
HIV VACCINES AND THE COMMUNITY

The Community Advisory Board Bulletin

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HAPPY HOLIDAYS

Bioethics Continued...

CAB Member Perspectives

In the last issue, we began reviewing and discussing some of the ethical issues that relate to HIV vaccine research and trials. We looked at the issue of externally sponsored research, and we touched on the issue of care provided to participants and what the UNAIDS guidelines suggest. In this issue, Rose McCullough, HVTN Global CAB member, and Luis Santiago, New York Blood Center CAB member, will help us to understand some of the ethical issues raised by the latest revision to the Helsinki Declaration.*

A look at the impact of the recent revisions to the Declaration of Helsinki

By Rose McCullough
HVTN Global CAB member

The World Medical Association (WMA) amended the Declaration of Helsinki in October 2000 after three years of discussion and debate. The impact of these changes on HIV vaccines trials remains unclear. The changes tighten the rules for clinical research and put new limitations on the risks to which patients may be exposed. The changes reduce some of the ambiguity in the earlier guidelines and may force changes in the design of future drug trials. Critics say that the changes are at odds with current common practices and are at odds with FDA requirements for placebo controlled trials for licensure.

The Declaration of Helsinki, a very important set of guiding principles for the ethical conduct of research, has no legal authority in the United States or elsewhere, and the practical effect the changes may have on medical research globally is not clear. The Federal Drug Administration (FDA) and the Office for Human Research Protections (OHRP) are currently reviewing the new language to determine how they will react to it. This is key for the effect on research funded by the US government.

The review that led to the recent changes began, in part, because of the controversy that arose over the use of placebo controlled studies to find inexpensive and easy ways to reduce the spread of HIV from pregnant women to their babies. The Declaration's original language contained a phrase suggesting that placebo use

A QUICK QUIZ

Take this fun little quiz to assess your knowledge

1. How many years have HIV vaccines been tested in humans?
2. What is a *clade*?
3. Has the HVTN begun a Phase III trial in humans yet?
4. True or False: The HVTN is researching therapeutic HIV vaccines?
5. What is a *cohort*?
6. How many trial sites are in the network?
7. What is the CAB PWG?
8. Who funds the HVTN research?
9. True or False: A protocol may be modified once the trial has begun?
10. Who is the PI at your site?
11. True or False: Your input can influence the research process in the development of an HIV vaccine.

(Answers can be found on the back cover)

should be restricted but the wording was not explicit. The Declaration was changed to say that any new treatments under study should be tested against "best current" treatments. Placebos can be used where no proven treatment exists.

New vaccine candidates against diseases for which there aren't any vaccines are tested against placebos. The Declaration's new language does not alter researchers' ability to ethically test these vaccines against placebos.

The issue of how to treat trial participants, who may through their own actions become infected with HIV during participation in a vaccine trial, is not completely resolved by the Declaration's new language. If the "best proven" standard required by the new language is applied to treatment provided to participants who become infected everywhere in the world, another ethical dilemma may result: can a potential trial participant freely give informed consent when trial participation is their best and perhaps only hope to obtain antiretroviral drugs if they become infected? This issue was controversial in the discussions that led

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to the May 2000 release of the *Ethical Considerations in Preventive HIV Vaccine Trials: UNAIDS Guidance Document*. It suggests a compromise that takes into account varying conditions around the world, such as national and individual autonomy. (See last month's issue: Volume 1 Issue 4 November 2000 p. 2).

The new language also asks researchers to disclose to participants how the trial is funded and whether the researchers have any conflicts of interest, and requests the publication or public availability of all data, negative as well as positive. Some researchers believe that there is little incentive to publish negative data and this may provide an incomplete picture about product efficacy.

