

**National Institute of Allergy and Infectious Diseases  
Division of Acquired Immunodeficiency Syndrome  
AIDS Research Advisory Committee**

**September 29, 2003  
Natcher Building, Conference Rooms E1-E2  
NIH Campus, Bethesda, Maryland**

The AIDS Research Advisory Committee (ARAC) met on September 29, 2003 at the Natcher Building on the National Institutes of Health (NIH) campus in Bethesda, Maryland.

Dr. Holmes chaired the meeting, which was open to the public. ARAC members (including NAAID Council AIDS Subcommittee members) in attendance were Drs. Jackson, Jacobs, R. Johnston, Kanki, Lewis, Martin, Marx, and Ruff; and *ex officio* members Drs. Deyton, Jaffe and Masur. Also present were DAIDS staff Drs. Dieffenbach, M. Johnston, Kagan, Montoya, Murguia, Lehrman, and Tramont; OAR staff Dr. Eisenger and Ms. Wertheimer; and DoD staff Dr. Birx. Ms. Siskind was Executive Secretary.

**Director's Report – Dr. Tramont**

**Budget Update:** The President's proposed fiscal year 2004 budget for NIH, subject to change by Congress, is \$27.9 billion; NIAID has become the second largest institute (after NCI) with \$4.3 billion, or 15.4% of the total. The NIAID budget is roughly divided into thirds among biodefense, HIV, and other activities. The total NIH AIDS budget is \$2.8 billion, divided among all of the institutes and centers, with NIAID receiving half of that. Within DAIDS, approximately 63% of the budget goes to clinical trials. This year \$100 million of the AIDS budget is passed through directly to the Global Fund; next year it might be a larger amount.

**Organizational and Personnel Changes:** The Division has added two new offices. The Office for Policy in Clinical Operations was established to address the increasing scientific, ethical, and legal complexities surrounding clinical trials, and will be led by Dr. Jonathan Fishbein. The Office of International Research, headed by Dr. Rod Hoff, was established to provide overarching coordination of the expanding international research portfolio, including oversight of CIPRA.

Dr. Tramont thanked Drs. Martin and Jacobs, who are rotating off of the ARAC, for their service. Dr. Jackson can, and has agreed to serve another term on ARAC and will also serve as the Committee's liaison to the OARAC.

Dr. Tramont concluded his Director's reported by reviewing ten of the Division's selected scientific accomplishments during FY 2003.

**HIV Vaccine Program – Dr. Tramont**

A vaccine is critical to controlling the HIV/AIDS epidemic and Dr. Tramont described the Division's comprehensive program. He reviewed the principle scientific impediments to identifying a vaccine as well as the long list of vaccine candidates currently in development.

**PAVE:** The Partnership for AIDS Vaccine Evaluation (PAVE) is a coordinated HIV vaccine research effort that includes the three government agencies most involved in this activity – NIH, Centers for Disease Control and Prevention (CDC) and the Department of Defense. The three agencies will work together to ensure that research protocols, standards, and measures are developed in a coordinated and harmonized manner so that outcomes can be compared across

trials. International non-government organizations (NGOs) and companies have expressed interest in joining in the partnership.

**Global Enterprise:** The concept of a Global Enterprise first took form in an article in *Science* in June, coauthored by Richard Klausner and several others, and was described as a strategic plan to accelerate HIV vaccine development. An expanded group of about 60 people met in August to further advance the initial ideas, and a handful of working groups will be developing a draft strategic plan over the next six months. Dr. Tramont noted that the Enterprise might be able to provide additional resources, particularly for activities that NIH cannot support, such as paying for bricks and mortar in resource poor settings and providing antiretroviral therapy to vaccine trial participants who become infected. He emphasized the desire not to create new bureaucratic obstacles but to fill in gaps where necessary.

