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The Ethics of Subject Selection for Testing Live-Attenuated HIV Vaccines

JEREMY GRUSHCOW†

Over 30 million people worldwide are infected with Human Immunodeficiency Virus (HIV), the virus that causes AIDS.1 More than 2 million people died of AIDS in 1997 alone, including 39,200 in the U.S. The best long term solution to the HIV pandemic is the development of an effective vaccine. However, vaccine testing must be performed on uninfected subjects, exposing them to uncertain risk and certain adverse social consequences.2 Three subject populations have been proposed for vaccine trials: doctors and health-care workers;3 terminally ill cancer patients;4 and citizens of developing countries.5 This paper considers the ethical merits of using each of these populations at different stages of vaccine testing and concludes that doctors are the most appropriate population for early stages of testing, that populations in developing countries are the

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2. One of the main quandaries posed by HIV vaccine testing is that test subjects will test positive in some or all tests for the virus, and may be subject to discrimination as if they were HIV positive. Chris Collins, Sustaining Support for Domestic HIV Vaccine Research: Social Issues Over the Long Haul of Human Trials, CAPS—Center for AIDS Prevention Studies, Occasional Paper #2 (July 1996) at <http://hivinsite.ucsf.edu/topics/vaccines/2098.2914.html>.


most appropriate for later stages, and that terminal cancer patients are wholly inappropriate subjects.

I. AN HIV VACCINE

A. THE NEED FOR A LIVE-ATTENUATED HIV VACCINE

As one physician has observed, "[i]f we're really going to kick [HIV] in the butt it's going to have to be with a vaccine."6 Despite the publicity generated by effective drug treatments in developed countries,7 a vaccine is superior to drugs. Because antiviral drugs do not fully eradicate HIV infection, but only keep it in check, they require that patients have long-term access to medical care. Unlike antibiotics, which can clear bacterial infections over a short course of treatment, antiviral drugs must be taken continually to prevent a resurgence of the viral infection. Because antiviral drugs must be taken long term, the costs of treatment mount quickly. Furthermore, long-term patient commitment is necessary. In contrast, vaccination often requires only one encounter with health care workers, so the benefits can be realized without a lifetime of medical treatment. Because the vast majority of HIV infected people worldwide will never be able to afford antiviral drug treatment8 and do not have access to the lifelong care such treatment requires, the development of an HIV vaccine is essential to bringing the global spread of AIDS under control.

Vaccines work by introducing the immune system to a virus in a modified form that cannot cause disease. This allows the body to learn to recognize the virus and respond effectively to it in the future.9 Three kinds of modified viruses have been used for vaccination: subunit vaccines, killed vaccines, and live-attenuated vaccines. Neither subunit vaccines nor killed vaccines are likely to be appropriate for clinical use. Subunit vaccines are the safest option because they introduce only a small, impotent portion of the virus. However, a subunit vaccine against HIV is not likely to be effective because HIV is much more variable than most viruses. Consequently, there are now five major and several more minor subtypes of HIV in the world, each of which differs by about 30 percent

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7. The CDC's latest published statistics show the first recorded decrease in the number of AIDS deaths in the U.S. CDC, 9 HIV/AIDS Surveillance Report 3 (mid-year ed 1997). However, the number of people infected with HIV continues to rise, with almost 65,000 new cases reported in the U.S. between June 1996 and June 1997. Id at 5.
8. “For example, Uganda ... [has] ... an annual per capita expenditure on health of $6 ... [compared to] ... the $12,000 to $15,000 annual cost for antiretroviral therapy.” Bloom, 279 Science at 187 (cited in note 5).
9. The immune system protects against future infection in two ways. First, it produces antibodies, which are molecules that bind to and neutralize a virus (“humoral immunity”). Second, the immune system maintains a small reserve of cells that remember the virus and can be multiplied and remobilized to fight a new infection with the virus (“cellular immunity”). It is unclear whether an HIV vaccine will need to induce either a cellular or humoral response, or both, in order to ensure that subsequent exposure to HIV will not result in an infection.
from the others. A subunit vaccine developed to fight against one subtype will not necessarily protect against other subtypes. Furthermore, a subunit vaccine developed against one subtype may not even protect against that same subtype months later due to the rapid mutation rate of the virus. Empirical data so far have supported the prediction that subunit vaccines will not work. Killed vaccines are the next safest alternative. However, the technology does not currently exist to produce a killed HIV vaccine. Given the problems associated with subunit and killed vaccines, a successful HIV vaccine will most likely take the form of a live-attenuated virus.

Live-attenuated vaccines are potentially the most dangerous but have historically been the most effective. The global eradication of Smallpox, and the victories against Rabies, Polio, Measles, Mumps, German Measles, Chickenpox and Shingles, among others, are testaments to the effectiveness of live-attenuated viruses for vaccination. So far, studies using animal models of HIV suggest that live-attenuated vaccines may be the best hope in this case as well. However,


