

**Report of the Working Group To Review the NIH Perinatal,  
Pediatric, and Adolescent HIV Research Priorities**

**Sponsored by**

**Office of AIDS Research  
National Institute of Allergy and Infectious Diseases  
National Institute of Child Health and Human Development**

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## Dartmouth-Hitchcock Medical Center

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January 5, 2000

Neal Nathanson, M.D.  
Director  
Office of AIDS Research  
National Institutes of Health  
Building 31, Room 4C-02  
Bethesda, Maryland 20892

Dear Dr. Nathanson:

Please find enclosed the report of the Working Group to Review the NIH Perinatal, Pediatric, and Adolescent HIV Research. The Working Group included academia, industry, and community constituency participants who represented a broad range of expertise and perspectives and who came from both developed and developing nations. Working Group members reviewed the current data on the demographics and natural history of the epidemic in the perinatal, pediatric, and adolescent populations in the United States as well as abroad. To gain a better understanding of ongoing research efforts and how they complement each other, the Working Group was presented with overviews of the key NIH-sponsored cohort-based, therapeutics, and prevention programs in each of these populations as well as overviews of studies supported by the Joint United Nations Programme on HIV/AIDS and the U.S. Centers for Disease Control and Prevention.

After two days of extensive discussions on June 10-11, the Working Group identified a series of key scientific issues and scientific priorities that were prioritized for the United States and developed nations as well as the developing nations. We appreciate the opportunity to participate in the review process and hope that these recommendations will guide the NIH pediatric AIDS research agenda. I thank the Session Chairs, the NIH Co-Chairs, and the members of the Working Group for their efforts in developing this report.

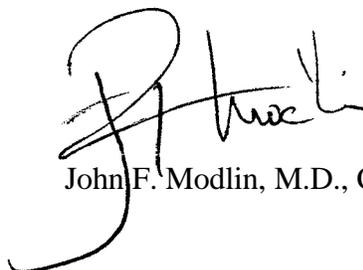
Sincerely,

John F. Modlin, M.D., Chair

Working Group to Review the  
NIH Perinatal, Pediatric, and  
Adolescent HIV Research Priorities

**Chair and Co-Chairs  
Working Group to Review the  
NIH Perinatal, Pediatric, and Adolescent HIV Research Priorities**

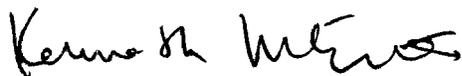
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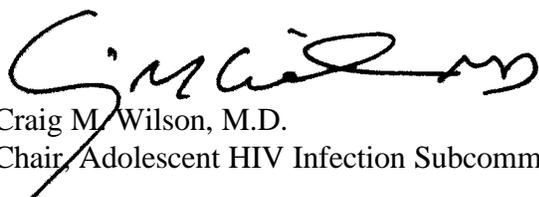
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## Executive Summary

Committee Chair: John Modlin, M.D.  
Executive Secretary: Robert W. Eisinger, Ph.D.

Since the beginning of the global AIDS epidemic, an estimated 4.8 million children have become infected with the human immunodeficiency virus (HIV), and more than 1 million children are now living with HIV infection or AIDS. Virtually all of these infections result from vertical transmission via HIV-infected mothers. While HIV disease is reported from virtually all nations, the vast majority of childhood cases occur in underdeveloped regions of the world where few resources exist to respond. The most gravely affected region of the world is sub-Saharan Africa, where populationwide HIV infection rates as high as 20 to 30 percent are observed. There, approximately 960,000 children under 14 years of age are living with HIV infection, and an estimated 1,600 new infections occur each day.

The bleak situation in the developing world contrasts sharply with the experience in the United States, where the incidence of perinatal AIDS cases reported to the Centers for Disease Control and Prevention (CDC) peaked in 1992 and has subsequently declined by nearly 75 percent. This reversal is attributed to enhanced efforts to universally counsel and test pregnant women for HIV antibody and to the demonstration in 1994 that maternal and perinatal zidovudine treatment will reduce the overall risk of vertical transmission from 25 percent to 8 percent. The recent introduction and use of more potent non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) to treat HIV-infected women, coupled with the growing recognition that vertical transmission risk correlates directly with maternal HIV viral load, has led to enthusiasm over the prospect of reducing vertical transmission rates well below those observed with zidovudine monotherapy. In fact, vertical transmission rates in the United States may be so low that the incremental benefit of elective cesarean section for infected mothers is now debated, despite the observation in a prospective, controlled trial that this procedure significantly reduces the risk of transmission in the absence of antiretroviral therapy. Unfortunately, the influence of a very low risk of vertical transmission is partially offset by the increase in HIV infection rates among women of childbearing age. High adolescent pregnancy rates among at-risk populations, failure to identify HIV infection during pregnancy, and inadequate prenatal care for HIV-infected women remain as barriers that must be overcome in order to further reduce the number of HIV-infected children born in the United States and other developed countries.

Highly active antiretroviral therapy (HAART) is the core of improved treatment options introduced for HIV-infected infants and children during the past decade. It is estimated that the median age of HIV-infected children in the United States has risen to 8 years. Increasing survival rates and the decreasing rate of new infections have resulted in a stabilization of the number of HIV-infected children followed at most centers and in the gradual aging of the HIV-infected population.

In contrast to newborn infants and children, among adolescents the HIV epidemic remains unchecked in the United States, where the burden of infection is estimated to be between 12,000 and 38,000. Recent surveillance data show virtually no change in annual incidence, but

new infections in adolescent females now equal or surpass new cases in adolescent males. Sexual transmission remains the predominant mode of HIV transmission among adolescents, with homosexual transmission accounting for an increasing number of cases among adolescent males.

With this background, a working group of 47 HIV experts (Appendix II) from the United States and several foreign countries (including Brazil, Canada, People's Republic of China, India, Italy, South Africa, Switzerland, and Zambia) met with program directors from the National Institutes of Health (NIH) and other Federal agencies (Appendix III) in Falls Church, Virginia, on June 10-11, 1999, to review current epidemiological data and contemporary knowledge regarding the prevention and treatment of pediatric HIV infection and to advise the NIH Office of AIDS Research on future research priorities. For logistical reasons, it proved useful to focus separately on three areas: (1) maternal HIV infection and prevention of vertical transmission (perinatal HIV infection), (2) management of HIV-infected infants and children (pediatric HIV infection), and (3) prevention and care of adolescent HIV infection (adolescent HIV infection). After examination of current data and formal discussion, the participants generated a list of scientific issues for the NIH pediatric HIV/AIDS research agenda and categorized these issues by priority. The workshop proceedings were then prepared, reviewed, and re-reviewed. The priorities identified in this document are to be viewed not as competing but as complementary. Answers to critical scientific questions in one realm may produce results that are important to another realm. It was recognized that NIH will need to work in collaboration with other agencies of the U.S. Department of Health and Human Services, such as CDC and the Food and Drug Administration (FDA), to achieve some of these goals.

Furthermore, the Working Group recognized that priorities for developing nations should be addressed independently, because the research questions emerging from the rapid spread of HIV infection in these nations clearly differ from those in the United States and other developed nations, though basic questions are shared by all nations affected by the epidemic. These questions and the search for solutions to the problems from which they arise are complex for many reasons. A wide array of economic, political, medical, ethical, and social factors influences both the strategies and the feasibility of research in these settings. The scope of the pediatric HIV epidemic outside the United States is formidable, and many questions urgently require answers as the devastation for children worldwide has many effects on the United States and other developed nations.

*The workshop participants universally recognized that, for NIH, one of the most critical issues that must be confronted to answer both perinatal and pediatric research questions posed by developing countries is the establishment of productive scientific collaborations with investigators and institutions in these countries. To be successful, such collaborative relationships must be long-term commitments, must include plans to build and strengthen local infrastructure, and must be based on scientific queries that are of high priority to a particular country.*

Within each of the three sections that follows, examples of the types of critical studies in each scientific area are listed. These studies are then divided into interventions for developed countries and for developing countries.

