

Testing Therapies Less Effective than the Best Current Standard: Ethical Beliefs in an International Sample of Researchers

David M. Kent, Tufts-New England Medical Center, Boston, USA

Mkaya Mwamburi, Tufts-New England Medical Center, Boston, USA; Africa Centre for Health and Population Studies, Mtubatuba, South Africa

Richard A. Cash, Harvard School of Public Health, Boston, USA

Tracy L. Rabin, University of Rochester School of Medicine and Dentistry, Rochester, USA

Michael L. Bennish, Tufts-New England Medical Center, Boston, USA; Africa Centre for Health and Population Studies, Mtubatuba, South Africa

Abstract

Objectives: To test the range of beliefs regarding the ethics of testing, in resource poor settings, new therapies that are less efficacious but more affordable and feasible than the best current therapeutic standard.

Design: Using a web-based survey, we presented a hypothetical scenario proposing to test a therapy for HIV disease (“therapeutic inoculation”) known to be less efficacious than highly active antiretroviral therapy (HAART). Respondents evaluated various trial designs as ethical or unethical.

Participants: 604 subscribers to two listservs for individuals interested in international health research ethics.

Main outcome measures: Proportion of respondents endorsing trials testing this “substandard” therapy, and proportion endorsing placebo-controlled trials.

Results: There were 215 respondents from 47 countries. Forty-five percent of respondents were from low or middle income countries; 96% devoted at least some time to research activities; and 75% had “some” or “considerable” research experience in developing countries. Of respondents, 97% (95% CI 94.7 to 99.4) endorsed testing therapeutic inoculation, without HAART, in patients with HIV disease; 86% (95% CI 81.4% to 90.7%) endorsed testing against placebo. Sixty-eight percent explicitly endorsed principles where the standard of care for subjects in clinical trials is determined by local, not universal, standards. There were no differences in responses based on respondent education-level or the income-level of their country of citizenship.

Conclusion: There was broad agreement that a therapy of potential local benefit may be tested, even when that therapy is known to be inferior to the standard of care in wealthy countries. Most agreed that a placebo control may be used in some circumstances.

Introduction

Following the 1994 ACTG 076 trial (Connor et al. 1994), which demonstrated that an intensive course of zidovudine (AZT) substantially reduced the risk of vertical transmission of the human immunodeficiency virus (HIV), a series of trials were conducted in developing countries to test less intensive AZT regimens that might be affordable and feasible in that context (Shaffer et al. 1999; Wiktor et al. 1999). These trials drew intense criticism (Lurie and Wolfe 1997; Angell 1997), primarily because the “short-course” regimens were compared to placebo.

Critics of these “short-course” trials based their argument on several related ethical principles, including principles articulated in the Declaration of Helsinki (Varmus and Satcher 1997) that required that “every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method” and prohibited placebo-control unless no proven therapy existed. The trials of modified anti-retroviral therapy clearly violated the Declaration, since no patient—in either the control or treatment arm—was assured of the “best proven” therapy (i.e. the AZT regimen used in the ACTG 076 trial), and placebo controls were used even where a proven (albeit inaccessible) therapy existed. Critics of the trials argued that universal standards of research ethics mandated universal standards of care; that is, trials that are unethical to conduct in industrialized countries should also be unethical in developing countries (Lurie and Wolfe 1997; Angell 1997).

It was, however, pointed out that, for resource poor settings, the demand for a standard of care defined by the “best proven diagnostic and therapeutic method” may conflict with the need for research relevant to the population from which subjects are drawn (Varmus and Satcher 1997; Wilkinson, Karim, and Coovadia 1999). Specifically, all clinical research aimed at measuring the effects of incremental improvements of care in resource poor settings would be proscribed, unless those improvements were at least as efficacious as the best proven standard available in resource-rich settings.

Despite the intensity of the debate, and despite its importance for clinical research in resource poor settings, there has been no scientific accounting of the beliefs and opinions of key stakeholders. We hypothesize that a survey may reveal a pattern of consensus that may be useful in guiding policy.

Methods

We sought to test the range of opinions and beliefs regarding the ethics of testing new therapies with the following characteristics:

1. The new therapy is known to be less efficacious than the “best proven” therapy.
2. The new therapy may be better than the current standard-of-care in the resource poor setting in which testing is proposed.
3. The new therapy is affordable and feasible in the resource poor setting in which testing is proposed.
4. Broad access to the “best proven” therapy is not feasible in the resource poor setting, and is not expected to become so in the foreseeable future.