11. "[V]accination with recombinant HIV immunogens induces high levels of antibodies but ... these do not bind to or neutralize the field virus." Safe, Effective AIDS Vaccine Highly Unlikely Within Ten Years, Reuters Health Information (Feb 2, 1998), reporting on Dr. David Baltimore’s keynote address to the 5th Conference on Retroviruses and Opportunistic Infections, at <http://www.ama-assn.org/special/hiv/newsline/conferen/retro98/020298a1.htm>. Furthermore, a summary of data from phase I and phase II trials found that nineteen vaccinated subjects nevertheless acquired HIV-1 infection, compared to four HIV infections among subjects who received a placebo. B.S. Graham, et. al., *Analysis of Intercurrent Human Immunodeficiency Virus Type 1 Infections in Phase I and II Trials of Candidate AIDS Vaccines*, 177 *J Infect Diseases* 310 (Feb 1998); "[W]e conclude that vaccination with rgp120 has had, to date, no obvious beneficial or adverse effects on the individuals we have studied." R.I. Connor, et al, *Immunological and Virological Analyses of Persons Infected by Human Immunodeficiency Virus Type 1 While Participating in Trials of Recombinant gp120 Subunit Vaccines*, 72 *J Virol* 1552 (1998). AIDS Vaccine Evaluation Study Group Results Presented In Vancouver, Reuters Health Information (July 8, 1996) at <http://www.ama-assn.org/special/hiv/newsline/conferen/aids11/708art12.htm>. More recent early stage clinical trials that use more highly immunogenic presentations of HIV subunits are ongoing. These may show more promise than earlier subunit vaccines.

12. Killed virus does not stimulate the immune system to nearly as great an extent as live virus. Therefore, in order to induce protective immunity with a killed vaccine, enormous quantities of virus are required. The cultivation of such quantities of HIV is beyond the ability of current technology.


14. "To date, vaccine approaches based on live attenuated SIV [simian immunodeficiency virus] have exhibited the greatest degree of efficacy and provide opportunities for defining correlates of immune protection." NIH Office of Aids Research (OAR), *General Information, HIV/AIDS-Related Research Program: Vaccines*, (last update Feb 17, 1998), at <http://www.nih.gov/od/oas/OARVACC.HTM>; "Historically and statistically, the vaccines with the best chance of succeeding are live-attenuated vaccines, which use weakened forms of the actual virus. Of the vaccines tested thus far, live-attenuated vaccines have provided the most consistent and broadest protection in SIV-infected monkeys." Deborah L. Shelton *AIDS Vac-
live-attenuated vaccines for HIV are ethically problematic because they risk giving subjects AIDS, which is incurable. A live-attenuated vaccine for HIV also poses a second problem. HIV is a retrovirus, which means that one of its first acts upon infecting a cell is to insert itself into the host cell's DNA where a copy resides permanently. This permanence means that even a successful attenuated vaccine would cause a life-long latent infection with weakened HIV.\textsuperscript{15} This is dangerous for two reasons. First, there is a theoretical possibility that ongoing low level viral replication could contribute to the development of cancer in vaccinated individuals. Second, it is theoretically possible that the integrated viral genome from the vaccine could recombine with virus from a later (accidental) exposure to reconstitute a potent infectious variety. Because both the risks and the benefits of a live-attenuated vaccine are great, such vaccines pose a significant ethical challenge to those responsible for evaluating the safety and efficacy of HIV vaccines.

B. DEVELOPING AN HIV VACCINE

In the U.S., monitoring the clinical trials of vaccines is the responsibility of the Center for Biologics Evaluation and Research (CBER) of the Food and Drug Administration (FDA). This authority was vested in the CBER and its predecessors in response to a dizzying history of abuse of research subjects.\textsuperscript{16} In submitting an application for clinical testing of an "Investigational New Drug (IND),"\textsuperscript{17}...
the sponsor must describe the safety of the manufacturing process, the laboratory (in vitro) and animal (in vivo) testing data, and the qualifications of the investigators.\textsuperscript{18} The FDA mandates three phases of clinical trials to demonstrate both the safety and the efficacy of an IND before it will approve the IND for commercial distribution.\textsuperscript{19}

Phase I and phase II clinical trials are primarily meant to evaluate safety. Phase I trials enroll a small number of (often healthy) subjects to test for safety and, in the case of vaccines, to test for indications that an immune response is being generated.\textsuperscript{20} Phase II trials expand on phase I data, optimize dosage regimens, and may compare the immunogenicity of different vaccines.\textsuperscript{21} Preliminary indications of efficacy in phase II are compared with cumulative data on safety and short-term side effects in order to decide whether to proceed to phase III. Phase III trials enroll large numbers of subjects to determine the efficacy of the IND and, in the case of vaccines, requires subjects who are at risk for the disease. Phase III trials for vaccines require several thousand participants.\textsuperscript{22}

With close to 16,000 people being infected with HIV every day,\textsuperscript{23} some have argued that "[f]ailing to proceed [with HIV vaccine development and testing] is unethical and violates basic human rights (emphasis added)."\textsuperscript{24} However, there is a competing ethical obligation to protect research subjects (and the public) from dangerous or ineffective products. In deciding whether and when to begin the clinical trials required by the FDA, research sponsors must be guided by the ethical framework set out in the Belmont Report.

\textbf{II. THE BELMONT REPORT}

The Belmont Report was prepared by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1979.\textsuperscript{25} The Commission was created by the National Research Act in 1974,\textsuperscript{26} and was

\textsuperscript{18} Id (citing 21 CFR 312 (1992)).
\textsuperscript{19} Id at 895.
\textsuperscript{21} Id.
\textsuperscript{22} The first planned phase III trial for an HIV vaccine is currently underway using 5,000 volunteers in the US and a further 2,500 in Thailand. Michael Balter, \textit{Impending AIDS Vaccine Trial Opens Old Wounds}, 279 Science 650, 650 (Jan 30, 1998).
\textsuperscript{23} UNAIDS and WHO \textit{Report on the Global HIV/AIDS Epidemic}, text accompanying Figure 2 (cited in note 1).
\textsuperscript{26} Grady, \textit{The Search for an AIDS Vaccine} at 41 (cited in note 16).
charged with formulating the "basic ethical principles that should underlie the conduct of research involving human subjects, and ... guidelines to assure that such principles are followed."27

The Belmont Report identifies three principles: autonomy, beneficence and justice. These principles were incorporated into the Department of Health and Human Services' (DHHS) regulations in 1981. By 1991, the DHHS regulations had become the basis for regulation of research on human subjects throughout the federal government's intra- and extramural research programs.28 The principle of respect for persons translated into the policy of informed consent29 and into special protection for vulnerable populations;30 beneficence into risk/benefit analysis;31 and justice into a policy of appropriate subject selection to ensure equitable distribution of the risks and benefits of research.32 The Belmont Report principles are challenged in new ways by the AIDS pandemic, and by proposals to test preventative HIV vaccines.