The three year period for considering revisions to the Declaration was marked by sharp debate and a campaign by Public Citizen to change the language. Robert Levine chaired a WMA task force that proposed language to clarify the ambiguous placebo language by allowing placebos if their use does not cause death or disability. The WMA rejected this language and another committee chaired by Dr. Anders Milton, head of the WMA, proposed the current language. Throughout this process, Public Citizen waged a campaign to end the use of placebos. Public Citizen and others criticized the placebo controlled "short course" or single injection of antiviral trials to study the ability to decrease mother to child transmission of HIV in Thailand and several African countries. They said that the control should be the standard treatment in the US and other developed countries: long course treatment with antiretroviral drugs. Proponents of these trials argued that quickly testing a potentially effective treatment that could be used in these countries and other parts of the developing world to prevent mother to child transmission of HIV was worth doing.

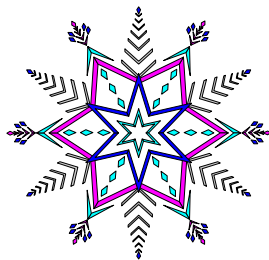
The reaction to these revised guidelines by the FDA and other national regulatory bodies, whose rules do have the force of law, will be an important indication of the effect on preventive HIV vaccine trials. The challenges of conducting multi-national trials are immense. We need to find ways to respect both an individual's rights and national autonomy; we must attain an ethical standard where the principles that guide us are universal. We can and do debate whether the application of these principles may be tempered by the realities in an unethical world: poverty, lack of access to basic health care services, wide differences in standard of living and income, and a host of other inequities. If HIV vaccine trials wait while we work on and solve these inequities, we risk another ethical dilemma: allowing the HIV pandemic to go on longer and effect more people. *

Another perspective

By Luis G. Santiago
New York Blood Center CAB Member
AVAC Board Member

Declaration of Helsinki, 2000

In October 2000, the World Medical Association (WMA)



adopted a revision of the Declaration of Helsinki. This is the fourth time the Declaration has been amended since its original adoption in 1964, when it became one of the pillars of clinical research ethics.

The most fundamental revision to the Declaration is related to the use of "placebos" as control arms in clinical research. It resolves the incoherence of the previous version on this subject. This previous version stated in Section II, 3 that "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." Since clinical studies are designed precisely to test a new method that differs from the "best proven method," this statement did not make much sense.

In the revised Declaration, WMA leaves no doubt as to what it believes should be required in a clinical trial. Section C, 29 states:

"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."

Several alternate positions were debated and discarded during three years of discussions. One proposed allowing placebos in trials where risks were minimal and there was no possibility of death or disability. It also supported the use of "the highest attainable and sustainable therapy" (which amounts to the "best" possible care available in the country where the study is being held) as controls. Others suggested that "proven, effective treatment," but not necessarily the best, was sufficient. This position appears to coincide with the one supported by the US National Bioethics Advisory Commission (NBAC), which is currently working on its own report entitled "Ethical and Policy Issues in International Research." NBAC recommends the term "established, effective treatment," which incorporates the notion of the widespread acceptance of the therapy.

Potential Impact of the Revised Declaration of Helsinki on Preventive HIV Vaccine clinical trials

The main impact of this revision on current and future preventive HIV Vaccine trials may be added pressure to provide the "best current therapy" to participants who get infected with HIV during the course of a study. Although these are "prophylactic" and not "therapeutic" studies, participants who get infected will still be followed up either in the original study or possibly in other subsequent studies. This is because the vaccine may have an impact on the course of the disease, even if it doesn't stop the initial HIV infection itself.

Unfortunately, there is a possibility that more pressure to provide the "best current treatment" may not result in more ethical trials, but in a delay in the start of new preventive HIV vaccine trials. This is particularly true for trials in least developed nations, where providing this level of treatment, even for the several hundred participants who potentially will get infected in studies that can include thousands, will be difficult to achieve.