#### **AIDS Vaccine Research Working Group (AVRWG): Update – Dr. Bradac**

The AVRWG held a meeting in New York City, immediately prior to the start of the AIDS Vaccine 2003 conference. At the meeting, three leaders of the European Vaccine Effort against HIV/AIDS (EuroVacc) presented their ambitious research agenda to the AVRWG and it is expected that they will look to collaborate with DAIDS/NIAID in the future. The AVRWG also reviewed the candidates in the pipeline and several questions were raised about whether there should be restrictions on support for new MVA candidates and how NIH should decide which candidates to move on to phase III trials, when capacity is limited. The AVRWG did not want to close off the pipeline to new MVA products but did express a desire to become more selective. It recommended that new candidates show improvements or uniqueness over existing candidates. A standardized assay panel should be used to make that evaluation.

#### **Concept Review: Vaccine and Prevention Research Program– Dr. Johnston**

Dr. Johnson offered a brief update on leading issues and promising approaches from FY '03 that they are trying to fast track:

- Adenovirus: Does prior exposure to adenovirus dampen the immune response to this vector, and if so, how might it be overcome?
- Four vaccine candidates have been advanced into phase I trials within the past 12 months, including those from the VRC.
- Ongoing prevention activities show that effect of nevirapine in preventing mother to child transmission is durable over time.
- The trial using canarypox + gp120 is about to start in Thailand.
- Six additional products are to enter phase I in 2003-2004.
- The first phase III microbicide trial is about to begin.
- EXPLORE results on behavioral interventions are due around the end of the calendar year.
- HVTN proof of concept trials of one or two vaccines will begin in the next year or two.

Key scientific challenges for vaccine development are eliciting broadly neutralizing antibodies – tied to a better understanding of envelop structure; inducing broader CTL responses to avoid viral escape; and advancing candidates into efficacy trials to evaluate potential correlates of protection.

Key scientific challenges for prevention are promoting development and evaluation of microbicides that build upon lessons from therapy – a combination of approaches and targets are more successful than a single approach; and formulation issues for consumer acceptance will require a series of skills that NIH traditionally has not developed.

Within this context Dr. Johnston presented several concepts for initiatives for the committee to review and approve.

***HLA Typing and Epitope Mapping to Guide HIV Vaccine Design:*** Renewal of this program for 5 years through a N01 mechanism is being requested, with first year costs of \$3 million. The purpose of the program is to guide the design, development, and evaluation of HIV vaccines by supporting the acquisition of HLA and related data. It aims to better understand both on an individual and on population levels what shapes HIV evolution and escape from immune control, toward improving vaccine design.

The first contract was awarded in May 2001, to study clade B infected non-Caucasians in the Americas and non-clade B individuals in South Africa. It has identified 17 new CTL epitopes to date. A second award was signed in July 2003 for sites in Peru, China, and Thailand.

The committee voted to approve the concept.

***Advanced HIV Vaccine Development:*** Request is being requested for expansion of an existing program to advance candidates beyond phase I and into phase II and III trials through the production of vaccines, reagents, and other products. The five-year cost is up to \$15 million, administered through a N01 mechanism as 2-4 contracts. Budgetary factors will determine whether the program is expanded in fiscal year 2004.

The program has two stages of funding: 1) the first stage of funding requires promising phase I data; the second requires being ready to produce the candidate vaccine, which means demonstrating the manufacturing capability at large scale.

The committee voted to approve the proposal.

***HIV Vaccine Design and Development Teams:*** Renewal and expansion of this program for five years is being sought, with a first year cost of up to \$10 million, through a N01 mechanism. The purpose is to advance candidates into phase I trials. It is a milestone-driven, completion, cost-reimbursement contract where contractors receive a portion of the “profit” as they achieve their predetermined milestones. If they do not meet their milestones, we can narrow the scope; narrow the budget; terminate the contract; or renegotiate the milestones.

Candidates must both be promising and have a milestone driven plan to advance it into a phase I trial. To date, one of the four contractors already has initiated their clinical trial and the other three have plans to do so by the end of the calendar year. Four additional awards are being announced that day. Additional areas where they hope to stimulate activity include eliciting broadly neutralizing antibodies; novel envelope constructs; improved methods to get a broader CTL response; inclusion of additional target genes; and mucosal immunity.

While this program does not provide access to screening and non-human primates, those resources are available to grantees through other mechanisms. The total number of grantees will remain the same, at 8-10, due to turnover.