A. AUTONOMY

The principle of autonomy reached its ascendancy in 1947, in the Nuremberg Code. This document, which comprised part of the judgment at the Nazi Doctors' Trial,33 placed the principle of informed consent above all other considerations. Whereas other provisions in the Code leave room for balancing priorities, the consent provision is absolute: "[t]he voluntary consent of the human subject is absolutely essential."34 Likewise, the Belmont Report's concern for autonomy is manifested in its requirement that a research subject give his "informed consent" to participate in a clinical trial.35

The current standard of informed consent for a particular clinical trial depends on two factors: the risk of the proposed experiment,36 and the capacity of the proposed subject to freely and deliberately assume the risks of the trial.37 Because of the uncertain but large risk associated with live-attenuated vaccine trials, a high level of autonomy must be demanded from all subject pools. A subject's autonomy can be assessed by monitoring three elements: information, comprehension, and voluntariness.38 The information must be provided "in language

30. 56 Fed Reg 28003, 28016 (§111(b)).
31. 56 Fed Reg 28003, 28016 (§111(a)(2)).
32. 56 Fed Reg 28003, 28015-16 (§§111(a)(1)(ii), 111(a)(3)).
36. Id at 11.
37. 56 Fed Reg 28003, 28016 ) (§116) (cited in note 29).
understandable to the subject, and the subject must be given “sufficient opportunity to consider” the information. A subject gives voluntary consent when he is “free of coercion or undue influence.” Each population’s capacity to make autonomous decisions about whether to participate in an HIV vaccine trial must be assessed separately.

The task of assuring subject autonomy for HIV vaccine trials may be more onerous than for other types of research because of the complexity of the subject matter. A recent empirical study of the willingness of high risk subjects to participate in phase III HIV vaccine trials identified several relevant issues. First, the study found that 37 percent of the men were initially certain of their willingness to participate in vaccine trials; but that one year later, almost half of them had changed their minds. This finding reveals the importance of allowing subjects sufficient time to consider the information presented; and suggests that the amount of time necessary to reach an autonomous decision may be considerably longer than is typically allowed. Disturbingly, the study also found a correlation between continued willingness to participate and lower levels of education. Furthermore, anecdotal evidence suggests that information about risks needs to be fully and carefully presented, even to highly educated subjects. For example, one physician volunteering for phase I HIV vaccine trials admitted, “I have this kind of Hollywood fantasy that, as a result of this clinical trial, someone is going to do something and have an ‘Ah-hah!’ moment that’s going to make the big difference.” Similarly, a volunteer at the AIDS Vaccine Evaluation Unit at the University of Washington explained his willingness to participate in HIV vaccine trials as follows: “I thought about how polio vaccine was developed, how those volunteers might have felt. I thought this would be a landmark study to be involved with.” Anyone with knowledge of the polio vaccine’s development would feel only terror at the prospect of participating in a repetition of that process. When large-scale trials of the first polio vaccines were undertaken in 1936, there was not adequate data on the safety or immunogenicity of the vaccines. Many of those inoculated developed paralysis, often in the inoculated limb. A further 260 cases of polio were caused by unsafe manufacturing of the vaccine at the Cutter plant in 1955. Of course, informed consent does not nec-

40. Id.
43. Id at 112.
44. Id at 110, 113.
46. AIDS Vaccine Evaluation Unit (AVEU), University of Washington, In Their Own Words—The Volunteers Speak (1996) at <http://weber.u.washington.edu/~vaccine/pages/InTheirOwnWords.html>.
47. Frederick C. Robbins, M.D., Polio—Historical, in Plotkin and Mortimer, eds, Vaccines 137, 137-8 (cited in note 13).
48. Id at 140.
essarily include an understanding of the history of vaccination. However, vaccine trials do present unique hazards which must be properly explained. Care must be taken to avoid overestimating the capacity of potential subjects to appreciate the consequences of participation.

B. BENEFICENCE

The second Belmont Report Principle, the principle of beneficence, is as old as medicine. Physicians taking the Hippocratic oath must swear the following: “I will follow that system of regimes which, according to my ability and judgment, I consider for the benefit of my patients, and abstain from whatever is deleterious and mischievous.” This oath has been called the “golden rule” of the medical profession.

A literal interpretation of the Hippocratic oath became problematic with the advent of vaccines. Jenner’s experiments with the cowpox virus in 1798 caused his subjects mild illness, and the occasional deaths following Pasteur’s inoculation of patients with live-attenuated rabies virus in 1885 were viewed as medical murder. Nevertheless, the vaccines that resulted from these experiments prevented countless deaths. A new concept of “public health” emerged sometime between Jenner and Pasteur, which embodied Jeremy Bentham’s relatively new philosophy of utilitarianism. In a modern interpretation of the Hippocratic maxim, the Belmont Report acknowledges that “even avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm.” The principle of beneficence now means ensuring that “[r]isks to subjects are reasonable in relation to ... the importance of the knowledge that may reasonably be expected to result.”