We used a scenario proposing to test a hypothetical modified anti-retroviral regimen that explicitly met the above four criteria, being much less expensive and easier to administer than highly active anti-retroviral therapy (HAART). For this reason, we chose to test a therapeutic inoculation, or “therapeutic vaccine”, which had no value preventing HIV infection, but which may be of some value in slowing the progression of the disease. We additionally stipulated that this “therapeutic vaccine” was found not to provide any incremental benefit for patients taking

HAART, and that there was no reliable data on the natural history of HIV disease directly applicable to this resource poor setting. Table 1 summarizes the core elements of the scenario, and each of the questions. (For the complete survey, see Appendix or www.tuftshealthsurvey.org.)

We asked respondents to indicate whether they believed that testing the therapeutic inoculation would be ethical with several different trial designs, including whether it could be tested against placebo (questions 1 and 2). For respondents who endorsed a particular trial design, we asked whether their selected trial could be ethically conducted in an industrialized setting where HAART is routinely available (question 3). Finally (question 4), respondents were asked to endorse one of four principles to define the required standard of care for the ethical conduct of a clinical trial. The first two choices (from the prior [South Africa, 1996] version (World Medical Association 1996) and recently revised [Scotland, 2000] Declaration of Helsinki (World Medical Association 2002)) used a universal standard of care regardless of the setting, while the second two choices required a standard of care determined by the local context.

Survey sample and procedures

Survey respondents were obtained from two e-mail lists:

- 1) The Harvard Bioethics listserv;
- 2) The NIH-Fogarty International Bioethics listserv.

The Harvard Bioethics listserv (n= 495 at the time of this survey) is a “snowball sample” which was originally comprised of participants of workshops of the Harvard Program on Ethical Issues in International Health Research. At the time of the survey, there had been six such workshops (held in Boston [June 1999, 2000, 2001], South Africa [July, 2000], Mexico [October, 2000] and India [January, 2001]). These workshops aimed to provide a comprehensive overview of contemporary ethical issues in international health research and were intended for individuals or organizations that fund, approve or conduct such research. The listserv was launched in May 2000 as a forum for the discussion of selected ethical issues in international research.

The NIAID-Fogarty International Bioethics listserv (n=162) was started following an NIAID-sponsored research ethics conference in Malawi (March, 2001) for a network of African malaria

Table 1: Survey Summary

Central Elements of the Scenario:

- The therapeutic vaccine is known to be less effective than HAART.
- The therapeutic vaccine is known not provide any additional benefit when given with HAART.
- HAART is not affordable, implementable or sustainable in the resource poor setting, and is not expected to become so in the foreseeable future.
- If the therapeutic vaccine is demonstrated to reduce morbidity, the local government and international sponsors have endorsed incorporating it into the care of HIV-infected patients.
- There is no reliable data concerning the natural history of HIV disease directly applicable to this resource poor setting.
- Trial subjects will not receive HAART, even when they become sick.

Question 1:

Would testing the therapeutic vaccine be ethical in the following scenarios:

- Scenario 1: The intervention group will receive the vaccine and the control group will receive a placebo. Although prophylaxis for opportunistic infections is available at some other clinics in the region, subjects in this trial will not receive any prophylaxis, as this may obscure some of the potential benefits in the treatment group.
- Scenario 2: As in the Scenario 1, the intervention group will receive a vaccine and the control group will receive a placebo. In this scenario, antibiotic prophylaxis is not available at any clinics in the region. Study participants in both the control and treatment group will not receive prophylaxis.
- Scenario 3: As in Scenarios 1 and 2, the intervention group will receive the vaccine and the control group will receive placebo. Although prophylaxis is not available at any clinic in the study area, subjects, in both the control and treatment group, will receive prophylaxis.

Question 2:[†]

Which of the following options best expresses your beliefs regarding the proposed trial:

- Despite the investigators' belief that the therapeutic vaccine will be far less effective than HAART, the control group should receive HAART.
- An observational trial should be performed to monitor for side-effects and to tests the feasibility and costs. If the vaccine proves feasible and well-tolerated, and there is not any apparent increase in poor outcomes, than use of such a therapy should be recommended under the assumption that treatment is likely to be better than no anti-retroviral therapy.
- It is unethical to test this sub-standard therapy under any circumstance. Until HAART becomes available, or until a feasible anti-retroviral regimen likely to be as effective as HAART is proposed, no anti-retroviral therapy should be offered to this population.
- Other (Please specify in a few sentences, taking care not to change the hypothetical conditions specified in this scenario):

Question 3:[‡]

Would the endorsed trial design also be ethical to conduct in the industrialized countries of Europe and North America, where HAART is widely available?

