to find a more feasible treatment. If a treatment was found to be somewhat less effective yet much more feasible, it would be a success since it provides the greatest benefit to the greatest number of people without sacrificing the individual.

Thus, we are now left with the fourth and final argument, that the placebo-controlled trial is the only definitive proof of an effective treatment in a particular environment, and is also able to provide definitive evidence of side-effects. Whereas the previous three arguments are disputed, this final argument has merit and is backed by the World Medical Association in the Declaration of Helsinki (2004): “[...] a placebo-controlled trial may be ethically acceptable, even if proven therapy is available [...] where by compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method” (Note of clarification on paragraph 29). The key here

is that placebo-controlled studies can be conducted if there are legitimate methodological and scientific reasons, including differences in the study environment and sample population that warrant further study. Indeed, the treatment of perinatal HIV transmission may fit under this category since the standard of treatment in developing countries, protocol 076, has only been proven effective in developed countries with high standards of healthcare. Furthermore, it is important to note that the ethicality of using placebo controlled tests is directly affected by the quality of scientific data collected through studies in the field. If current studies find that a particular treatment is indeed effective in developing countries, then placebo-controlled studies would be unethical. In lieu of such a discovery, placebo-controlled studies are ethical and necessary. Thus, in order to determine if placebo controlled studies for treatment against perinatal transmission of HIV are ethical in the present, we must examine the wealth of information that has been generated by placebo-controlled studies conducted up to now and see if there has been definitive findings on successful treatments.

As reasoned above, studies begun in the mid-1990s were justified in the use of placebo-controlled trails of shortened courses of protocol 076 in developing countries such as in Thailand and Africa. These studies have yielded a wealth of evidence concerning the efficacy of different treatments against perinatal transmission of HIV in developing countries. The primary problem, it appears now, is the inability of mothers in developing countries to refrain from breast feeding because of the lack clean water for baby formula. There is also social stigma surrounding not breast feeding because to do so would reveal one's HIV positive status. These problems dramatically affect the efficacy of zidovudine, as shown by recent studies.

For example, placebo-controlled studies of zidovudine in Thailand and Africa, in which mothers agreed not to breast feed showed that zidovudine was quite effective: "A short course of twice-daily oral zidovudine was safe and well tolerated and, in the absence of breastfeeding, can lessen the risk for mother to child HIV-1 transmission by half" (Shaffer, 1999, Interpretation). This is similar to the results of the PACTG protocol 076 study (Connor, 1993), in which participants did not breastfeed. Moreover, this study indicated that shortened forms of the zidovudine treatment that required only oral medication was still effective in developing countries, which dramatically improves the feasibility of implementing widespread zidovudine treatments against perinatal transmission of HIV.

Furthermore, recent studies in the United States also indicate that shortened courses of protocol 076 can be nearly as effective as a full course. According to a study conducted by Wade (1998), "When treatment was begun in the prenatal period, the rate of HIV transmission was 6.1 percent [...] when begun within the first 48 hours of life,

the rate was 9.3 percent [...] when begun on day 3 of life or later, the rate was 18.4 percent [...]. In the absence of zidovudine prophylaxis, the rate of HIV transmission was 26.6 percent" (p. 1). This shows that even if zidovudine was given 48 hours after delivery, there is not a substantial decrease in efficacy. Although larger and more detailed studies need to be conducted, these results show that it is highly probable that zidovudine is effective in shortened course forms both in the United States and in developing countries, provided that there is no breast feeding. Taken together, these two studies indicate two important points: first, shortened courses of zidovudine would be more feasible than the original protocol 076, and second, shortened zidovudine courses can be used as active-controls in developing countries for non-breastfeeding populations.