The committee voted to approve the proposal.

***Microbicide Design and Development Teams:*** Approval was given to launch the program in FY 2004 and this request seeks to expansion; this is a five-year program, with a first year cost of up to \$7.5 million. Funding would be made through a N01 mechanism. There is a critical need for

the program because major pharmaceutical companies are even more reluctant to enter into the development of microbicides than they are to engage in HIV vaccine research because it is an unproven technology. Those companies that are involved in this area of research are small and underfunded. The phase III trial with nonoxynol-9 (N-9) was not successful. Other candidates are about to enter phase III. The focus of the program is on non-detergent candidates and on combining products that use different mechanisms of action to achieve protection. Peer review will evaluate *in vitro* data to determine the most promising candidates to move forward.

The committee voted to approve the proposal.

**Concept Review: International Research Branch – Dr. Hoff**

***Comprehensive International Program of Research on AIDS (CIPRA):*** Approval is being sought for a five-year renewal of the program that provides long-term support for epidemiologic, laboratory, and clinical studies to lay the foundation for research on practical and affordable methods for prevention and treatment of HIV/AIDS in developing countries. First year funding is \$15 million (\$13.5 million CIPRA, \$1.5 million monitoring) awarded through three grant mechanisms: 1) R03 – planning and organizational grants of up to \$50,000 for a maximum of 2 years; 2) U01 – exploratory and developmental research of up to \$500,000 for a maximum of 5 years and U19 – multi-project research awarded on a 5-year, renewable basis.

The FY 2003 CIPRA budget of \$12.8 million is supporting:

- R03: 23 grants, totaling \$1 million
- U01: 1 grant for six months, totaling \$0.3 million
- U19: 3 grants, totaling \$10 million
- Monitoring/operations totaling \$1.5 million

Additional funding would expand the program's ability to build multi-disciplinary research capacity, support DAIDS network activities, provide regional balance to the international portfolio, and fulfill commitments to host countries. The increased funds would support 10-12 U19 applications and a handful of U01s.

The committee voted to approve the concept.

**Concept Review: Office for Policy in Clinical Research Operations – Dr. Fishbein**

***DAIDS-wide Clinical Trials Site Monitoring and Training Program:*** Approval is being sought for renewal of a contract for seven years, with a first year cost of \$18 million. Funding would be provided through a N01 mechanism. The contract permits DAIDS provide monitoring and training its clinical trial sites throughout the world, as required. The scope covers all DAIDS-funded clinical research units – more than 900 sites in 41 countries involved in approximately 200 protocols with more than 40,000 subjects.

Discussion focused on the need for flexibility, and creativity in terms of monitoring a wide range of trials conducted in very different regions of the world.

The committee voted to approve the concept.

**Concept Review: Biostatistics Research Branch – Dr. Gezmu**

***Statistical Methods in HIV/AIDS Research:*** Renewal is being sought for five years of R01 and R03 programs totaling \$1 million in the first year. The purpose is to stimulate innovative research

in statistical methods to advance the study of HIV/AIDS vaccines, therapies and pathogenesis. The current portfolio consists of 24 grants totaling \$6.3 million.

The problem of choosing which vaccine candidates to advance from phase II to phase III trials was raised during discussion. It was suggested that innovative statisticians and researchers knowledgeable in the design of clinical trials be paired to try to come up with some new paradigms for clinical trials that will help guide this decision making process, hopefully using smaller sample sizes.

The committee voted to approve the concept.

## **Developing a Model for Clinical Research Networks in a Global Environment**

### ***Visions and Goals – Dr. Tramont***

The Division of AIDS' budget for all of its clinical trials networks is currently about \$320 million, or two-thirds of the DAIDS operating budget (minus indirect costs). Given the need for an expanded international research agenda, and a leveling of the funds be directed to HIV/AIDS, the Division of AIDS needs to adjust and refocus its priorities.