## **Perinatal HIV Infection**

Subcommittee Chair: Catherine Wilfert, M.D.

Subcommittee Co-Chair: Lynne Mofenson, M.D.

### **I. Background**

#### **A. Global Epidemiology of Perinatal Infection**

Worldwide, an estimated 14,000 adults acquire HIV infection each day. Approximately 40 percent of these new infections are among women. It is estimated that 1,600 HIV-infected infants are born daily. As is true for HIV infection among adults, most perinatal infection is occurring in the developing world. The highest incidence is in sub-Saharan Africa, and exponential increases are being observed in Southeast Asia and South Asia, particularly India and China.

Perinatal transmission also accounts for almost all new pediatric HIV infections in the United States, where more than 16,000 HIV-infected children were born through 1995. The magnitude of the epidemic is far less in the United States than in the developing world. Even though an estimated 6,000 infants are born each year in the United States to HIV-infected women, fewer than 300 are infected because of the use of zidovudine and other effective antiretroviral regimens during pregnancy and the postnatal period. New HIV infections in women continue to occur, primarily due to heterosexual transmission, and the proportion of women in the infected population continues to increase, particularly among adolescents and women of color.

#### **B. Prevention of Perinatal Transmission**

The face of the pediatric HIV epidemic in the United States and other developed countries was changed after February 1994, when the results of Pediatric AIDS Clinical Trials Group (PACTG) protocol 076 became available. The increase in use of antiretrovirals in the subsequent 5-year period has been accompanied by a marked decrease in perinatal transmission, with significant declines observed as early as 1995. Transmission rates of 3 to 6 percent with zidovudine prophylaxis have been reported in recent studies. Potent combination antiretroviral regimens, which are now the standard of care in the United States and which often reduce the maternal viral load to levels below detection, may lower the risk of transmission even further. Alternatively, elective cesarean section reduces perinatal transmission in women not receiving antiretroviral therapy. A meta-analysis of 15 studies concluded that transmission in women receiving zidovudine was significantly lower with elective cesarean delivery compared to vaginal delivery (2.0 percent versus 7.3 percent). However, in a prospective clinical trial, transmission rates in women receiving zidovudine were similar between those undergoing elective cesarean delivery and those delivering vaginally (2.1 percent versus 3.3 percent). Transmission risk is likely to be very low for women with low HIV ribonucleic acid (RNA) copy numbers, and it is unclear that elective cesarean delivery would provide any added benefit in such circumstances.

The dramatic advances achieved in the developed world in preventing perinatal transmission

have so far had little impact on perinatal infection in developing countries, where most infections occur. Short-course zidovudine and zidovudine/lamivudine regimens have been shown to decrease perinatal HIV transmission to breast-feeding infants. Even though breast-feeding results in some diminution in efficacy over time, infection rates in the zidovudine-receiving infants remain lower than in infants not on this regimen. Recent data from a breast-feeding population in Uganda (HIV Network for Prevention Trials [HIVNET] protocol 012) demonstrate that a simple regimen of nevirapine, given as one dose to women at the onset of labor and one dose to their infants at 48 to 72 hours of age, reduces perinatal transmission by 47 percent compared to a short zidovudine regimen. This nevirapine regimen and a regimen of zidovudine and lamivudine given intrapartum and to the mother and neonate for 1 week, as evaluated in the Perinatal Transmission (PETRA) trial, are the only antiretroviral regimens that have been proven in clinical trials to diminish transmission when administered during labor.

The HIVNET 012 trial results now provide developing countries with the challenge of implementing an effective and less expensive antiretroviral prophylaxis regimen. The cost in U.S. dollars for the nevirapine regimen is approximately \$4, compared to \$50 to \$100 for the short-course zidovudine regimens. However, developing countries have not yet been able to implement such regimens on a nationwide basis because of inadequacies in the existing maternal-child health care services and infrastructure, difficulties in integrating HIV counseling and testing into antenatal care, and the economic reality of severely limited resources to pay for health care.

## **II. Key Scientific Issues**

*While many scientific issues are already being addressed in ongoing NIH-sponsored studies, the global nature of the perinatal HIV epidemic and changes in the character of the epidemic in the United States warrant an increased focus on international collaboration(s). The Working Group recognizes that an increase in research related to the perinatal epidemic in the developing world does not negate the fact that there continue to be critical research questions related to perinatal infection in the United States that must be addressed simultaneously.*

In the United States and other developed countries, where antiretroviral prophylaxis is received by most women identified as HIV-infected and who are receiving prenatal care, transmission rates are as low as 3 to 5 percent. Therefore, many questions relevant to perinatal transmission among non-breast-feeding populations will be difficult to address, because the patient numbers required to evaluate the efficacy of new interventions in randomized, comparative phase III trials are so large that these trials could not realistically accrue a significant number of patients in a timely manner. The effort and expense required to conduct such trials are considerable, making it imperative to develop alternative methodologies to assess these questions. It is likely that a significant proportion of this research will require collaboration between developed and developing countries.

Innovative strategies are needed to detect potential short- or long-term adverse consequences of *in utero* and/or neonatal antiretroviral drug exposure, particularly for the large number of infants who will now not be infected due to antiretroviral prophylaxis. A number of nucleoside analogue drugs are carcinogenic in some rodent studies and can induce mitochondrial

dysfunction, and mutagenicity for experimental animals has recently been demonstrated with some protease inhibitors. While zidovudine prophylaxis appears safe in the short term for women and infants followed as long as 6 years, long-term data are not available. However, minimal information exists regarding the safety of therapy with other antiretroviral drugs during pregnancy. Followup of exposed children for an adequate period of time will present many challenges.

Research related to perinatal transmission in developing countries, where implementation of proven effective antiretroviral regimens remains difficult and where postnatal breast-milk transmission is of concern, has a different focus than in developed countries. The development of effective, inexpensive, and safe interventions to decrease perinatal transmission, while ensuring optimum nutrition by breast-feeding, remains a critical need. A clinical trial in Kenya demonstrated that use of formula decreased postnatal transmission by nearly 50 percent. This trial, however, was conducted in an urban area where safe water was available and where careful instruction of the mothers took place; these results are not generally applicable to rural communities and poor families where a sustainable supply of formula may not be possible and appropriate education about preparation is lacking. Additionally, breast-feeding is the cultural norm in many developing countries, and infected women may fear that formula-feeding their infant would reveal their HIV serostatus and subject them to discrimination or violence. A recent study has suggested that exclusive breast-feeding (no additional water, tea, etc.) may result in transmission rates comparable to those observed with formula feeding. This study requires urgent confirmation, as exclusive breast-feeding for the first 3 to 6 months of life would allow provision of adequate nutrition to the infant.

## **1. Develop additional interventions that would further reduce the risk of transmission in the developing and developed world.**

### *United States and Other Developed Countries*

- Obtain data related to the pharmacokinetics and safety of new antiretroviral agents and combinations. This may occur in classic phase I trials or by developing innovative strategies to evaluate patients receiving therapy for clinical care.
- Evaluate the feasibility and acceptability of rapid HIV counseling and testing during labor of women without prenatal care or of unknown HIV serostatus.
- Evaluate the efficacy of postexposure infant prophylaxis in women first identified as infected during labor (e.g., comparing the HIVNET 012 intrapartum/postpartum nevirapine regimen to a combination antiretroviral regimen). These studies will require multinational collaboration and may require innovative epidemiologic approaches rather than classic phase III clinical trials.
- Develop collaborations between research groups in the United States and international sites in other developed and mid-developed countries to address research issues of high priority for countries in which antiretroviral prophylaxis is now the standard of care. The scientific questions that are addressed must be relevant to all of the

collaborating countries.

- Develop innovative alternatives to randomized clinical trials (e.g., nonrandomized observational trials) capable of reliably addressing issues related to interventions to further reduce perinatal transmission in developed countries.
- Conduct phase I and phase II trials of current and new HIV vaccine products in newborns of HIV-infected women. (Initial trials of vaccine products will likely be conducted in developed countries, but phase I and II studies of vaccine products specific for viral subtypes in developing countries also will be required.)