While an HIV vaccine has enormous potential for societal benefit, the substantial risks to trial subjects “carry special weight” under the Belmont Report’s beneficence principle. Foremost among these risks is the likelihood that participants in live-attenuated HIV vaccine trials will test positive in most, if not all, commercially available HIV tests. This presents a risk of social harm equal to that of actually having HIV. This risk can be minimized by providing verification of the subject’s participation in the trial and of their (hopefully) negative HIV status. In the future, this risk may be eliminated by the widespread applica-

49. An excellent discussion of the specific information which should be provided in informed consent documents in vaccine trials can be found in OTA, Adverse Reactions to HIV Vaccines (cited in note 20).
51. Id.
54. 56 Fed Reg 28003, 28015-6 (§111(a)(2)) (cited in note 29).
56. OTA, Adverse Reactions to HIV Vaccines at 52 (cited in note 20).
57. Id at 53.
tion of testing methodologies that can reliably differentiate between vaccinated and infected subjects.

A second risk to potential subjects is the difficulty of identifying a useful and safe trial endpoint. In the case of an influenza vaccine, the endpoint is the clinical manifestation of flu symptoms, and the subsequent determination of the exact nature of the infectious agent. Waiting for symptoms of AIDS to manifest themselves is an ethically unacceptable method of monitoring the effectiveness of an HIV vaccine. Current standards of care in the U.S. mandate aggressive antiviral treatment at the first sign of HIV infection. Because subjects cannot presently rely on commercially available methods of testing, the trial sponsor must proactively test for super-infection by naturally occurring strains of HIV throughout the patient’s life.

Aside from these benefits and risks, which apply to all HIV vaccine trials, each potential subject population will be subject to unique risks and benefits. Therefore, a risk/benefit analysis must be applied to each population separately.

C. JUSTICE

The third principle identified by the Belmont Report, the principle of justice, requires “that there be fair procedures and outcomes in the selection of research subjects.”58 In order to ensure that subjects are selected fairly, the selection process “needs to be scrutinized in order to determine whether some classes ... are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied.”59 Vaccine research in particular has often been conducted on impoverished populations in developing countries.60 Such instances have caused concern that the development of anti-HIV therapies could lead to the unjust “exploitation of those with the least access to health care.”61 Regardless of the population that is ultimately selected, the sponsor of the trial must provide any product that results from the research to the community which

59. Id at 9-10.
60. The first large-scale field trial of a typhoid vaccine took place in 1896 using four thousand volunteers from the Indian army at a time when there remained great controversy over the vaccine’s use in Britain. Waldemar Haffkine, faced with an outbreak of the plague in Bombay in 1897, produced a killed plague vaccine and inoculated himself and 8,000 other people. In 1968, after its approval for use in Japan, but before it was licensed in the U.S., the Centers for Disease Control conducted large-scale trials of a vaccine against Japanese encephalitis virus in Northern Thailand. In 1977, small-scale trials of a typhoid vaccine were carried out on a volunteer group in the U.S., followed by large-scale trials in Egypt in 1982, and in Chile in 1987. Plotkin and Plotkin, A Short History of Vaccination, 1, 4-7 (cited in note 52).
hosted the trial. In this way, the benefits of the research will be assured to the community that bears the burden of the research.62

D. CONFLICT BETWEEN THE PRINCIPLES OF AUTONOMY AND JUSTICE

The most significant challenge for HIV vaccine testing is the conflict between the requirements of autonomy and the requirements of distributive justice. This problem arises only in the context of testing treatments for preventable diseases such as AIDS. A subject who adequately understands and appreciates the risks of HIV infection will be more likely to use adequate safeguards or abstain from engaging in high risk activity. This is demonstrated by the falling HIV infection rates in Uganda which have resulted from “open and concerted” education efforts.63 As autonomous agents, such subjects are ideal for vaccine trials. However, subjects who use adequate safeguards and abstain from high risk activity will probably never need a vaccine. Since such subjects will never benefit from the research, it is unjust to impose the burdens of vaccine testing on them.

The problem extends beyond ethical concerns of justice. Subjects who completely avoid risk of infection are scientifically useless for evaluating the efficacy of a vaccine. When vaccine testing is done on animals, researchers intentionally challenge vaccinated animals with the live virus to test the protective capability of the vaccine. If the vaccine has worked, the animal will remain healthy. If the vaccine has failed, the animal will get the disease. In human vaccine testing, of course, vaccinated subjects cannot be intentionally challenged with live virulent HIV. Instead, studies must compare the number of HIV infected individuals in placebo and vaccinated groups. The lower the incidence of HIV infection in the overall population of subjects, the larger the enrollment needs to be in order to yield statistically significant results regarding the efficacy of the vaccine. In a completely autonomous population that safeguarded itself against infection, it would be impossible to evaluate vaccine efficacy. However, no population is so completely rational. Each potential pool of subjects is exposed to HIV with some frequency. Analyzing the suitability of a subject pool for vaccine trials requires an evaluation of the relative weight of autonomy and justice concerns in that population.

62. Although there is wide agreement that the research sponsor should provide the benefits of the research to the communities that participated in the trial, there is a great deal of controversy about the details of how and to what extent this should be done. For example, how broadly is community defined? Should products be provided free, or at reduced cost? For how long? These questions are beyond the scope of this paper.