[†] For those that believe a placebo-controlled trial is unethical under any of the conditions in question 1.

[‡] For those that endorsed a specific trial design in either question 1 or question 2.

Question 4:

The following statements are alternative descriptions of the medical care that subjects in clinical trials are entitled to. Please read the statements carefully and select the version that most closely matches your opinion. For the purposes of this survey, “best proven therapy” and “best current therapy” should be interpreted as referring to universal standards of care, regardless of where the trial is being conducted. “Best attainable and best sustainable” refers to the highest standards of care that can be maintained in the community in which the trial is based after the trial has ended.

- In any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.
- The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
- In any medical study, every patient including those of a control group, if any – should be assured of the best attainable and sustainable diagnostic and therapeutic method.
- In any medical study, every patient – including those of a control group, if any – should be assured of a standard of care that is no worse than the standard of care otherwise available.

researchers and members of their local Institutional Review Boards (IRB). The purpose of this listserv was to provide researchers and IRB members with information, such as postings regarding changes in regulations concerning human subject research and notification of funding sources for bioethics research projects. The listserv membership was subsequently expanded at a network meeting for Program Directors of the Fogarty International Bioethics Training Program (Bethesda, USA, April 2001), and by "word-of-mouth".

The survey was conducted between December 1, 2001 and January 11, 2002. To increase the survey response rate, an initial e-mail requesting participation was followed-up by three reminder e-mails. As an incentive, a US \$10 donation was made on behalf of each respondent to one of two charitable organizations, as selected by the respondent.

Results

A total of 619 e-mails were sent. Fifteen were sent to inactive addresses, leaving 604 potential respondents.

There were 215 respondents from 47 countries. Characteristics of respondents are shown in Table 2. Almost all respondents were involved research activities, three-quarters had at least some research experience in developing countries, most had doctorate-level degrees and about half were from lower or middle income countries.

Responses to proposed clinical trials testing the therapeutic inoculation against placebo are shown in Table 3. Almost all respondents felt it was unethical not to provide antibiotic prophylaxis, if such therapy might be available at nearby clinics. Thirty percent felt that testing the thera-

Table 2. Study Sample Characteristics of Participants (N = 204)

	Proportion of Participants n (%)
Age Group	
Less than 40	71 (33.0)
Between 40 and 59	176 (58.6)
Greater than 60	18 (8.1)
Continent of Residence	
Africa	36 (16.9)
Australasia	47 (22.0)
Latin America	18 (8.5)
Europe	17 (8.0)
North America	95 (44.6)
Income Group of Country of Residence - World Bank Classification by 2000 GNI per capita	
Low Income (\$755 or less)	20 (23.3)
Lower Middle Income (\$756- \$2,995)	22 (10.3)
Upper Middle Income (\$2,996- \$9,265)	25 (11.7)
High Income (\$9,266 or more)	117 (54.7)
Medical Profession (Doctors and Nurses)	105 (48.8)
Doctorate Holders (Doctors and PhD)	146 (67.9)
Institutional Affiliation	
Hospital	37 (17.2)
University	118 (54.8)
Government Body	53 (24.7)
Non-Government Industry	37 (17.2)
Percentage of Time Devoted to Research	
None	8 (3.7)
1% - 25%	50 (23.3)
26% - 50%	54 (25.1)
51% - 75%	50 (23.3)
76% - 100%	53 (24.7)
Involvement in Medical Research based in Developing Country	
Never	
Some	51 (23.7)
Considerable	67 (31.2)
	97 (45.1)
Formal Education in Medical Research Ethics Received	
CME course	
University Course	67 (31.2)
Ethics Specialist	88 (40.9)
	39 (18.1)

Table 3: Endorsement or Acceptance of Scenarios Presented in the Study

	Proportion of All Participants n (%) (N=215)	Proportion of Participants From Low and Middle Income Countries n (%) (N=97)
Endorsed Scenario 1 (placebo control, no prophylaxis, prophylaxis available at some regional health centers)	7 (3.3)	7 (7.1)
Endorsed Scenario 2 (placebo control, no prophylaxis, prophylaxis unavailable at some regional health centers)	63 (29.3)	19 (19.6)
Endorsed Scenario 3 (placebo control, prophylaxis provided, prophylaxis unavailable at some regional health centers)	177 (82.3)	79 (81.4)
Endorsed Placebo Controlled Design (Any of the above Scenarios)	185 (86.1)	80 (82.5)