### *Developing Countries*

- Evaluate the feasibility, acceptability, and implementation of prenatal HIV counseling and testing in general, including rapid HIV testing during labor and expanded access to HIV counseling and testing for family members.
- Conduct longitudinal assessments of the intrapartum/postpartum antiretroviral regimens (HIVNET 012 nevirapine and PETRA zidovudine/lamivudine) to determine efficacy through the weaning period in the breast-feeding population. It is reasonable to expect the HIVNET 012 regimen of nevirapine to become the standard of comparison because of its low cost and feasibility for use in developing nations.
- Evaluate the efficacy of nonantiretroviral interventions for prevention of transmission, including nutritional interventions, vaginal microbicides, antenatal/intrapartum antibiotic prophylaxis of chorioamnionitis, and passive and/or active immunization. Consideration will need to be given to clinical trial design in light of the new results from Uganda (e.g., inclusion of two-dose nevirapine as the standard of care in both the control and study arms).
- Conduct phase I and II trials of current and new HIV vaccine products for specific viral subtypes. These trials would be conducted in developing countries in newborns of HIV-infected women.
- Evaluate interventions, including exclusive breast-feeding, to reduce the risk of breast-milk transmission, the use of antiretroviral or immunologic prophylaxis during the early breast-feeding period combined with early weaning, and the use of breast-milk substitutes to reduce the morbidity and mortality in both uninfected and infected infants.
- Evaluate whether the availability of culturally sensitive family planning services provides acceptable options that are utilized to prevent pregnancies among serologically discordant and seropositive couples.

**2. Define the mechanisms and timing of breast-milk HIV transmission and the role of maternal virologic factors and maternal and infant immunologic (cellular and humoral) and genetic factors in postnatal breast-milk transmission in developing countries.**

- Assessment of the role of maternal/infant immune response in breast-milk transmission, including humoral (e.g., immunoglobulin M [IgM], surface immunoglobulin A [SIgA]) and cellular (e.g., cytotoxic T cells, natural killer cells, and antibody-dependent cellular cytotoxicity) immunologic factors.
- Evaluation of the role of virologic factors (e.g., cell-associated/cell-free load, phenotype, genotype, chemokine receptor use) in breast-milk transmission.
- Studies to better define the influence of maternal factors (e.g., mastitis) and infant factors on breast-milk transmission.
- Clinical trials to assess the efficacy and impact of interventions to reduce breast-milk transmission, including exclusive breast-feeding, antiretroviral interventions, vaccines, early weaning, and/or breast-milk substitutes and alternatives.
- Meta-analysis of data on the timing and incidence of postnatal transmission in selected clinical trials in developing countries to improve the design of intervention studies.
- Evaluation of the influence of genetic factors on breast-milk transmission, including host genetic factors such as the human leukocyte antigen (HLA) haplotype and chemokine receptors and genotypes.

**3. Define effects of *in utero* antiretroviral drug exposure on the fetus and infant.**

- Evaluations *in vitro* and/or in animal models to assess potential mutagenesis or other effects of *in utero* antiretroviral drug exposure on the fetus.
- Laboratory-related evaluation of potential effects of *in utero* antiretroviral exposure in human infants, including evaluation of nucleoside analogue antiretroviral drug incorporation into host deoxyribonucleic acid (DNA); mutagenic potential; chromosomal and/or mitochondrial abnormalities; and the durability of any such changes after antiretroviral prophylaxis has been stopped.
- Studies that continue to evaluate the long-term consequences of antiretroviral drug exposure.
- Studies to develop innovative followup and/or surveillance strategies for long-term followup of antiretroviral-exposed infants not followed in current studies.

**4. Define the mechanism and timing of *in utero* and intrapartum HIV transmission and the role of maternal virologic, immunologic (cellular and humoral), and other genetic factors (e.g., chorioamnionitis) in perinatal transmission.**

In developed countries, it will be important to monitor factors associated with HIV transmission in women receiving antiretroviral therapy (e.g., failures of antiretroviral prophylaxis). For developing countries, risk factors for transmission that are relevant to conditions in the developing world (e.g., infections with other sexually transmitted diseases [STDs] or viral genetic subtypes) are important to identify, especially any factors that might be amenable to simple interventions.

- Evaluation of the influence of maternal virologic factors on HIV transmission in the developing world, such as viral subtype.
- Assessments of trends in the transmission of antiretroviral drug-resistant virus and the impact of drug resistance on the effectiveness of perinatal transmission interventions over time in developed countries. These trends also should be monitored in developing countries as short-course antiretroviral prophylaxis regimens are implemented.
- Evaluation of the influence of maternal and neonatal immunologic factors, particularly cell-mediated immune responses, on transmission.
- Evaluation of the influence of chorioamnionitis and/or other placental abnormalities on transmission.
- Assessment of the influence of genital tract virology and immunology on perinatal transmission and on the factors associated with genital HIV shedding, including antiretroviral therapy.
- Studies on female reproductive tract mucosal immunology and physiology, local immune defense mechanisms, and endogenous and exogenous factors that affect vaginal immune defense mechanisms (including vaginal microbicides) that could influence susceptibility to HIV infection.
- Evaluation of the influence of genetic factors on transmission (including human host genetic factors such as HLA haplotype) and the influence of chemokine receptor genotype on transmission. This effort will require research on populations of varying genetic make-up.
- Investigations to further develop animal models of perinatal HIV infection.

**5. Define barriers and the means to enhance the implementation of interventions known to be effective in reducing HIV transmission (e.g., short course zidovudine or nevirapine prophylaxis and/or use of breast-milk alternatives).**

- Evaluation of social/behavioral factors associated with the acceptance of prenatal HIV counseling and testing by pregnant women in developing countries and immigrant women from these countries who are now living in developed countries, and evaluation of the factors associated with their return for HIV test results.
- Evaluation of the implementation and acceptability of different models of prenatal HIV counseling and testing.

**6. Define the benefits and risks of elective cesarean delivery to reduce perinatal transmission.**

- Studies to evaluate the role of elective cesarean delivery in the era of HAART. A population-based epidemiologic approach rather than a randomized clinical trial will likely be required, due to the requirement for extremely large numbers of patients in a clinical trial when transmission rates are very low.
- Studies to evaluate the complications of operative delivery in HIV-infected women.

**III. Scientific Priorities**

**A. United States and Other Developed Countries**

**High Priority**

1. Develop mechanisms to evaluate the potential adverse consequences of exposure to prenatal, perinatal, and postnatal antiretroviral therapy, as an estimated 6,000 infants per year are exposed.
2. Evaluate pharmacokinetic and safety data and preliminary virologic effectiveness for new antiretroviral drugs and combinations of drugs in pregnant women and neonates (including classic phase I trials but also utilizing new innovative methodologies to obtain such data, including observational data on women receiving antiretroviral drugs).
3. Evaluate the effects of combination antiretroviral therapy, non-zidovudine containing regimens, virus burden, and drug resistance on the risk of transmission over time. These assessments would likely need to be done through observational epidemiologic studies.

## **Medium Priority**

1. Continue to evaluate the seroincidence of HIV in reproductive-aged women and seroprevalence in pregnant women.
2. Conduct phase I and II vaccine trials on safety and immunogenicity in pregnant HIV-infected women and their newborns.
3. Evaluate interventions to prevent HIV transmission to women (e.g., microbicides).
4. Evaluate the efficacy of elective cesarean section for reducing HIV transmission in women receiving combination antiretroviral regimens. Evaluate the morbidity of operative delivery in infected women.
5. Evaluate the acceptance and feasibility of rapid HIV counseling and testing of women during delivery.
6. Better define the pathogenesis of fetal HIV infection.

## **Low Priority**

1. Evaluate the effect of genital mucosal factors on perinatal transmission.
2. Evaluate the reproductive decision making of HIV-infected women and discordant couples.