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The Vanderbilt University HVTU

Past, Present and Future

By Mary Braeuner

Over 13 years ago, in the fall of 1987, preventive HIV vaccine research became a reality at Vanderbilt University. Our unit, known then as the AIDS Vaccine Evaluation Unit (AVEU), has grown from the original three people to today's group of close to 20. Helping to find a safe, effective, preventive HIV vaccine has been the driving force and commitment of the staff. Composed of a diversity of peoples and races, the staff represents, in microcosm, a sampling of the larger world that is in such desperate need of a vaccine. The Vanderbilt HIV Vaccine Trials Unit (HVTU) is pleased to be working with its Sub-Unit in Port-au-Prince, Haiti. We have also been involved in some of the start-up staff training for the sites in Brazil and Trinidad. The unit looks forward to continuing its role in the international fight against HIV. The vaccine unit joined a long standing tradition of vaccine research at Vanderbilt University. Numerous pediatric vaccines have proceeded through research studies at Vanderbilt. Many have succeeded in making major contributions to the control of infectious diseases around the world.

The HVTU team at Vanderbilt is composed of people in many disciplines. Researchers with whom people may have the most contact with include:

Co- Principal Investigators:

Barney S. Graham, MD, PhD
Paul Spearman, MD
Peter Wright, MD

Research Coordinator:

Lois Wagner, MSN, RN, FNP, CCRC

Clinic Staff:

Kyle Rybczyk, MSN, RNC, FNP
Katie Crumbo, MSN, RNC, FNP

Recruitment/Educator:

Mary Braeuner, BSN, RN
Susan Montgomery, BSN, RN

Data / Systems Coordinator:

Roberta Cornell

Vanderbilt University is a 127 year old institution dedicated to education, research and service. It is located in Nashville, Tennessee, a robustly growing community of over 1 million people. Most people recognize Nashville and environs as the home of country music, which it is. It is also the home of numerous volunteers who have chosen to participate in the HIV vaccine studies here at Vanderbilt. On Feb. 29, 1988 the first volunteer at Vanderbilt was

enrolled in a vaccine study. We've come a long way since then. Some 500 men and women have been entered into a vaccine study. Primarily, they come to us from the middle Tennessee area but they have also participated from as far away as Kentucky, Alabama and Georgia.

The staff make numerous community presentations. While the major recruitment and educational activities are the function of the nurse recruiters/educators, recruitment is everyone's focus. All of the investigators, nurses and staff participate in their sphere of influence to reach out to educate the public about the vaccine trials and to recruit volunteers. This is also true of increasing the community networking that is so important. The Community Advisory Board (CAB) also plays a major role in community outreach, education and support. The dedicated members of the CAB always bring a fresh new dimension to the work of the unit.

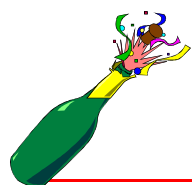
Over the years a good working relationship with the press and media has proven very beneficial. A well done TV news spot can provide hundreds of callers seeking information about the studies. Because of fear, lack of knowledge and misinformation surrounding HIV and research, the unit is always acutely aware of the need to provide clear, correct information to the community. This is especially true in the minority communities.

There is a strong emphasis on providing prevention education to the various racial and ethnic communities that make up greater Nashville.

Nashville is basically a young community with approximately 90% of its population 65 and under. Forty three percent are 44 years of age and younger. While everyone will benefit, this group in particular will be major beneficiaries of a safe, effective, preventive HIV vaccine. Vanderbilt University houses the world's most complete collection of television news broadcasts. Started in 1968 it contains a record of all the major news events of

our lifetime such as: Kennedy's assassination, Watergate, walks on the moon and the counting of chads. The goal of this HVTU is to add another great news event to the archives and to the history of mankind. It will read "HIV Vaccine Found". We, at all the sites across the world, will be proud to have been a part of its discovery.*

Imagine a World...
...without AIDS
Help us find a vaccine to prevent HIV!
• HIV negative volunteers, 18-60, are needed.
• It is not possible to get HIV from the vaccines.
• Volunteers are reimbursed for their time.
call 322-HOPE
or 1-888-559-HOPE
AIDS Vaccine Evaluation Unit Vanderbilt University Medical Center



CONGRATULATIONS to the Vanderbilt HVTU for vaccinating the first participants in the Protocol 203 trial on December 14, 2000 !!!