Table 4: Trial endorsed by respondents who believed that a placebo-controlled trial would not be ethical (n=25)

	Proportion of among respondents believing placebo-controlled trial unethical (n=25) n (%)	Proportion of All Participants (n=215) %
Test against IIAART	11 (44)	5.1
Observational Trial	7 (28)	3.3
Testing vaccine unethical	2 (8)	0.9
Other	5 (20)	2.3
Ethical to Test Therapeutic Vaccine	19 (76)	97.2
Unethical to Test Therapeutic Vaccine	6 (24)	2.8

Table 5: Would the selected trial be ethical in industrialized countries where IIAART is available?

	Proportion of Respondents (n=215) n (%)
Ethical	91 (42.3)
Unethical	113 (52.6)
No trial endorsed	11 (5.1)

Table 6: Ethical principles defining the required standard of care for subjects participating in clinical research

Standard Of Care Described	Proportion of Participants n (%)	Reference for Standard of Care	Proportion of Participants n (%)
"Best Proven"	29 (13.5)	Universal	68 (31.6)
"Compared to Best Current"	39 (18.1)		
"Best Attainable and Sustainable"	102 (47.5)	Contextual	147 (68.4)
"...No Worse than the Standard of Care Otherwise Available"	45 (20.9)		

peutic inoculum against placebo would be ethical, without provision of antibiotic prophylaxis, if such therapy would not otherwise be available. Eighty-four percent of respondents believed testing against placebo is ethical, when anti-bacterial prophylaxis is provided to all. In total, 86% of respondents believed that, at least under some conditions, the therapeutic vaccine could be tested against placebo.

As only 14% of respondents felt that testing the therapeutic vaccine against placebo would not be ethical, there were only 25 responses to question 2, which concerned

non-placebo-controlled alternative designs, summarized in Table 4. Even among this subgroup that believed all the placebo-controlled trials were unethical, 76% indicated that the therapeutic vaccine could be tested, either in an observational trial, or against a different control (i.e. HAART). Thus, in total 97% of respondents agreed that the therapeutic vaccine could be ethically tested in HIV-infected subjects in this resource poor setting, without ensuring that all study subjects receive the best proven therapy.

Income-level or geographic location of the respondent's country of citizenship or the education-level of the respondent did not have a significant effect on whether the respondent was likely or not to endorse a trial design using a placebo control.

Responses to question 3 and 4 are shown in Tables 5 and 6.

Discussion

Almost all respondents to our survey (97%) felt that a therapy that was known to be less effective than the best proven therapy (HAART) could be tested in a clinical trial in which HAART would not be given to HIV-infected participants in the treatment arm, (even when study subjects become sick), when HAART was locally unavailable and unfeasible. Further, the vast majority of respondents (87%) felt that the therapy could be tested against a placebo control, under some circumstances.

There are a number of reasons that this hypothetical trial might have elicited different responses compared to the short-course trials for mother-to-child prophylaxis, since critics of the short-course AZT trials raised additional concerns that do not apply here. These concerns are related to the following claims: 1) that there was pre-trial evidence that short-course AZT might be as beneficial as the full 076 AZT regimen, and therefore the proper trial design might have been an equivalency trial (Lurie and Wolfe 1997, 1998) (i.e. testing short-course against the 076 AZT regimen); 2) that historical controls could have been used; 3) that the proposed short-course therapy would anyway be unaffordable and unfeasible in the developing world (Annas and Grodin 1998). The results of our survey are not relevant to these concerns, but are relevant to the central principle of the critics argument, contested during the revisions of the major ethical guidelines for research on human subjects¹: that universal standards of care should apply in clinical trials regardless of the standards otherwise available to trial participants outside the context of the trial.

While the controversy centered around the need to provide equal treatment for research subjects regardless of the setting, critics of the short-course trials applied this concern mainly to subjects in the control arm (Lurie and Wolfe 1997; Angell 1997), not those in the treatment arm receiving short-course AZT (nor to those receiving single dose nevirapine (Lurie and Wolfe 1999), when this was tested (Guay et al. 1999)). This asymmetric concern is reflected in the current Declaration of Helsinki (World Medical

Association Declaration of Helsinki 2000), which was revised in the midst of the controversy and explicitly privileges the control group to receive the "best current" therapy, but does not specify any required standard of care for the treatment group (see choice B, question 4). A properly articulated ethical principle should presumably apply equally to the control and treatment group.