## **B. Developing Countries**

### **High Priority**

*The Working Group recognizes that most scientific questions, including those of the highest priority, cannot be addressed without investment in the infrastructure within the developing countries in which the research will be conducted. This includes development of clinical and laboratory facilities and professional resources.*

1. Evaluate simple and inexpensive interventions to decrease transmission, including:
  - a) Approaches specifically targeted toward prevention of postnatal transmission through breast milk, including antiretroviral intervention and other approaches such as exclusive breast-feeding, vaccine interventions, early weaning, and use of breast-milk substitutes. Studies designed to better understand the timing and mechanisms of breast-milk transmission would complement this research.
  - b) Non-antiretroviral interventions targeted to prevent intrapartum transmission.

2. Evaluate the factors associated with successful implementation of effective regimens (including the assessment of the feasibility and effectiveness of various methods to enhance antenatal care and implement prenatal HIV counseling and testing) and evaluate the factors associated with the acceptance of HIV counseling and testing by pregnant women and those factors that influence their return for test results.
3. Evaluate the seroincidence of HIV in reproductive-aged women and seroprevalence in pregnant women.
4. Develop and evaluate new methods for rapid diagnosis of HIV infection in women during labor and at delivery (including blood or saliva tests) and evaluate the feasibility of implementing such rapid testing for women of unknown HIV serological status at the time of labor.

### **Medium Priority**

1. Evaluate adverse consequences of antiretroviral prophylaxis for women and their infants.
2. Evaluate interventions to prevent HIV heterosexual transmission to women (e.g., use of microbicides).
3. Evaluate the impact of HIV subtypes on perinatal transmission and implications for diagnosis of infection in the infant.
4. Evaluate risk factors for intrauterine and intrapartum transmission relevant for the developing world (e.g., malaria, HIV subtype).
5. Evaluate interventions to reduce unwanted pregnancy.



## **Pediatric HIV Infection**

Subcommittee Chair: Kenneth McIntosh, M.D.  
Subcommittee Co-Chair: James McNamara, M.D.

### **I. Background**

#### **A. United States and Other Developed Countries**

HIV-infected children in the United States are, for the most part, started on antiretroviral drugs shortly after the diagnosis of HIV-infection is made. This is in contrast to some western European countries, where about one-third of children with known HIV infection have not yet started treatment with antiretroviral drugs, and half of those who have been treated have not received protease inhibitors.

Studies of pediatric HIV infection over the past 15 years, including natural history cohorts, treatment protocols, and studies on the pathogenesis of vertically transmitted infection, have expanded greatly the knowledge base for this disease in children. Many of these studies have involved children on either no antiretroviral treatment or on nucleoside reverse transcriptase inhibitors. Treatment regimens including PIs or other potent combinations have only been in use in pediatrics since about 1997, and studies of their effects on the natural history of HIV disease and long-term studies on their impact on HIV-infected children are ongoing.

#### **B. Developing Countries**

While the epidemic has stabilized in the United States and Western Europe, the number of new infections in children in the rest of the world is rising rapidly. In the developing world, very few children have received antiretroviral treatment.

It is estimated that there are approximately 960,000 children under 14 years of age living with HIV infection in sub-Saharan Africa. Worldwide, an estimated 600,000 new infections occur each year, but due to the high death rates without antiretroviral treatment, an estimated 500,000 HIV-infected children die annually. In southern Africa, the HIV epidemic in children threatens to wipe out gains made in infant and child survival through childhood immunization and oral rehydration programs.

Progression from initial HIV infection to severe disease and death is more rapid in children in developing countries than in industrialized countries. This is probably due to the increased risk of infection associated with ubiquitous pathogens (particularly those causing diarrhea and pneumonia), poor nutrition, and the lack of access to standard medical care.

Many HIV-infected children in these settings go without diagnosis, owing to the lack of adequate resources and a fatalistic view of the disease in the absence of specific treatment. Although treatment with antiretroviral drugs may be beyond the resources of many developing countries, nonantiretroviral treatments such as vitamin supplementation and other nutritional interventions, and prophylaxis of opportunistic infections (OIs) with inexpensive antibiotics such as

trimethoprim/sulfamethoxazole may be feasible to evaluate.

Although the primary mode of acquisition of HIV infection in the developing world is perinatal transmission, horizontal infection remains a threat. For example, in Romania, an epidemic of pediatric HIV infection was found to be secondary to injections of institutionalized and hospitalized children with inadequately sterilized needles and syringes.

Finally, the ravages of the pediatric HIV epidemic are not confined to the infected children themselves. It is estimated that deaths due to HIV infection in parents have resulted in over 8 million uninfected children who have been orphaned due to HIV disease. This is a problem of growing and overwhelming proportions.

## **II. Key Scientific Issues**

### **A. United States and Other Developed Countries**

#### **1. Obtain data on the pharmacokinetics and safety of new antiretroviral drugs and combination therapies in infants and children.**

New drugs and biological agents for the treatment of HIV infection and its complications will continue to be developed by the pharmaceutical industry. The safety, tolerability, and pharmacokinetics of these agents will need to be assessed in children in a timely manner to allow early licensure for infected individuals of all ages. Phase I and II data (e.g., pharmacokinetics, safety) will need to be obtained for promising interventions in infants and children. Conducting these studies poses particular challenges such as the development of suitable formulations for children as well as the complicated assessment of toxicity, tolerability, palatability, and pharmacokinetic properties of new agents in the context of combination therapies. Classical phase I and phase II trials as well as innovative approaches to obtaining the data are needed.

#### **2. Define treatment strategies and options for HIV-infected children at all stages of HIV disease.**

How to best use the treatments that are currently available for children remains an important issue. The following treatment strategy questions remain important today in optimizing and implementing effective therapies for infected children: What is the best treatment option when initiating treatment? When should treatment be initiated? What criteria should be used to initiate a switch of antiviral therapies? What are the simplest regimens that will provide durable antiviral responses with the least toxicity? When is prophylaxis for OIs no longer needed for the infected individual with immunologic recovery?

Children living with HIV infection in the United States today are themselves at all stages of clinical progression of HIV infection or AIDS. This situation is likely to continue for an indefinite period of time. But the majority are children older than 2 years. Some are in excellent health, with almost intact immune systems; some have advanced disease, with virus that has developed multidrug-resistance mutations and with heavily damaged

immune systems. Most of the infected children are in various stages between these two extremes. All of these children are gradually aging, with all the attendant questions of physiological, psychological, and social development during these critical years. The management and treatment of these children pose enormous challenges with many unknowns that need to be studied.

Within the broader population of HIV-infected children, there are several distinct populations that pose both separate and overlapping scientific questions.

- *Children who are treatment naive or who have early HIV infection.* Small numbers of infants in this population are being studied intensely to answer a variety of pathogenesis-related questions concerning the effects of treatment on viral load and viral reservoirs during acute and early HIV infection and the impact of treatment on the immune system, particularly its anti-HIV immune responses. Clinically, the goal of these studies is to assess if early, intensive treatment leads to better control of virus both in the first years of life and in the long term. In the United States, the small number of new HIV infections in infants dictates the need for a coordinated national agenda to answer the questions of highest priority as well as the establishment of collaborations with other developed nations to answer mutually important questions in a timely manner.
- *Older antiretroviral-experienced children with stable HIV infection.* The older treated child with HIV infection presents somewhat different questions. Major issues that are particularly important in these children are those related to adherence with complex treatment regimens; to the assessment of resistance in the pediatric setting, where viral loads are higher than in adults, as well as the impact of treatment on other critical pediatric targets such as the developing nervous system; to the entrance into puberty; and to general issues of growth and development. Other questions include those related to the evaluation of immune modulators that may lead to the enhancement of HIV-specific immune responses.
- *Children with prior antiretroviral therapy and advanced HIV disease.* Advanced HIV disease is different in children, and therefore there are special needs for research in this area. Studies in this group are targeted at evaluating new therapies in the context of both treatment failure and multidrug-resistant viral strains and that of evaluating virologically successful interventions for evidence of immune reconstitution. This group also is at greatest risk for the development of infectious and noninfectious complications of HIV infection. Studies to improve the prevention and treatment of these complications are needed.

