June 4, 2002

Elias Zerhouni, MD
Director
National Institutes of Health
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Building 1, Room 126
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Dear Dr. Zerhouni:

The Infectious Diseases Society of America (IDSA) and HIV Medicine Association of IDSA (HIVMA) congratulate you on your recent confirmation as director of the National Institutes of Health (NIH). At NIH, you join many notable experts in the field of infectious diseases (ID) research, for whom we hold the deepest admiration and respect. These individuals primarily work within the National Institute of Allergy and Infectious Diseases (NIAID), Office of AIDS Research (OAR) and Fogarty International Center (FIC). We look forward to working with you to further the important ID research activities that NIH is pursuing.

Together, IDSA and HIVMA are the principal organizations representing ID and HIV/AIDS physicians and other scientists devoted to patient care, education, research and community health planning. Given the dynamics of the global HIV epidemic and the recent anthrax attacks in the United States, we believe that this is a critical time for ID research in the United States. As such, IDSA and HIVMA, on behalf of our combined membership of 7,000 experts, would like to provide you and other senior NIH leaders with a list of ID research priorities for you to consider and pursue. Together, NIH and its stakeholders must continue to work to meet new and daunting global challenges as well as to maintain ongoing ID research, such as basic and clinical research that leads to the development of new diagnostics, therapeutics and preventive technologies, research that further investigates the link between chronic diseases and infection, and similar ID-related priorities. We have highlighted for you below our research priorities related to both ongoing and future research activities.

1. Development of New Therapeutics, Preventatives, Diagnostics and Approaches to Treat, Prevent, Diagnose and Manage Significant Pathogens

The short- and long-term availability of essential tools, such as therapeutics, preventatives (e.g., vaccines and microbicides) and diagnostics to fight ID is a critical, ongoing concern for both IDSA and HIVMA members. In recent years, many of the important products our members use to prevent and treat ID have experienced shortages as a result of manufacturing problems or had their availability restricted due to pharmaceutical companies pursuing the development of more trendy or profitable products. Affected products have included injectable antimicrobial agents such as ganciclovir, piperillin/tazobactam, caspofungin injection, penicillin G, meripenem, cephazolin, gentamicin and nafcillin; antiparasitic agents, which are critical for immigrants, travelers, military personnel, and international settings; and routine vaccines, including influenza vaccine, DTaP (diphtheria, tetanus and pertussis), MMR (measles, mumps and rubella), PCV-7 (pneumococcal conjugate vaccine), varicella (chicken pox), Td (tetanus and diphtheria) and even hepatitis.
Although NIH may not play a central role in alleviating shortages of ID products, NIH does play a vital role in the development, and thus the availability, of new products and approaches for the effective management of infectious diseases. To achieve future successes in this area, we urge NIH to expand its investment in the development of these products and approaches and increase its public/private partnership initiatives in order to motivate an increase in private investment. Future investments should highlight the development of:

- novel compounds in ID treatment
- promising vaccine directions including multiple antigens in single doses
- new approaches toward biodefense and tropical agents
- biotherapy and biointerference strategies to replace antimicrobial use

We also strongly encourage new investments in:

- diagnostics research to develop tools that more rapidly detect ID
- improved infection control methods

As NIH’s scientists work to achieve these research goals, we ask that you consider mechanisms that will make these new therapeutics, vaccines, diagnostics and approaches useful and accessible in the United States as well as globally (i.e., the research protocols used in product development must reflect the ethnic profiles of the individuals who will use them; new products must be affordable to the individuals who desperately need them, etc.).

The development of antimicrobial and antiviral resistance also has significantly limited the usefulness of existing products. Research is urgently needed to:

- better define the basic mechanisms of resistance
- develop more rapid, sensitive and specific tests for resistance
- identify drug use strategies that minimize resistance development

Specific to HIV/AIDS, we support the:

- identification of new targets for AIDS drug therapy and stimulation of pre-clinical research in this area. New therapies other than reverse transcriptase or protease inhibitors should be targeted, and new NIH/industry partnerships should be pursued
- establishment of international sites for HIV therapeutic research that are closely linked with sites performing vaccine research and prevention strategies so that synergies can be created and maintained. This effort, if coordinated with the domestic therapeutic effort, could greatly enhance the effectiveness of AIDS vaccine and prevention research and will facilitate the development of the knowledge base and the infrastructure required to optimally deliver contemporary HIV therapy in resource-limited settings.
- continued emphasis on microbicides research as these products can be important tools in the arsenal to prevent transmission of sexually transmitted diseases, including HIV/AIDS

In addition, tuberculosis (TB) has reemerged as an enormous global public health problem. TB is the second leading cause of death due to an infectious disease worldwide and the leading cause of death
among HIV-infected patients globally. The World Health Organization estimates that 8 million new patients will develop TB this year and more than 2 million will die as a result. Moreover, multi-drug resistant TB has developed in numerous parts of the world, especially in the former Soviet Union and in Asia. Despite its long history and devastating impact, no novel drugs have been developed to fight TB in more than 30 years. To address this global issue that is certain to continue to creep into the United States, IDSA and HIVMA strongly support increased TB research, including:

- new treatments, especially those that are safe and effective for drug-resistant tuberculosis
- new rapid diagnostic tests
- an effective vaccine
- research to better understand the mechanism of infection and pathogenesis

The Institute of Medicine (IOM) has called for an annual U.S. investment of at least $280 million in research to better prevent, treat and control tuberculosis, an amount that is significantly higher than is currently spent. IDSA and HIVMA support the IOM’s recommendation.