Indeed, it has been pointed out that if there were an ethical requirement to provide the best proven therapy to research subjects then testing any new therapy might be considered unethical, unless all subjects are simultaneously provided with the best proven therapy (Levine 1999). A less prohibitive interpretation would permit new therapies to be tested only if they are likely to be at least as efficacious as the best current therapy. With such a standard, the testing of short-course AZT or single-dose nevirapine should not have been permitted at all, regardless of the control group, and indeed it is difficult to imagine the testing of these therapies in industrialized settings. Applying the principle of the universal standard of care to the scenario in our survey, testing the "therapeutic vaccine" without HAART would clearly be ethically inappropriate; 97% of respondents, however, endorsed one of the trials testing this "substandard" therapy.

These summary results obscure a considerable degree of variation in the individual responses. Similar to the debate following the mother-to-child transmission trials, there appeared to be more uneasiness among respondents regarding the use of placebos, than the use of a therapy known to be worse than the best current therapy. Indeed, 76% of those who felt that a placebo-controlled trial would be unethical endorsed the testing of this "substandard" therapy, not known to be any better than placebo. Additionally, only about 30% of respondents felt that providing control subjects with placebo alone (plus usual care) would be ethical in this setting. Approximately half of respondents believed medical care not ordinarily available (i.e. antibiotic prophylaxis) was required to make a placebo-controlled trial ethical. Additionally, 21% of respondents endorsed guidelines that appeared to conflict with their selected trial design. Discordance between a respondent's preferred trial design and guideline may indicate the difficulty of abstracting general principles for application to complex cases (even among sophisticated respondents), or it may suggest that, for some respondents, the hypothetical trial represents an "exception to the rule".

This discordance (between the selected trial and the selected principle) is consistent with other evidence that, despite the consistency of the main results, some respondents remain conflicted regarding the dilemma. A few respondents selected trials that are difficult to justify scientifically (e.g. treating the control arm with HAART does not provide any scientifically relevant information and violates the principle of equipoise (Freedman 1987)). And a substantial minority of respondents indicated that the vaccine could be tested as described even in industrialized countries. We hypothesize that these answers may, in some cases, represent cognitive errors resulting from a

strong motivation to (falsely) reconcile the two conflicting terms of the dilemma.

There are several important limitations of this study:

1. We used a convenience sample based on two listservs. However, this sample included a diverse population of informed researchers and would presumably be more representative than opinions expressed in editorial pages, which preferentially reflect those of a very few editors, or which, in the interest of presenting a “balanced” perspective, may systematically over-sample minority opinions.
2. Even if the sample accurately reflects the beliefs of international clinical researchers, this population should not necessarily be the ultimate arbiters of research ethics. Indeed, the beliefs of informed community representatives, especially potential research subjects, government representatives and others are crucial.
3. A true ethical dilemma is by its nature not wholly resolvable (by a survey or otherwise), since it is comprised of (at least) two terms that can not be simultaneously satisfied. Subtle changes in the details of the scenario may alter respondents’ choices.
4. A significant minority of respondents interpreted the trial in such a way that they believed testing this “sub-standard” therapy could be ethical, even in industrialized countries where HAART is routinely available. The trial may have been interpreted as potentially ethical (in both industrialized and resource poor settings) if respondents misunderstood the trial as involving only patient-subjects at very early stages of infection. However, even eliminating the responses of those who interpreted the trial as potentially ethical in industrialized settings does not substantially change the main results. Among the remaining 125 respondents, 96% endorsed a trial testing the therapeutic vaccine and 89% endorsed a trial using a placebo-control.

The broad consensus endorsing the testing of a therapy in a resource poor settings known to be inferior to the best current standard (even among those who believe a similar trial would be unethical in industrialized countries) should not be surprising. As discussed, there were no strong ethical concerns raised in the medical or popular press regarding the use of short-course AZT (unlikely more effective, and potentially less effective, than the current standard) or nevirapine (clearly less effective than combination therapies contemporaneously used routinely in industrialized countries). Meanwhile, controversy regarding the standard of care for the control group has been a matter of deep, and unresolved, contention not only in editorial pages, but also during recent revisions of major international guidelines for biomedical research². If indeed there is consensus that,

under certain circumstances, therapies likely to be less effective than the best proven standards can be tested, than uncovering the ethical principles that underpin such broad agreement and permits the testing of such therapies may be useful in creating guidelines concerning the standard of care for all trial subjects (whether in the treatment or control group).