### **3. Evaluate the long-term efficacy and toxicity of antiretroviral drugs in HIV-infected children.**

All children with HIV infection also pose a particular challenge in relation to long-term treatment. It is likely, from the information available so far, that early treatment can be successful in suppressing virus and allowing normal or near-normal development of the

immune system. However, no regimen is successful for all infants, and even those infants with optimal suppression of virus seem to lack an immune response to HIV. The future for these children or other HIV-infected children on drug treatments is not clear, and it appears that all of these children will require potent treatment, using multiple antiretroviral drugs, possibly in conjunction with nonspecific or antigen-specific immunologic enhancing agents.

The efficacy and toxicity of these drugs and biologicals in this setting of long-term chronic treatment is not known. It also is not known how to minimize toxicity while keeping the viral infection suppressed. There is a lack of information on immunologic or virologic markers as prognostic identifiers of delayed HIV disease progression. In some children who develop potent natural defenses against HIV or who are infected with less virulent viral strains, long-term outcomes might be improved by beginning treatment later in childhood.

#### **4. Evaluate HIV vaccines in children.**

As potentially effective vaccines to prevent HIV infection are developed, children will become an important public health focus for these vaccines. Vaccine studies aimed at the prevention of horizontal transmission in children, while not of first priority in the early development of vaccines, will eventually become a critical part of the deployment of such vaccines. The use of HIV vaccines as a therapeutic intervention is also of considerable interest to augment lagging HIV-specific immune responses in virologically suppressed children.

### **B. Developing Countries**

#### **1. Develop methods for early diagnosis relevant to developing countries.**

The study of pediatric HIV infection requires accurate diagnosis. During the critical first months of life, routine serologic assessments for HIV cannot be used. Thus, there is a need for simple, inexpensive techniques for detecting the presence of HIV that are both sensitive and specific. Polymerase chain reaction (PCR), the method used most frequently in the United States and Europe, is not available in most developing countries, and HIV antigen-based techniques may be more applicable. Once HIV infections are routinely identified, the nature of the illness and its complications in infants and children in all parts of the world can be defined clearly.

#### **2. Develop strategies to manage HIV infection in children that are relevant to conditions in developing countries and that can be implemented.**

It is clear that most public health programs in countries around the world cannot afford the intensive treatment of children that is the standard of care in the United States. Developing countries may decide on an individual basis that an investment in prevention of mother-to-child transmission takes precedence. Still, in all countries of the world, infants and children are being infected and require some organization of their HIV health care. In these countries, management schemes can be constructed that fit with the available resources,

and research designed to optimize these schemes becomes an important objective.

### **3. Evaluate the impact of parental death due to HIV on uninfected children (AIDS orphans).**

In many countries, the care of HIV-uninfected children who are orphaned by the epidemic has become a problem of enormous proportions because of the tremendous toll taken by HIV infection on young women with families. This also is a situation for which solutions are not readily available and where research is likely to yield palpable benefits to society.

## **III. Scientific Priorities**

*Since high-risk behaviors for transmitting HIV infection begin in the adolescent years, prepubertal children are clearly a major, if not the major, target for widespread immunization by any vaccine with proven preventive activity. The Working Group felt that, once a successful HIV vaccine candidate has been identified, research to examine the safety, immunogenicity, and efficacy of such preventive vaccine candidates in prepubertal children is the highest priority in both the developing and the developed world.*

### **A. United States and Other Developed Countries**

#### **High Priority**

1. Developing and testing new drugs and immune-enhancing agents.

New and better drugs are urgently needed, particularly against new viral targets, to improve the virologic efficacy of currently available drugs.

The Working Group supports the idea that NIH should continue to invest in the development and testing of drugs and other therapies against HIV and the infectious and noninfectious complications of HIV, as well as the development and testing of immune modulators that may help to augment the immunologic reconstitution of children with advanced HIV disease. This testing must include not only the customary studies of pharmacology, immediate toxicity, and virologic efficacy, but also, for useful drugs that enter the marketplace, drug interactions with other agents used in HIV-infected children and long-term toxicity, which has become an issue of increasing concern.

2. Obtain pediatric-specific pharmacological data.

While some pharmacological studies are performed to support drug licensure in the pediatric population, all too frequently many pharmacological questions remain about the appropriate dosing of children in some populations (particularly the newborn, infant, and adolescent).

- a) New pharmacological approaches are needed to maximize the information that is available from limited sampling approaches.
  - b) Research support is needed to study developmental changes in infant and child drug metabolism to allow better modeling of drug pharmacokinetic profiles.
  - c) The development of child-friendly drug formulations and delivery regimens (pleasant tasting, reasonable volumes, long-dosing intervals) is urgently needed.
3. Develop strategies for children requiring prolonged treatment.

Most HIV-infected children in the United States and other developed countries require prolonged treatment. This raises many questions that were identified as of high priority by the Working Group, including the following:

- a) What are the best treatment alternatives for children with advanced HIV disease?
- b) When should therapies be switched in children who are failing treatment?
- c) What strategies should be used for treating children with multidrug-resistant strains of HIV?
- d) What are the long-term consequences and toxicity of combination regimens in infants and children, and how can they be optimally identified, avoided, or treated? These consequences include the psychological burden of prolonged, rigorous drug regimens, as well as the metabolic changes induced in lipids, mitochondrial function, and other physiologic functions.

### **Medium Priority**

1. Treatment strategies for early infection that are unique to pediatrics.

HIV-infected infants present a unique challenge in treatment. A serious concern remains as to how to optimally use new interventions for newborn infants and small children with developing immune systems and, potentially, long lives of chronic viral infection.

2. Immune reconstitution.

While it is clearly important to reduce HIV viral load to the lowest possible level, the evaluation of the impact of markedly reduced viral load levels on the recovery of the immune system is also critical. Several Working Group members stressed the unique features of immune recovery in children where the thymic environment is more robust than that seen in most adults. Studies felt to be important are those that help define the extent of immune reconstitution based on lymphocyte phenotypic and functional

characteristics, the markers to identify thymic function, and the durability of these responses. Data in adults and children suggest that immunologic recovery may be augmented by using immune modulators such as cytokines (interleukin-2, interleukin-7, interleukin-12, and granulocyte macrophage colony stimulating factor). This area of research merits further investigation in the pediatric population. Therapeutic immunization strategies to induce or expand HIV-specific immunity deserve further exploration.

3. Virologic evaluations.

The Working Group supported the concept that more detailed viral load evaluations are needed beyond clinically available plasma HIV RNA copy measurements. Studies on potentially sequestered viral compartments in the body and latent HIV viral pools were identified as priority areas.

4. Natural history of treated disease.

Ongoing natural history studies have provided important information on HIV pathogenesis. Presently available treatment options have changed the course of the HIV epidemic and have altered how we think about this disease. OIs have been markedly curtailed, but questions remain about what the most important infectious disease complications are today and what the impact is on uniquely pediatric problems such as lymphoid interstitial pneumonitis, as well as what the new opportunistic diseases will be in the future. Recent findings on chemokines, chemokine receptors, and their genotypes as they relate to pediatric disease progression suggest that additional research is needed in this area. Working Group members also noted that, as the HIV-infected pediatric population ages, understanding growth and the many changes associated with puberty and young adulthood should be considered a priority.

## **B. Developing Countries**

### **High Priority**

1. Developing and testing management schemes (including antiretroviral drugs).

While substantial strides are being made in preventing maternal-infant transmission, there are no low-cost, effective treatment strategies for children diagnosed with HIV infection. The Working Group considered it a high priority to conduct studies that addressed affordable, practical treatments for the following:

- a) HIV and its complications.
- b) Infections associated as co-factors of HIV disease progression.
- c) Prevention of OIs.

2. Social, behavioral, and legal issues.

The Working Group acknowledged the wide range of issues raised by the HIV epidemic. Examples include AIDS orphans, the impact of AIDS on economic development, and culture-specific issues on preventive strategies. The group suggested that further NIH-sponsored research should address many of these issues as stand alone initiatives or efforts integrated into other research projects.