III. PROPOSALS FOR SUBJECT SELECTION

By applying the principles of autonomy, beneficence, and justice, the following section will show that ethical imperatives can be satisfied for all phases of vaccine testing. Three populations have been proposed for testing a live-attenuated HIV vaccine. The International Association of Physicians in AIDS Care (IAPAC), in conjunction with Dr. R. Desrosiers and Therion Biologics Corp., have proposed phase I safety testing on physicians and health care workers. Dr. J. Sullivan has proposed using terminal cancer patients with untreatable solid tumors for phase I trials. Finally, citizens of developing countries, notably Thailand and Uganda, are currently hosting phase III trials of subunit vaccines, and are likely candidates for testing a live-attenuated vaccine.

A. PHYSICIANS

Physicians are ethically the most appropriate pool of subjects for phase I safety trials of live HIV vaccines. Physicians already involved in AIDS treatment are nearly ideal candidates when it comes to satisfying the requirements of the principle of autonomy. As in any HIV vaccine trial, the potential for great benefit to society merits strong consideration under the principle of beneficence. However, no interpretation of distributive justice comes out in favor of using physicians as subjects in the trial, since physicians face a greater risk of HIV infection from the trial than from their normal occupation. The tradeoffs between autonomy and justice suggest that the participation of physicians be restricted to phase I testing.

According to the Belmont Report, "there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension, and voluntariness." While physicians involved in AIDS care are already well informed about the consequences of infection from a live vaccine, the knowledge required to treat patients is distinct from a knowledge of the science behind the vaccines being proposed. Therefore, physicians will need to be educated about the nature of the vaccine and the degree of risk associated with the trial. The unique advantage of physician subjects is their manifest ability to comprehend the information at a high level. The Belmont Report identifies

65. Id. Many of the arguments that apply to terminal cancer patients also apply to death row inmates: since they will die in any case, vaccine testing will not really harm them. However, the additional risk of coercion in the prison setting makes death row inmates particularly unsuitable candidates.
“intelligence, rationality, maturity and language” as requisite traits for comprehension. Not only are these traits job requirements for physicians, but their strengths in these areas are directly related to their ability to comprehend the type of information likely to be presented in informed consent documents for an HIV vaccine trial. Physicians are as near to ideal participants as is possible as far as information and comprehension are concerned.

Voluntariness, however, is as difficult an issue for physicians as it is for any other subject pool. The IAPAC, which is calling for volunteers to participate in the trials, has characterized participation in vaccine trials as a “moral imperative,” and emphasized that “[t]here are millions of lives at stake.” These are strong words that have particularly great resonance for physicians in general, who are sworn to protect lives, and for AIDS physicians in particular, who are acutely sensitive to the social and moral problems associated with HIV. Dr. Mike Youle, director of HIV clinical research at the Royal Free hospital in London and a trial volunteer, says “[o]f course I am putting myself at risk and so will any other volunteers, but I think there is a certain moral imperative to do this.” The Belmont Report warns that “[u]njustifiable pressures usually occur when persons in positions of authority or commanding influence ... urge a course of action for a subject.” Among individuals in a peer group of physicians, no one possesses authority to a degree that should trigger concern. However, a “commanding influence” is exerted when a professional organization as a whole takes a stance. It is important to distinguish the laudable altruism of physician-subjects from decisions that may have been induced by “undue influence.” It would be possible to ameliorate this problem by disqualifying members of IAPAC from participation in trials sponsored by their organization. While other physicians might initially be less familiar with the risks of the trial, they are equally competent to comprehend and accept those risks. However, such a rule would exclude some of the best informed subjects, many of whom would probably volunteer even in the absence of external influences. A less drastic solution might be to appoint a consent auditor for the trial in order to provide some extra protection for the participants. In any case, careful subject selection from among the physician volunteers could allay concerns about voluntariness. Once these concerns have been addressed, trials on physician subjects will meet the requirements of the ethical principle of autonomy.

To determine whether a trial satisfies the ethical principle of beneficence, the risks of the trial must be weighed against the benefits. In the case of a live-attenuated vaccine, there is a risk that the vaccine will actually cause AIDS or cancer over the lifetime of the subject. According to the Belmont Report, the

69. Id at 12.
"manifest voluntariness" of the subject is an acceptable counterweight to high levels of risk under the principle of beneficence. The Nuremberg Code even allows for the possibility of experiments that carry a risk of "death or disabling injury ... in those experiments where the experimental physicians also serve as subjects." This is not an abstract proposition in the history of vaccine research. Waldemar Haffkine was his own first subject when he developed a killed vaccine for the plague in India in 1897. In 1987, Dr. Daniel Zagury injected himself with the first HIV vaccine tested on humans. Thus, the strength of the informed consent that physicians can provide mitigates some of the risks involved in being a subject in an HIV vaccine trial.

Under the principle of beneficence, we are instructed to look not only at the risks and benefits to the individual patient, but also to "the importance of the knowledge that may reasonably be expected to result." In the case of physician-subjects, there is almost no possibility of direct benefit to the individual subjects. Therefore, the analysis for this patient population depends on whether the benefit to society justifies the risk to individual subjects. In the 1994 edition of Vaccines, Susan and Stanley Plotkin argue that:

[The impact of vaccination on the health of the world's peoples is hard to exaggerate. With the exception of safe water, no other modality, not even antibiotics, has had such a major effect of mortality reduction and population growth.]

In a utilitarian calculation, the potential benefit of preventing over two million deaths a year carries heavy weight. This benefit, in combination with the "manifest voluntariness" of the subjects, outweighs the considerable risk associated with phase I trials of live-attenuated vaccines. Therefore, the risk/benefit calculation comes out in favor of using physicians as subjects.