However, breast feeding is a seemingly unavoidable problem in most developing countries. This drastically lowers the effectiveness of protocol 076 and shortened courses of it, to the point at which it may not necessarily be more effective than placebo, ruling out zidovudine as an active-control for studying breastfeeding populations. According to the Petra Study Team (2002), "The bad news from our trial is that when a combined endpoint of HIV-1 infections and child mortality is taken, very little benefit remains after 18 months of follow-up [for short-course zidovudine and lamivudine treatments]. This may be ascribed to continued breastfeeding with resultant HIV-1 transmission and to high infant mortality rates in East Africa" (Discussion).¹

There is hope, however, in the possibility of a new treatment in the form of nevirapine, a significantly cheaper drug that appears to be much more effective than zidovudine. In an active-controlled study known as the HIVNET 012 randomized trial conducted from 1997 to 1999 in Uganda, nevirapine treatment was shown to have a transmission rate of 15.7% compared to a 25.8% transmission rate for short course zidovudine at 18 months (Jackson, 2003, Interpretation). This finding contains two important indications. First, nevirapine is far more effective than zidovudine in breast feeding populations and is also more feasible because it is given in only two doses: one to the mother during labor and another to the newborn 72 hrs after birth. Second, it is important to note that the

¹ It may be of interest to note that the ethicality of the placebo-controlled Petra study was questioned before its results were revealed due to its use of a placebo control. The ethical issues debated were similar to the ones discussed in this paper. In hindsight, the authors note that "it is worth drawing attention to the difficulties that would have been incurred in interpretation of results if the placebo group had not been included [...] the degree of effectiveness of all three experimental groups would have been overestimated. The implications of these miscalculations for policy and further operational studies would have been quite serious" (Petra Study, 2002, Discussion).

zidovudine effectiveness of 25.8% is not much better than placebo treatment in other studies. Although one should be wary about cross-comparing results from different studies, this large transmission percentage supports the idea that zidovudine treatment in a breastfeeding population is ineffective.

So what do all of these studies mean? Do they show conclusively that there is an effective standard of treatment for developing countries, and therefore require that all future studies use it as a control instead of placebo? The answer depends on what kind of study one is conducting. If one were to conduct studies in which subjects are not allowed to breastfeed, then it would be unethical to use a placebo control because it has been shown conclusively that short course zidovudine is an effective standard treatment. However, studies involving breast feeding subjects are still ethical because the evidence is not so conclusive. Zidovudine has been shown to be ineffective, and nevirapine needs to be tested against placebo.² Therefore, efforts should be made to affirm the effectiveness of nevirapine in breastfeeding women, when tested against placebo. If such tests do in fact show that nevirapine is effective, then placebo-controlled trials would become unethical.

Overall, the use of a placebo-controlled study can not be justified by the low standard of care in the study location, by local support without ethical approval in the sponsoring country, or by the infeasibility of implementing the active-control in the country. Indeed, the World Medical Association states in the Declaration of Helsinki (2004) that a placebo-control, "in general [...] should only be used in the absence of existing proven therapy" (Note of clarification to paragraph 29). In the case of protocol 076, there has been substantial evidence in recent years indicating that the breakthrough protocol that works effectively in industrialized countries can be shortened and still be effective in developing countries for non-breastfeeding populations. These recent studies used placebo controls and did so ethically because there was a state of equipoise—of uncertainty that protocol 076 or modified forms of it were superior to placebo. However, that state of equipoise no

longer exists because of the results of these studies. Future studies, in non-breastfeeding populations, therefore, can not be justified on the grounds of equipoise. Studies of breastfeeding populations using placebo-controls, however, are still ethical because of the lack of a proven treatment i.e., a genuine state of equipoise still exists. Once an effective treatment is found however, all subsequent studies must be tested against an active control. 🍌

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² The HIVNET 012 nevirapine trial started out with a placebo control, but when the Thai trials of zidovudine showed that zidovudine was effective 6 months after birth, the placebo control was dropped due to ethical reasons similar to the ones discussed in this paper. Subsequent trials, as explained in this paper, showed that zidovudine was actually not effective when extended to 18 months after birth in breastfeeding populations.