Finally, we believe that NIH’s institutes and centers must learn to better coordinate and leverage off of each other’s common efforts. For example, both NIAID and the National Institute of Diabetes, and Digestive and Kidney Diseases are working on hepatitis C co-infection and metabolic issues. Similarly, both NIAID and the National Heart Lung and Blood Institute are researching long-term cardiovascular risks. Steps should be taken to ensure that benefits derived from these similar efforts are shared between both entities and that redundancies are avoided.

2. Continued Investigation of the Link Between Chronic Diseases and Infectious Agents

The classic research paradigm that views chronic disease research and infectious disease research separately is most artificial and limiting and is not suitable for modern interdisciplinary challenges. Cancer is caused by such diverse infections as the herpesviruses (HHV-8, EBV), human papillomaviruses, hepatitis B virus, *H. pylori*, *Schistosoma haematobium*, and many others. Heart disease may be exacerbated by *Chlamydia pneumoniae* and its interplay with atherosclerosis. Diseases as diverse as multiple sclerosis and diabetes mellitus may well demonstrate an infectious etiology or co-factor, during your time as NIH director. Even when an infection is not a direct cause of chronic disease, it may contribute indirectly through immunomodulation, including immunosuppression or immunostimulation. The relationship of Burkitt’s lymphoma and hyperendemic malaria may be due to non-specific immune stimulation from chronic infection with malaria and subsequent dysregulation of the host immune system.

We are concerned about the level of ID involvement at the institutes whose mandates include cancer, heart disease, rheumatic diseases, neurological diseases, and other chronic infectious diseases. Are the very best ID investigators deeply engaged in some of these efforts? When ID investigators are involved, are they teamed up with the very best chronic disease researchers? Are we making progress rapidly enough? We suggest that the NIH institute and center directors discuss the ways whereby these disparate communities can cross-pollinate, perhaps with strategically written research funding agreement.

3. International Research Investments to Address Tuberculosis and Malaria Control and
HIV/AIDS Care and Prevention, Especially Research on Best Approaches to Implement HAART in Resource-Limited Settings

International research efforts to fight ID and in particular, AIDS, TB and malaria are very important to IDSA’s membership. IDSA and HIVMA agree strongly with NIH leaders’ recent expressions of support for international research related to these three diseases. We are specifically supportive of NIH’s efforts to advance HIV/AIDS therapeutic research in developing countries, particularly as the cost of these drugs has plummeted from $12,000 per year just four years ago to under $400 (using Indian generics) per year today. We acknowledge that the long-term approach to HIV control must be built upon prevention, including microbicides, vaccines, STD control, and behavioral change. However, the therapeutic agenda is most vital to stem immediately the economic and human losses in Africa, Asia, Latin America, the Caribbean and Eastern Europe and will enhance the effectiveness of prevention research.

We believe that NIH’s initial foray into international therapeutics research through the Comprehensive International Program Research on AIDS (CIPRA) and the International AIDS Clinical Trials Group (ACTG) is important, but more will need to be done to fully meet the urgent research priorities internationally. NIH’s gracious financial support for the special conference IDSA and HIVMA co-sponsored on October 24, 2001 to develop an HIV/AIDS therapeutic research agenda for resource-limited countries acknowledges the Agency’s support for advancements in this area. IDSA and HIVMA are grateful to NIH for its financial commitment to this conference. Through NIH’s support, we were able to bring together experts from 22 countries to work toward developing an HIV/AIDS therapeutic research agenda for NIH to consider and to implement. We enclose for your consideration a list of 11 suggested research concepts that emerged from the conferences’ working groups. We stand ready to work with you as necessary to develop protocols related to these recommendations.