Conclusion

There is broad consensus that a therapy known to be less effective than the best standard of care can be tested in resource poor settings where the best therapy is normally unavailable and difficult to implement. Further, most also support the use of a placebo-control to test such a therapy in some circumstances. The above findings are consistent across respondents from all geographic areas, regardless of the income-level of the respondent’s country of residence or citizenship. ☺

Acknowledgement of financial support:

This study was supported, in part, by a grant from the John Lloyd Foundation. Dr. Mwamburi is supported by a grant from The NIH - International Training in Medical Informatics (ITMI) (Forgarty Grant No. 5D43TW01083). Dr. Bennish is supported by a Mid-career Investigator Award in Patient Oriented Research from the National Institute for Allergy and Infectious Diseases of National Institutes of Health (1 K24 AI/HDO01671), and by a grant from the Wellcome Trust.

Notes

1. See, for example, various letters by P Lurie and SM Wolfe at www.citizen.org/press, including Letter to J Esparza (UNAIDS), January 15, 1999, Letter to H Shapiro (National Bioethics Advisory Commission), November 13, 2000, and Letter to D Human (World Medical Association) July 31, 2000.

2. Indeed, because of “confusion in the research world” regarding the Declaration’s position on placebo-controlled, the World Medical Association issued a “note of clarification” in October 2001 relaxing its restriction against placebo controls to permit their use, even if proven therapy is available, where there are “compelling and scientifically sound reasons”. www.wma.net/e/policy/17-c_e.html (accessed June 14, 2002). And the Council for International Organizations of Medical Sciences (CIOMS), which has initiated a process of revising their 1993 guidelines on international biomedical research involving human subjects in May of 1999, as of their last posting on January 2002, been unable to resolve the issue; multiple conflicting versions of guideline 11, regarding the use of placebos, appear in the draft version of this document (www.cioms.ch/guidelines_january_2002.html, accessed June 4, 2002).

References

- Angell, M. 1997. The ethics of clinical research in the Third World. *New England Journal of Medicine* 337:847-9.
- Annas, G. J., and M. A. Grodin. 1998. Human rights and maternal-fetal HIV transmission prevention trials in Africa. *American Journal of Public Health* 88(4): 560-3.
- Connor, E. M., R. S. Sperling, R. Gelber et al. 1994. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *New England Journal of Medicine* 331:1173-80.
- Freedman, B. 1987. Equipoise and the ethics of clinical research. *New England Journal of Medicine* 317:141-5.
- Guay, L.A., P. Musoke, T. Fleming et al. 1999. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomized trial. *Lancet* 354:795-802.
- Levine, R. J. 1999. The need to revise the Declaration of Helsinki. *New England Journal of Medicine* 341:531-4.
- Lurie, P., and S. M. Wolfe. 1997. Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries. *New England Journal of Medicine* 337:853-6.
- . 1998. Ethics and international research. Comparison of short and long zidovudine regimens is appropriate. *British Medical Journal* 316:626.
- . 1999. HIVNET nevirapine trials. *Lancet* 354:1816-7.
- Shaffer, N., R. Chuachoowong, P.A. Mock et al. 1999. Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: A randomised controlled trial. Bangkok Collaborative Perinatal HIV Transmission Study Group. *Lancet* 353:773-80.
- Varmus, H., and D. Satcher. 1997. Ethical complexities of conducting research in developing countries. *New England Journal of Medicine* 337:1003-5.

Kent, D. M., M. Mwamburi, R. A. Cash, T. L. Rabin, and M. L. Bennish. 2003. Testing therapies less effective than the best current standard: Ethical beliefs in an international sample of researchers. *The American Journal of Bioethics* 3(2): W28-W33.

Wiktor, S.Z., E. Ekpini, J. M. Karon et al. 1999. Short-course oral zidovudine for prevention of mother-to-child transmission of HIV-1 in Abidjan, Cote d'Ivoire: A randomized trial. *Lancet* 353:781-5.

Wilkinson, D., S. S. Karim, and H. M. Coovadia. 1999. Short course anti-retroviral regimens to reduce maternal transmission of HIV. *British Medical Journal* 318:479-80.

World Medical Association. 1996. *Declaration of Helsinki*. Rev. ed. Somerset West, Republic of South Africa 48th WMA General Assembly, October.

———. 2000. *Declaration of Helsinki*, as amended at the 52nd WMA General Assembly, Edinburgh, Scotland, October. Available from: www.wma.net/e/policy/17-c_e.html.