The DAIDS-funded clinical research networks include the Adult AIDS Clinical Trials Group, the Pediatric AIDS Clinical Trials Group, the Acute Infection and Early Disease Research Program, the Community Programs for Clinical Research on AIDS, the HIV Prevention Trials Network, the HIV Vaccine Trials Network, and the Evaluation of Subcutaneous Proleukin in a Randomized International Trial (ESPRIT). All of the existing networks will be recompeted at the same time in FY 2006. To do this, DAIDS will extend some of the existing networks so that they all come up for review at the same time.

The clinical trials networks foster broad input on key clinical scientific questions; involve multiple, diverse sites and populations; provide a forum for investigator exchanges; develop lab and clinical standards; share databases, SOP, and training modules; and significantly improve DAIDS efficiency in management and oversight. They are the most visible aspect of DAIDS/NIAID and are constantly under scrutiny by the community, the NIH hierarchy, the press, and Congress.

In previous meetings with the network leadership and DAIDS, discussions focused on ways to improve the effectiveness and efficiency of the clinical research effort. It was emphasized that while this is a “competitive renewal,” one initiative or more initiatives and one or more networks may emerge. The timeline for the review and application process is as follows:

2003	Consultations
2004 January	Draft concept paper for the future of the networks
2004 May	Final review
2004 Fall	Release of RFA(s)
2004 Fall	Pre-application meeting
2005 Spring	Receipt of applications
2005 Summer	Review and awards for work to begin in FY 2006

### ***Discussion of Scientific Priorities and Integration – Drs. Lehrman and M. Johnston***

The goal is to end the epidemic through a coordinated research plan that is designed to:

- Stop new infections by protecting uninfected persons and reducing infectiousness of those already infected.
- Keep infected persons healthy

- Continue to pursue innovative translational research

There are several challenges in positioning trials along the continuum of approaches that might be taken; this can be thought of as a series of trade-offs that must be made, such as:

- “Optimal” therapies ↔ cost effective and deliverable interventions
- Slower, resource intensive investigation ↔ “quick and dirty”
- Randomized Controlled Efficacy Trials ↔ Community Based Trials
- Individual ↔ family focused
- Domestic ↔ international “agendas”
- Long-term clinical outcomes ↔ surrogate markers

Vaccines: With regard to vaccines, unanswered questions remain with regard to whether clade and HLA or other genetic traits significantly affect the protective ability of a vaccine. While this has not been a problem with other vaccines, one cannot simply assume that this will be the case with HIV. Multi-country trials will be required to resolve the issue. Current plans envision:

- Conducting 2-3 efficacy trials that look at infection endpoints; and continue to follow subjects to determine the impact on disease progression, further transmission, and other secondary endpoints.
- Selecting and improving the most promising candidates will be an iterative process that likely will have many cycles. The trials must be constructed in a way that generates the information necessary to make this possible.
- Evaluation of the impact of passive transfer of antibodies from mother to child will be challenging.

Microbicides: Developing microbicides is difficult because of the lack of surrogate models; issues of adherence; and design of the control arm, where any placebo gel may have some protective barrier effect. The first trial will have two control arms – placebo gel and condom-only.

Other Prevention Interventions:

- Coinfection therapies and possibly vaccines that might reduce the risk of HIV infection
- Behavioral interventions, individual, group and community.
- Barrier protections, male and female

The latter two are not NIAID strengths and will require extensive collaboration with other institutes.

Keeping Infected Persons Healthy: Questions that are as applicable in a developing setting as they are in the US are:

- When to start ART; with what, and when to switch
  - Trade-offs of early or deferred intervention
  - Issues of adherence, conservation of classes of drugs, and cost-benefit for society
- Resistance and salvage
- Immune preservation or restoration
- Coinfections and concomitant medications
  - Tuberculosis
  - Hepatitis: B, C, and GBV-C
  - Malaria

- Natural products and how those might interact with ART
- Reduce or control complications of disease and therapy
- Simplify and make sustainable diagnostics used in detecting infection and treating and monitoring disease, and deliver care.

*Coordination and Integration at the Scientific Level:* Examples include:

- Common trials, where networks and entities decide to work jointly on a single trial. An example is the first phase II vaccine trial, which was a joint effort of the AIDS Vaccine Evaluation Group (AVEG) and HIVNET.
- Simultaneous trials done at common sites. Examples are the HPTN 052 and AACTG 5175, and the subsequent AACTG 5190.
- Trials conducted at the same setting, without coordination
- Data sharing may possibly answer some questions, as the AIERDP program is doing.