**Medium Priority**

1. Natural history questions.

Research needs to be conducted to define a broad range of pathogenesis questions related to HIV complications and risk factors for disease progression in the diverse settings of developing nations. The Working Group emphasized the importance of identifying the most important OIs (including lymphoid interstitial pneumonitis), cancers, and other complications of HIV infection in developing nations. Additionally, a better understanding of host genetic factors and immunologic responses—as well as the potential impact that different viral subgroups may have on disease progression—will foster a better understanding of the epidemic in these countries so that affordable and appropriate intervention strategies can be developed.

2. Diagnostic methods.

Simpler and cheaper methods to diagnose HIV infection in young infants are needed.

## Adolescent HIV Infection

Subcommittee Chair: Craig M. Wilson, M.D.  
Subcommittee Co-Chair: Audrey Smith Rogers, Ph.D.

### I. Background

#### A. United States

In contrast to the attenuation of the AIDS epidemic in infants in the United States, HIV infection rates are unchanged in adolescents and young adults. In 1998, there were 727 new HIV infections reported among 13- to 19-year-olds and 1,999 new infections reported among 20- to 24-year-olds. In the 13- to 19-year-old group, 62 percent were female, and in the 20- to 24-year-old group, 43 percent were female. As with infants/children and women, the majority of all reported new HIV infections are in minority populations, with 62 percent in the 13- to 24-year-old age group. The primary mode of transmission for reported AIDS cases among adolescent females has always been heterosexual transmission, while the primary mode of transmission in adolescent males became prominently male-to-male sexual transmission in 1995. Thus the picture of the expanding adolescent HIV epidemic based on reports to the CDC is one that is increasingly female, minority, and related to sexual transmission (i.e., heterosexual activity in females and homosexual activity in males).

Accurate information on how many teens in the United States are HIV-infected remains elusive. The Multicenter AIDS Cohort Study (MACS) showed that age at seroconversion was a significant predictor of time to AIDS. An extrapolation would suggest that the median age at which AIDS would occur in individuals infected at the age of 13 years occurs 11.6 years later at age 24.6 years. MACS data also would seem to indicate that it is unlikely that more than 10 percent of the individuals infected at age 13 would have developed AIDS while they were still teenagers. Based on these data, if one assumes an annual 1 to 3 percent rate of progression to AIDS in teens, the size of the HIV-infected pool required to generate the 1997 incidence of AIDS cases in 13- to 19-year-olds would be 12,000 to 38,000; the corresponding pool in 20- to 24-year-olds would be 62,000 to 185,000.

Primary prevention research efforts supported by NIH have generally concentrated in investigator-initiated (R01) single studies or limited multicenter studies. In the current NIH portfolio of active projects, over 27 adolescent-specific studies are identified as developing and evaluating social and behavioral interventions to reduce HIV transmission. More than 22 adolescent-specific studies are identified as examining the determinants and processes influencing HIV-related risk and protective behaviors, including one national probability sample of youth surveyed in part for some HIV-specific information.

Information on the manifestations and progression of HIV disease is critical to the development and evaluation of a therapeutic agenda. NIH has supported two prospective observational studies of HIV-infected youth designed to collect data about growth, development, and disease progression: one in youth with hemophilia who had been infected through blood products (Hemophilia Growth and Development Study); the other, in youth (13 to 18 years) infected

through sexual behavior (the REACH Project of the Adolescent Medicine HIV/AIDS Research Network). The latter examines sexually transmitted infection, co-morbidity, and the behavioral consequences of HIV disease on psychosocial well-being and clinical management as well.

Adolescent-specific therapeutic interventions are just now emerging, notably PACTG 381 (Establishment and Maintenance of Long-Term Undetectable Plasma HIV-1 RNA: Correlation with Immunologic Reconstitution and Viral Dynamics B), which is now actively accruing adolescent participants. Clinical research on HIV-infected youth has been hampered by the disproportionately small number of the estimated HIV-seropositive youth who are identified and successfully linked to health care. Consequently, there exists no broad-based clinical research infrastructure for HIV-infected adolescents with their particular challenges and unique management demands comparable to those established to address adult and pediatric HIV-infected populations.

## **B. Developing Countries**

Eleven million of the 33 million people living with HIV/AIDS worldwide are between the ages of 15 and 24 years; of the 5.8 million new infections, half occur in youth. Worldwide, infections in young people happen at the rate of five per minute. Enhanced risk is exhibited in the particular social and biologic vulnerabilities of young women in many societies; the exploitation and abuse of youth in countries with civil unrest or economic upheaval; and the exceptionally dangerous intersection of drugs, sex, and prostitution.

In the strictly behavioral arena, several adolescent-specific R01s have been funded to examine risk and protective factors related to HIV transmission in sub-Saharan African countries. In general, adolescents and young adults have not been consistently identified as distinct groups in NIH-funded population-based prevention efforts in resource-poor countries.

## **II. Key Scientific Issues**

### **A. United States and Other Developed Countries**

#### **1. Primary prevention efforts.**

Current efforts related to behavioral interventions that incorporate skill-building programs need to be expanded and coordinated among the NIH Institutes. Support should be continued for basic social science research on the influence of family, social, and sexual networks on sexual debut, on alcohol and drug use, and on subsequent high-risk activity. There is a need to explore primary prevention efforts for adolescents that combine different approaches (e.g., the treatment of STDs, the use of barrier methods, and the use of microbicides). Additional work is needed to understand the maturation of the mucosal immune response in adolescents for further development of mucosal vaccines.

HIV-infected youth are now appearing in health care in increasing numbers, so there is an emerging opportunity to assess why and how prior prevention strategies and programs failed. Studying the particular constellation of risk(s) that led to HIV infection in

seropositive adolescents may produce insights into targeting strategies toward subpopulations at increased risk. Further study also is required to identify which factors constitute barriers to the effective utilization of preventive programs in the infected population.

## **2. Discovering windows of therapeutic opportunity.**

Recent data provide evidence for significant differences in the immune system between male and female youth; the long-term implications of this disparity need to be established. Other data demonstrate high levels of naive CD8 cells in response to HIV infection in adolescents with CD4 cell counts over 500 cells/microliter, suggesting functioning thymic tissue in some HIV-seropositive adolescents. These observations may indicate that the immune system in HIV-infected adolescents may be capable of better responses to neoantigens and better cytotoxic T-cell responses to HIV than the immune system of infected children or adults. The majority of adolescent HIV infection is acquired through sexual activity during or immediately post-puberty and therefore may represent an infection in process of becoming established. The effects of early, aggressive therapy need to be studied, as well as the immunologic potential of adolescents and the development of methods for enhancing their HIV-specific cellular immune responses. Alternatively, study is needed on the effect(s) of delaying treatment when clinical parameters exhibit no apparent damage and the probability of drug adherence is low. A question that also needs to be addressed is whether there are specific immunogenetic markers in this population to guide decision-making on the initiation of therapy.

Chronic, complicated therapeutic regimens initiated during the behavioral changes of adolescence present difficulty for most teens. Efforts to simplify regimens are needed. The pharmacokinetics of available agents need to be studied to determine the feasibility of less frequent dosing. In addition, the profiling of specific biotransformation or elimination pathways may permit the individualization of therapy, taking advantage of longer drug half-lives that are naturally occurring or are induced by another agent (e.g., hydroxyurea and dideoxyinosine [ddI]).

## **3. Behavioral consequences and implications of HIV infection.**

All HIV-infected youth are faced with the social and physical developmental challenges of puberty that make the acceptance of chronic illness, of complex drug regimens, and of disclosure to peers an intense and complicated endeavor. The consequences of HIV infection for adolescents is a profoundly understudied area demanding attention. In addition, there are few adolescent-specific studies to develop strategies to improve treatment adherence and to prevent or minimize the negative physical, psychological, cognitive, and social consequences of HIV infection, particularly during the critical developmental periods of adolescence. Preliminary data indicate that less than 41 percent of youth who have been prescribed antiretroviral therapy actually use it as indicated. Failure to achieve treatment adherence in a population with continuing unprotected sexual activity has both individual and public health implications for drug resistance and requires further study.