It is the third Belmont principle, justice, that presents a particular challenge to the use of physicians as vaccine trial subjects. The principle of justice demands that "research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research." Aside from their exposure at work, there is no reason to think that physicians are at any higher risk of acquiring HIV than members of comparable demographic groups. In the entire history of HIV in the U.S., only 114 health care workers have ever acquired HIV through occupational transmission. This is because the

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73. Id at 17.
75. Plotkin and Plotkin, A Short History of Vaccination, 1, 4 (cited in note 52).
77. 56 Fed Reg 28003, 28015-6 ($111(a)(2)) (cited in note 29).
78. Plotkin and Plotkin, A Short History of Vaccination at 1 (cited in note 52).
80. Fifty-two of these cases have been documented and confirmed. The remaining 62 have not been proven, but "[these health care workers have been investigated and are without identifiable behavioral or transfusion risks; each reported percutaneous or mucocutaneous occupational exposures to blood or body fluids, or laboratory solutions containing HIV." 9 HIV/AIDS Surveillance Report at 15 (table 11, 3) (cited in note 7).
use of universal precautions for sterility in medicine has effectively prevented infection of health care workers on the job. Therefore, physicians are unlikely to benefit directly from the development of a vaccine.

The problem of justice is not insurmountable. The Belmont Report requires only that “research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research (emphasis added).” The inclusion of the modifier “unduly” suggests that some mismatch between benefits and burdens is acceptable when the benefits of the research are substantial. The main focus of the Belmont Report’s discussion of justice is the protection of vulnerable populations such as prisoners and the poor, who have historically been exploited as research subjects. Certainly, the principle of justice was not elaborated in the Belmont Report for the purpose of protecting physicians. Furthermore, while the Belmont Report assigns no priority to its three principles, one could argue that the acceptability of physicians with respect to the principles of autonomy and beneficence outweigh their inappropriateness with respect to the principle of justice. By this analysis, physicians are excellent candidates for phase I clinical trials of vaccine safety and immunogenicity. However, because of their low baseline rate of infection, physicians are not scientifically useful for phase II or phase III trials, which require rates of infection high enough to test the efficacy of the vaccine in a reasonably sized cohort.

B. TERMINAL CANCER PATIENTS

Terminal cancer patients are not ethically acceptable subjects for HIV vaccine trials. Traditionally, terminal patients have been regarded as poor subjects from the standpoint of autonomy. Patients facing death may be easy targets for coercion and may be unduly influenced to cling to improbable hope. However, these undue influence concerns are absent in the case of HIV vaccine trials. Nevertheless, cancer patients are unacceptable subjects from the standpoint of beneficence because of the possibility of hastening their deaths. Furthermore, by participating in HIV vaccine trials these patients will be unsuitable subjects for experimental cancer protocols. Finally, the principle of justice argues that terminal cancer patients should not be used in HIV vaccine trials because they will not benefit from the research.

Cancer patients raise two concerns about the ability of research subjects to make autonomous decisions. First, the absolute dependence of the patient on his physician makes almost any suggestion by the physician coercive. As one commentator explains:

When “informed consent” is obtained, it is not the student, the destitute bum, or the prisoner to whom, by virtue of his condition, the thumb screws of coer-

Second, there is a degree of desperation that (legitimately) accompanies a terminal illness and that may interfere with the ability of the patient to comprehend his situation and the possible consequences of a proposed trial. However, when asking a terminal patient to participate in research for another illness, it is likely that both of these concerns can be minimized. It is unlikely that a cancer patient’s oncologist will also be an investigator for a clinical trial of an HIV vaccine. Therefore, the oncologist could legitimately reassure her patient that his care would not be affected by his decision. Furthermore, it is clear even to the most desperate cancer patient that no clinical benefit will come to him from participation in an HIV vaccine trial. Therefore, the only consideration which could motivate a terminal cancer patient to participate in such a trial would be altruism. This is a legitimate motive for any person of sound mind, and is in some ways similar to the risk we allow otherwise healthy kidney donors to assume for the benefit of others. Therefore, terminal cancer patients are acceptable subjects for HIV vaccine trials from the standpoint of autonomy.

The most common argument in favor of using terminal patients for clinical trials of any sort is that they have “nothing to lose.” If this were true, HIV vaccine trials for terminal cancer patients would fall under the “minimal risk” exemption of the DHHS regulations. The Supreme Court rejected a similar argument in 1979 in *United States v Rutherford*, based on the fact that “with diseases such as cancer it is often impossible to identify a patient as terminally ill except in retrospect.” A patient who recovered from their cancer because of a new treatment or an unexplained remission would face a small risk of a second terminal illness from the HIV vaccine. Even in the case of a correctly diagnosed terminal patient, there is a small risk that damage to their immune system caused by the vaccine would hasten their death. Most importantly, enrollment in a clinical trial for an HIV vaccine causes harm to terminal cancer patients by disqualifying them from participation in clinical trials of experimental cancer therapies. The only aspect of the risk/benefit analysis which weighs in favor of

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83. Of course, the benefit in the case of organ donation is direct and tangible compared to the more abstract benefit gained from some unquantifiable progress in the fight against AIDS.
84. 56 Fed Reg 28003, 28013 (§102(1)) (cited in note 29).
85. 442 US 544, 551 (1979). Based on the FDA guidelines in force at the time, the Supreme Court held that there was no exception to the safety and efficacy requirements even for terminally ill cancer patients seeking access to the experimental drug Laetdle.
87. The pace at which new treatments are developed means that the definition of “terminal” is fluid, and provides a poor basis for subject selection. For example, Dr. Sullivan proposed using “terminal cancer patients with untreatable solid tumors” in 1997. *Proposed Live HIV Vaccine Trials*, 12/1/97 AVAB, 1997 WL 9577778 (cited in note 4). This is precisely the type of patient who would have been considered terminal at the time of Dr. Sullivan’s proposal, but would now be considered an excellent candidate for trials of new anti-angiogenic compounds.
using terminal cancer patients is that they are already subject to medical interventions. Therefore, travel to the hospital, injections, and taking of blood samples, which would be substantial burdens for healthy patients, would not significantly change a terminal cancer patient’s normal routine. These risks are not balanced by any benefits, because there is no possibility that the cancer patients will experience any direct benefit from the HIV vaccine.