Other suggestions of where integration might occur:

- Impact of prevention and ART on transmission
- Treatment of HIV+ women in developing countries and the impact on MTCT
- Treatment and preventive vaccine research
- Studies of acute infection likely will impact all areas
- Crosscutting laboratory research on diagnostics and monitor to create more appropriate, and sustainable technology in these settings.
- Cross-cutting background issues of nutrition, traditional therapies, and endemic infections

***ARAC Input and Key Questions for Consideration – Dr. Holmes***

Since globalization is the general theme of reorganizing the networks, the following questions were raised for consideration:

- Which research priorities require a global multi-center network structure and which can be addressed adequately and more efficiently at a single site?
- Based on the current need for prevention and therapy research in developing countries to determine efficacy of new products and approaches, or to rigorously assess the effectiveness in developing countries of existing products or approaches shown to be effective, what should be the balance of NIAID support for these options? Should NIAID become more involved in operational research on HIV/AIDS treatment as funding for treatment is scaled-up in developing countries?
- What should be the balance of Network support after 2005 for developing and sustaining infrastructure vs. conducting actual research?

***DISCUSSION***

***Advantages and Disadvantages of the Networks:*** From a historical perspective, the networks have been successful. Years ago, instead of funding individual R01-type approaches, the networks were funded as networks to initiate a whole new area of science; to invest in developing the scientists and create the infrastructure to begin the whole activity. DAIDS was successful in doing that. There have been multiple generations of scientists that have emanated from these networks, and a large and sustained commitment to AIDS research by industry has followed. The networks have stimulated the whole depth and breadth of AIDS research around the world.

The networks also bring researchers together, which is an important intellectual benefit. They provide a good way to set priorities and make sure that people are studying things in a compatible and comparable manner. Network interactions improve protocol designs and statistical analysis; however, they significantly delay the work getting done. There is a great deal of time devoted to conference calls and other network type activities that keep people from doing actual research.

The question was raised as to whether different types of research might call for different structures and interactions. There is also concern that those who are not part of the network are shut out of the process. The problem is that if a network is charged with a mission, then those resources must be directed to that mission and not be diluted with use by those outside of the network.

### ***FDA Influence***

It was noted that the FDA is a driving force for DAIDS research design and conduct. There was discussion as to the extent to which FDA standards and regulations should drive NIH-funded global research. It was pointed out that host governments want the studies being done in their countries to be conducted according to the same standards as if we were doing them in the US. Many of the international regulatory agencies in developing countries either lack the ability or the self-confidence to review and approve trials without the FDA blessing. Nonetheless, the urgent need to respond more rapidly to the HIV epidemic in developing countries may warrant greater flexibility on regulation standards, for example in some operational research.

### ***International Issues***

It was generally recognized that the need for prevention, care and treatment research at international sites is needed; however, the cost will be great. The issue of limited US resources was discussed in the context of the breadth and scope of international research priorities. In addition, all international sites do not need to be held to the standard of doing independent research. The goal of doing operational research does not necessarily need to lead to the ability to do more sophisticated research in all of these countries.

### ***Alternative Funding Mechanisms***

It was suggested the rather than put such a substantial amount of the budget into clinical research networks, DAIDS should consider putting a large portion into translational research through competitive, focused program announcements. Another portion could be divided among international and long-term studies. This would require the creation of clinically oriented study sections. However, it was pointed out that individual trials could require as much administrative manpower as a network. There are models, however, with no networks, in which core resources could be made available to individual and network researchers.

It was pointed out that the network approach is not conducive to the need for speed that DAIDS is seeking and a more entrepreneurial approach, such as that of working with the South African military, might be more efficient.

### ***Next Steps***

A draft concept from DAIDS was requested for the Committee to review and comment on at the January meeting. It was also suggested that there are other groups and NIH Institutes that participate in clinical trials, who are not part of this review process, and should be included.