#### **4. Biologic consequences of HIV infection and its treatment.**

The long-term consequences of the newer drug therapies with demonstrated metabolic effects administered to adolescents during periods of pronounced growth and sexual maturation are unknown and require investigation. As these more effective antiretroviral agents are used more widely in youth, the resulting improved survival may permit the emergence of HIV-related malignancies. Recent data indicate that the rates of cervical human papillomavirus (HPV) infection and squamous intraepithelial lesions were higher among HIV-seropositive female adolescents than in HIV-uninfected girls despite similar sexual risk behaviors and the relatively healthy state of the HIV-seropositive participants. The effect of this co-morbidity and others requires continued evaluation. The seroprevalence of hepatitis B (HBV), as measured by HBV core antibody (HBcAb), in the HIV-seropositive participants of the REACH cohort was 23.7 percent overall (48/202): 28 percent in the males (14/50) and 22.3 percent (34/152) in the females. Of the HBcAb seropositive participants, 21 percent (10/48) had evidence of active HBV infections: 15 percent (5/34) of the females and 36 percent (5/14) of the males. The seroprevalence of hepatitis C virus in the REACH cohort was 1.6 percent and was similar in males and females.

#### **5. Rapid transfer of information to community programs.**

Current behavioral approaches to primary prevention are wide and varied. A mechanism for identifying and disseminating information on the factors involved in successful strategies that can be generalized needs to be established; such a mechanism also should include information on the circumstances under which such strategies fail. Immediate and useful dissemination of research findings to community-based organizations struggling under the weight of the HIV epidemic must be considered a key part of any research agenda.

#### **B. Developing Countries**

The overwhelming extent and devastating consequences of sexual transmission of HIV in adolescents and young adults in resource-poor countries coupled with the cost of individual treatment and the prevention of perinatal transmission necessitates an emphasis on strategies to prevent further HIV infection in youth. Behavioral approaches and biologic, chemical, or physical barrier protection strategies must be directed toward youth. These types of behavioral interventions require careful attention to the social, political, and religious dimensions of the issues to be addressed. Consequently, primary prevention efforts need to:

- Be community-based with broad consultation and alliances with community leaders (formal and informal), honoring supportive familial or cultural traditions.
- Preserve traditional practices that advance societal connectedness and cohesion while understanding traditions, such as gender power imbalance, that will impede successful implementation.

- Recruit, train, and empower youth as peer educators and outreach workers.
- Acknowledge and incorporate positive components of the evolving global youth culture.
- Test feasibility and acceptability of messages and methods with local youth.
- Provide interventions that combine more than one prevention modality and coordinate health prevention efforts with economic and educational efforts, since the effect of education and economic empowerment of women in patriarchal cultures on delaying the sexual debut of young women has been well demonstrated.

### **III. Scientific Priorities**

#### **A. United States and Other Developed Countries**

*Inherent in this listing of priorities for the adolescent research agenda is the understanding that specific attention must be directed toward building an adolescent medicine multidisciplinary research infrastructure to implement the domestic research agenda in collaboration with existing research groups. The base activities of this infrastructure would also include evaluating approaches to identify HIV-seropositive and at-risk adolescents and their linkage(s) to care. Other than primary prevention efforts, the research agenda cannot be accomplished without this infrastructure.*

#### **High Priority**

1. Primary prevention of new infections:
  - a) Continuing the current efforts to develop behavioral interventions that incorporate skill-building programs aimed at community, social network, family, dyadic, and individual levels;
  - b) Coordinating behavioral research efforts with research into acceptable and feasible biologic, chemical, and barrier protection studies; and
  - c) Continuing basic social science research into the influence of family, social, and sexual networks on sexual debut, alcohol and drug use, and subsequent high-risk activity.
2. Therapeutics:
  - a) Optimizing therapy through management trials evaluating simple therapeutic regimens and long-term adherence interventions; and
  - b) Evaluating the complications of therapy, particularly metabolic and cardiovascular consequences of protease inhibitor therapy during sexual

maturation and adolescent growth.

### **Medium Priority**

1. Preventive vaccine preparedness studies examining acceptability and feasibility of a preventive vaccine initiative as well as the ethical considerations inherent in vaccine program implementation.
2. Secondary prevention by preserving health in HIV seropositive youth through:
  - a) Characterizing adolescent-specific immune responses to HIV infection, including both mucosal and systemic immune responses and the influences of adolescent-specific characteristics such as reproductive immaturity and hormonal changes. The effects of factors common in adolescents such as the presence of STDs and substance use also should be examined.
  - b) Adolescent-specific HPV-associated malignancies (cervical and anal).
3. Therapeutic trials to explore capacity for immune recovery.

### **Low Priority**

1. Study efforts to inform HIV-infected youth about the particular constellation of risks that can result in HIV infection.
2. Examine the barriers HIV-infected youth face that prohibit the full use of community HIV/STD prevention programs.
3. Study the role of mental illness, including conduct disorder, in influencing HIV-related risk behaviors.
4. Study the effect that the availability of efficacious antiretroviral therapy has on HIV-related risk behaviors among HIV-uninfected adolescents.
5. Characterize the immune response in HIV-uninfected adolescents (mucosal and systemic), examining hormonal influence and co-infection with commonly occurring sexually transmitted diseases in adolescents.
6. Characterize immunologic, immunogenetic, and virologic factors in perinatally infected adolescent nonprogressors.
7. Study disorders of growth and body composition that result from the effects of HIV disease on the hypothalamic pituitary axis.
8. Therapeutics:

- a) Pharmacokinetic profile of pubertal effects on the cytochrome P450 system.
- b) Effective salvage strategies for treatment-experienced adolescents who are failing treatment.
- c) Therapeutic vaccines.

9. Behavioral research:

- a) Studies on the determinants of effective HIV health care utilization, including effective methods of identifying and linking HIV-infected youth to health care.
- b) Studies on the psychosocial consequences of HIV infection and the predictors of mental health and optimal functioning.
- c) Studies on the determinants of disclosing HIV serological status and the derivation of theoretically based strategies for facilitating appropriate disclosure of HIV serological status.
- d) Studies on the determinants of continuing high-risk behaviors and failure to adopt preventive measures.
- e) Studies on the effects of therapy-induced viral suppression on family, career, and life-planning decisions (e.g., pregnancy, family planning attitudes and practices).
- f) Studies on the effects of therapy-induced viral suppression on continuing high-risk behaviors.
- g) Studies on the impact of therapy on quality of life and normal adolescent development.

## **B. Developing Countries**

### **High Priority**

1. Primary prevention community-based efforts honoring supportive familial or cultural traditions, involving youth in the design and implementation, and providing interventions that combine more than one prevention modality.