4. Research Capacity and Infrastructure Development in Resource-Limited Nations

ID research will never be the same in the United States as it was in the pre-AIDS and pre-bioterrorism era. Global issues are now local issues. NIH’s domestic and evolving international experiences have provided the agency with unique insight into the capacities that are needed to do effective ID treatment and prevention research in the developing world. To best capitalize on this experience, IDSA and HIVMA call on NIH to investigate and pursue the following approaches intended to build research capacity and infrastructure in resource-limited nations:

- expand programs that transfer domestic expertise to foreign investigators (such as CIPRA)
- expand U.S.-foreign partnerships in training and research, such as the AIDS International Research and Training Program (AIRTP), International ACTG, HIV Prevention Trials Network (HPTN) and HIV Vaccine Trials Network (HVTN). Recent OAR support of HPTN sites is an exceptional example of how NIH can jump-start international research by focusing on “missing links.”
- pursue research activities that may become sustainable and design research activities so that they may justify their own investment (this will help to provide context for infrastructure building)

Moreover, greater research capacity and health infrastructure can be achieved in resource-limited nations through better coordination and leveraging of resources within the U.S. government’s own
evolving international program. For example, the Centers for Disease Control and Prevention (CDC) now has employees working on the Global AIDS Program in dozens of countries. CDC also has recently announced an international emerging infections program with sites being established in Thailand and Africa. These public health oriented staff and service infrastructures would be highly suitable for NIH research collaboration, if NIH and CDC could hammer out agreements to make this possible. Secondly, the U.S. Agency for International Development’s (USAID) operations research agenda dovetails nicely with NIH’s research. Attention must be given within both agencies to better coordinate and mutually reinforce international prevention and care research for infection control. An NIH/USAID partnership directed at developing comprehensive approaches to AIDS care would be particularly effective. A third example is the Health Resources and Services Administration’s (HRSA) domestic and evolving international programs, such as AIDS Educational Training Centers (AETCs), which could be used to advance international research training in ID care. The AETCs, in particular, provide excellent front-line AIDS care training opportunities, which could target lower technology clinical settings such as those that exist in developing nations. This is a terrific opportunity to exploit a valuable HRSA investment to train international researchers in modern HIV care.

5. Fogarty Training Resources for International Infectious Diseases Research in Care and Prevention, Highlighting A Cadre of Experts from Nursing, Medicine, Social Service, and Allied Health Sciences

We are well aware of the fine research training programs in HIV/AIDS, emerging pathogens, tuberculosis and malaria that currently exist at NIH’s Fogarty International Center. IDSA and HIVMA previously have expressed to NIH our support for these programs and our concern about the limited resources Fogarty has available to support these programs. Simply stated, the available resources are inadequate to fit existing and evolving research training needs in nursing, medicine, social services and allied health services. HIV care, tuberculosis and biodefense come to mind as conspicuous gaps in the current FIC training portfolio. While the AIDS International Training and Research Program (AITRP) has been a backbone of the FIC agenda, the AITRP has never focused on treatment issues due to the prohibitive cost of HAART. As HAART becomes more affordable, these training programs need to adapt to the new universe of solutions for fighting AIDS globally. Investments that target the training of new research leaders in treatment issues are now most vital and could easily justify a doubling of resources for the FIC agenda. The overlap in expertise in tropical and global health with current needs in biodefense research is notable and also gives NIH an opportunity for wise investments. Moreover, given the morbidity and mortality associated with TB on a global scale, there is a critical need to infuse significantly more resources into FIC’s Tuberculosis International Training and Research Program (TBITRP). Finally, additional investments are needed to transfer greater knowledge and research skills related to other major pathogens, including malaria, diarrheal and respiratory pathogens, and parasitic diseases.

6. International Infectious Diseases Training Opportunities for American Students (from All of the Health Sciences), Residents and Fellows

IDSA and HIVMA support the creation of a modest scholarship program ($10,000-$15,000/student/year) for medical, nursing, and public health students interested in international research. The objective of these scholarships would be to allow students to engage in a year of mentored research at a developing country research site. Such opportunities for selected students are an
important component of developing a cadre of American researchers competent in international health. It also is quite possible to link this to the new biodefense initiatives as this expertise very much depends on the kind of training offered in international settings where trainees will have the opportunity to see anthrax, botulism, arboviruses, and other key diseases first hand.

7. Continued Efforts in the Domestic HIV/AIDS Therapeutic Research Program

Recognizing that there are many unanswered questions in spite of recent antiviral successes, we believe that the United States’ domestic HIV/AIDS therapeutic research agenda should address current gaps in knowledge related to:

- when to start therapy
- the usefulness of strategic treatment interruptions
- the usefulness of therapeutic vaccination
- how to minimize resistance
- how to assess and minimize side effects (both short-term and long-term)
- how to stimulate maximum drug adherence
- how to manage acute HIV infection (current expert guidelines do not adequately help clinicians)

We thank you and other senior NIH leaders for your consideration of the research priorities that we have outlined above. Again, we welcome you to your new role as head of the world’s premiere research organization. Our ID expert members are prepared to help you in any way that we can to ease you into your new position as well as to assist NIH senior leaders as they work to develop appropriate ID research agendas and protocols. Please do not hesitate to contact us with any questions that you may have through Robert J. Guidos, JD, IDSA’s director of public policy at 703-299-0202.

Sincerely,

David N. Gilbert, MD
President, IDSA

William Powderly, MD
Chair, HIVMA

Enclosure

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