Finally, cancer patients are unsuitable subjects for an HIV vaccine trial according to the principle of distributive justice. Since they are in a hospital environment, terminal cancer patients are at very low risk for becoming infected with HIV. Therefore, they are poor vaccine trial subjects under the principle of distributive justice. Also, as low risk subjects, terminal cancer patients are scientifically inappropriate for phase II or phase III clinical trials.

For phase I trials, terminal cancer patients have a slight advantage over physicians under the principle of autonomy because they are largely free from undue influence or coercion in trials not related to their illness. However, their capacity to understand the informed consent material will likely be substantially less than that of physicians and they likely cannot be allowed sufficient time for reflection. Furthermore, the participation of terminal cancer patients in HIV vaccine trials risks hastening their death, and precludes their participation in potentially beneficial cancer therapy trials while providing no direct benefit to them whatsoever. Finally, because they are at low risk of acquiring HIV, the principle of justice also dictates that terminal cancer patients are inappropriate subjects for any phase of HIV vaccine testing.

C. CITIZENS OF DEVELOPING COUNTRIES

The population ethically and scientifically best suited for larger scale trials is a population of subjects from developing countries with a high incidence of HIV infection. Current guidelines for international research require that the principles of respect for persons, beneficence, and justice guide experimentation in developing countries. The controversy surrounding trials in developing countries is fueled by desperate calls to relax these ethical guidelines in response to the magnitude of the AIDS pandemic. Opponents of these trials fear ethical relativism and claim that “[t]he refusal or disinclination of populations in developed countries to enroll in studies should serve notice that they are equally unaccept-

88. “Risks to subjects are minimized ... by using procedures already being performed on the subjects for diagnostic or treatment purposes.” 56 Fed Reg 28003, 28015 (§11(a)(1)(ii)) (cited in note 29).
90. Bloom, 279 Science at 186 (cited in note 5); Edward Mbidde, Bioethics and Local Circumstances, 279 Science 155, 155 (Jan 9, 1998).
able in the developing world.” However, both of these opinions ignore the possibility that different outcomes in different countries can still be legitimate under the Belmont Report’s normative principles. First of all, citizens of developing countries have demonstrated their autonomy by their capacity to understand and act on information about HIV. Second, risk/benefit calculations that take local circumstances into account can determine whether a trial in a particular developing country satisfies the principle of beneficence. Finally, the principle of distributive justice argues strongly in favor of conducting vaccine trials in developing countries with a high incidence of HIV, since citizens of those countries stand to benefit most from the knowledge and products that result. Where adequate medical and ethical safeguards are taken, developing countries provide the best testing grounds for phase III determinations of vaccine efficacy.

One of the common objections to clinical trials performed on citizens of developing countries is that such populations will be unable to meet the requirements of the principle of autonomy. Proponents of this argument point out that citizens of developing countries are more vulnerable than citizens in developed countries, and that tribal interests take priority over individual rights in most African systems of customary law. These arguments are specious and paternalistic. The success of public health campaigns in reducing the number of new HIV infections in Uganda indicates that developing countries are capable of disseminating relevant information, and that their citizens are capable of understanding, processing, and acting on such information. Furthermore, community-mindedness is a major motivation for volunteers in vaccine trials throughout the developed world, and does not per se indicate a deficiency in information, capacity, or voluntariness.

Beneficence and non-maleficence arguments provide the strongest case for phase III trials in developing countries. A subject that is at high risk of becoming infected with HIV will receive substantial beneficial effects even from a vaccine that is only partially protective. The beneficial effects of a treatment can be conceived of as being composed of two variables: the magnitude of the benefit, and the probability of the benefit. The probability of the benefit depends on the probability that the vaccine will be successful and on the probability that a given subject will be exposed to HIV. Taking magnitude and probability into account yields a value that reflects the expected benefit of the treatment to an individual.
subject. This approach to evaluating the beneficial effects of a treatment mirrors the risk calculation component of the beneficence analysis. As the Belmont Report points out, the term risk commonly refers "both to the chance (probability) of experiencing a harm and to the severity (magnitude) of the envisioned harm." Furthermore, an expected benefit approach to analyzing the beneficial effects of a treatment is justified by the Belmont Report's admonition that "the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible."

In the case of a drug that is given to a person who has been diagnosed with a particular illness, the probability of exposure to the illness is one; that is, the patient definitely has the illness and will definitely benefit from any protective effect of the drug. Therefore, the beneficial effect of the drug can be described simply by quantifying the probability of success of the drug. In the case of a vaccine, the beneficial effect can only be fully characterized if both the probability of success and the probability of exposure are taken into account. Thus, in evaluating the beneficial effect of a vaccine on a particular subject, we must take into account both the effectiveness of the vaccine and the likelihood that the subject will be exposed to the pathogen. Therefore, the more prevalent the disease, the greater the beneficial effects of the vaccine. For example, a subject who bears a 40 percent risk of contracting HIV by virtue of belonging to a high risk population will receive a 28 percent beneficial effect from a vaccine that is 70 percent effective in protecting people from contracting HIV. This means that if a subject is vaccinated, he will have a 28 percent chance of being exposed to HIV but not contracting it. Even if the vaccine carries a 1 percent risk of giving the subject HIV, the total chance of the subject getting HIV is reduced.