## Appendix I

### Working Group To Review the NIH Perinatal, Pediatric, and Adolescent HIV Research Priorities

June 10-11, 1999

DoubleTree Hotel at Tysons Corner  
Falls Church, VA

#### AGENDA

#### Thursday, June 10, 1999

#### Morning Session

8:30 Introduction and Welcome

*Dr. Neal Nathanson  
Office of AIDS Research, NIH*

Goals and Objectives

*Working Group Chair:  
Dr. John Modlin  
Dartmouth-Hitchcock  
Medical Center*

#### **PERINATAL AGENDA**

8:45 Epidemiologic Overview: *Perinatal Transmission*

Domestic

*Dr. Mary Glenn Fowler  
Centers for Disease Control  
and Prevention*

International

*Dr. Joseph Saba  
Joint United Nations  
Programme on HIV/AIDS*

9:15 Natural History Agenda

Women and Infants Transmission Study  
(WITS)

*Dr. Celine Hanson  
Texas Children's Hospital*

Perinatal AIDS Collaborative Transmission  
Study (PACTS)

*Dr. Mark Bulterys  
Centers for Disease Control  
and Prevention*

**Thursday, June 10, 1999**

**Morning Session**

9:45 Prevention Agenda

Pediatric AIDS Clinical Trials Group  
(PACTG) Agenda

*Dr. Gwendolyn Scott  
University of Miami School  
of Medicine*

HIV Network for Prevention Trials (HIVNET)  
Agenda

*Dr. Brooks Jackson  
Johns Hopkins University*

Centers for Disease Control and Prevention  
(CDC) Agenda

*Dr. Mary Glenn Fowler*

UNAIDS Perinatal Work Group

*Dr. Joseph Saba*

Summary of NIH Portfolio

*Dr. Lynne Mofenson  
National Institute of Child  
Health and Human  
Development, NIH*

11:00 **BREAK**

11:15 Discussion of Research Needs

*Session Chair:  
Dr. Catherine Wilfert  
Elizabeth Glaser Pediatric  
AIDS Foundation*

*NIH Session Co-Chair:  
Dr. Lynne Mofenson*

12:45 **LUNCH**

**Thursday, June 10, 1999**

**Afternoon Session**

***ADOLESCENT AGENDA***

Focus on Adolescent-Specific/Unique Research  
Issues and Opportunities

1:45 Epidemiologic Overview: Focus on *Adolescents*

Domestic

*Dr. Donna Futterman  
Montefiore Medical Center*

International

2:05 Natural History Agenda

Research for Excellence in Adolescent Care  
and Health (REACH)

*Dr. Barbara Moscicki  
University of California,  
San Francisco*

**Thursday, June 10, 1999**

**Afternoon Session**

2:25 Prevention Agenda (including Behavioral Research)

Centers for Disease Control and Prevention Programs

Summary of NIH Portfolio

NIH Panel for Questions and Answers

*Ms. Janet Cleveland  
Centers for Disease Control  
and Prevention*

*Dr. Audrey Rogers  
National Institute of Child  
Health and Human  
Development, NIH*

*Dr. Christine Bachrach  
National Institute of Child  
Health and Human  
Development, NIH*

*Dr. Rodney Hoff  
National Institute of Allergy  
and Infectious Diseases, NIH*

*Dr. Willo Pequegnat  
National Institute of  
Mental Health, NIH*

*Dr. Vince Smeriglio  
National Institute on  
Drug Abuse, NIH*

3:25 Therapeutic and Adherence Agenda

Pediatric AIDS Clinical Trials Group (PACTG)

Research for Excellence in Adolescent Care and Health (REACH)

*Dr. Patricia Flynn  
St. Jude Children's  
Research Hospital*

*Dr. Craig Wilson  
University of Alabama  
at Birmingham*

3:45 **BREAK**

4:00 Discussion

*Session Chair:  
Dr. Craig Wilson*

*NIH Session Co-Chair:  
Dr. Audrey Rogers*

5:30 **ADJOURN**

Friday, June 11, 1999

Morning Session

**PEDIATRIC AGENDA**

8:30 Epidemiologic Overview: Focus on *Infected Children*

*Dr. Pascale Wortley  
Centers for Disease Control  
and Prevention*

Domestic

International

8:50 Natural History Agenda

Women and Infants Transmission Study  
(WITS)

*Dr. Celine Hanson*

Perinatal AIDS Collaborative Transmission  
Study (PACTS)/Pediatric Spectrum of  
Disease Surveillance (PSD)

*Dr. Marc Bulterys  
Centers for Disease Control  
and Prevention*

Summary of NIH Portfolio

*Dr. James McNamara  
National Institute of Allergy and  
Infectious Diseases, NIH*

9:20 Treatment Agenda

Pediatric AIDS Clinical Trials Group (PACTG)

*Dr. Steven Spector  
University of California,  
San Diego*

NCI Clinical Intramural Program

*Dr. Robert Yarchoan  
National Cancer Institute, NIH*

Pediatric European Network for Treatment of AIDS  
(PENTA)

*Dr. Carlo Giaquinto  
Pediatric European Network for  
Treatment of AIDS*

10:35 **BREAK**

10:45 Discussion

*Session Chair:  
Dr. Kenneth McIntosh  
Children's Hospital, Boston*

*NIH Session Co-Chair:  
Dr. James McNamara*

12:15 **LUNCH**

Friday, June 11, 1999

*SUMMARIES*

1:15 Perinatal Agenda

1:45 Pediatric Agenda

2:15 Adolescent Agenda

2:45 **BREAK**

3:00 Integration of Research Agendas and Final Comment  
Opportunities

Closing Remarks

4:00 **ADJOURN**

Afternoon Session

*Session Chair:*  
*Dr. Catherine Wilfert*

*NIH Session Co-Chair:*  
*Dr. Lynne Mofenson*

*Session Chair:*  
*Dr. Kenneth McIntosh*

*NIH Session Co-Chair:*  
*Dr. James McNamara*

*Session Chair:*  
*Dr. Craig Wilson*

*NIH Session Co-Chair:*  
*Dr. Audrey Rogers*

*Working Group Chair:*  
*Dr. John Modlin*

*Dr. Neal Nathanson*

## Appendix II

### Working Group To Review the NIH Perinatal, Pediatric, and Adolescent HIV Research Priorities

June 10-11, 1999

DoubleTree Hotel at Tysons Corner  
Falls Church, VA

#### WORKING GROUP MEMBERS

##### Chair

John F. Modlin, M.D.  
Professor of Pediatrics and Medicine  
Infectious Disease Section  
Dartmouth-Hitchcock Medical Center

##### Perinatal Session Chair

Catherine M. Wilfert, M.D.  
Scientific Director  
Elizabeth Glaser Pediatric AIDS Foundation

##### Adolescent Session Chair

Craig M. Wilson, M.D.  
Assistant Professor of Pediatrics  
Division of Geographic Medicine  
Clinical Research Director, REACH Project  
University of Alabama at Birmingham

##### Pediatric Session Chair

Kenneth McIntosh, M.D.  
Chief, Division of Infectious Diseases  
Principal Investigator  
Children's Hospital, Boston

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Elaine J. Abrams, M.D.  
Director, Pediatric AIDS Program  
Department of Pediatrics  
Harlem Hospital Center  
Columbia University

William A. Blattner, M.D.  
Professor and Associate Director  
Institute of Human Virology  
University of Maryland

Arthur J. Ammann, M.D.  
President  
Global Strategies for HIV Prevention

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## Appendix III

### Working Group To Review the NIH Perinatal, Pediatric, and Adolescent HIV Research Priorities

June 10-11, 1999

DoubleTree Hotel at Tysons Corner  
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## Appendix IV

### Glossary

<b>AIDS</b>	acquired immunodeficiency syndrome
<b>AZT</b>	azidothymidine (also known as ZDV)
<b>CDC</b>	Centers for Disease Control and Prevention
<b>ddI</b>	dideoxyinosine
<b>DNA</b>	deoxyribonucleic acid
<b>FDA</b>	Food and Drug Administration
<b>HAART</b>	highly active antiretroviral therapy
<b>HBV</b>	hepatitis B virus
<b>HbcAb</b>	hepatitis B virus core antibody
<b>HIV</b>	human immunodeficiency virus
<b>HIVNET</b>	HIV Vaccine Efficacy Trials Network for Prevention Trials
<b>HLA</b>	human leukocyte antigen
<b>HPV</b>	human papilloma virus
<b>MACS</b>	Multicenter AIDS Cohort Study
<b>NIH</b>	National Institutes of Health
<b>NNRTI</b>	non-nucleoside reverse transcriptase inhibitor
<b>OIs</b>	opportunistic infections
<b>PACTG</b>	Pediatric AIDS Clinical Trials Group
<b>PCR</b>	polymerase chain reaction
<b>PETRA</b>	Perinatal Transmission Trial
<b>PI</b>	protease inhibitor
<b>R01</b>	investigator-initiated research project
<b>REACH</b>	Reaching for Excellence in Adolescent Care and Health
<b>RNA</b>	ribonucleic acid
<b>STD</b>	sexually transmitted disease

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