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My position

On the one hand, I disagree with those who say that offering the “best current treatment” to HIV-infected participants is an “undue inducement” to join a preventive HIV vaccine study. These trials already provide routine checkups as well as other benefits that are not commonly available to the general population. Besides, this opinion is based, at least partially, on the idea that once people join the study they will increase higher-risk practices, particularly if they know they will have access to anti-retroviral treatment, which is something we are not seeing in the current studies.

I would prefer that the “best current treatments” be incorporated in all preventive HIV vaccine trials in developing countries, if it were possible. However, I believe a trial is “ethical” if it provides a “proven effective treatment” (or “established, effective treatment” using NBAC’s terminology) that includes anti-retroviral therapy and is at least as good as what everyone else in the country receives, even if it is not the “best current treatment”.

This is different from the “highest attainable and sustainable therapy,” because this last one may or may not include anti-retroviral therapy. For example, in many African countries, prophylaxis against Opportunistic Infections, with no effective anti-retroviral combination, is the norm. An “established, effective treatment” must include anti-retroviral medication (if and when it is indicated, which may be years after initial infection).

As community vaccine advocates in a country that provides, in general, access to HAART therapy, considered the “best current treatment” for HIV disease and AIDS, what is our role regarding preventive HIV vaccine clinical research in developing countries that do not regularly provide HAART to its HIV-infected population? I believe, first and foremost, that we should support all initiatives to expand access to HAART in these countries to all people infected with HIV. And secondly, but of equal importance, we should promote the development of prophylactic HIV vaccine clinical trials with sound ethical standards, without raising this ethical bar so high as to prevent the trials from getting started in the first place. *

CALENDAR OF EVENTS

CAB PROTOCOL WORKING GROUP CONFERENCE CALL:

January 3, 2001 12 p.m. EST, 9 a.m. PST. ***Note new date and time***

GLOBAL CAB CONFERENCE CALL:

January 11, 2001 7 p.m. EST, 4 p.m. PST (non-staff)

COMMUNITY EDUCATION/RECRUITMENT COORDINATION CALL:

January 16, 2001 2:30 p.m. EST, 11:30 p.m. PST (staff)

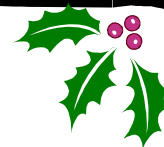
COMMUNITY EDUCATORS/RECRUITERS MEETING :

February 12-13, 2001 New York



Save the date:

CAB Retreat in Seattle, WA
August 16-18, 2001



Answers to the fun little quiz:

1. Over 12 years.
2. A clade, also called a subtype, is a group of related HIV isolates classified according to their degree of genetic similarity. There are currently two groups of HIV-1 isolates, M and O. M consists of at least nine clades.
3. Not yet. The first Phase III trial for the network is projected to begin in 2002.
4. False. The HVTN is currently researching only preventive vaccines. There are plans to work with the Adult and Pediatric AIDS Clinical Trial Groups to test future vaccine candidates.
5. A cohort is a group of individuals who share one or more characteristics in a research study and who are followed over time. For example, a vaccine trial might include two cohorts, a group at low risk for HIV and a group at higher risk for HIV.
6. There are presently 10 funded sites and over 20+ trial locations worldwide.
7. The CAB PWG is the CAB Protocol Working Group. This is a group of CAB members who sit on a call once a month to discuss some of the important issues that come up from the individual protocol teams that they represent.
8. The HVTN research is funded by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH).
9. True. However, it may only be modified after approval of all trial sponsors and Institutional Review Boards (IRBs)
10. If you don't know, go find out and introduce yourself. You may find that she/he is a very interesting and delightful person, who has been waiting to talk to you!
11. True. As a CAB member, you can be part of protocol teams and scientific committees and influence the research from its very early stages of pre-trial development.

Please send suggestion, questions and article submissions to:
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HIV VACCINE
TRIALS NETWORK