98. This conception of beneficial effect can be described by the following equation:

\[
\text{beneficial effect} = \text{expected benefit} = (\text{magnitude of benefit}) \times (\text{prob. of benefit})
\]

99. Belmont Report at 15 (cited in note 25). The risk calculation can be depicted as follows:

\[
\text{risk} = \text{expected harm} = (\text{magnitude of harm}) \times (\text{prob. of harm})
\]

100. Id at 16.

101. This explains, for example, why Thai authorities have authorized phase III trials of subunit vaccines that showed no preliminary evidence of effectiveness in phase I and II trials in the U.S. The risk of the subunit vaccines has been proven to be minimal in phases I and II. Whereas a protective effect too small to be detected in phase II provides small incremental benefit to U.S. populations, the incidence among some communities in Thailand is so high that even a tiny protective effect translates into significant numbers of lives saved.

102. This result is reached by plugging the risk of being exposed to HIV and the effectiveness of the vaccine into the equation set out in footnote 97 as follows:

\[
\text{beneficial effect} = 70\% \times 40\% = 28\%
\]

Because of the availability of epidemiological data, this type of calculation will often be fairly easy to carry out. Note that the magnitude of the harm of contracting HIV and the magnitude of the benefit of avoiding HIV are the same. Because these magnitudes appear on both sides of the risk/benefit analysis, they cancel each other out and so the magnitude variable can be ignored.

103. This risk would be unacceptably high in the U.S., since the overall prevalence of HIV in the U.S. is approximately 0.1 percent. A one percent risk of getting HIV from a vaccine would be ten times higher than the risk of getting HIV with no vaccine at all.
from 40 percent to 13 percent.\textsuperscript{104} Because the beneficial effects of a trial increase with the incidence of HIV in the population, high-risk populations in developing countries will often be ideal for HIV vaccine trials.

There is a problem with this analysis. The beneficial effect of a vaccine to subjects in developing countries depends on the subjects being at high risk for HIV. However, ethical considerations require that we take every possible measure in parallel with vaccination to ensure that subjects take action to avoid infection. If these measures, such as public education, really matched prevention efforts in developed countries, they should be able to reduce infection rates in the developing country to the rates observed in the sponsoring nation. However, there is a point at which continued education by the sponsor will reduce the number of new HIV cases in the subject population less than the reduction expected from the vaccine. At this point, the incidence of HIV infection in the developing country might still be higher than in the sponsoring country, but the sponsors can be said to have adequately met their ethical obligation to educate the subjects.

Trials of HIV vaccines in developing countries are also strongly supported by arguments of distributive justice. Trial subjects come from high risk populations, so it is appropriate to ask them to bear the burden of participating in research trials. Their participation, however, imposes an obligation on the part of the sponsor “to make vaccine available to the community in which the trial was conducted ... for free or at cost” at the conclusion of the trial.\textsuperscript{105} Furthermore, there is an ethical and scientific imperative to perform vaccine trials with virus subtypes appropriate to those prevalent in the subject population.\textsuperscript{106} These procedures ensure that, having borne the burden of participation, the host community shares in the benefits that result.

Even according to the rigorous standards of the Belmont Report, phase III vaccine efficacy trials in developing countries are ethical. The 1993 CIOMS guidelines advocate “applying ethical standards in local circumstances.” In the case of using subjects from developing countries, such application reveals a very powerful beneficence argument that is unique to populations with a high incidence of HIV. Furthermore, the justice of performing trials on a population that stands to benefit greatly from the resulting vaccine is attractive. Finally, concerns about the vulnerability of citizens of developing countries are paternalistic, and ignore the existence of sophisticated mechanisms for scientific and ethical review which are in place in the countries participating in vaccine efficacy trials.\textsuperscript{107} The same characteristics that make developing countries appropriate hosts for phase III trials also make them appropriate hosts for phase II trials.\textsuperscript{108}

\textsuperscript{104} Thirteen percent is the chance that the vaccine failed to protect against environmental exposure (40% - 28% = 12%) plus the chance that the vaccine gave the subject HIV (1%).
\textsuperscript{105} OTA, \textit{Adverse Reactions to HIV Vaccines} at 75-76 (cited in note 20).
\textsuperscript{106} Id at 73 (cited in note 20).
\textsuperscript{107} Mbidde, \textit{Bioethics and Local Circumstances}, 279 Science at 155 (cited in note 90).
\textsuperscript{108} Bloom, \textit{Bioethics and Local Circumstances}, 279 Science at 188 (cited in note 5).
IV. CONCLUSION

This paper considered the appropriateness of three subject pools for testing live-attenuated HIV vaccines. Each population was evaluated for its suitability according to the three Belmont Report principles: autonomy, beneficence, and justice. This analysis revealed that physicians are the most suitable subject population for phase I trials because of their great capacity to make autonomous decisions. Terminal cancer patients are unacceptable for any phase of HIV vaccine testing because their participation would preclude their participation in cancer treatment trials; therefore, trials involving terminal cancer patients do not meet the requirements of beneficence. Finally, citizens of developing countries are the most appropriate populations for phase II and phase III trials because the expected benefit of such trials will be relatively high due to the prevalence of HIV in these populations.