### ***Summary Recommendations***

- A clear consensus of ARAC members was that the overarching challenge for DAIDS in global HIV/AIDS research is to define and support the most appropriate and efficient mechanisms for very high quality research on prevention and treatment of HIV infection.
- There was clear recognition and consensus that the current HIV treatment and prevention networks represented an innovative approach to developing research capacity where little or none existed. These have been highly productive and have brought credit to DAIDS, NIAID, NIH and those who have conducted the research and have had a major positive impact on HIV/AIDS care and treatment. Further, these networks now concentrate valuable expertise and experience in therapeutic and prevention research trials.
- Several ARAC members noted that over time, as HIV/AIDS research has matured, the role and modus operandi of HIV/AIDS research networks much adjust to the changing dynamics of the epidemic in a manner that most efficiently utilized their expertise and capabilities. For example, now that many clinical investigators have become highly experienced in HIV/AIDS clinical research, and the numbers experienced in international research are growing, the need for intensive scientific oversight by DAIDS has clearly changed. There appears to be a danger of letting efforts to develop the “perfect protocol” become the enemy of conducting feasible and essential good research. We must avoid “paralysis by analysis” by avoiding recurring vetting and re-vetting of protocols.
- Another observation was that the mechanisms that worked well for conducting the multi-site, one-size-fits-all domestic research trials involving new drug development may be unnecessary and even counter-productive today for many of the most urgent needs for treatment and prevention research in developing countries. Multi-center Phase III vaccine trials will certainly be needed. However, it is noteworthy that of the key studies carried out in HIV treatment and prevention in developing countries, thus far (e.g., nevirapine for perinatal prophylaxis, the Mwanza, Rakai and Masaka studies of STI treatment for HIV prevention, the ten N-9 microbicide trials, the Thai short course AZT trials) few were multi-country studies.
- Specific suggestions that generated the most enthusiasm among ARAC members and that may help DAIDS staff in future planning include the following:

1. Increase efficiency:

- Decrease the number of international sites on a rational, competitive basis, and focus on strengthening capabilities of those that remain.
- Streamline the protocol development and review process, both for network and non-network research.
- The recent HPTN external review recommended larger number of Phase II studies and fewer mega-budget Phase III prevention studies. Similarly, for treatment research in developing countries, DAIDS can balance the funding for multi-site trials of new therapeutic regimens and the funding for smaller, local studies of the effectiveness of new approaches for delivery of care in developing countries. In the current era, as new funding for treatment rapidly becomes available, the need for the latter type of research is especially urgent. NIH must vigorously pursue ways to help other federal and inter-governmental agencies scale-up the treatment effort in a cost-effective manner now!

2. Developing country Centers of Excellence for HIV/AIDS research. Strive for the availability of multidisciplinary capabilities to address HIV vaccine, prevention and treatment research in developing country Centers of HIV/AIDS Research Excellence. Partner/collaborate with other NIH Institutes and Centers, other government agencies, foundations, and non-government organizations that support a broad range of related research activities in supporting these Centers. This need not include simultaneous involvement of multiple networks or institutes on exactly the same protocol.

3. Create incentives for actual conduct of research as opposed to maintaining infrastructure or prolonged protocol development. Core support for creating research infrastructure in developing countries is clearly essential at the beginning, and ongoing needs for sustaining core support are disproportionately greater in developing countries than in the US. However, alternative mechanisms are clearly needed now to redirect research funds into cost-effective conduct of actual research. The CIPRA program provides one clear mechanism for supporting basic core capacity that can equally and even simultaneously serve treatment, prevention, and vaccine research, including research led by the networks. Support from research trials for infrastructure maintenance could be tightly tied to research productivity (e.g., on a per study enrollment basis) to incentivize productivity.
4. Increase emphasis on the DAIDS research portfolio on international research activities, according to scientific needs and opportunities.
5. Encourage and support research with family and/or community based research approaches (to include adults, children and adolescents together).
6. DAIDS should proceed in developing a draft proposal/concept for discussion and review by the ARAC. The ARAC and/or individual members should be utilized in any capacity necessary before the January 2004 meeting in order to facilitate this process.